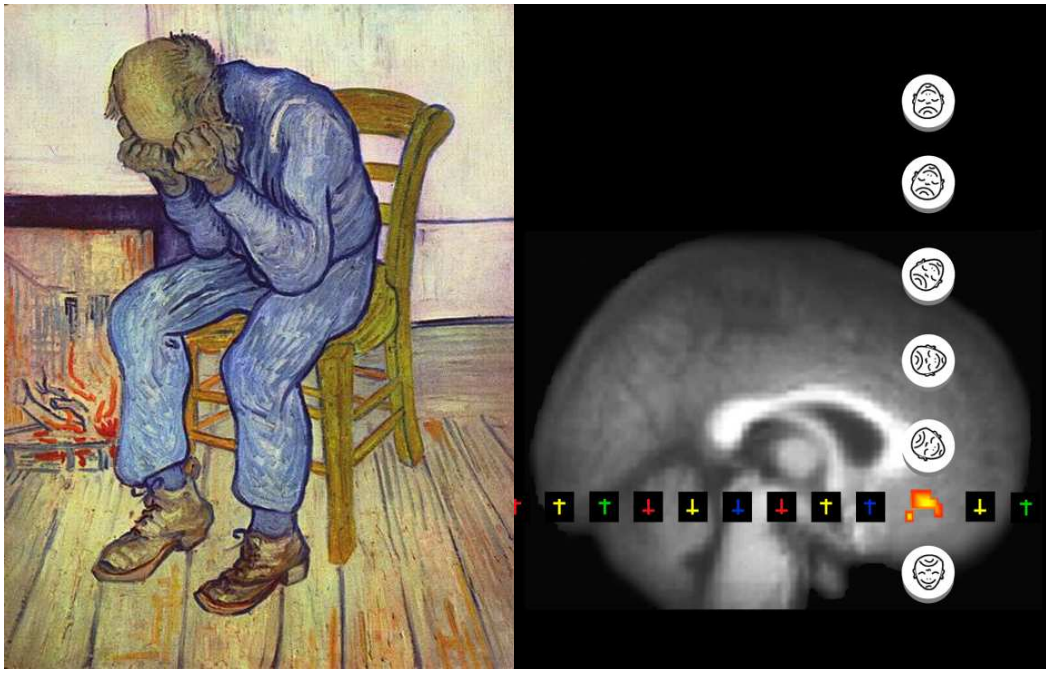
Université de Liège
Faculté de Médecine

Attentional deficits in major depression

A combined approach by clinical and functional magnetic resonance imaging studies



Martin DESSEILLES

Centre de Recherches du Cyclotron et Service de Psychiatrie
Université et Centre Hospitalier Universitaire de Liège
Promoteurs : Professeurs Pierre MAQUET et Marc ANSSEAU

Thèse présentée en vue de l'obtention du grade de
Docteur en sciences médicales
2008-2009

Cover. Left panel: *On the Threshold of Eternity* by Vincent Willem van Gogh, 1890; right panel: illustration by Sophie Schwartz adapted from Desseilles, Balteau et al. 2009.

"Si la matière grise était rose, personne
n'aurait plus d'idées noires."

Pierre DAC, Pensées, 1972.

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Summary

The major depressive disorder (MDD) is a frequent, chronic and debilitating illness characterized by affective, cognitive, motor and autonomic symptoms (DSM-IV-TR) (American Psychiatric Association 2000). Symptoms cause major distress to patients and their families. Invalidity and morbidity, including suicide, associated with this illness constitute important social and economic problems. According to the World Health Organization, depression is the 4th cause of disability and projections predict that depression will be the 2nd cause of disability in 2020 (Murray and Lopez 1997).

However, the pathophysiology of MDD is not yet elucidated. Here, we will use functional neuroimaging methods to study the cerebral mechanisms involved in MDD. We propose that a combined clinical and functional brain imaging approach to MDD will contribute to our understanding of this psychiatric disease, and will open new perspectives on cognitive and affective deficits associated with MDD.

From a cognitive point of view, MDD patients have impairments encompassing several domains of executive, memory, and attentional functioning (Austin, Ross et al. 1992; Beats, Sahakian et al. 1996; Purcell, Maruff et al. 1997; Murphy, Sahakian et al. 1999; Porter, Gallagher et al. 2003). In particular they have deficits for complex tasks including attention and short-term memory (Williams, Hagerty et al. 2000).

In MDD, functional brain imaging at rest showed impairments in polymodal associative cortices (prefrontal and parietal) and in limbic/paralimbic regions (including anterior cingulate cortex, amygdala, hippocampus) (Cummings 1993; Drevets, Price et al. 1997; Goodwin 1997; Drevets 1998; Rogers, Bradshaw et al. 1998; Price 1999; Teasdale, Howard et al. 1999; Drevets 2000; Davidson, Lewis et al. 2002; Drevets 2003; Lacerda, Nicoletti et al. 2003; Phillips, Drevets et al. 2003a; Phillips, Drevets et al. 2003b). At rest, MDD patients typically show a diminution of glucose consumption in prefrontal and parietal areas (Drevets, Price et al. 1997). Functional neuroimaging studies also revealed a deficit of activation in these areas when MDD patients performed cognitive tasks, as compared to normal controls. For instance, there is a significant correlation between frontal hypoperfusion and

cognitive alterations in MDD, in particular for tasks requiring a mental effort (Rogers, Bradshaw et al. 1998).

The brain is organized in a modular, hierarchical and recurrent manner. Firstly, modules at low hierarchical levels code for simple sensorial attributes (e.g. orientation of visual stimulus) and receive information from modules at higher hierarchical levels, which themselves code for progressively more complex attributes (e.g. faces). Secondly, at each hierarchical level of information processing, neuronal activity is modulated by the information provided by inferior and superior levels, forming a system of recurrent loops (Friston and Price 2001; Lee and Mumford 2003). The most extensively studied example concerns how attention can modulate the activity in low-levels sensory cortices (Felleman and Van Essen 1991).

In the context of MDD, this organization implies that dysfunctions at higher cortical levels (associative polymodal) may result in major changes at lower-level of information processing, including primary sensory cortices.

Using attention as a paradigmatic example of such “top-down” effects, we initially proposed and constructed an original attentional paradigm to manipulate and explore these top-down effects in healthy subjects and patients.

Using this attentional paradigm, we measured cerebral activity in 14 MDD patients and 14 healthy controls using functional magnetic resonance imaging (fMRI) while they performed attentional tasks. Our research project aimed at a better understanding of how affective and cognitive dysfunctions interfered with normal functioning in early cortical areas in MDD patients.

Finally, using the same paradigm, we conducted whole-brain correlation with clinical scores derived from the Hamilton Rating Scale for Depression in order to explore the neurobiological bases of suicidality in major depression.

To introduce the experimental studies described in the second part of this manuscript, we will first review the current knowledge about depression, including signs and symptoms of depression, stress axis and autonomic dysfunctions, cognitive abnormalities, suicide ideations and attempts, sleep impairments, brain abnormalities.

We will then propose an overview of human attention in particular how attentional processes interact with other cognitive and perceptual processes.

1. Theoretical introduction

1.1. Depression

1.1.1. Introduction

Major depressive disorder (MDD) or unipolar depression is a psychic disorder which is typically characterized by a pervasive low mood, low self-esteem, and loss of interest or pleasure in normally enjoyable activities (American Psychiatric Association 2000).

The term MDD was selected in 1980 by the American Psychiatric Association (APA) for the third version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and has become widely used since. In the DSM-III, MDD refers to a symptom cluster classified under mood disorders

The term “depression” is often overworked as it is used to describe the disorder (i.e. major depressive episode) and the symptom (i.e. depressed mood). This is the reason why a more specific terminology is favored by clinical and basic neuroscientists.

Major depression is a disabling condition which adversely affects a person's family, work or school life, sleeping and eating habits, and general health. In the United States around 3.4% of people with major depression commit suicide, and up to 60% of all people who commit suicide have depression or another mood disorder (Mann 2003).

As often in psychiatric practice, the diagnosis of MDD is based on the patient's self-reported feelings and behavior, observations by relatives or friends, and a mental status exam by a specialist.

Even if there is no specific laboratory test for major depression, physicians usually request tests for physical conditions that may cause similar symptoms (differential diagnosis) (Halbreich 2006).

While this illness can be present at any age, time of disease onset is most commonly seen between the ages of 30 and 40 years, with a later peak between 50 and 60 years.

Major depression occurs about twice as frequently in women as in men, and men are at higher risk for suicide (Sadock and Sadock 2005).

The majority of the depressed patients are treated in the community with antidepressants, psychotherapy or counseling (Sadock and Sadock 2005). Psychological treatments may be based on psychoanalysis (Blatt 1998), interpersonal communication (Dobson 2008), learning theory (Abrams 1964; Lazarus 1968), and cognitive schemata structuring personality (Beck 2008). In cases with associated self-neglect or a significant risk of harm to self or others, hospitalization may be necessary (Sadock and Sadock 2005). A minority of patients are treated either with electroconvulsive therapy (ECT), under a short-acting general anaesthetic (Pagnin, de Queiroz et al. 2004) or with transcranial magnetic stimulation (Loo and Mitchell 2005), deep brain stimulation (Glannon 2008) or surgery (Juckel, Uhl et al. 2009).

The time course of the disorder varies widely across patients, from a lifelong disorder with recurrent major depressive episodes to a single episode lasting a few months (Benazzi 2006).

Importantly, depressed individuals have shorter life expectancies than those without depression. This is due in part to being more susceptible to serious medical conditions (Carney, Blumenthal et al. 2003; Carney, Blumenthal et al. 2005; Steptoe 2006; Janszky, Ahlbom et al. 2007; Steptoe 2007).

Over the centuries, the understanding of the nature and causes of depression has evolved. Psychological (Beck 2008), biological (Nestler, Barrot et al. 2002; Mann 2005; Belmaker and Agam 2008), social (Klerman and Weissman 1978; Fullilove 2002) and evolutionary (Nesse 1999; Nettle 2004; Hendrie and Pickles 2009) causes have been proposed. An important role for monoamines (serotonin, norepinephrine, and dopamine) in depression has also been suggested, because the efficiency of most antidepressants is mediated by an increase in monoamines levels (Mann 2005; Belmaker and Agam 2008). Nevertheless, many aspects of depression are still now not fully understood.

These various issues are developed in the following introductory sections.

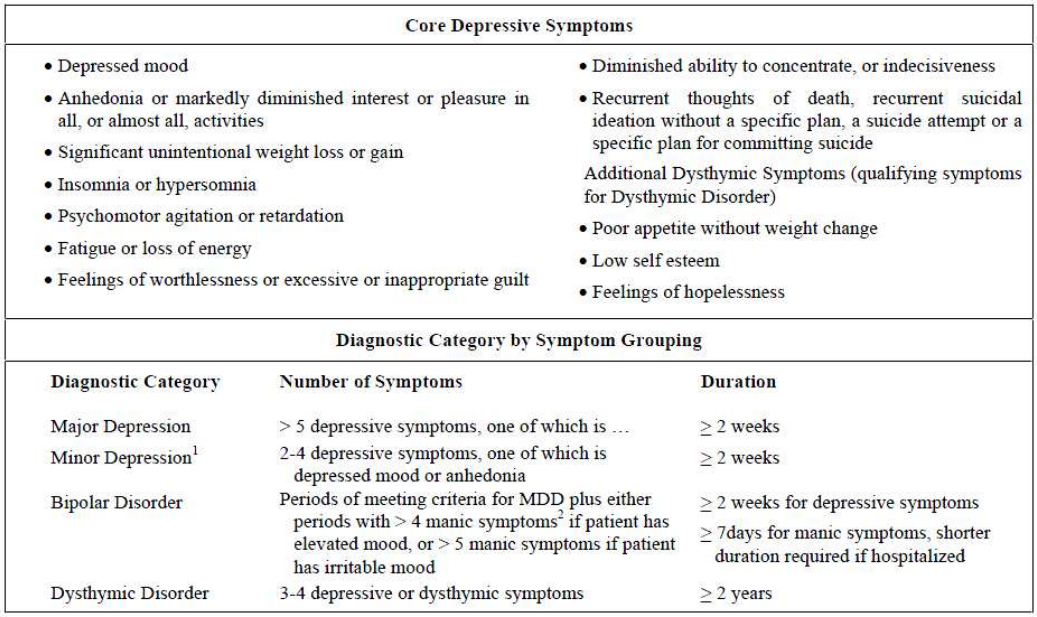
1.1.2. The spectrum of mood disorders

The term “mood disorder” refers to a cluster of different conditions in the Diagnostic and Statistical Manual of Mental Disorders 4th Revision (DSM-IV-TR) (American Psychiatric Association 2000) classification system. In that cluster, a modification in the person's emotional mood is thought to be the major underlying aspect. The same nosological cluster is known as mood / affective disorders in the chapter V (Mental and behavioural disorders) of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization 2005).

Affective disorder was first proposed as a category including all emotional disorders. Mood disorder replaced then this term to refer more specifically to the underlying emotional state, whereas affective disorder now mainly refers to the external expression observed by others.

At present, there is a broad recognition of a division between two groups based on whether the patient presented at some point with a manic or hypomanic episode: (i) depressive disorders including major depressive disorder also called major depression, and (ii) bipolar disorder, formerly called "manic depression" and characterized by intermittent periods of manic and depressed episodes, sometimes with mixed states (both states simultaneously).

Depressive disorders correspond a range of clinical presentations such as major depressive disorder (MDD), atypical depression, melancholic depression, psychotic depression, catatonic depression, postpartum depression, seasonal affective disorder and dysthymia (American Psychiatric Association 2000).



Core Depressive Symptoms

- Depressed mood
- Anhedonia or markedly diminished interest or pleasure in all, or almost all, activities
- Significant unintentional weight loss or gain
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Diminished ability to concentrate, or indecisiveness
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a suicide attempt or a specific plan for committing suicide

Additional Dysthymic Symptoms (qualifying symptoms for Dysthymic Disorder)

- Poor appetite without weight change
- Low self esteem
- Feelings of hopelessness

Diagnostic Category by Symptom Grouping

Diagnostic Category	Number of Symptoms	Duration
Major Depression	> 5 depressive symptoms, one of which is …	≥ 2 weeks
Minor Depression[1]	2-4 depressive symptoms, one of which is depressed mood or anhedonia	≥ 2 weeks
Bipolar Disorder	Periods of meeting criteria for MDD plus either periods with > 4 manic symptoms[2] if patient has elevated mood, or > 5 manic symptoms if patient has irritable mood	≥ 2 weeks for depressive symptoms ≥ 7days for manic symptoms, shorter duration required if hospitalized
Dysthymic Disorder	3-4 depressive or dysthymic symptoms	≥ 2 years

Figure 1 : Depressive symptoms and diagnostic criteria for depressive disorders (American Psychiatric Association 2000). [1] Minor depression is not yet a full categorical diagnosis in the DSM-IV but is included as a research diagnostic category. [2] Manic symptoms include elevated or irritable mood, inflated self-esteem or grandiosity, decreased need for sleep, increased talking or pressured speech, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in pleasurable activities that may have a high potential for painful consequences.

• According to the DSM-IV-TR, major depressive episode (MDE) happens when (**A**) Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (**1**) depressed mood or (**2**) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations. The nine symptoms are: (**1**) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood; (**2**) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others); (**3**) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains. (**4**) insomnia or hypersomnia nearly every day; (**5**) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down); (**6**)

fatigue or loss of energy nearly every day; (**7**) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick); (**8**) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others); (**9**) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. (**B**) The symptoms do not meet criteria for a Mixed Episode. (**C**) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. (**D**) The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism). (**E**) The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation (Figure 1).

- The diagnosis of Major depressive disorder (MDD, or major depression or unipolar depression) is considered when a person has two or more major depressive episodes. Unipolar depression describes depression without periods of mania because the mood remains at one pole / emotional state.

- Atypical depression is characterized by mood reactivity and positivity, significant weight gain or increased appetite, hypersomnia or somnolence, a sensation of heaviness in limbs known as leaden paralysis, and significant social impairment as a consequence of hypersensitivity to perceived interpersonal rejection.

- Melancholic depression is characterized by anhedonia (a loss of pleasure) in most or all activities, a failure of reactivity to pleasurable stimuli, a quality of depressed mood more pronounced than that of grief or loss, a worsening of symptoms in the morning hours, early morning waking, psychomotor retardation, excessive weight loss, or excessive guilt.

- Psychotic depression is the term for a major depressive episode, particularly of melancholic nature, where the patient experiences psychotic symptoms such as

delusions or hallucinations. These are often mood-congruent (i.e. content coincident with depressive themes such as ruin or death).

- Catatonic depression is a rare and severe form of major depression involving disturbances of motor behavior as a core symptom. The person is mute, stuporous, and either immobile or exhibits purposeless or bizarre movements. Catatonic symptoms also occur in schizophrenia, manic episode, or in neuroleptic malignant syndrome.

- Postpartum depression refers to the intense, sustained, and disabling depression experienced by women after giving birth. It has incidence rate of 10–15%, typically sets in within three months of labor, and lasts as long as three months.

- Seasonal affective disorder happens when at least two depressive episodes happen during the autumn or winter, and resolve in spring with no other episodes at other times over a two-year period or longer.

- Dysthymia, a chronic, milder mood disturbance is diagnosed when a person reports a low mood almost daily over a span of at least two years. Symptoms are not as severe as those for major depression, although people with dysthymia are vulnerable to double depression, which is a secondary episode of major depression.

- Depressive Disorder Not Otherwise Specified (DD-NOS) correspond to depressive disorders that are impairing but do not fit any of the officially DSM specified diagnoses such as Recurrent Brief Depression, and Minor Depressive Disorder.

- Recurrent brief depression (RBD) happens in people who have depressive episodes about once per month, with individual episodes lasting less than two weeks and typically less than 2–3 days. It requires that several episodes occur over the span of at least one year and, for female patients, independently of the menstrual cycle. People with major depression can develop RBD, and conversely. In addition, both illnesses have similar risks. Thus this diagnosis is distinguished from MDD primarily by differences in duration.

- Minor depression refers to a depression that does not meet full criteria for major depression but in which at least two symptoms are present for two weeks.

Bipolar disorders include subtypes such as: bipolar I, II and cyclothymia.

- Bipolar disorder is described by alternating periods of (hypo)mania and depression. For both Bipolar I and II, there are a number of specifiers that indicate the presentation and course of the disorder, including “rapid cycling”, “mixed states”, and “psychotic symptoms”.

- Bipolar I is characterized by at least one manic or mixed episodes with or without major depressive episodes.

- Bipolar II is characterized by recurrent intermittent hypomanic and depressive episodes.

- Cyclothymia is a milder form of bipolar disorder, characterized by recurrent hypomanic and dysthymic episodes, without any more severe ones occurring.

1.1.3. Signs and Symptoms of depression

Major depression is a severe mental illness that affects several domains including personal (familial) and / or professional (work or school) life, major physiological functions such as sleep and eating habits, sexual drive, motor abilities, and cognitive functions. It is a chronic and highly debilitating disease as showed by the study of Hays and collaborators (Hays, Wells et al. 1995). They have conducted a 2-year observational study of 1790 adult outpatients with several mental and physical disorders including depression, diabetes, hypertension, recent myocardial infarction, and/or congestive heart failure. They showed that depressed patients have significant and long-lasting impairments in multiple areas of functioning and well-being that equal or exceed those of patients with chronic medical illnesses (Hays, Wells et al. 1995). Overall, general (mental and physic) health of those patients is highly impaired.

People suffering from major depressive episode (MDE) usually exhibit a low mood diffusing into all facets of life. An inability to experience pleasure in previously enjoyable activities is frequent. They may ruminate over thoughts, feelings of worthlessness, inappropriate guilt or regret, helplessness or hopelessness (American Psychiatric Association 2000).

Additional symptoms include reduced concentration, poor memory, withdrawal from social situations, and abandonment of activities, reduced sexual drive, and negative thoughts about death or suicide. Sleep disorders are common, with a typical pattern of insomnia when patient wakes very early and is unable to get back to sleep. Hypersomnia, or oversleeping, may be present but are less common. Diurnal fatigue is often present in both cases (insomnia or hypersomnia) (American Psychiatric Association 2000). Appetite typically decreases, with consequential weight loss. Nevertheless increased appetite, with resulting weight gain, occasionally occurs.

Physical complaints may be the first presenting problem in several population and cultures such as in Zimbabwe, a developing country, where fatigue and headaches are the most common presentation of depression (Patel, Abas et al. 2001). In fact, nearly all depressions present with various somatic complaints in addition to cognitive and affective ones. About one half of all depressions seen by primary care physicians

initially present either mostly or exclusively with somatic symptoms and are called “masked depression” because affective symptoms are masked by somatic ones. Unfortunately, many of these masked depressions are not recognized or are misdiagnosed and consequently mistreated. Fisch hypothesized that the proportion of depressions that are masked is positively correlated to the tendency of the patients to “somatize” and negatively correlated to the ability of the medical practitioner to recognize depressions that hide behind somatic complaints (Fisch 1987).

Psychomotor symptoms are an important diagnostic clue (Schrijvers, Hulstijn et al. 2008). People close to the patient may observe that his / her behavior is either agitated or lethargic. Theoretically, a mismatch between motor activity and psychic activity may occur. For instance psychic agitation may be concomitant with motor stupor. In addition, impulsive-aggressive behaviors may be present and such behaviors have been shown to increase suicidal risk (McGirr and Turecki 2007). Interestingly, a serotonin deficiency has been implicated in a broad range of psychiatric conditions, including depressive and anxiety disorders, suicidal and aggressive behaviors as well as impulsive control disorders. Once again affective symptoms may be masked by impulsive ones. This raises the question about what should be considered a primary cause in this form of depression: the underlying disturbance of impulsivity, or the mood disorder (Lopez-Ibor 1992).

Patients with depression may experience thought disorders such as crowded thoughts or ruminations. Crowded thoughts may be conceptualized as a pathological thought process characterized by the occurrence of too many thoughts that co-exist almost simultaneously in consciousness, and that give to the subject a sense of constant and unpleasant agitation in his/her own thinking (Koukopoulos and Koukopoulos 1999). Ruminations are generally defined as “a constant preoccupation such as thinking about one single idea or theme” (Sadock and Sadock 2005). When depressed people ruminate, their thoughts are usually focused on the causes, meanings and consequences of depressive symptoms (Nolen-Hoeksema 1991). They have repetitive thoughts concerning their present distress and the circumstances surrounding their sadness (Conway, Csank et al. 2000). Depressive rumination is intimately associated to depressive mood (Papageorgiou 2004). While depressive mood might occur in the absence of ruminations (the subject is feeling permanent emotion of sadness but

his/her mind is so inhibited that he/she is unable to think), depressive ruminations are always associated with depressive mood (the subject is feeling sadness and emotional suffering while he/she is repetitively thinking about the circumstances of his sadness). In depressive ruminations, people report repetitive thoughts about a single, or sometimes a few themes, but they may not report being overwhelmed by numerous ideas dealing with possibly many themes. Moreover, in crowded thoughts patients are not able to control the stream of their thoughts and focus on any single one, while in rumination on the other hand they seem not able to change voluntarily from one topic to another one.

Within the sphere of affective disorders, subtypes of depression will have various presentations. For instance, *reactive* depression occurs as a result of an identifiable precipitating stress and symptoms include initial insomnia, anxiety, emotional lability, and multiple somatic complaints. *Melancholic* patients appear profoundly sad, disheveled and malnourished, and slowed in all aspects. Others symptoms according to DSM-IV-TR include diurnal variation of affective symptoms where depression is worse in the morning, early morning wakening, severe psychomotor retardation and severe anhedonia. Symptoms in depression occurring in *pregnancy* or in *postpartum* are the same as for major depressive episodes.

Depressed *children* present more often than adults symptoms as agitation, anxiety, somatic complaints, sad appearance, and even, mood-congruent hallucinations, compared to adults. *Adolescent* may present delinquency aggressive behavior, substance abuse, rejection hypersensitivity in addition to overeating, oversleeping, poor hygiene, and restlessness (Carlson and Kashani 1988; Ryan and Redding 2004). *Older* depressed persons may have cognitive symptoms of recent onset, such as forgetfulness, and a more noticeable slowing of movements. In severe cases, depressed people may have symptoms of psychosis such as delusions or, less commonly, hallucinations, usually of an unpleasant nature (Koenig 1991; Meyers 1995).

1.1.4. Stress axis and autonomic dysfunctions in depression

There is a large body of evidence showing that depression is associated with disturbances of hypothalamic-pituitary-adrenocortical (HPA) axis function including the metabolism of cortisol and autonomic function (Steptoe 2006; Pariante and Lightman 2008).

HPA axis is considered to be the "final common pathway" for a considerable part of the depressive symptomatology. A major part of the genetic and environmental risk factors for major depressive disorder appear to correlate with increased HPA-axis activity in adulthood. For instance, child abuse or early maternal separation constitute risk factors for later depression and are accompanied by HPA-axis hyperactivity (Swaab, Bao et al. 2005; Tarullo and Gunnar 2006). Interestingly, a spontaneous remission, the use of antidepressants or electroconvulsive therapy in animal models of depression or in patients with major depression episode is linked with a normalization of the HPA-axis function (Nemeroff 1996).

The secretion of adrenocorticotrophic hormone-releasing factor (CRF) and vasopressin (AVP) from the paraventricular nucleus (PVN) of the hypothalamus, through hypophyseal portal vessels, activates the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland, which finally causes the secretion of the glucocorticoids from the adrenal cortex (i.e. cortisol in humans and corticosterone in rodents) (Figure 2). These glucocorticoids are responsible for feedback inhibition both on CRF and AVP from the hypothalamus and directly on secretion of ACTH from pituitary corticotropes where they interact with their receptors. In addition, the HPA axis regulates bodily peripheral functions including metabolism and immunity and has deep effects on the brain. For instance, glucocorticoids can regulate neuronal survival, cause neurogenesis, modulate the size of the hippocampus, control the acquisition of new memories and organize the emotional appraisal of events (Herbert, Goodyer et al. 2006). Thus, HPA axis activities play roles at the interface between brain functioning and stress and has been found abnormal in several psychiatric disorders, and in particular in major depression.

HPA dysregulation is observed in approximately 50 % of patients with unipolar depression and it may contribute to the association between depressive symptoms and

many types of physical disorders including, for instance, diabetes, obesity, heart disease, chronic fatigue and cancer (Steptoe 2006). These depressed patients have been found to have increased levels of cortisol in the saliva, plasma and urine, and increased size and activity of the pituitary and adrenal glands (Nemeroff and Vale 2005). These changes in HPA activity may be different depending on the subtypes of depression (Stewart, Quitkin et al. 2005).

On the other hand, oxytocin (OXT) inhibits ACTH release providing an example of the various "ying-yang" actions of AVP and OXT (Legros 2001; Neumann 2008). Moreover, activation of OXT neurons has been related to decreased appetite and weight loss in depression, and particularly in melancholic subtype of depression where loss of weight is one of the key characteristics due to the central effects of this neuropeptide as a satiety hormone (Gimpl and Fahrenholz 2001; Meynen, Unmehopa et al. 2007).

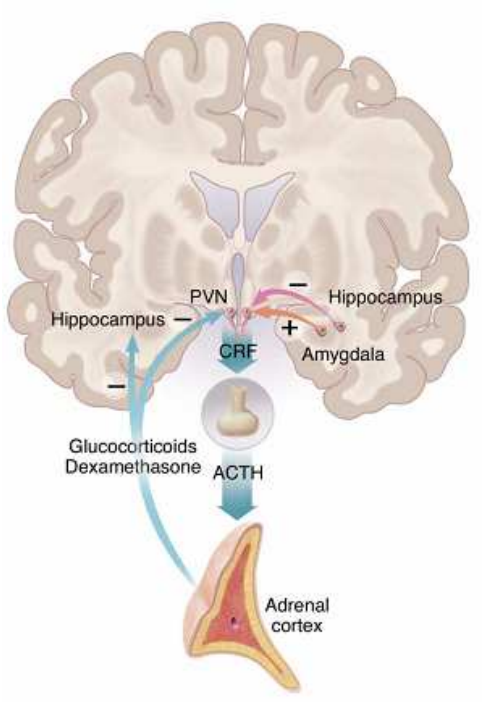


Figure 2 : Regulation of the HPA axis CRF-containing parvocellular neurons of the PVN of the hypothalamus integrate information relevant to stress (Nestler, Barrot et al. 2002). Prominent neural inputs include among other (i) excitatory afferents from the amygdala, (ii) inhibitory afferents from the hippocampus, and (iii) direct and indirect inputs from ascending monoamine pathways including the norepinephrine (from the locus coeruleus or LC) and the serotonin (from the dorsal raphé or DR) (not shown).

In addition to HPA axis function, the paraventricular nucleus (PVN) of the hypothalamus is involved in autonomic nervous system (ANS) regulation. It influences brainstem autonomic control nuclei. The hypothalamus in turn receives inputs from the limbic system, particularly from the central nucleus of the amygdala (the major output way from the amygdala), which operates in tight association with the prefrontal neocortex in order to integrate affective / emotional and motivational behaviours. It has been suggested that the ANS dysregulation underpins the increased risk of heart disease in depressed patients.

Several aspects of the ANS activity have been explored, including heart-rate levels and autonomic control processes governing baroreceptor reflex sensitivity and cardiac sympathovagal balance. This latter aspect has been assessed either with simple temporal measures, or with more complex power spectrum analysis. Heart-rate-variability (HRV) is typically computed by spectral methods. In spectrum analysis, high-frequency power is thought to reflect parasympathetic or vagal tone, while low-frequency power probably reflects sympathovagal balance and baroreceptor receptor reflex modulation of heart rate. Low level of heart-rate variability and low parasympathetic tone predict future cardiac heart disease in apparently healthy individuals (Steptoe 2006).

Comparisons between depressed patients and healthy controls have shown increased sympathetic nervous system activity in patients, but methodological issues have to be pointed out since controls for smoking, body mass and physical activity, altering neuroendocrine function, are often lacking. Sympathetic activation and reduced vagal tone are also known to reduce the threshold for cardiac ventricular fibrillation and to stimulate ventricular arrhythmias. In addition, if there is large evidence that resting heart rate is higher in depressed patients than healthy individuals, data concerning HRV and sympathovagal balance are more mixed and this mechanism has become increasingly difficult to study in clinical sample because of the large use of beta-blockers. Nevertheless, depression was associated with alteration of cardiac autonomic tone towards decreased parasympathetic activity and an increased sympathetic activity (Udupa, Sathyaprabha et al. 2007).

Major depression is a risk factor for medical morbidity and mortality in patients with coronary heart disease (CHD). In addition to elevated levels of plasma catecholamines and elevated heart rate, dysregulation of the ANS as been shown through low heart rate variability, exaggerated heart rate responses to physical stressors, high variability

in ventricular repolarization, and low baroreceptor sensitivity. Interestingly, all of these indicators have been linked to increased risks of mortality and cardiac morbidity in patients with CHD (Carney, Freedland et al. 2005).
Moreover, patients suffering from depression show a two to fourfold increase in sudden death and a sevenfold increase in ventricular arrhythmia (Carney, Freedland et al. 2005). These cardiac risks are hypothesized to result partly from elevated noradrenergic and sympathetic autonomic function, together with reduced parasympathetic tone on the heart rate (Carney, Freedland et al. 2005).

Various autonomic dysfunctions occur according to the subtype of depression (Rechlin, Weis et al. 1994). For instance, patients with reactive depression did not show any differences in auconomic function when they were compared with a control group. Patients with major depression had lower values of the high-frequency peak of spectral analysis than in the other depression subgroups, indicating decreased parasympathetic activity.

Given the interconnections between autonomic functions and depression, it is likely that a common neurobiological dysfunction contributes to both depression and cardiac autonomic changes in the illness. Indeed, the medial prefrontal cortex (mPFC) and associated limbic structures (including amygdala) give forebrain inflection over visceral control structures in the hypothalamus and brainstem. Dysfunction in this network can account for the neuroendocrine impairment and disturbances in ANS regulation associated with MDD (Drevets, Price et al. 2008). Firstly, amygdala stimulation of the locus ceruleus, lateral hypothalamus and periaqueductal gray matter (PAG) increases sympathetic autonomic arousal in rodents (Gold and Chrousos 2002; LeDoux 2003). Secondly, the parasympathetic tone on the heart-rate is partly regulated by projections from the infralimbic cortex (which putatively forms the posterior segment of the human subgenual anterior cingulate cortex) to the nucleus of the tractus solitarius of the vagus nerve, and structural lesions of this area reduce the parasympathetic tone on the heart in rodents (Frysztak and Neafsey 1994). The combined effect of the hyperactivity within the amygdala and reduced infralimbic cortex function could account for the increased sympathetic tone on the heart rate seen in patients with depression (Carney, Freedland et al. 2005).

1.1.5. Cognitive abnormalities in depression

Several cognitive models aimed at describing mechanisms of depression. *Beck's cognitive model* proposes that unpleasant events during childhood lead to the development of negative automatic cognitive schemata, activated by stressors later in life (Beck, Rush et al. 1979; Wright and Beck 1983; Beck 2008). These schemata drive cognitive distortions that contribute to the maintenance of negativity directed at the *self* (i.e. self-focused ruminations), *world* and *future* (Beck's negative triad) (Figure 3). The *learned helplessness model* proposes that adverse experiences lead to subjects accepting that their actions cannot modulate outcomes, i.e. a state of helplessness, which impedes motivation and cognitive learning processes (Seligman 1972; Miller and Seligman 1975; Miller, Seligman et al. 1975; Klein, Fencil-Morse et al. 1976; Miller and Seligman 1976; Seligman 1978; Nolen-Hoeksema, Girgus et al. 1986). The *Seligman's attribution model* proposes that patients suffering from depression attribute the causes of perceived failures inappropriately to internal, global, and stable factors (Seligman, Abramson et al. 1979; Raps, Peterson et al. 1982; Alloy, Peterson et al. 1984).

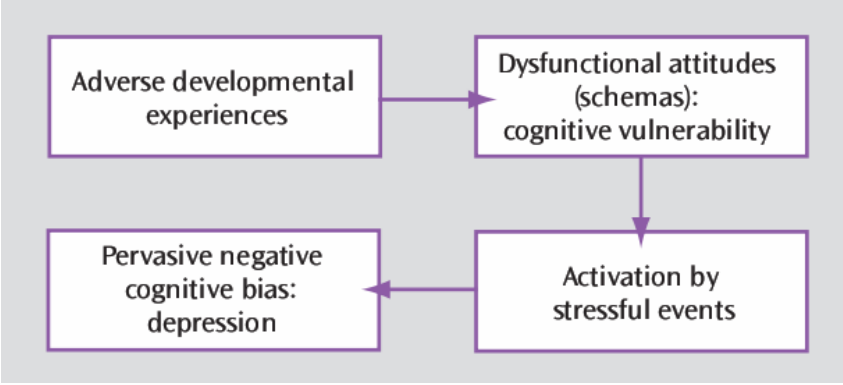


Figure 3 : Developmental model of depression based on vulnerability diathesis and stressful life events, from (Beck 2008).

Cognitive distortions are multiple (Beck, Rush et al. 1979; Kleftaras 2004): (i) *All-or-Nothing Thinking:* This type of thinking is characterized by absolute terms like *always*, *never*, and *forever*. However, few situations are ever this absolute and they present generally more nuances. (ii) *Overgeneralization:* taking an isolated case or cases and assuming that all others are the same. (iii) *Mental Filter:* mentally singling out only the adverse events in the life and overlooking the positive. (iv) *Disqualifying*

the Positive: taking the positive in a situation and turning it into a negative. (v) *Jumping to Conclusions:* expecting the worst and beginning to prepare early for the disappointment. (vi) *Magnification and Minimization:* looking at all the positive through the wrong end of the telescope and the negative through the other end. (vii) *Emotional Reasoning:* basing the assessment of the situation on how it makes the subject *feel* and not how it really is. (viii) *Should Statements:* thinking things *should* be a certain way even if they aren't. (ix) *Labeling and Mislabeling:* labelling himself / herself as bad, lazy and hopeless. (x) *Personalization:* taking all the responsibility for how (bad) another person is doing in life or how horrible is a situation in the world.

Psychological approaches based on these models have led to cognitive psychotherapies aiming at (i) training patients to focus on the interactions between affects, cognition and behaviour, (ii) evaluating validity of client's thoughts and beliefs to assess what the client expects and predicts and (iii) assessing client's attributions for causes of events and to try alternative conceptualisations (Socratic questioning and cognitive restructuring) (Beck 1993; Beck 1997).

Early neuropsychological investigations used pen-and-paper approaches and shed light on abnormalities in cognitive flexibility and the retrieval of work lists in patients with mood disorders (Breslow, Kocsis et al. 1980; Calev, Korin et al. 1986). Recent neuropsychological investigations used computerized diagnostic tools such as those in the Cambridge neuropsychological test automated battery (CANTAB) (Cambrige Cognition Accessed february 07, 2009). Attentional deficits during depressive episodes are described in the DSM-IV (American Psychiatric Association 2000), i.e. “reduced ability to think or concentrate”. Similarly, psychomotor retardation during cognitive task is also a criterion of DSM-IV depression. A major issue of neuropsychological experimentation is the development of objective tests aiming at (i) detect the onset, (ii) monitor the course of major depression, and (iii) assess the efficacy of various treatments.

Several neuropsychological studies have shown that several cognitive domains are consistently impaired in patients suffering from major depression, including (i) early information processing, (ii) attention, (iii) memory and (iv) executive functioning (Fossati, Ergis et al. 2002; Ottowitz, Dougherty et al. 2002; Taylor Tavares, Drevets

et al. 2003; Chamberlain and Sahakian 2004; Chamberlain and Sahakian 2006; Drevets, Price et al. 2008) while other studies did not found such abnormalities (Channon, Baker et al. 1993; Purcell, Maruff et al. 1997; Grant, Thase et al. 2001). Discrepancies might come from methodological heterogeneities including heterogeneous patients groups, medication status, and differences in cognitive paradigms used which are thought to assess the same cognitive functions.

Inspection time (minimum stimulus presentation time necessary for near perfect performance on a two-choice visual discrimination task), thought to assess the speed of *early information processing* independent of motor speed or cognitive strategy, was shown to be longer in patients than in controls (Tsourtos, Thompson et al. 2002).

Even if subjective impairments of attention and concentration are frequently reported in major depressive episodes, standard measures depending on traditional neuropsychological test batteries have failed to identify clear, consistent patterns of deficits in MDD (Elliott, Sahakian et al. 1996; Purcell, Maruff et al. 1997; Grant, Thase et al. 2001; Ravnkilde, Videbech et al. 2002), probably due in part to the absence of tasks designed specifically for this clinical population (Drevets, Price et al. 2008).

Selective attention and working memory (Landro, Stiles et al. 2001; Stordal, Lundervold et al. 2004; Rose and Ebmeier 2006) were shown to be impaired in patients with major depression. Nevertheless some discrepancies remain (Purcell, Maruff et al. 1997). For instance, Purcell and collaborators did not find any impairment in short-term memory capacity, spatial working memory, planning ability and cognitive speed in 20 young patients with unipolar depression, compared with 20 matched healthy subjects (Purcell, Maruff et al. 1997).

A*ffective processing biases* have frequently been described, e.g. patients suffering from depression have excessive recall of negative (autobiographical) material as compared to positively toned information (Williams and Scott 1988; Brittlebank, Scott et al. 1993; Bradley, Mogg et al. 1995; Murray, Whitehouse et al. 1999); present more interference with depression-related negative (compared to happy or neutral) words on emotional stroop tasks (attentional paradigm that works by examining the

response time of the participant to name colours of emotional words) (Gallardo Perez, Banos Rivera et al. 1999; Broomfield, Davies et al. 2007); respond more rapidly to sad versus happy words in an affective Go/No-Go task (affective attention shifting task - requiring a motor response as quickly as possible to affective words fitting with only one category such as sad versus happy) when they are medicated (Murphy, Sahakian et al. 1999), or unmedicated (Erickson, Drevets et al. 2005); attend preferentially to faces with sad expressions in a face dot-probe task (assessing the allocation of attention between neutral or emotional faces) (Gotlib, Kasch et al. 2004a; Gotlib, Krasnoperova et al. 2004b); interpret more negatively ambiguous words (Mogg, Bradbury et al. 2006) and situations (Nunn, Mathews et al. 1997) as compared with healthy participants.

Moreover, abnormal response to *negative feedback*, leading patients to ruminate over their perceived failures (Elliott, Baker et al. 1997), has been described in depressive patients using the new tower of London test of planning and the delayed matching to sample test of memory from the CANTAB. In the first test there are two boards with pegs and several beads with different colours and the examiner uses the beads and the boards to present the examinee with problem-solving tasks (a computerised variant, known as the Stockings of Cambridge test, is available as part of CANTAB); in the second test, the subject is shown a complex visual pattern (the sample) and then, after a brief delay, four similar patterns. The subject must touch the pattern which exactly matches the sample. Indeed, the probability of failing a problem given that the previous one was failed increases significantly selectively in depressed patients (Elliott, Sahakian et al. 1997). This observation suggests that depressed patients fail to use negative feedback as a motivational (goal directed) encouragement to improve their performance. Thus, unlike controls, depressed patients might not improve their performance after an error, and after the perception of a wrong performance they might allocate their attentional resources more toward themselves than toward the task (Ingram 1990).

Several studies suggest that cognitive deficits in major depression may depend on age, severity of illness and presence of psychotic or melancholic features (Mossner, Mikova et al. 2007). Cognitive deficits in depression could be associated with both trait and state features and raise questions regarding the long-term cognitive

functioning in patients with major depressive disorders. These deficits may be explained by structural or functional changes associated with the severity of illness, ageing effects or a possible cumulative pathologic effect of depression on brain structure and function across recurrent episodes of illness (Mossner, Mikova et al. 2007). These residual cognitive deficits, occurring independently of mood state, include psychomotor slowing, impaired memory and impaired sustained attention (O'Brien, Sahakian et al. 1993; Silverstein, Harrow et al. 1994; Tham, Engelbrektson et al. 1997; Ferrier, Stanton et al. 1999; Rubinsztein, Michael et al. 2000; Clark, Iversen et al. 2002; Clark, Kempton et al. 2005; Paelecke-Habermann, Pohl et al. 2005; Goswami, Sharma et al. 2006).

1.1.6. Suicide ideations and attempts

Around one million of fatal suicide (FS) and ten million suicide attempts (SA) occur worldwide each year. Frequently, suicide is consecutive to a psychiatric disorder, most commonly a mood disorder (see for example Beautrais, Joyce et al. 1996). Several other psychiatric conditions or traits have been related to suicide, including schizophrenia (Perenyi and Forlano 2005), alcoholism (Murphy, Wetzel et al. 1992), substance abuse (Murphy 1988), personality disorders (Krysinska, Heller et al. 2006), aggressive/impulsive, hopelessness or pessimistic traits (Brezo, Paris et al. 2006), a history of physical or sexual abuse during childhood (Joiner, Sachs-Ericsson et al. 2007), a history of head injury (Wasserman, Shaw et al. 2008) or neurological disorder (Faber 2003) (Figure 4).

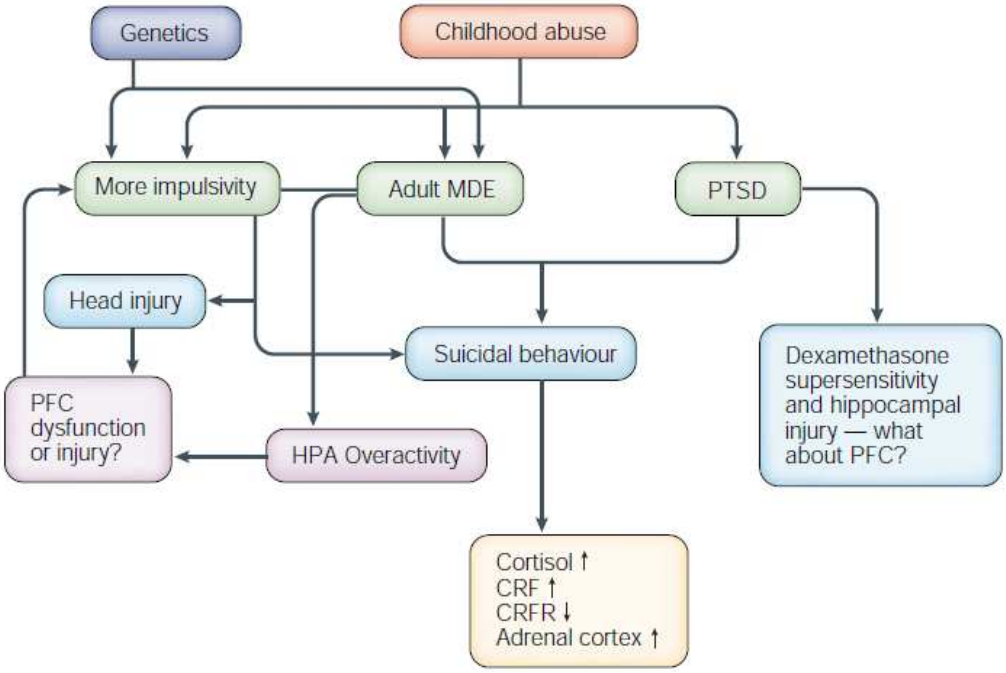


Figure 4 : Effects of genetics, head injury and childhood abuse on mood disorders and impulsivity in relation to suicidal behaviour. Impulsivity in combination with a mood disorder or post-traumatic stress disorder (PTSD) increases the risk of suicidal behaviour. CRF, corticotrophin releasing factor; CRFR, CRF receptor; HPA, hypothalamic pituitary adrenal; MDE, major depressive episode; PFC, prefrontal cortex (Mann 2003).

In addition, various psychosocial factors correlate with suicidal behaviour, including rural areas, high rates of gun ownership, poverty, unemployment, social isolation (Smith, Mercy et al. 1988; Beautrais, Joyce et al. 1996) and imitation (Gould 1990; Johnson, Cohen et al. 2002).

Neurobiological correlates of the diathesis-stress model of suicidal acts involve the serotonergic dorsal raphe (DR), noradrenergic locus coeruleus (LC), and the ventromedial prefrontal cortex (vmPFC).

The diathesis–stress model is a psychological theory explaining behaviours as resulting from both (i) biological and genetic factors ("nature"), and (ii) life experiences ("nurture"). This model assumes that a disposition towards a certain disorder may result from a combination of genetic background and early learning (e.g. as occurring during sexual abuse). The term "diathesis" refers to a genetic

predisposition toward an abnormal condition and this predisposition, in combination with certain kinds of environmental stress, results in abnormal behaviours.

Neurochemical correlates (including indices of neurotransmitters, signal transduction and cellular morphology) of suicidal behaviour have been studied mainly through post-mortem brain tissue analysis. This kind of analysis presents some limitations that include confounding effects of ante-mortem drug treatment and the possibility of examining the brain only at one point in time.

A large majority of post-mortem studies of suicide examined the *serotonergic* system because early studies (Stanley, Virgilio et al. 1982; Stanley and Mann 1983) identified fewer presynaptic serotonin (5-HT, 5-hydroxytryptamine) transporter sites in several brain areas including vmPFC (Arango, Underwood et al. 1995). In addition, upregulation of 5-HT1A receptor in the vmPFC was observed (Mann and Arango 2001). The same area is involved in behavioural and cognitive inhibition that may be important in order to diminish aggressive or suicidal feelings. There have been fewer studies about *noradrenergic* neurotransmission. Overall, they showed fewer noradrenergic neurons (Arango, Underwood et al. 1996), lower noradrenaline levels and higher number of alpha-2 adrenergic receptors in the LC of suicide victims (Ordway, Widdowson et al. 1994) and higher beta-1 adrenergic receptor binding (Mann, Stanley et al. 1986) with lower alpha-adrenergic binding (Arango, Ernsberger et al. 1993) in PFC, indicating respectively a brainstem noradrenergic hypoactivity and a cortical noradrenergic overactivity. The latter could have conducted to the former. Although the *dopamine* system is abnormal in depression, available studies are too scarce to determine whether it can be implicated in suicide.

Genes by environment interactions have been pinpointed. For instance, peer-reared monkeys have lower serotonergic activity, persisting into adulthood and reflected in greater impulsivity and aggression, as compared to maternally raised monkeys (Higley, Thompson et al. 1993). Stress increases noradrenergic system, HPA axis and cortisol release (Pittenger and Duman 2008). One simple extrapolation may be made with child abuse resulting sometimes in post-traumatic stress disorder (PTSD). This example illustrates the impact of parenting (i.e. neglect, physical or sexual abuse) and

stress, two environmental factors interacting with serotonergic and noradrenergic activity.

Specific genes that promote suicide risk independently of an associated psychiatric disorder are unknown. The majority of genetic studies have been candidate-gene association studies examining the relationship between genetic variation in serotonin-related genes (including tryptophan hydroxylase – the rate-limiting enzyme of serotonin, the serotonin transporter or SERT, several serotonin receptors and the monoamine oxidase promoter (Mann 2003), and both suicidal behaviour and impulsive aggression. For instance, SERT promoter region has two allelic variants which differ in a 44-base pair stretch: a long and a short form. In mood disorders associations have been reported between the short form and violent suicide attempts (Bellivier, Szoke et al. 2000).

Ventromedial prefrontal cortex (vmPFC) and its connections with the amgydala have been involved in decision-making (Bechara, Damasio et al. 2000) and in volitional acts (Ingvar 1994). It suggests that a decrease of activity within the vmPFC, that provides insights into consequences of future actions, including self-harm suicidal acts, could increase impulsive acts. Orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) have been proposed to suppress emotions, through inhibition of the amygala (Davidson, Putnam et al. 2000). For instance, lower vmPFC activity and impaired serotonergic responsivity were proportional to the lethality of the SA and may act as a go-between the effects of suicide intent and impulsivity on lethality.

The risk of suicidal behaviour is increased in the first month after starting antidepressants (including amitriptyline, fluoxetine and paroxetine), in particular during the first nine days (Jick, Kaye et al. 2004). This increase of deliberate acts of self-harm is thus not uncommon and has been hypothesised to be due to a mismatch in symptom improvement. That is, physical energy gets better first while resolution of negative thoughts, including suicidal ideations and hopelessness, is slower. Congruently to this hypothesis, other studies observed a significantly higher risk of SA during the first week of antidepressant treatment compared to later weeks (Simon, Savarino et al. 2006; Simon and Savarino 2007). In addition, the relative risk of FS among patients who were first prescribed an antidepressant within 1 to 9 days before the date of suicidal behaviour (index date) was 38.0 compared with those who were

first prescribed an antidepressant 90 days or more before their index date (Jick, Kaye et al. 2004).

While studies highlighted increase of SA or FS following antidepressant use, we should nevertheless keep in mind (i) that symptoms of depression, including negative mood and suicidal ideations, are the reason why antidepressants are prescribed, and (ii) that the risk of suicide declines sharply after starting treatment with antidepressants (Simon, Savarino et al. 2006). Indeed, management of a suicidal patient includes (i) the diagnosis and treatment of a possible psychiatric disorder, (ii) the assessment of suicide risk and the maintenance of a distance from the most lethal methods for suicide, and (iii) a specific treatment aiming at reducing the nature-nurture interaction contributing to SA.

1.1.7. Sleep and depression

Another major symptom of depression is sleep impairment. In fact, nearly 90 % of depressed patients show alterations of sleep observed polysomnographically (Wilson and Nutt 2008).

Insomnia and depression are closely linked, suggesting a neurobiological overlap, but intimate mechanisms are still hypothetical (Adrien 2002). A combination of various factors (including neurotransmission polymorphisms, HPA hyperactivity, and impaired plasticity) is thought to cause sleep changes in depression. To make these mechanisms more clear, recent technologies involving functional brain imaging associated to traditional polysomnography are interesting.

Depression and insomnia have a reciprocal relationship: (i) depressed patients exhibit higher rates of insomnia than the general population (American Psychiatric Association 2000; Peterson and Benca 2006) and (ii) insomnia is a risk factor for depression (Ford and Kamerow 1989; Hohagen, Rink et al. 1993; Breslau, Roth et al. 1996; Chang, Ford et al. 1997; Roberts, Shema et al. 2000; Franzen and Buysse 2008). Yet the “chicken or the egg” causality dilemma remains as “which came first, the depression or the insomnia?”, that is whether insomnia is a premorbid trait of

depression or a precursor leading to depression, or alternatively an independent risk factor (Riemann, Berger et al. 2001; Riemann 2007).

Sleep troubles, including both insomnia and hypersomnolence, constitute part of the diagnostic criteria for mood disorders. Depressed patients often complain of at least one of the following difficulties: falling asleep, fragmented sleep, disturbing dreams, early morning awakening, nonrestorative sleep, daytime sleepiness, decrease amount of sleep (Perlis, Giles et al. 1997; Ohayon 2002; Ohayon 2005). A minority of patients presents hypersomnolence during their depression, in particular those with bipolar and atypical depression (Wilson and Nutt 2008).

In patients with depression, there is a poor correlation between subjective insomnia and objective sleep parameters, possibly due to (i) misperceptions by the patient, or (ii) failure to measure the appropriate physiological parameters, (iii) severity of depression (proportional relationship with the accuracy of subjective sleep assessment), (iv) Age (proportional relationship with the poor accuracy of subjective sleep assessment), (v) greater proportion of light sleep (inversely, subjectively more restorative sleep might be correlated with increases in slow-waves sleep (SWS) (Argyropoulos, Hicks et al. 2003; Tsuchiyama, Nagayama et al. 2003).

Polysomnography shows the similarities in the sleep parameters that are affected in insomnia and depression: in both disorders, compared with normal individuals, (Benca, Obermeyer et al. 1992) there is a reduction of (i) total sleep time, (ii) sleep efficiency, (iii) SWS time and percentage, (iv) and sleep latency is increased. Rapid Eye Movement (REM) sleep parameters are not clearly altered in patients suffering from insomnia, contrarily REM latency is decreased and the percentage of REM sleep is increased in patients with depression.

Sleep disturbances can continue even during periods of depression remission suggesting that insomnia could be a trait of depression (Ohayon and Roth 2003; Taylor, Lichstein et al. 2005; Kaneita, Ohida et al. 2006; Ohayon and Hong 2006; Peterson and Benca 2006). Insomnia has also been considered as the most common refractory symptom of mood disorders, such as depression (Nierenberg, Keefe et al. 1999). In that way, persistence of insomnia after a depressive episode has been shown

to be predictive of increased severity and recurrence of mood disorders (Dew, Reynolds et al. 1997; Bauer, Grof et al. 2006).

On the other hand, insomnia could be considered as a precursor leading to depression since patients with insomnia are up to 10 times more likely to have depression than normal sleepers (Taylor, Lichstein et al. 2005; Kaneita, Ohida et al. 2006; Ohayon and Hong 2006), and those with persistent insomnia, as compared with those who have no sleep complaints, have a significant higher risk of developing new-onset depression (Ford and Kamerow 1989; Breslau, Roth et al. 1996; Chang, Ford et al. 1997). The temporality between insomnia and depression is shaped with insomnia tending to precede or co-occur with mood disorders; in contrast it tends to present at the same time or following onset of an anxiety disorder (Ohayon and Roth 2003).

Several biological mechanisms might explain altered sleep patterns in depressed patients: including (i) deficits in monoaminergic neurotransmission, (ii) abnormalities in circadian genes, (iii) overactivity of the hypothalamic–pituitary–adrenal (HPA) axis, and (iv) impaired functioning of plasticity-related gene cascades.

(i) *Deficits in monoaminergic neurotransmission*. During normal sleep, electroencephalograph (EEG) activity typically reveals progressive transitions from “light” sleep to “deep sleep”, and the alternation across the night of non-rapid eye movement (NREM) sleep (including slow-waves sleep (SWS) with episodes of REM sleep. This latter stage is initiated when the monoamines (serotonergic and noradrenergic) activity decreases and cholinergic activity increases, and ceases with the opposite changes (Pace-Schott and Hobson 2002). In patients with depression, REM sleep propensity is increased, conducting to reduced REM latency, increased proportion of REM sleep, and an increase in the number of eye movements (REM density) (Benca, Obermeyer et al. 1992). Additionally, time spent in SWS and the proportion of overall sleep that is SWS are also decreased (Benca, Obermeyer et al. 1992). Depression may be worsened when levels of monoaminergic neurotransmitters are decreased and antidepressant drugs that increase monoaminergic drive apparently reverse

these abnormalities, increasing REM sleep latency and decreasing REM density (Thase 1998; Argyropoulos and Wilson 2005) (Figure 5) .

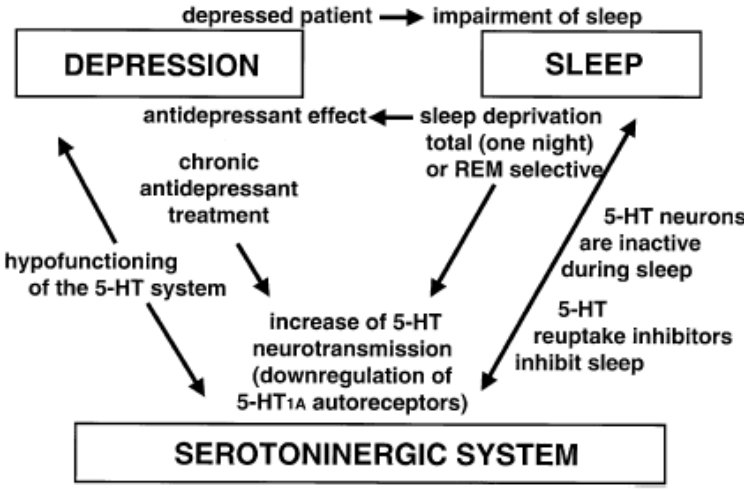


Figure 5 : Summary of the relations between sleep, depression, and the serotoninergic system (Adrien 2002).

(ii) *Abnormalities in circadian genes*. Circadian genes involved in the control of biological rhythms are another link between depression and insomnia. The central pacemaker within the suprachiasmatic nuclei (SCN) of the anterior hypothalamus controls circadian rhythms (Glass, Hauser et al. 1993). Among the genes supposed to interact with the SCN pacemaker, irregularities in the Circadian Locomotor Output Cycles Kaput (CLOCK) gene might have a major influence on sleep patterns. Recent studies showed that a polymorphism (C to T nucleotide substitution) in the 3′ flanking region of the human CLOCK gene is associated with diurnal preferences of human healthy subjects, with higher "eveningness" in subjects carrying at least one copy of the C allele (Benedetti, Serretti et al. 2003). Patients presenting a major depressive disorder who have a C/C variant polymorphism in their CLOCK gene are more likely to experience lifetime insomnia, have a significant higher recurrence of initial insomnia, and experience significantly worse insomnia during antidepressant treatment than patients without this variant (Serretti, Benedetti et al. 2003; Serretti, Cusin et al. 2005). In addition to CLOCK gene, period gene

(PER) and timeless gene (tim) have been involved in mental disorders (Lamont, Legault-Coutu et al. 2007).

(iii) *Overactivity of the hypothalamic–pituitary–adrenal (HPA) axis*. Hypothalamus is also involved in HPA axis abnormalities that are considered as the "final" common pathway for many depressive symptoms. HPA overactivation has been involved in the development of mood disorders (Bao, Meynen et al. 2008) and sleep disturbance (Nestler, Barrot et al. 2002; Steiger 2007). Corticotrophin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus play a key role in HPA axis activity. Several evidences link insomnia and depression since CRH neurons are activated in depression, CRH mRNA is increased in the paraventricular nucleus, antidepressants decrease CRH levels, and CRH antagonists have potential in the treatment of depression (Steiger 2007; Bao, Meynen et al. 2008) while, on the sleep side, growth hormone inhibits the HPA axis, growth hormone-releasing hormone (GHRH) stimulates NREM sleep, CRH reduces NREM cycles, suppresses SWS and may enhance REM sleep (Holsboer, von Bardeleben et al. 1988; Tsuchiyama, Uchimura et al. 1995; Steiger 2007).

(iv) *Impaired functioning of plasticity-related gene cascades*. Neural plasticity is closely linked to learning, memory, sleep, and cortisol regulation (Dang-Vu, Desseilles et al. 2006). Indeed genes related to plasticity are mainly expressed during waking, whereas genes related to synaptic downscaling are expressed during sleep, and particularly during SWS (Tononi and Cirelli 2006). It is possible that sleep is needed for the downscaling of synapses on a daily basis, and that disturbances in sleep and/or mood disorders could affect this course (Tononi and Cirelli 2006). On the other hand, sleep deprivation might increase plasticity-related gene expression during wakefulness, strengthening synapses in brain regions that are involved in mood regulation, and thus accounting for the acute antidepressant effects of sleep deprivation therapies (Manji, Quiroz et al. 2003; Zarate, Singh et al. 2006).

Sleep deprivation (SD) has been consistently shown to provoke a rapid, striking, and temporary antidepressant effect in patients with depression (Wu and Bunney 1990).

The degree of improvement after only one night of SD seems to be equivalent to the response rate for six weeks of antidepressant treatment (Gillin, Buchsbaum et al. 2001). Nevertheless, total SD for one whole night improves depressive symptoms in 40-60% of treatments and the degree of clinical change spans a continuum from complete remission to worsening (in 2-7%) (Giedke and Schwarzler 2002). This somatic therapy has other side effects such as sleepiness and (hypo-) mania. Often the temporal course of amelioration is (i) in the SD night or on the following day, but (ii) 10 to 15% of patients respond after recovery sleep only, and (iii) after recovery sleep 50-80% of day 1 responders have a complete or partial relapse, (iv) nevertheless enhancement can last for weeks (Giedke and Schwarzler 2002). Interestingly, SD treatment effects may be stabilised by antidepressant drugs, lithium, shifting of sleep time or light therapy. The best predictor of a therapeutic effect is a large variability of mood. Current opinion is that partial SD in the second half of the night is equally effective as total SD. There are, nevertheless, indications that total SD has better effects (Giedke, Klingberg et al. 2003).

Many hypotheses have been proposed to explain the rapid antidepressant actions of sleep deprivation (Wu and Bunney 1990; Wirz-Justice and Van den Hoofdakker 1999) through a direct regulation in neurotransmission. For instance, serotonin-mediated effects have been shown to decrease sensitivity of serotonergic 1A auto-receptors after total sleep deprivation (Gardner, Fornal et al. 1997) (Figure 5).
Interestingly, the anterior cingulate cortex (ACC) has been involved in antidepressant response to sleep deprivation using various experimental paradigms showing an hyper activity at baseline in SD responders and a normalisation after SD (Ebert, Feistel et al. 1991; Wu, Gillin et al. 1992; Wu, Buchsbaum et al. 1999; Clark, Brown et al. 2006; Clark, Brown et al. 2006).

1.1.8. Brain abnormalities in depression

Over the last decade, different models of brain mechanisms associated with mood disorders and major depression have been proposed. I will first present the model proposed by Mayberg and collaborators, and then the model developed by Drevets and colleagues.

1.1.1.1. The limbic-cortical dysregulation model

Mayberg and collaborators proposed that major depression results from a failure in the coordination of interactions within a distributed network of cortical, subcortical and limbic areas (Mayberg 1997; Mayberg 2003). In this model, brain areas with known anatomical interconnections and that also show synchronized changes using positron emission tomography (PET) in three behavioral states (normal transient sadness in controls, baseline depressed in patients and post-treatment in patients) are grouped into three compartments (Figure 6).

- The attention-cognition-context compartment (or dorsal compartment) includes both neocortical and superior limbic elements. It is thought to mediate cognitive aspects of negative emotion such as apathy, psychomotor slowing and impaired attention and executive function.
- The autonomic-circadian compartment (or ventral compartment) is composed of limbic, paralimbic and subcortical regions that are known to mediate circadian and vegetative aspects of depression: sleep, appetite, libidinal and endocrine disturbances.
- The gating compartement (or rostral) includes rostral cingulate area (rCg24a) and subcortical regions. It is isolated from both the ventral and dorsal compartments based on its cytoarchitectural characteristics and reciprocal connections to both dorsal and ventral anterior cingulate. Metabolism in this region uniquely predicts antidepressant response in acutely depressed patients (Mayberg, Brannan et al. 1997).

The dorsal-ventral segregation additionally identifies those brain regions where an inverse relationship has been demonstrated in converging PET experiments (Mayberg 1997). Sadness and depressive illness are both associated with decreases in dorsal

neocortical regions and relative increases in ventral limbic and paralimbic areas. Mayberg's model, in turn, proposes that illness remission occurs when there is appropriate modulation of dysfunctional limbic-cortical interactions (Figure 6, solid black arrows) – an effect facilitated by various forms of treatment (such as placebo, antidepressant drug, surgery and cognitive-behavioral therapy). Mayberg and collaborators postulated that initial modulation of unique subcortical targets by specific treatments promotes possible adaptive changes in particular pathways necessary for network homeostasis and conducting to clinical recovery. Three regions are separated from their compartments in the model to emphasize their important primary interactions both within and between 'levels' for the integration of self-referential (dorsal medial frontal or mF9), emotionally salient (rostral anterior cingulate or rCg24), and exogenous stimuli relevant to reward, punishment and learning (medial orbital frontal cortex or oF11).

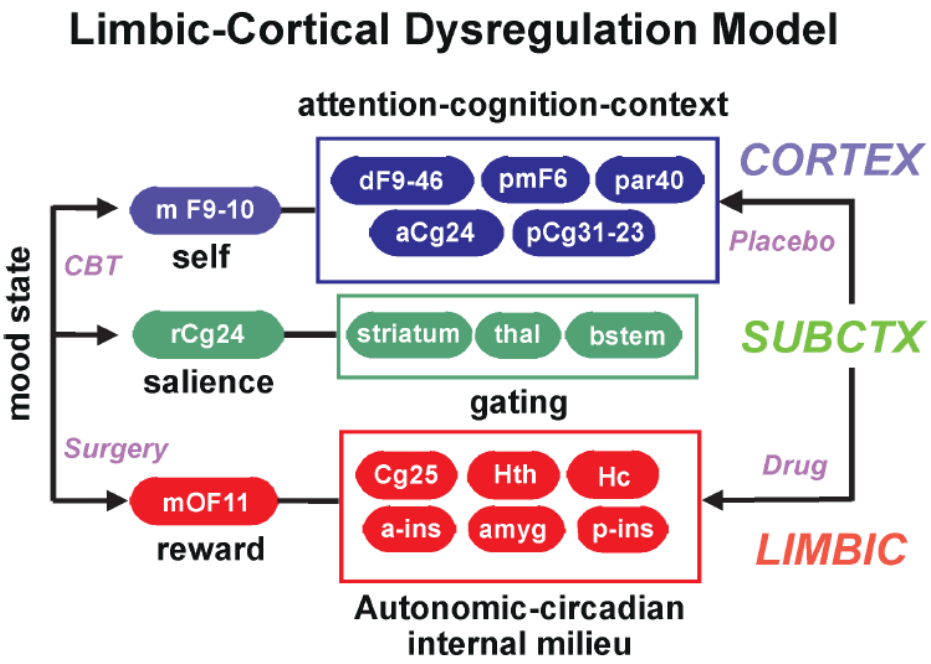


Figure 6: from (Mayberg 2003) illustrating the "limbic-cortical dysregulation model". Abbreviations: mF, medial prefrontal; dF, prefrontal; pm, premotor; par, parietal; aCg, dorsal anterior cingulate; pCg, posterior cingulate; rCg, rostral cingulate; thal, thalamus; bstem, brainstem; mOF, medial orbital frontal; Cg25, subgenual cingulate; Hth, hypothamus; Hc, hippocampus; a-ins, anterior insula; amyg, amygdala; pins, posterior insula. Numbers are Brodmann designations.

1.1.1.2. The three circuits model

Based on neuroimaging, neuropathological and lesions data, Drevets and collaborators identified brain networks regulating the evaluative, expressive and experiential aspects of emotional behavior in the pathophysiology of mood disorders (Phillips, Drevets et al. 2003b; Drevets, Price et al. 2008; Phillips, Ladouceur et al. 2008).

These neural circuits include the (i) limbic-cortical-striatal-pallidal-thalamic circuits (LCSPT), and two extended cortical circuits from the orbital and medial prefrontal cortex: (ii) the orbital prefrontal network and (iii) the medial prefrontal network.

The *LCSPT* is formed by connections between the orbital and medial prefrontal cortex (OFPFC), amygdala, hippocampal subiculum, ventromedial striatum, mediodorsal and midline thalamic nuclei and ventral pallidum (Ongur, Ferry et al. 2003). This circuits has been found to be involved in emotional behavior on the basis of its anatomical connectivity with visceral control structures that mediate emotional expressions, such as the hypothalamus and periaqueductal gray matter (PAG) (Nauta and Domesick 1984). In addition, impairments in transmission through the LCSPT can produce the emotional symptoms found in major depression (Drevets, Gadde et al. 2004).

The *orbital prefrontal network* is mostly related to the central and lateral orbital areas and includes sensory association areas such as visual associated areas in the inferior temporal cortex and somatic-sensory associated areas in the insula and frontal operculum, as well as olfactory and taste cortex (Ongur and Price 2000; Saleem, Kondo et al. 2008). This network codes for sensory integration and for affective characteristics of stimuli such as reward, aversion, and relative value.

The *medial prefrontal network* includes the dorsomedial / dorsal anterolateral prefrontal cortex, the mid- and posterior cingulate cortex, a region in the anterior superior temporal gyrus and sulcus, and the entorhinal and posterior parahippocampal cortex (Kondo, Saleem et al. 2005; Saleem, Kondo et al. 2008). This network has major connections with limbic structures and visceral control structures

(hypothalamus and PAG) (Ongur and Price 2000), and is thus mainly involved in introspective functions such as mood and emotion, and visceral reactions to emotional stimuli (Figure 7). This network shares some similarities with the "default" network, that become activated during resting state conditions and deactivated during tasks that require attention to external stimuli (Gusnard, Akbudak et al. 2001; Fox, Snyder et al. 2005).

Brain region	Gray matter volume	Cell counts, cell markers	Glucose metabolism, CBF	
	Dep versus Con	Dep versus Con	Dep versus Con	Dep versus Rem
Dorsal medial/anterolateral PFC (BA9)	↓	↓	↓	↓
Frontal polar C (BA 10)		↓	↓	↓
Subgenual anterior cingulate C	↓	↓	↓/↓[a]	↓
Pregenual anterior cingulate C	↓	↓	↓	↓
Orbital C/ventrolateral PFC	↓	↓	↓	↓
Posterior cingulate	↓		↓	↓
Parahippocampal C	↓	↓ BD	↓	↓
Amygdala	↓/↑[b]	↓ MDD	↓	↓
Ventromedial striatum	↓		↓	↓
Hippocampus	↓	↓ BD	n.s.	n.s.
Superior temporal G/temporopolar C	↓			↓
Medial thalamus			↓	↓

Figure 7 : Neuroimaging and histopathological abnormalities in the visceromotor network (Ongur, Ferry et al. 2003) in early-onset, recurrent major depressive disorder (MDD) and/or bipolar disorder (BP). (a) In the subgenual anterior cingulate cortex the apparent reduction in CBF and metabolism in PET images (Drevets, Price et al. 1997) of depressed subjects is thought to be accounted for by the reduction in tissue volume in the corresponding cortex, as after partial volume correction for the reduction in gray matter the metabolism appears increased relative to controls (Drevets and Price 2005). (b) The literature is in disagreement with respect to the amygdala volume in mood disorders. In MDD, the volume appears reduced in cases whose MDE show a chronic or intermit course C cortex, Dep versus Con unmedicated depressives versus healthy controls, Dep versus Rem unmedicated depressives versus themselves in either the medicated or unmedicated remitted phases, G gyrus, n.s. differences generally not significant, PFC prefrontal cortex. Empty cells indicate insufficient data. Adapted from (Drevets, Price et al. 2008).

Various treatment for mood disorders have shown a decrease or a suppression of pathological activity within visceromotor network structures such as the subgenual anterior cingulate cortex (SgACC), amygala, and ventral striatum (Drevets, Bogers et al. 2002; Drevets and Price 2005; Mayberg, Lozano et al. 2005).

The neural model of depression proposed by Drevets and colleagues involves the dysfunction of the medial prefrontal cortex (mPFC) resulting in a disinhibition of limbic transmission through the amygdala (Figure 8). This dysfunction might lead to the emotional, cognitive, endocrine, autonomic and neurochemical manifestations of

depression (Drevets, Price et al. 2008). The basolateral amygdala sends efferent projections to the central nucleus of the amygdala and the bed nucleus of the stria terminalis. The efferent projections from these structures to the hypothalamus, PAG, nucleus basalis, locus ceruleus, raphé, and other diencephalic and brainstem nuclei then organize the neuroendocrine, neurotransmitter, autonomic, and behavioral responses to stressors and emotional stimuli (Davis and Shi 1999; LeDoux 2003). The mPFC shares reciprocal projections with all of these structures and potentially modulates limbic outflow and thus several facets of related emotional expression (Ongur, Ferry et al. 2003).

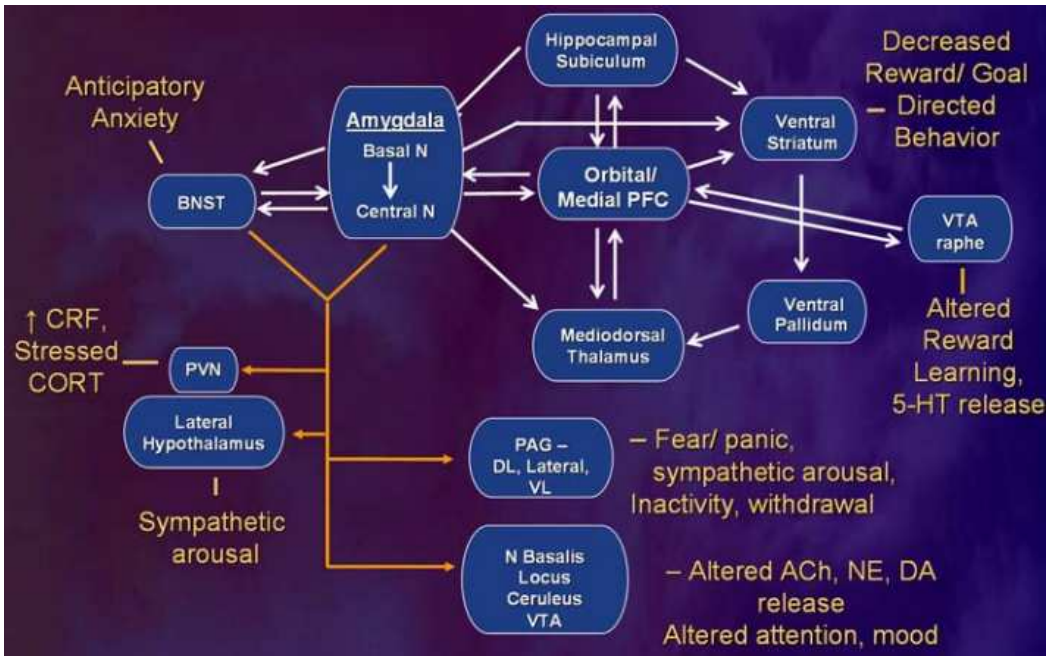


Figure 8 : Dysfunction of mPFC and amygala in major depression (Drevets, Price et al. 2008). Solid white lines indicate some of the major anatomical connections between structures, with closed arrowheads indicating the direction of projecting axons. Solid yellow lines show efferent pathways of the ACe and BNST. Abbreviations: 5-HT serotonin, ACe central nucleus of the amygdala, ACh acetylcholine, BNST bed nucleus of the stria terminalis, DA dopamine, DL dorsolateral column of PAG; N nucleus, NE norepinephrine, NTS nucleus tractus solitarius, PAG periaqueductal gray, PVN paraventricular N of the hypothalamus, VL ventrolateral column of PAG, VTA ventral tegmental area.

1.1.1.3. A central role for the anterior cingulate cortex

In early depression research, the limbic loop containing the anterior cingulate cortex was shown as the common denominator of change and therapy effects in depressive states (Ebert and Ebmeier 1996) (Figure 9).

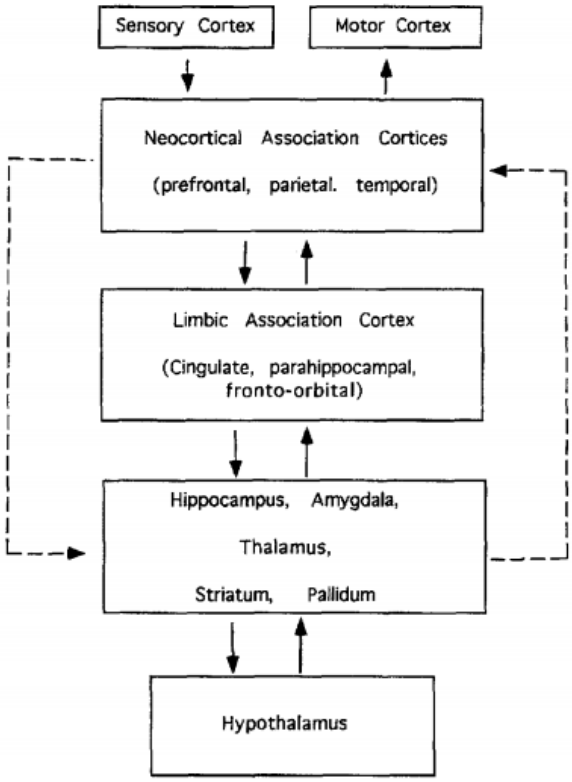


Figure 9 : Basic description of the role of the cingulate in intracerebral information processing in depression. The limbic association cortex is well placed to connect neocortical association cortices activated in cognition, sensory, and motor phenomena, to phylogenetically older areas involved in the domains of emotion, drive, and vegetative functions through major neuronal pathways (solid arrows). Minor pathways exist between neocortical areas and ventral striatum, amygdala, and thalamus (dashed arrows), but there are no direct connections between hypothalamic nuclei and neocortical association areas. The cingulate is in good position to be implicated in the mediation of cognition and emotion, and that dysfunctions of the cingulate might lead to a functional dissociation of these two domains. Adapted from (Ebert and Ebmeier 1996).

Several somatic therapies of major depressive disorder have been linked with the activity (mainly a decrease) of subgenual cingulate cortex

- Antidepressant treatment. Clinical improvement in unipolar depressed patients treated with fluoxetine was associated with subgenual cingulate brain glucose metabolism decrease (Mayberg, Brannan et al. 2000).
- Electroconvulsive therapy (ECT). After ECT, widespread and highly significant decreases in regional cerebral metabolic rate for glucose was observed in the subgenual region of left medial frontal gyrus in patients with major depression (Nobler, Oquendo et al. 2001).
- Repetitive transcranial magnetic stimulation (rTMS). The lower the measured regional Cerebral Blood Flow (rCBF) before the rTMS treatment in the ACC,

the greater was the antidepressant effect of the applied rTMS course (Mottaghy, Keller et al. 2002). In addition, rTMS to dorsolateral prefrontal cortex (DLPFC) increased the activity in the ACC (Paus, Castro-Alamancos et al. 2001).

- Ablative surgery. Higher preoperative rates of metabolism at left subgenual prefrontal cortex was associated with subsequent improvement in depressive symptom severity following cingulotomy (Dougherty, Weiss et al. 2003).
- Deep brain stimulation. Use of high-frequency stimulation in the subgenual cingulate white matter (adjacent to the subcallosal cingulate region, SCG or Cg25 for Broadman area 25) is accompanied with a deactivation of a hyperactive Cg25 and with a sustained remission of depression (Mayberg, Lozano et al. 2005).

Interestingly, it has also been proposed that connections of Cg25 with a subset of areas (i.e., brainstem, hypothalamus and insula) are involved in the deregulation of circadian rhythm commonly associated with depression (such as sleep, appetite, libido or neuroendocrine changes) (Jurgens and Muller-Preuss 1977; Ongur, An et al. 1998; Drevets 2000; Freedman, Insel et al. 2000; Barbas, Saha et al. 2003). In addition, reciprocal pathways linking Cg25 to another set of areas (i.e., orbitofrontal, medial prefrontal, as well as parts of the anterior and posterior cingulate cortices) constitute the neuroanatomical substrates by which primary basic processes (e.g. autonomic and homeostatic) influence various aspects of cognition such as learning, memory, motivation and reward which are all impaired in depressed patients (Vogt and Pandya 1987; Carmichael and Price 1996; Barbas, Saha et al. 2003; Haber 2003). In particular, animal data (Sullivan and Gratton 1999) suggest that the left subgenual PFC abnormalities in depression may participate to the heightened HPA-axis activity and sympathetic autonomic arousal of depression and that right subgenual PFC activity may increase emotional reactivity, which is consistent with the findings that metabolic activity in this area correlates positively with depression severity (Drevets 2000).

1.1.9. Therapies in depression

Several therapies are used to treat depression. These therapies have a various degree of invasiveness (Figure 10). Therapies are classically divided into psychotherapies and somatotherapies. Psychotherapies (Clarkin, Pilkonis et al. 1996) are either expressive (such as psychoanalysis) or supportive (such as psychotherapy, including cognitive-behavioural therapy). somatotherapies include sleep deprivation (Giedke and Schwarzler 2002), antidepressant medication (Mann 2005), transcranial magnetic stimulation (TMS) (Lam, Chan et al. 2008), magnetic seizure therapy (Lisanby, Schlaepfer et al. 2001), electroconvulsive therapy (ECT) (Lisanby 2007), vagus nerve stimulation (VNS) (Fitzgerald and Daskalakis 2008), deep brain stimulation (DBS) (Mayberg, Lozano et al. 2005; Hauptman, DeSalles et al. 2008) and neurosurgery (Nicolaidis 2005). Interestingly, ECT has been considered as the most efficient and rapidly acting long-term somatic treatment in psychiatry (Servais, Ansseau et al. 2008) (see section 7.1Electroconvulsive therapy in depression).

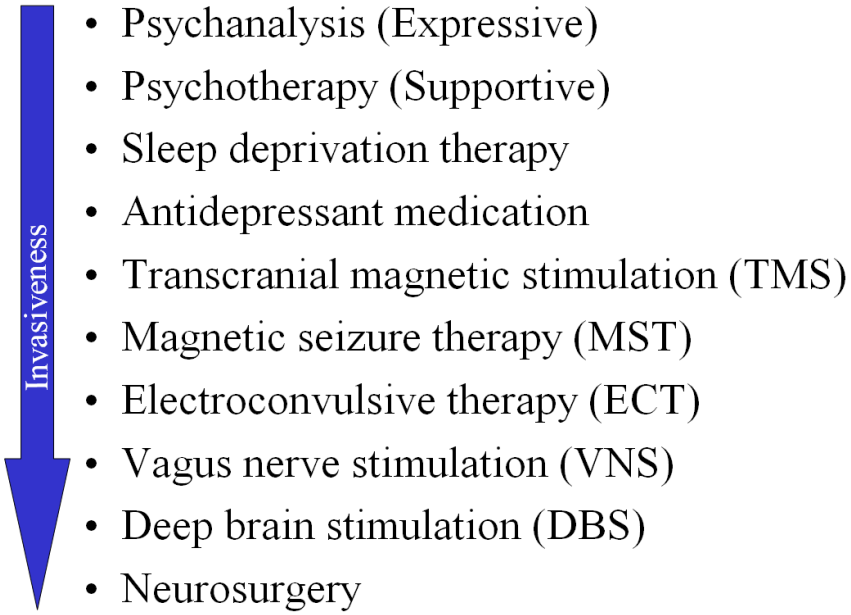


Figure 10 : List of several therapies used in major depressive disorder ordered following their somatic invasiveness.

1.1.10. Biological markers of depression

Several biological markers of depression exist and reflect either the causes or consequences of depression (Mossner, Mikova et al. 2007) (Figure 11). Genetic factors include polymorphisms of the serotonin receptors. Environmental factors include abnormalities of the brain development (e.g. hypoxia, viruses, and trauma) and adult life disorders (e.g. stress). Neuroimaging markers include functional (e.g. glucose metabolism or blood oxygen level dependant signal) and structural brain features (e.g. grey and white matter abnormalities). Cognitive markers include attention, memory and executive functioning dysfunctions. Other markers include immune factors (e.g. interleukin abnormalities), low molecular weight species abnormalities (e.g. folate or cyanocobalamin deficiency), endocrine disorders (e.g. increase of cortisol), neurotransmission abnormalities (e.g. decrease of brain derived neurotrophic factor, norepinephrin, dopamine, and serotonin), and electrophysiological markers (e.g. event-related potential abnormalities).

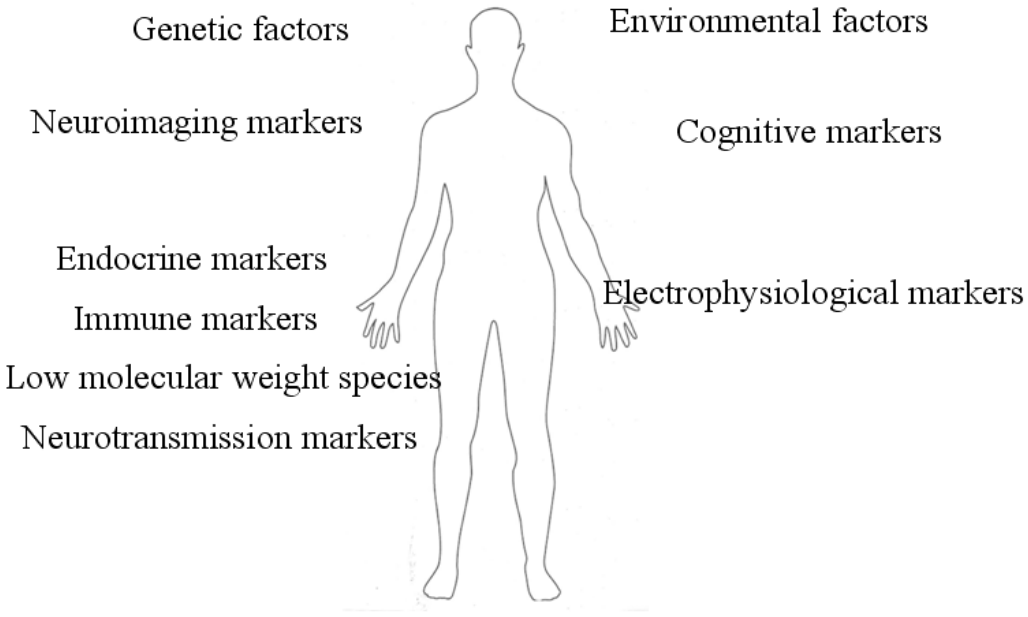


Figure 11 : Biological markers of depression. Adapted from (Mossner, Mikova et al. 2007).

1.2. Attentional processes

Interactions between attention and perception are multiple and complex. Here, we first describe attentional networks and then how “bottom-up” (ascending stream of information) and “top-down” mechanisms (descending stream of information) interact across hierarchically-organized, distributed and specialized brain regions, and how such brain architecture ensures a large capacity for adaptation. We then describe how voluntary attention and depression may influence perceptual processing.

1.2.1. Attentional networks

At any moment in time, we only attend to a small portion of the stimuli in our environment. Thus attention selects the information that will access conscious awareness. Several networks of attention have been described (Posner and Raichle 1999; Posner and Rothbart 2007): (i) a network for visual orienting is used to orient attention overtly by moving our eyes to a location in order to allows the image to fall on the part of the retina with the highest acuity; (ii) a network for executive attention is used when we need to shift our attention to a new location, that is the conscious execution of an instruction in order to detect an object; (iii) a network for vigilance or alerting is used in order to maintain a sustained state of altertness in order to perform a task.

These three networks that allow orienting to sensory stimuli, exercising executive control, and maintaining an alert state of vigilance rely on the functioning of several cortical and subcortical areas (Fan, McCandliss et al. 2005) that act in concert to form an unified attentional system. This system underlies the unity of our subjective experience of the world around us (Posner and Raichle 1999).

1.2.2. Bottom-up and top-down mechanisms

Any scene from our everyday life contains many visual objects that can simultaneously project onto the visual cortex. Given the limited processing capacity of the visual system, visual objects compete for neural representation at different levels along the visual pathways (Duncan, Humphreys et al. 1997; Desimone 1998;

Duncan 1998; Aston-Jones, Desimone et al. 1999; Kastner and Ungerleider 2001) to eventually access to consciousness (Driver, Vuilleumier et al. 2001; Whatham, Vuilleumier et al. 2003; Sergent, Baillet et al. 2005; Bahrami, Lavie et al. 2007; Kouider and Dehaene 2007). Several factors influence neural competition between visual objects. For example, if you are looking for a given friend in a crowd, you may remain blind to another acquaintance who may pass in front of you (Levin, Drivdahl et al. 2002; Levin, Simons et al. 2002; Simons, Chabris et al. 2002; Varakin and Levin 2006). However, no matter how important it is for you to find your friend, your attention might still be automatically attracted by an unusual visual event or object, such as for example, someone close to you suddenly falling on the ground or flames coming out of a building nearby, thereby distracting you from your main search task. This example illustrates that competition between multiple objects in the visual cortex can be biased by so-called "top-down" mechanisms such as voluntary or goal-directed attention, but also by "bottom-up" influences from sensory information with high perceptive saliency or high cognitive impact (Hopfinger, Buonocore et al. 2000; Corbetta and Shulman 2002).

Recent functional brain imaging studies showed that, either in the presence or in the absence of visual stimulation, biased signals due to selective attention can modulate neuronal activity within visual cortices, including the primary visual cortex (V1) (Kastner, Pinsk et al. 1999; Tootell and Hadjikhani 2000; Vanduffel, Tootell et al. 2000; Schwartz, Vuilleumier et al. 2005). While attention can affect early stages of visual processing, top-down effects on entering visual information have been shown to originate from a network of frontal and parietal cortical regions (Kastner, Pinsk et al. 1999). Moreover, because processing resources are limited, one single object presented in the visual field is processed more easily than if it is presented together with another competing object (Duncan 1998; Reynolds, Alborzian et al. 2003; Lavie 2005).

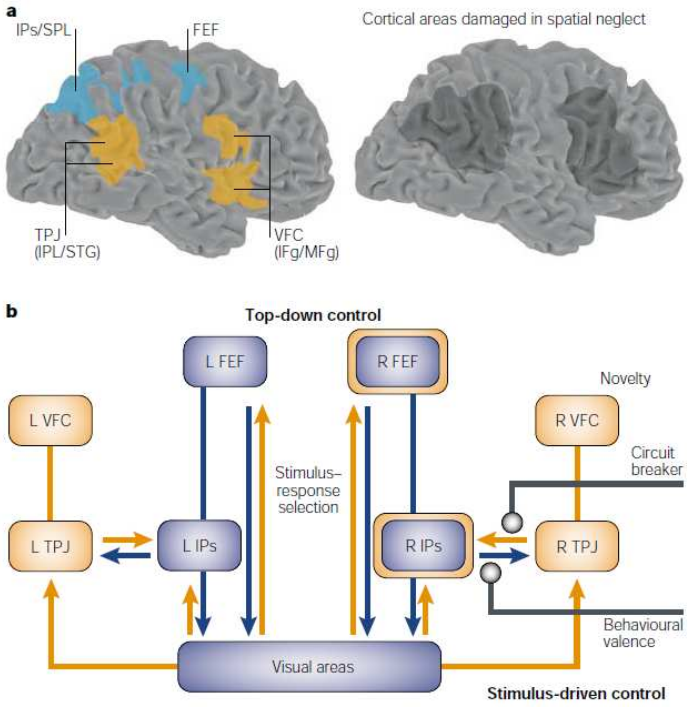


Figure 12 : Neuroanatomical model of attentional control. (a) Dorsal and ventral frontoparietal networks and their anatomical relationship with regions of damage in patients with unilateral neglect. Areas in blue indicate the dorsal frontoparietal network. FEF, frontal eye field; IPs/SPL, intraparietal sulcus/superior parietal lobule. Areas in orange indicate the stimulus-driven ventral frontoparietal network. TPJ, temporoparietal junction (IPL/STG, inferior parietal lobule/superior temporal gyrus); VFC, ventral frontal cortex (IFg/MFg, inferior frontal gyrus/middle frontal gyrus). The areas damaged in neglect (right) better match the ventral network. (b) Anatomical model of top-down and stimulus-driven control. The IPs–FEF network is involved in the top-down control of visual processing (blue arrows). The TPJ–VFC network is involved in stimulus-driven control (orange arrows). The IPs and FEF are also modulated by stimulus-driven control. Connections between the TPJ and IPs interrupt ongoing top-down control when unattended stimuli are detected. Behavioural relevance is mediated by direct or indirect (not shown) connections between the IPs and TPJ. The VFC might be involved in novelty detection. L, left; R, right. Image and caption from (Corbetta and Shulman 2002)

Thus, attentional processes can be divided into top-down and bottom-up processes. In everyday life, visual attention is controlled by both cognitive (or *top-down* because the flow of information goes from 'higher' to 'lower' centres) factors, such as knowledge, expectation and current goals, and *bottom-up* factors, so called because sensory stimulation processing proceeds in a single direction from sensory input, through perceptual analysis, towards motor output (Corbetta and Shulman 2002) (Figure 12). Other factors that affect attention, such as novelty and unexpectedness, reflect an interaction between cognitive and sensory influences. The dynamic interaction of these factors controls where, how and to what we pay attention in the visual environment (Corbetta and Shulman 2002).

In conclusion, bottom-up and top-down attentional mechanisms interact to guide neural competition between simultaneous sensory stimuli. Accordingly, bottom-up influences such as the perceptual salience of an external stimulus might interact with top-down influences such as the viewer's intentions or current goals. The search for a friend in a crowd provides an illustration of the dynamic links between these two mechanisms. We describe below how these mechanisms can act at multiple levels of functional organization in the human brain.

1.2.3. Modular and hierarchical organization of central nervous system

How does the external world project onto cortical layers? Numerous somato-sensory and motor maps have been described that represent proprioceptive, perceptual experiences as well as actions (Sereno 1998). For example, information from the visual field that stimulates retina cells projects in a spatially-organized manner onto the cortical surface, hence forming retinotopic maps in the primary visual cortex (Van Essen, Lewis et al. 2001; Wandell, Brewer et al. 2005). Similarly, tonotopic maps represent the frequency composition of sounds in an organized manner along the cortical surface of the primary auditory cortex (Guimaraes, Melcher et al. 1998; Talavage, Ledden et al. 2000; Formisano, Kim et al. 2003). Several other "topies" exist for the main sensory modalities, including spatial maps for the target locations of voluntary saccades in the parietal cortex (Sereno, Pitzalis et al. 2001; Silver, Ress et al. 2005; Hagler and Sereno 2006; Sereno and Huang 2006; Hagler, Riecke et al. 2007).

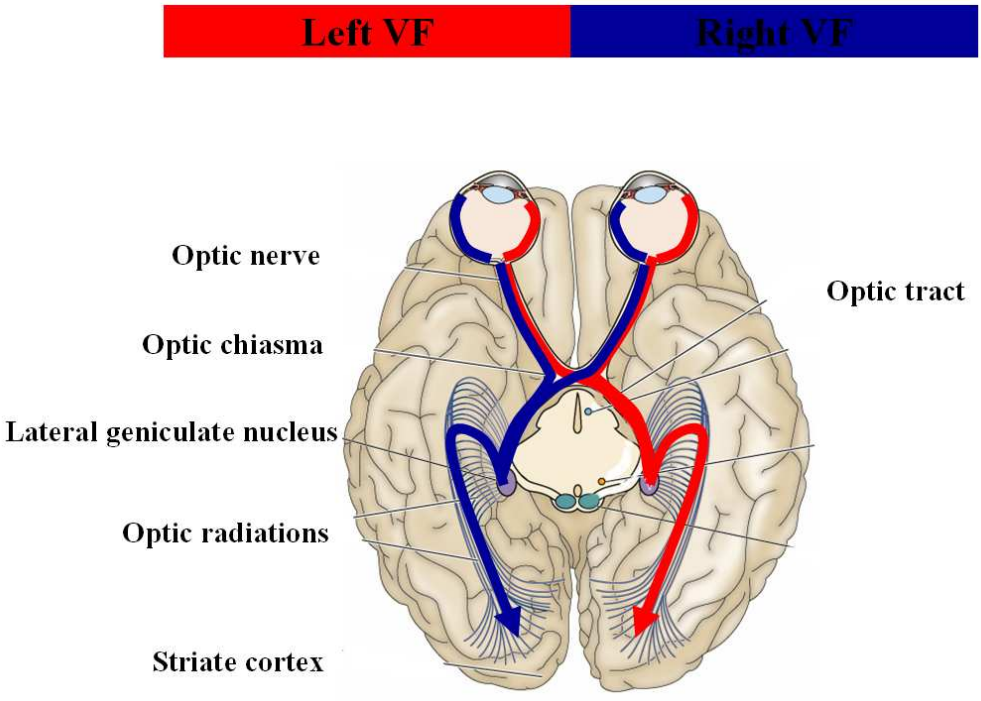


Figure 13 : Visual information from the retina to the primary visual cortex.

According to the traditional hierarchical model of visual processing (Van Essen, Lewis et al. 2001), visual information travels from the retina along the optic nerve to the lateral geniculate nucleus (LGN) located at the back of the thalamus, then projects to the primary and secondary visual cortical areas (V1, V2) (Figure 13). From there, separable features of the stimulus are distributed across various regions coding for colors (V4/V8 (Hadjikhani, Liu et al. 1998; Bartels and Zeki 2000; Tootell and Hadjikhani 2001; Tootell, Nelissen et al. 2004), motion (MT/V5 (Dumoulin, Bittar et al. 2000; Vanduffel, Fize et al. 2001), but also integrated objects (lateral occipital cortex, LOC; (Grill-Spector, Kushnir et al. 1999; Ciaramelli, Leo et al. 2007; Golarai, Ghahremani et al. 2007) and specific object categories such as faces (face fusiform area, FFA; (Kanwisher, McDermott et al. 1997; Grill-Spector, Knouf et al. 2004; McKone, Kanwisher et al. 2007), body parts (extrastriate body area, EBA; (Astafiev, Stanley et al. 2004; Downing, Chan et al. 2006; Morris, Pelphrey et al. 2006), places

(parahippocampal place area, PPA; (Epstein and Kanwisher 1998; Epstein, Harris et al. 1999), etc. (Figure 14).

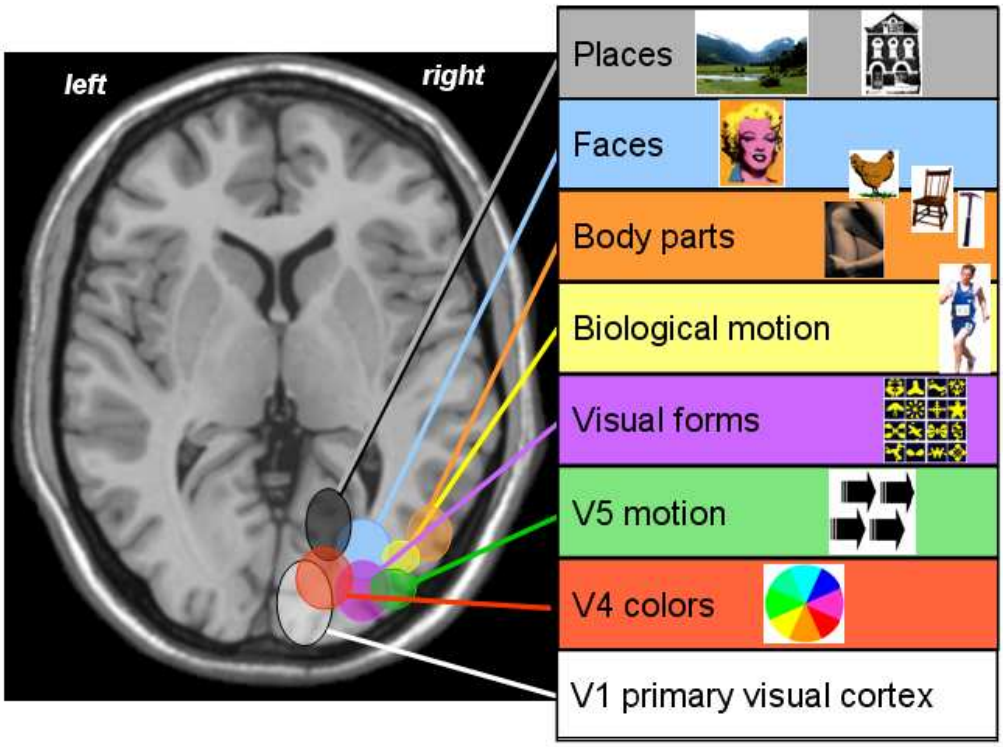


Figure 14 : Anatomical segregation of specialized functional visual regions (see main text for references).

Such a modular organization of visual processing might serve voluntary action. Indeed, any action or thought has to adapt to available information and current goals. This implies that information has to be integrated in time and across multiple levels of processing. Recent microscopic studies in cat revealed that descending projections between two neuronal population are often denser than ascending projections (Van Horn, Erisir et al. 2000). For example, the LGN projects ascending axons to the primary visual cortex, while neurons in the primary visual cortex project back nearly 10 times more descending axons to the LGN (Bear, Connors et al. 1997; Van Horn, Erisir et al. 2000; Bickle 2001). Consistent with these anatomical data, electrophysiological studies with implanted electrodes in monkeys showed that feedback from V1 can modulate the response of neurons in the lateral geniculate nucleus (LGN) (Webb, Tinsley et al. 2002).

Taken together, these studies suggest both a high degree of selectivity and connectivity across visual regions, with top-down connections outnumbering bottom-up afferences (Bullier 2004).

1.2.4. Effects of attention on perception

Lavie's theory of attention resolves a long-standing debate between early and late selection of information to process. She proposes that perceptual capacity is limited and that, only within the limits of these processing capacities, perception is automatic. Thus, the processing demands (low versus high attentional load) of a relevant task would determine the processing of irrelevant distractors (Lavie 2005).

This theory was tested in a functional magnetic resonance imaging study where relevant task was a linguistic task of low or high attentional load, and irrelevant distractors where motion in the periphery of the display. The study showed a reduced motion processing during the high load condition, thus fulfilling Lavie's prediction (Rees, Frith et al. 1997).

Schwartz et al. (2005) used as relevant task a rapid stream of coloured stimuli presented at central fixation and as distractors flickering checkerboards presented in the periphery. In the low-load task subjects had to detect any shape of one colour while in the high-load task, they had to detect specific conjunctions of colour and shape (Schwartz, Vuilleumier et al. 2005). The study showed that neural response related to the task-irrelevant distractors was decreased when the attentional load of the central task was high.Such effects of load occurred in V1 and were larger for successive extrastriate areas through to V4.

Phelps and Carrasco combined emotional and attentional effect on perception in a behavioural study. They showed that emotion enhances contrast sensitivity irrespective of attention. Moreover emotional faces (fear) potentiated the effect of attention on contrast sensitivity. Thus the conjunction of emotional and attentional manipulation increased perception of contrast more than only one change in either emotional or attentional characteristics (Phelps, Ling et al. 2006).

Overall these studies showed that attention clearly alters perception and thus the neural representation of “external” objects. Moreover the effect of attention can act in conjunction with other “modalities” like emotion in order to modulate perception.

1.2.5. “Indirect” consequences of depression on perceptual systems

From a behavioral point of view, depression is characterized by memory, emotional and attentional impairments (e.g. Chamberlain and Sahakian 2006).

From a neurological point of view, depressed patients present dysfunctions in the cortices underpinning memory (e.g. hippocampus, frontal cortex), emotional (e.g. limbic and paralimbic, anterior cingulate cortex, amygdala) and attentional (e.g. fronto-parietal cortex) functions (e.g. Drevets, Price et al. 1997; Malizia 2005).

In addition, as described above, the central nervous system is organized in a modular, hierarchical and recurrent manner. Thus, in the context of major depression, this recurrent organization of central nervous system supposes that all dysfunctions of high-level cortices (that is associative polymodal cortices) would be accompanied by an impairment of the modulation of subjacent cortices and even primary cortices.

This might mean that top-down modulations (e.g. attentional or motivational) from high-level cortices on low-level cortices would be impaired as a consequence of the dysfunction of the source of top-down processes (e.g. fronto-parietal cortices) in depression.

Sensory processing (i.e., visual, olfactory, auditory, gustatory, tactile) might thus be altered by dysfunctions within higher-level cortices.

Modulation of low-level cortices by high-level cortices might biais the competition between top-down and bottom-up mechanisms for the neuronal representation of objects seen in a scene of everyday life (such as color, familiar face, etc.), which may have major consequences for MDD patients’ everydaylife functioning.

2. Objective

2.1. Why and how to explore attentional process in depression?

While top-down and bottom-up attentional processes interact to afford efficient processing of sensory information, we propose that this subtle interaction might be disrupted in pathological conditions, such as depression.

Several biological markers of major depression exist. Functional magnetic resonance imaging (fMRI) has a growing place in psychiatry and its innocuous effect allows repetitive examinations in order to study the pathophysiological mechanisms of depression

Traditional neuropsychological test batteries have failed to identify clear patterns of deficits in major depressive disorders and it is thought to be due, at least in part, to a lack of tasks designed specifically for patients suffering from depression (Drevets, Price et al. 2008). Our first objective was to construct an attentional task allowing us to explore attention in healthy subjects and MDD patients.

2.2. Is there an abnormal neural filtering in patients with depression?

Early information processing deficits in MDD have been only studied through inspection time. This is measured as the minimum stimulus presentation time necessary for near perfect performance on a two-choices visual discrimination task and is thought to assess the speed of early information processing independent of motor speed or cognitive strategy. This measure was shown to be longer in patients than in controls indicating that unipolar depression is associated with a slowing of speed of information processing (Tsourtos, Thompson et al. 2002).

Our second objective was to use our attentional task simultaneously with fMRI in order to evaluate the early information processing in MDD patients and to test whether attentional influences from fronto-parietal networks on the processing of visual stimuli differ in depression as compared to healthy subjects, in particular when these stimuli are irrelevant to the task.

2.3. Could a modulation of attentional load impact on mood?

Mood interacts with cognition and manipulation of cognition is used in several psychotherapies (Simons, Garfield et al. 1984; Beck 2008). Our third objective was to test with fMRI whether varying attentional demands can transiently modulate activity in emotional-limbic networks.

2.4. Exploration of the neurobiological basis of suicidality

Suicide is a major public health problem that typically occurs in the context of a depression. Using fMRI, our fourth objective was to reveal the neurobiological correlates of suicidality in depressed patients.

3. Methodological considerations about functional magnetic resonance imaging (fMRI)

fMRI measures the variations in brain perfusion related to neural activity, using a method based on the assessment of the BOLD (blood oxygen-level-dependent) signal. The BOLD signal relies on the following principles (Kastler 2003). When a brain area is activated, it locally induces an increase in cerebral blood flow and a proportionately less important increase in oxygen consumption. This results in an excess of oxyhemoglobin in venous capillaries of the activated area, and therefore a relative decrease in deoxyhemoglobin concentration. Because of its paramagnetic properties, the deoxyhemoglobin is associated with a signal decrease due to a magnetic susceptibility effect. The local decrease in deoxyhemoglobin concentration thus leads to a slight signal increase in the activated area. BOLD effects are measured using rapid volumetric acquisition of images (echo planar or EPI T2 or T2*-weighted sequences); the whole brain volume is thus covered in a few seconds only (2.13 sec in our specific sequences; other parameters were : 32 slices, 3mm-thick slices, spatial resolution of 3.4 x 3.4 x 3 mm^3 voxel size) (Figure 15). The obtained signal increase in activated areas is weak (about 2-5%), which requires a high number of measurements or trials (e.g. events; see below). The BOLD contrast also increases with the intensity of the scanner magnetic field (B0), because of an improved sensitivity to the differences in magnetic susceptibility when B0 is higher. That is why fMRI sequences usually require at least a 1.5 Tesla scanner (our fMRI device is a 3 Tesla scanner). As for PET images, BOLD fMRI data are coregistered and mapped onto precise structural MRI images for interpretation of results.

Two main types of experimental design are used in fMRI studies : ‘block’ and ‘event-related’. *Block-design,* which is the design used in our studies, is commonly used to characterize the brain areas activated by a specific cognitive task. In this case, the subject during fMRI recording is submitted to an alternation of task-related (e.g. presentation of images) and control (e.g. presentation of a standard fixation cross) periods or ‘blocks’ of predetermined duration. The statistical analysis will seek for

significant correlations in each voxel between the ‘on-off’ time course of experimental paradigm and the obtained BOLD haemodynamic response. In *event-related* fMRI, the statistical analysis aims at finding correlations between the obtained haemodynamic response and the occurrence of spontaneous events (e.g. slow waves or spindles during sleep) or delivered stimuli (e.g. brief tones).

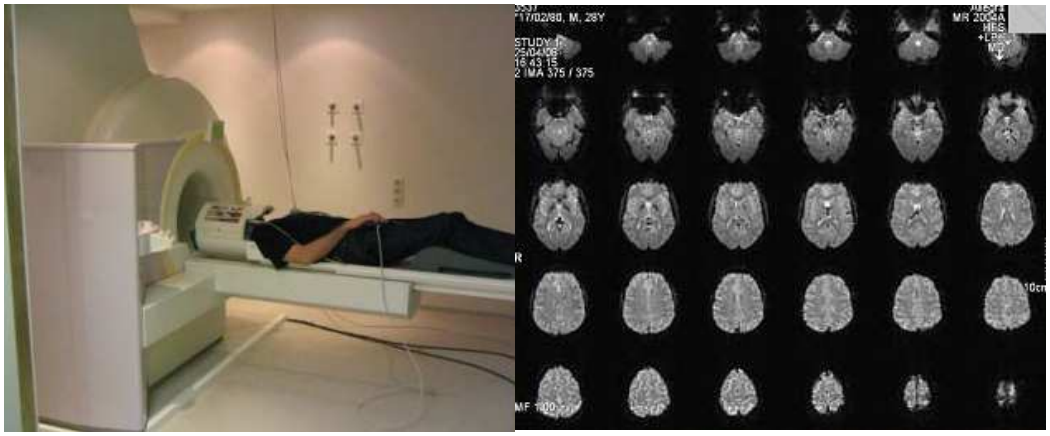


Figure 15 : 3 Tesla Simens Allegra MRI scanner device (left). 32-slices fMRI EPI sequence (right); the whole brain is covered in 2.13 sec.

The main advantage of the fMRI technique is its higher temporal resolution compared to PET, which makes possible the assessment of neural responses associated with brief events such as visual stimulation (Figure 16). The spatial resolution is also better compared to other imaging techniques such as PET and SPECT. The technique is non-invasive and requires no injection of contrast product. The main drawback is the discomfort of the scanning environment (including noise, which is reduced by earplugs and headphones).

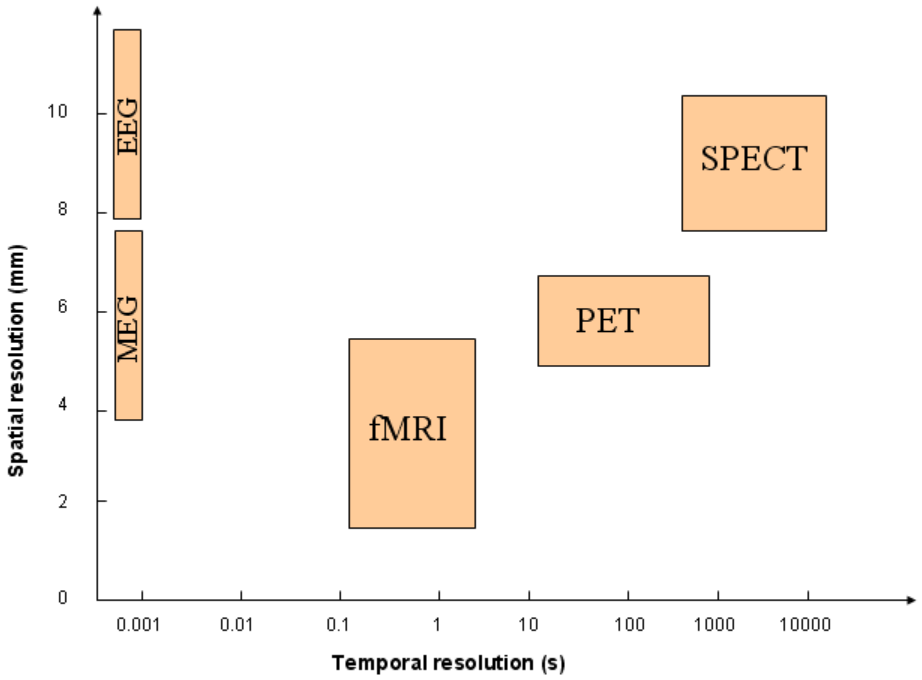


Figure 16 : Spatial and temporal resolution in the study of brain function. Schematic illustration of the ranges of spatial (in mm) and temporal (in seconds, logarithmic scale) resolution of various experimental techniques for studying the function of the brain. Note the superior temporal and spatial resolution of fMRI compared to PET, and the high temporal but poor spatial resolution of EEG. MEG = magneto-encephalography; SPECT = single-photon emission computed tomography. Adapted from (Churchland and Sejnowski 1988).

3.1. Statistical analysis of functional brain imaging data

We used Statistical Parametric Mapping (SPM - http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab to analyze functional brain imaging data (Figure 17). fMRI data were computed using SPM2 implemented in Matlab 7.1. Data processing may vary from one user to the other and from one protocol to the other. Only the procedures used in this thesis will be described.

3.2. Spatial processing

Before any statistical analysis is computed, fMRI data undergo several preprocessing stages. The first step of the preprocessing aims at realigning all data onto the first brain volume acquired, using the rigid body registration method (for a complete description of this method see (Ashburner and Friston 2004a). This first step takes into account the movements of the participant from one scan to the next. Although

usually limited, these movements change the origin of the signal recorded in the 3-dimensional space of the scanner. Six vectors are generated at this stage, one for each movement direction (3 translations and 3 rotations). Each vector contains values that represent the displacement of each scan as compared the first scan.

Functional images are then precisely matched, or coregistered, to a high resolution anatomical MRI image of the subject (Friston 2004). This image is recorded in a separate session, using acquisition settings privileging spatial resolution.

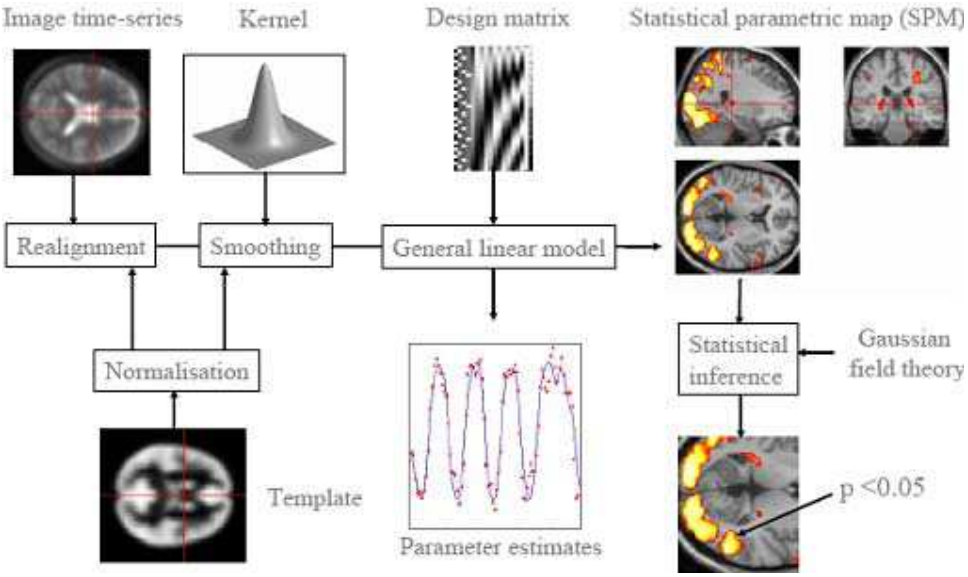


Figure 17 : Schematic representation of the preprocessing and statistical analysis of functional brain imaging data using SPM (Friston 2004).

Functional and high resolution anatomical images are then normalized to a standard space in order to allow between-subjects comparisons (for a complete description of the method see (Ashburner and Friston 2004b). This standard space is similar to the 3-dimensional space set by Talairach and Tournoux (Talairach and Tournoux 1988) which used three orthogonal planes to assign coordinates to every part of the brain. However, Talairach and Tournoux based their description on two dead brains in which displacement of the neural tissues had occurred. The standard space now used in SPM is a mean brain of about 350 anatomical images recorded at the Montreal Neuroscience Institute (MNI) and is referred to as the MNI space.

In the last preprocessing step, functional data are smoothed (using a Gaussian Kernel; Full Width at Half Maximum or FWHM 16 or 8 mm) in order to improve the signal-to-noise-ratio and reduce residual inter-individual differences (Friston 2004).

3.3. General linear model, design matrix and regressors

The statistical analysis uses a general linear model (GLM) to describe the signal X in a voxel I of each acquired brain volume j in terms of a linear combination of the regressors R of the design matrix, plus a constant term K, and an error term ε, representing the unexplained variability: $X_{i,j}=\beta_{1,i} \times R_{1,j} + \beta_{2,i} \times R_{2,j} + \beta_{3,i} \times R_{3,j} + \ldots + \beta_{y,i} \times R_{y,j} + K_i + \varepsilon_i$ where $\beta_{y,i}$ is a parameter estimate and represents the relative contribution of the Ry regressor to the signal recorded in voxel i (Kiebel and Holmes 2004). It is estimated using a method of ordinary least squares, which aims at reducing the sum of the squared differences between the actual and the fitted values.

All conditions of the experiment are modelled in columns of a design matrix that contains all relevant factors of the experimental design and relates them to the preprocessed functional data (Kiebel and Holmes 2004). A column is a continuous regressor that contains functions that indicate the precise time of each trial type and its duration. In the case of fMRI data, regressors are convolved with the haemodynamic response function (HRF) to match the characteristics of the recorded BOLD signal (Kiebel and Holmes 2004).

The design matrix attempts to comprehensively describe the experimental design, and also comprises a mean term. Regressors also include the conditions of interest (e.g. high attentional load) and the realignment parameters computed during preprocessing (note that realignment parameters are not convolved with the HRF).

3.4. Fixed effects – Random effects

For each individual, once the solution of the GLM is found, parameter estimates of all voxels can be entered in statistical tests (t, F) using linear contrasts (c) (fixed effects analysis) (Penny and Holmes 2004). These contrasts are applied at each voxel and result in contrast images that can be inspected to detect significant voxels. Linear contrasts can include a single regressor. The resulting contrast image will then represent the main effect of this regressor.

Contrasts can also compute the difference between regressors. The resulting images will then represent the difference between the regressors. The statistical tests computed take into account the size of the effect ($cT \times \beta i$) but also its variance. Summary statistics images are fed in a second level analysis (random effects analysis) taking into account inter-subject variability and allowing inferences on the general population from which the subjects were drawn (Penny and Holmes 2004). Summary statistics images are further smoothed (using a Gaussian Kernel; FWHM: 6mm) before being fed into the random effects analysis. Statistical inferences are carried on the parameter estimates computed at the random effects.

3.5. Inferences

The brain volume is composed of more than 100,000 voxels. The likelihood of obtaining voxels significantly affected by an experimental condition by chance is therefore high (e.g. with $p = 0.001$, we would obtain at least 100 significant voxels by chance). Data are corrected for multiple comparisons to prevent this type of error. The correction method takes into account the spatial correlation between voxels of the functional data to compute the number of independent measures of the data set, and define the Z-value threshold required to reach significance (Brett, Penny et al. 2004). If a significant activation can be expected in a given location (based on the literature), correction for multiple comparisons can be computed on a small (generally spherical) volume (generally 10 mm radius) around the a priori location of interest. If no a priori is available for a given location, this activation has to survive the more conservative multiple comparison correction over the entire brain volume to be considered significant (Brett, Penny et al. 2004). A basic assumption of classical statistics is that the data variances are independent and identically distributed across factors. When this assumption is falsified, a correction for non-sphericity is applied, for instance when regressors of a design matrix are correlated (Glaser and Friston 2004). This correction was applied in our sleep fMRI studies.

4. Reviews and experimental studies

4.1. Introduction

4.1.1. Usefulness of neuroimaging in psychiatry

From

Muselle A et Desseilles M, Utilité de la neuroimagerie en psychiatrie. Acta Psychiatrica Belgica, 108(6), 2008, 1-9.

Summary

Brain neuroimaging has a growing place in psychiatry. First only structural, it allows a better understanding in the pathophysiology of psychiatric illnesses by its functional applications. Even if early use of brain imaging in psychiatry was confined to scientific research, a lot of potential roles for diagnosis and treatment emerge. In this paper we present the different structural and functional neuroimaging tools. Then we evoke the place of these tools in psychiatric research and clinic. Finally, we describe briefly brain areas involved and clinical illustrations of brain neuroimaging in five frequent psychiatric illnesses (attentional deficit hyperactivity disorder, depression, obsessive-compulsive disorder, post-traumatic stress disorder and schizophrenia).

Utilité de la neuroimagerie en psychiatrie

A. Muselle[1], **M. Desseilles**[2]

Brain neuroimaging has a growing place in psychiatry. First only structural, it allows a better understanding in the pathophysiology of psychiatric illnesses by its functional applications. Even if early use of brain imaging in psychiatry was confined to scientific research, a lot of potential roles for diagnosis and treatment emerge. In this paper we present the different structural and functional neuroimaging tools. Then we evoke the place of these tools in psychiatric research and clinic. Finally, we describe briefly brain areas involved and clinical illustrations of brain neuroimaging in five frequent psychiatric illnesses (attentional deficit hyperactivity disorder, depression, obsessive-compulsive disorder, post-traumatic stress disorder and schizophrenia).

Key words : Neuroimaging, Psychiatry

Introduction

La neuroimagerie occupe une place de plus en plus importante en psychiatrie. Au départ uniquement structurelle, elle a permis ensuite par son versant fonctionnel une utilisation de plus en plus importante dans la compréhension des maladies psychiatriques. Actuellement, bien que l'utilisation de la neuroimagerie en psychiatrie soit surtout confinée à la recherche scientifique, les rôles potentiels en clinique pour le diagnostic ou le traitement semblent être de plus en plus nombreux.

La neuroimagerie structurelle, qui permet une analyse anatomique du cerveau, comprend la Tomodensitométrie Computérisée (TDC) et l'Imagerie par Résonance Magnétique (IRM). La neuroimagerie fonctionnelle, qui permet une mesure de l'activité cérébrale, comprend l'IRM fonctionnelle (IRMf), la Tomographie par Émission de Positons (TEP), la Tomographie par Émission Simple de Photons (SPECT), la Spectroscopie IRM (spIRM) et la Spectrométrie proche de l'infrarouge (NIRS). D'autres examens, qui ne sont pas à proprement parler des examens d'imagerie, permettent également une analyse du fonctionnement cérébral avec une grande précision temporelle. Il s'agit des Potentiels évoqués (PE), de l'Electroencéphalographie (EEG) et de la Magnétoencéphalographie (MEG).

Nous présentons d'abord les différents outils d'imagerie structurelle et fonctionnelle. Ensuite, nous évoquons la place de ces outils en psychiatrie que ce soit en recherche ou en clinique (outil diagnostique ou de validation d'un traitement). Enfin nous passons brièvement en revue cinq maladies psychiatriques fréquentes (le trouble du déficit de l'attention avec hyperactivité, la dépression, le trouble obsessionnel compulsif, le stress post-traumatique et la schizophrénie) en précisant (i) les régions cérébrales concernées, (ii) les fonctions cognitives impliquées et (iii) les applications cliniques de la neuroimagerie.

Outils en neuroimagerie cérébrale

De plus en plus de techniques de neuroimagerie (Laureys et al., 2002 ; Mazziota et Frackowiak, 2000 ; Shulman, 2001) sont utilisées, certaines couramment, d'autres dans des situations spécifiques ou dans le cadre de recherches. On peut classer ces techniques selon différents critères : utilisation structurelle ou fonctionnelle et résolution spatiale ou temporelle. Ainsi, certaines techniques ont une très grande résolution temporelle et une faible résolution spatiale (EEG, MEG, PE) et d'autres une bonne résolution spatiale et par contre une résolution temporelle plus faible (TEP, SPECT, fIRM) ou nulle (TDC, IRM). L'association de ces différents types d'examens chez un même sujet permet d'obtenir simultanément une analyse spatiale et temporelle (par exemple IRM+EEG) ou fonctionnelle et structurelle à la fois (par exemple TEP+TDC), ou encore structurelle, fonctionnelle et temporelle (par exemple IRM+IRMf+EEG).

La tomodensitométrie computérisée (TDC)

La TDC cérébrale est basée sur l'absorption des rayons X par les structures traversées. Le degré d'absorption, et donc l'image obtenue, dépendra de la densité des structures. La détection se fait grâce à des détecteurs placés autour du crâne. Une reconstruction algorithmique permet d'avoir une image tomographique.

La TDC a pour avantages d'être rapide, d'avoir une grande disponibilité, de permettre une bonne visualisation de l'os et du sang. Elle est pour ces raisons d'une grande utilité en urgence, notamment dans les cas de traumatismes et d'hémorragies intracrâniennes. Par contre, elle présente de la radioactivité et ne permet pas une bonne visualisation des contrastes.

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L'utilisation d'un produit de contraste permet d'améliorer la sensibilité de l'examen, notamment pour une meilleure observation de l'œdème et de l'ischémie.

L'Imagerie par Résonance Magnétique (IRM)

L'IRM est basée sur l'observation de la résonance magnétique nucléaire des protons de l'eau. On applique deux champs magnétiques, un premier, statique, qui permet l'orientation des moments magnétiques (spins) des noyaux et un second, sous forme d'impulsions brèves, qui fera passer les noyaux de l'état fondamental à l'état excité. On obtient ainsi la résonance, et le spin passe à un niveau d'énergie supérieur. Lorsque l'on va supprimer le second champ magnétique, les protons auront tendance à revenir à leur alignement initial, c'est la relaxation (T1 et T2), qui engendre un signal. C'est ce signal qui correspond, une fois transformé, au spectre de l'IRM, et qui est défini en terme d'intensité. Les temps de relaxation vont varier selon les tissus. Selon ces variations on pourra différencier les tissus et l'on pourra, voir dans un tissu les modifications liées à la présence d'une lésion. Le rôle des agents de contraste va être de diminuer ce temps de relaxation afin d'augmenter l'intensité des signaux.

Il existe différentes méthodes d'IRM qui permettent une analyse structurelle plus fine des structures cérébrales. La morphométrie voxel par voxel (Voxel Based Morphometry, VBM) mesure la concentration des différentes matières cérébrales. Il s'agit d'une analyse de la substance grise. L'imagerie par tenseur de diffusion (Diffusion Tensor Imaging, DTI) va, quant à elle, étudier la substance blanche. Cette technique est basée sur l'étude de la diffusion des molécules d'eau, qui est favorisée dans le sens des fibres et nulle perpendiculairement aux fibres (anisotropie). Grâce à cette propriété, on peut obtenir des images des fibres de la substance blanche : il s'agit de la fraction d'anisotropie (analyse locale de la substance blanche) et de la tractographie (analyse régionale des grands faisceaux de substance blanche).

L'IRM ne soumet pas le patient à la radioactivité, mais à un champ électromagnétique, et présente une meilleure résolution et une meilleure visualisation des contrastes que le CT scan.

D'un autre côté, il est moins disponible, plus coûteux et demande plus de temps que le CT scan. Il ne permet pas l'analyse des tissus osseux. De plus, il présente plusieurs contre-indications : la claustrophobie, la présence de prothèse et de matériel ferromagnétique, la présence de dispositifs tels un pace-maker.

L'IRM fonctionnelle (IRMf)

L'IRM fonctionnelle se base sur l'observation des variations de l'oxygène dans le sang. Cette observation est réalisée grâce à la différence entre l'oxyhémoglobine et la déoxyhémoglobine. En effet, si l'oxyhémoglobine n'a pas d'influence sur le champ magnétique, la déoxyhémoglobine, quant à elle, va modifier le champ. En libérant l'oxygène, le fer ferrique de l'hémoglobine se transforme en fer ferreux. Deux électrons non appariés vont donc apparaître dans l'hémoglobine et ceux-ci vont conférer à la déoxyhémoglobine ses propriétés paramagnétiques. Lors de l'acquisition des images IRM, les champs à proximité de l'oxyhémoglobine et de la déoxyhémoglobine sont donc différents, ce qui provoque l'hétérogénéité magnétique. Grâce à cela, au cours de l'activation de certaines régions cérébrales, et donc au cours de l'apport en oxygène de ces régions, on pourra enregistrer un signal.

L'IRM fonctionnelle permet donc une analyse du métabolisme cérébral. Ses inconvénients sont ceux de l'IRM.

La Tomographie par émission de Positons (TEP)

Il s'agit d'un examen de médecine nucléaire. Il est basé sur l'injection d'un traceur radioactif qui sera soit distribué dans la circulation sanguine, soit utilisé en intracellulaire, soit fixé sur un récepteur spécifique. Un métabolite cellulaire souvent utilisé est le déoxyglucose lié à un traceur radioactif, le fluor-18 (18-FDG). Le 18-FDG va participer au processus cellulaire et sera détecté. Par exemple, dans un tissu tumoral, la glycolyse est augmentée, le transporteur GLUT 1 est produit en excès et le 18-FDG qui ne peut être transformé par les étapes de la glycolyse va s'accumuler en intracellulaire et il y aura un hypersignal lors de sa désintégration.

La TEP permet donc une analyse fonctionnelle. La résolution spatiale est moins bonne que celle de l'IRMf, cependant l'évolution rapide des techniques réduit de plus en plus ce déficit. Par ailleurs, la résolution spatiale est uniforme. La résolution temporelle quant à elle est assez faible. L'avantage de la TEP, par rapport à l'IRMf, est qu'elle permet l'analyse de certains neurorécepteurs afin d'étudier la physiologie de leurs ligands (par exemple dopamine, sérotonine, noradrénaline, benzodiazépines, acide gamma-aminobutyrique, …) en utilisant des radioligands (traceurs radioactifs) spécifiques.

Enfin, elle expose le patient à une radioactivité, présente un coût important et est peu disponible à l'heure actuelle.

La Tomographie par émission Simple de Photons (SPECT)

Le principe est similaire à celui de la TEP, c'est-à-dire l'utilisation d'un radiotraceur. Mais dans le cas de la SPECT, il s'agit d'une émission monophotonique. Les images sont des projections qui seront ensuite reconstruites pour obtenir des images en trois dimensions.

L'examen est moins cher et plus disponible que la TEP. De plus, les traceurs utilisés ont une demi-vie plus longue, cela permet un intervalle entre l'injection et l'acquisition de l'image.

Cependant cet examen présente aussi quelques inconvénients : il est moins sensible, la résolution spatiale n'est pas uniforme et les traceurs disponibles sont moins nombreux.

La spectroscopie IRM

Il s'agit au départ d'une technique qui permet l'étude de la structure de molécules chimiques. Comme l'IRM, elle utilise un champ magnétique pour activer les noyaux, mais la mesure n'est pas, pour la spectroscopie, uniquement celle de H+, mais celle de tous les noyaux (31P, 13C, 19F, etc.).

La spIRM permet une analyse fonctionnelle cérébrale par l'observation du métabolisme et cela sans avoir recours à des radiotraceurs. Par exemple, la spIRM du proton (H+) permet l'identification de marqueurs de viabilité neuronale (N-acétyl-aspartate) et la spIRM du phosphore (31P) permet une analyse du métabolisme énergétique cellulaire (phosphocréatine, phosphate inorganique, ATP). La spIRM est, à l'heure actuelle, utilisée uniquement en recherche.

La spectrométrie proche de l'infrarouge (NIRS)

La spectrométrie proche de l'infrarouge se base sur l'absorption des rayonnements électromagnétiques par la matière. L'oxygénation et l'hémodynamique d'un tissu sont évaluées grâce à la différence d'absorption des rayons selon l'oxygénation de l'hémoglobine et de la myoglobine.

On obtient donc une image de l'activité cérébrale. Cette technique est aussi, pour l'instant, un outil de recherche.

Les Potentiels évoqués (PE)

Cette technique a pour principe l'enregistrement des ondes électriques perçues au niveau du système nerveux central. Les PE exogènes enregistrent les réponses des voies nerveuses à des stimuli spécifiques (auditifs, visuels ou somesthésiques). Les PE endogènes ou PE cognitifs sont, quant à eux, l'observation de certaines ondes au moment de la réalisation de tâches cognitives.

Pour les PE exogènes, on distinguera (i) les PEV ou potentiels évoqués visuels étudiant les voies visuelles, de l'œil aux aires visuelles ; (ii) les PEA ou potentiels évoqués auditifs étudiant les voies auditives, de la cochlée aux aires auditives et (iii) les PES ou potentiels évoqués somesthésiques étudiant les voies sensitives, des récepteurs sensitifs périphériques aux aires sensitives. Pour les PE endogènes on distinguera (i) le P300 ou onde ayant une déflexion positive survenant après 300 millisecondes lors d'une tâche cognitive comme la détection de stimuli ; (ii) la VCN ou Variation Contingente Négative, liée à l'anticipation d'un stimulus et (iii) la MMN (Mismatch negativity) ou négativité de discordance, traduisant un changement de stimulus.

La résolution temporelle des PE est très bonne, et ils permettent également une analyse précise des voies nerveuses. Un autre avantage est qu'il s'agit d'une technique peu coûteuse et très disponible.

Electroencéphalographie

L'EEG permet la mesure de l'activité corticale au cours du temps grâce aux électrodes qui enregistrent l'activité électrique. L'examen est surtout utilisé en neurologie, notamment dans le diagnostic de l'épilepsie, mais il a aussi un rôle en psychiatrie, en association par exemple avec la mesure des PE cognitifs.

Le tracé montre différents rythmes (rythme alpha : 8-13 Hz, bêta : 18-30 Hz, gamma : 30-200 Hz, delta : 0.5-4 Hz, thêta : 5-8 Hz, mu : 7-11 Hz) en fonction de l'activité cérébrale sous-jacente. Ces ondes, corrélées à l'activité cérébrale sous-jacente des sujets, représentent une imagerie cérébrale à haute résolution temporelle.

Elle a comme les PE un coût peu élevé et une très bonne disponibilité.

La Magnétoencéphalographie

Technique proche de l'EEG, la MEG est basée sur la mesure des champs magnétiques créés par les flux électriques. Elle permet de la même façon que l'EEG, d'avoir une image de l'activité cérébrale, avec une haute résolution temporelle. Cependant, l'analyse est plus fine et permet des mesures cognitives plus complexes qu'avec l'EEG. Elle a aussi une meilleure résolution spatiale que l'EEG.

Par contre, le dispositif et l'équipement nécessaires à cet examen sont plus coûteux et moins disponibles que pour l'EEG.

Utilisation de la neuroimagerie en psychiatrie

Introduction

La neuroimagerie structurelle sert au diagnostic différentiel en clinique psychiatrique afin d'exclure un trouble dit neurologique (par exemple, un scanner cérébral en urgence permettant d'exclure une hémorragie cérébrale). La neuroimagerie fonctionnelle est quant à elle un outil de recherche en psychiatrie alors qu'elle est utilisée en clinique neurologique notamment pour les maladies dégénératives de type maladie d'Alzheimer. Pourtant, la neuroimagerie cérébrale fonctionnelle permet de faire le lien entre de multiples pathologies psychiatriques et leurs substrats neuroanatomiques. Plusieurs circuits ont déjà été mis en évidence comme dans les troubles de l'attention, la dépression, le trouble obsessionnel compulsif, la schizophrénie et le stress post-traumatique. Dans certaines pathologies on peut aussi mettre en évidence des liens plus précis, non plus seulement entre la pathologie générale et le changement d'activité cérébrale, mais, plus spécifiquement, entre un symptôme de cette pathologie et un changement d'activité au niveau d'un site particulier cérébral. Cela a été étudié notamment dans le trouble obsessionnel compulsif et la dépression.

Certaines études ont analysé l'activité cérébrale (1) au repos, (2) d'autres au cours de tâches : (i) exécutives, mnsésiques ou cognitives, (ii) constituées de stimuli externes comme des images de visages ou des sons, ou de stimuli internes comme des images mentales, (iii) spécifiques ou non à la pathologie

observée, par exemple en induisant des symptômes spécifiques (tristesse, obsession, etc.). Ces différents modèles permettent de différencier une anomalie présente au repos d'une anomalie, déficit ou hyperactivation, se déclarant lors d'activités cérébrales précises, ce qui permet souvent une définition plus précise des anomalies décelées (Remijnse et al., 2006).

La difficulté en psychiatrie vient de la grande hétérogénéité des pathologies, de la grande variabilité (i) interindividuelle pour une même pathologie (comme la dépression) et (ii) intraindividuelle, au cours du temps, pour un même patient. Cela engendre une faible reproductibilité des études réalisées et nécessite de la part des chercheurs une bonne description des échantillons cliniques afin de mieux interpréter les résultats observés.

Endophénotype

Le génotype spécifique des pathologies psychiatriques est difficile à mettre en évidence. Par contre, le phénotype des pathologies psychiatriques est bien connu, ce sont les troubles psychiques rapportés et les comportements observés tant par le patient que par le spécialiste. Pour tenter d'approcher le génotype, le concept d'endophénotype ou phénotype intermédiaire a été proposé. L'endophénotype n'est pas directement observable – contrairement au phénotype – mais est plus facilement quantifiable et est plus proche du génotype que le phénotype. Un endophénotype doit être (i) associé à la maladie, (ii) contrôlé au moins partiellement par la génétique, (iii) objectivement mesurable et (iv) plus simple à étudier que le phénotype (Bigos et Hariri, 2007 ; Hariri et Weinberger, 2003 ; Mitterschiffthaler et al., 2006).

Le fait que certaines pathologies ont un caractère génétique est communément admis. La question reste cependant de savoir quelle est l'anomalie transmise génétiquement. Dans le but d'une meilleure compréhension des maladies psychiatriques et de cette transmission génétique, la neuroimagerie peut permettre de faire un lien avec la génétique et servir à mettre en évidence des endophénotypes liés à une pathologie. Il s'agit de faire le lien entre certains polymorphismes génétiques et des circuits nerveux liés directement à des pathologies psychiatriques. L'imagerie cérébrale a déjà permis de faire ce lien dans différentes pathologies. Dans la schizophrénie par exemple, on a mis en évidence un lien entre le polymorphisme du gène de la catécholamine O-méthyltranférase (COMT) et des différences en IRMf au niveau du cortex préfrontal durant des tâches mnésiques, alors que la tâche en elle-même (phénotype) n'était pas différemment réalisée (Mitterschiffthaler et al., 2006).

Le fait d'utiliser la neuroimagerie pour mettre en évidence des endophénotypes permet d'être plus précis, plus sensible, plus objectif et plus proche de la génétique. Grâce à cela on pourrait mettre en évidence des sous-groupes à l'intérieur des pathologies et ainsi cibler des traitements appropriés.

Diagnostic

En dehors de la psychiatrie, la neuroimagerie possède un rôle diagnostique primordial. La neuroimagerie structurelle peut permettre, entre autres, la mise en évidence de tumeurs cérébrales, de certains foyers épileptogènes et de certains accidents vasculaires cérébraux. La neuroimagerie fonctionnelle quant à elle peut apporter des arguments en faveur d'un diagnostic de dégénérescence cérébrale, telle la maladie d'Alzheimer.

En psychiatrie, la neuroimagerie n'est pas utilisée pour le diagnostic précoce de pathologie, car la clinique prime de manière générale pour le diagnostic. Cependant, elle peut avoir une utilité dans certains troubles complexes où le diagnostic n'est pas clair cliniquement, ou lorsque le patient répond mal à un traitement. Dans de telles situations, une imagerie fonctionnelle peut mettre en évidence des anomalies de l'activité cérébrale, pouvant se révéler typiques d'une pathologie. Par exemple, dans le trouble du déficit de l'attention avec hyperactivité (TDAH), on retrouve des anomalies qui seraient spécifiques du trouble (Rubia et al., 1999 ; Rubia et al., 2005) et qui pourraient se révéler utiles devant une interrogation diagnostique chez un enfant.

Grâce aux techniques de neuroimagerie fonctionnelle, on peut aussi tenter de subdiviser les maladies psychiatriques en sous-types, selon les symptômes et leur corrélation en imagerie (Gustafsson et al., 2000).

Actuellement, les techniques de neuroimagerie ne sont pas utilisées dans la pratique habituelle de la psychiatrie, mais l'expansion de ces techniques et la compréhension grandissante des substrats neuroanatomophysiologiques des maladies psychiatriques pourraient, dans le futur, conférer un rôle diagnostique de plus en plus important à ces techniques.

Traitement

La neuroimagerie pourrait aussi devenir un outil important dans le traitement des maladies psychiatriques.

L'activité cérébrale observée avant traitement chez les patients qui sont par la suite de bons répondeurs au traitement pourrait être utilisée comme standard prédictif d'une bonne réponse à ce traitement. Ceci a été réalisé pour comparer des traitements pharmacologiques, mais aussi d'autres comme la thérapie comportementale dans le Trouble Obsessionnel Compulsif (Evans et al., 2006 ; Kobayashi et al., 2007).

On peut aussi comparer l'activité cérébrale de différentes pathologies qui sont traitées avec la même molécule chimique. Ces comparaisons permettent d'avoir une meilleure compréhension du mécanisme des médicaments utilisés. Ainsi par exemple, on a pu déterminer que, si la fluoxétine était active dans la dépression et dans les TOC, ce n'était cependant pas par le même mécanisme d'action. En effet, les patterns d'activité pré- et post- traitement, et donc l'action du médicament, ne sont pas du tout les mêmes dans les deux pathologies (Evans et al., 2006).

La neuroimagerie peut s'avérer également utile dans la neurochirurgie des troubles psychiatriques. Tout d'abord elle permet une visualisation précise en préopératoire, ainsi qu'un contrôle postopératoire. Mais elle peut aussi, comme pour les

traitements pharmacologiques et psychothérapeutiques, apporter un indice prédictif de la réponse au traitement chirurgical.

Grâce aux valeurs prédictives obtenues par la neuroimagerie, il serait alors possible de préconiser un traitement plutôt qu'un autre selon la prédiction d'efficacité. Cela pourrait être particulièrement intéressant dans les cas où le traitement est onéreux, ou dans les cas où le traitement présente des risques d'effets secondaires ou des risques de complications, comme c'est le cas en neurochirurgie.

Illustrations cliniques de l'intérêt de l'imagerie cérébrale en psychiatrie

Nous allons discuter de cinq pathologies psychiatriques pour lesquelles plusieurs études utilisant la neuroimagerie fonctionnelle ont été réalisées. Il ne s'agit bien sûr pas d'une revue exhaustive de ce qui a été étudié par la neuroimagerie en psychiatrie, mais bien d'illustrations d'application en recherche et en clinique. Pour chacune des pathologies présentées, nous allons préciser (i) les aires cérébrales impliquées, (ii) les fonctions cognitives perturbées et (iii) les applications cliniques qui en découlent.

Il faut signaler que les pathologies étudiées sont très hétérogènes et que les résultats des différentes études réalisées ne sont pas toujours concordants (reproductibilité variable des études). C'est pourquoi il est encore difficile à l'heure actuelle de définir, par des résultats statistiquement significatifs, les sites exacts impliqués et les processus cognitifs perturbés dans ces différentes pathologies. Parfois le nombre de sujets étudiés est faible et il est alors difficile d'obtenir des résultats statistiquement concluants au niveau de la population. Par ailleurs, il faut bien se rendre compte que plus une étude est sélective et contrôlée, plus elle sera reproductible, mais plus on s'éloignera des patients rencontrés en pratique clinique.

Dépression

Aires cérébrales impliquées. Les anomalies décelées sont un déficit de perfusion au niveau cortical (préfrontal ventromédial, cingulaire et pariétal postérieur), des anomalies au niveau sous-cortical et limbique (région striatale, amygdalienne, hippocampique et thalamique) (Andreasen, 1997 ; Beauregard et al., 1998 ; Drevets, 1998 ; Drevets, 2003 ; Elliott et al., 1997 ; Evans et al., 2006 ; Mitterschiffthaler et al., 2006).

Fonctions cognitives. De nombreux déficits cognitifs (mnésiques, attentionnels ou exécutifs) ont été mis en évidence dans la dépression par l'utilisation de différents tests (Chamberlain et Sahakian, 2006). De plus, certaines caractéristiques de la dépression ont été étudiées (exemple : l'humeur dépressive, l'attention spécifique pour des stimuli négatifs, les ruminations, l'agressivité liée à la dépression) (Dougherty et al., 2004 ; Mitterschiffthaler et al., 2006).

Implications générales et applications cliniques. La neuroimagerie permet une meilleure compréhension de la maladie en faisant le lien entre la neurophysiologie et certaines caractéristiques de la dépression (Mitterschiffthaler et al., 2006). Ainsi, différentes études ont cherché à subdiviser la dépression en plusieurs sous-types et à voir quels étaient les corrélats cérébraux des différents symptômes du syndrome dépressif. Par exemple, Dougherty et al. ont comparé, en utilisant la TEP, (i) les épisodes dépressifs majeurs avec crise d'agressivité (MDD+A), (ii) les épisodes dépressifs majeurs sans crise d'agressivité (MDD-A) et (iii) des sujets contrôles au cours de l'induction de la colère (Dougherty et al., 2004). Ils ont ainsi vu que l'induction de la colère induisait une hyperactivation au niveau ventromédial du cortex préfrontal. Cette hyperactivation était significativement moins importante chez les sujets MDD+A. De plus, chez le sujet contrôle l'hyperactivation est associée à un déficit d'activation au niveau de l'amygdale, alors que chez le sujet MDD+A les variations préfrontales et amygdaliennes vont dans le même sens. Comme on connaît par ailleurs les liens entre le cortex ventromédial préfrontal et l'activité de l'amygdale (Johnstone et al., 2007), on comprend mieux que la régulation émotionnelle perturbée chez les patients déprimés est le résultat d'une dysconnectivité dans un réseau cortical et sous-cortical (Greicius et al., 2007 ; Seminowicz et al., 2004).

Par ailleurs, l'IRM fonctionnelle permet d'obtenir des images prédictives de l'efficacité d'un traitement (Evans et al., 2006 ; Kobayashi et al., 2007), grâce aux patterns d'activité cérébrale en pré-traitement qui varient selon qu'il s'agit d'un bon répondeur ou non. Au niveau thérapeutique, signalons aussi l'utilisation de la neuroimagerie en neurochirurgie fonctionnelle (cingulotomie) dans les cas de dépressions sévères et réfractaires aux thérapeutiques habituelles. Celle-ci permettrait une visualisation préalable des sites à atteindre en chirurgie, une visualisation durant l'opération (système de neuronavigation), une visualisation ultérieure de l'acte réalisé, mais aussi peut-être une valeur prédictive de la neurochirurgie tout comme dans les traitements médicamenteux.

Trouble obsessionnel compulsif (TOC)

Aires cérébrales impliquées. Une hyperactivation a été observée au niveau cortical (orbitofrontal et cingulaire antérieur), ainsi qu'au niveau sous-cortical (région striatale et thalamique) (Evans et al., 2006 ; Menzies et al., 2008 ; Mitterschiffthaler et al., 2006 ; Saxena et Rauch, 2000 ; Whiteside et al., 2004 ; Whiteside et al., 2006). Dans d'autres études, une réduction de l'activité corticale frontostriatale et une hyperactivité (peut-être compensatrice) des régions corticales (préfrontale dorsolatérale et cingulaire), ainsi qu'au niveau hippocampique et parahippocampique ont été mises en évidence (Rauch et al., 1997).

Fonctions cognitives. De nombreux tests ont mis en évidence plusieurs déficits cognitifs chez les patients obsessionnels-compulsifs (Chamberlain et al., 2005). Les inhibitions cognitive et comportementale pourraient être des marqueurs endophénotypiques du trouble. Utilisant un autre paradigme dans ce

trouble (tâche d'apprentissage réversible qui consiste à apprendre à détecter une cible d'une manière puis de la manière inverse) une étude a exploré les circuits de la récompense, ceux de la punition et les changements affectifs qui découlent de l'activation de ces deux circuits (Remijnse et al., 2006).

Implications générales et applications cliniques. Certaines études ont subdivisé le trouble obsessionnel compulsif par symptômes (Mitterschiffthaler et al., 2006) (lavage, vérification et accumulation) et elles tendent à montrer que les différents symptômes sont influencés par des voies nerveuses distinctes (Mataix-Cols et al., 2004).

La neuroimagerie peut aussi servir à la prédiction de réponse au traitement (Evans et al., 2006 ; Kobayashi et al., 2007). Il existe, tout comme pour la dépression, des patterns d'activité cérébrale en prétraitement différents pour les répondeurs ou les non répondeurs au traitement. Par exemple, les bons répondeurs au traitement par inhibiteurs sélectifs de la capture de la sérotonine (ISRS) auraient une hypoactivation orbitofrontale gauche, alors qu'au contraire, les bons répondeurs au traitement par thérapies comportementales auraient plutôt une hyperactivation de ce site (Evans et al., 2006). Dans une autre étude, un lien entre un déficit de l'activité orbitofrontale, une hyperactivité du cortex cingulaire postérieur et une bonne réponse au traitement par fluvoxamine a été mis en évidence chez des patients spécifiquement atteints de TOC avec thème de contamination (Rauch et al., 2002). Certaines recherches ont aussi été réalisées pour tenter de trouver des loci qui pourraient prédire une bonne réponse à la neurochirurgie. Une étude a ainsi été réalisée, de façon rétrospective chez des patients présentant un TOC et ayant subi une cingulotomie antérieure. Une relation entre les bons répondeurs (évalués selon l'échelle Y-BOCS) et une augmentation du métabolisme au niveau cingulaire postérieur droit a été mise en évidence (Rauch et al., 2001).

Le stress post traumatique (PTSD)

Aires cérébrales impliquées. Les anomalies décelées dans le PTSD se situeraient au niveau cortical (préfrontal médial, frontal inférieur, cingulaire antérieur) et au niveau limbique (régions amygdalienne et hippocampique) (Bremner, 2007 ; Hull, 2002 ; Phan et al., 2006 ; Rauch et al., 2006 ; Rossi et al., 2006 ; Shin et al., 2004). Des études réalisées en TEP comparent des vétérans de la guerre du Vietnam avec et sans PTSD et des sujets contrôles (Rauch et al., 2006 ; Shin et al., 2004). Une étude montre un déficit d'activité au niveau du cortex préfrontal médial et une hyperactivité au niveau amygdalien, ces deux anomalies étant inversement proportionnelles, durant la symptomatologie du PTSD (reviviscence des événements traumatisants) (Rauch et al., 2006). Par contre, dans une autre étude, les deux zones citées sont hypoactivées et les anomalies observées seraient proportionnelles à l'ampleur des symptômes (Shin et al., 2004).

Fonctions cognitives. De nombreuses fonctions cognitives seraient perturbées, comme les troubles mnésiques (Bremner, 2007 ; Hull, 2002 ; McNally, 2006), le conditionnement à la peur, l'habituation, l'extinction, les interactions cognitives et émotionnelles, le traitement d'informations émotionnelles relatives à soi et aux autres (Liberzon et Sripada, 2008 ; Rauch et al., 2006).

Implications générales et applications cliniques. Les études en imagerie cérébrale ont permis de mieux comprendre la physiopathologie du PTSD. (i) De manière générale, le système limbique serait relié à la mémoire autobiographique épisodique, à l'anxiété et à la peur. L'amygdale aurait un rôle dans l'acquisition des associations engendrant la peur et l'hippocampe dans l'appréciation de la sécurité de l'environnement, dans l'apprentissage et la mémoire (Rauch et al., 2006). (ii) Au niveau cortical, le cortex préfrontal aurait un rôle dans l'attention portée aux stimuli liés au traumatisme, dans les réponses à la peur et dans la mémoire verbale (Hull, 2002 ; Rauch et al., 2006). De plus, le cortex médial préfrontal serait impliqué dans la contextualisation des stimuli, et la dérégulation de cette fonction de contextualisation jouerait un rôle clé dans la constitution des symptômes du PTSD (Liberzon et Sripada, 2008). Au niveau frontal inférieur, l'aire de Broca jouerait un rôle dans l'expression, la communication et la description de l'expérience traumatisante. Enfin, le cortex cingulaire aurait un rôle dans les réponses émotionnelles (Hull, 2002).

Les applications cliniques décrites jusqu'à présent sont surtout d'ordre thérapeutique. Premièrement, la neuroimagerie a un rôle dans la recherche de cible thérapeutique (Hull, 2002 ; Rossi et al., 2006) : par exemple, on cherche à prévenir, stopper ou inverser les dommages hippocampiques (Hull, 2002). Ensuite, une hypothèse a été émise selon laquelle la stimulation transcrânienne magnétique au niveau dorsolatéral préfrontal serait bénéfique dans les symptômes d'évitement et d'anxiété (Rossi et al., 2006). Enfin, grâce à la neuroimagerie, on a pu faire le lien entre la difficulté à réaliser des thérapies basées sur l'expression verbale dans le PTSD et l'hypoactivité perçue au niveau de l'aire de Broca (Hull, 2002).

Schizophrénie

Aires cérébrales impliquées. Les anomalies mises en évidence se situent au niveau cortical (préfrontal -déficit d'activation-, temporal –suractivation-, pariétal et cingulaire), au niveau souscortical et limbique (striatal, thalamique et parahippocampique) et au niveau du cervelet (Andreasen, 1997 ; Haenschel et al., 2007 ; Heckers et al., 1999 ; Hugdahl et al., 2004 ; Rubia et al., 2001).

Fonctions cognitives. De nombreux domaines cognitifs sont altérés chez les patients schizophrènes : l'attention, les fonctions exécutives, la mémoire de travail verbale et visuospatiale, d'autres types de mémoire comme la mémoire sémantique et épisodique, et l'apprentissage (Frangou et al., 2008 ; Kuperberg et Heckers, 2000 ; Mortimer, 1997 ; Sharma et Antonova, 2003 ; Tyson et al., 2006 ; Weinberger et Gallhofer, 1997).

Implications générales et applications cliniques. La neuroimagerie permet de proposer des sous-types cliniques (endophénotypes) de la schizophrénie. On a pu, par exemple, montrer que

les anomalies frontales étaient plutôt associées à une schizophrénie déficitaire (prédominance de symptômes négatifs), alors que les anomalies temporales étaient plutôt associées à une schizophrénie non déficitaire (Heckers et al., 1999).

Une autre façon de caractériser la schizophrénie est de la différencier sur un mode temporel. Ainsi, on a essayé d'établir la différence entre l'état psychotique et le trait psychotique. Pour un même patient, l'activité cérébrale sera différente dans le temps, suite à la prise du traitement neuroleptique. Le déficit d'activation fronto-thalamo-cortical gauche est plutôt lié au trait psychotique, alors que le déficit au niveau du circuit droit est plutôt lié à l'état psychotique (Mendrek et al., 2004).

Différents troubles cognitifs ont pu être associés à des modulations du métabolisme cérébral. L'IRM fonctionnelle associée à des tâches arithmétiques a montré une diminution de l'activation au niveau préfrontal et une suractivation (peut-être compensatrice) au niveau pariétal (Hugdahl et al., 2004). Certaines études ont étudié les hallucinations. On a pu montrer des diminutions du flux sanguin au niveau du centre de la parole et de l'aire motrice secondaire chez les personnes présentant des phénomènes hallucinatoires. Des examens réalisés durant les hallucinations ont pu, quant à eux, montrer une activation au niveau du cortex cingulaire antérieur, du striatum, du thalamus, au niveau parahippocampique et du cervelet (Andreasen, 1997). D'autres études ont étudié la mémoire : par exemple une étude a utilisé les PE pour étudier la mémoire de travail (Haenschel et al., 2007). Grâce aux PEV et à l'IRM fonctionnelle, associés à des tâches de mémoire visuelle (encodage et restitution), elle a pu mettre en évidence un déficit visuel (au niveau des potentiels évoqués) et une diminution de l'activation des aires visuelles associées en IRM fonctionnelle. Cela suggère un déficit précoce de traitement de l'information (processing) dans la schizophrénie.

Trouble du déficit de l'attention avec hyperactivité (TDAH)

Aires cérébrales impliquées. La majorité des études montrent des anomalies au niveau cortical sous forme soit d'une hypoactivité (ventrolatéral préfrontal et cingulaire antérieur) soit d'une hyperactivité (aires sensitives primaires) ainsi que des anomalies sous-corticales (striatum) et cérébelleuses (Bush et al., 1999 ; Bush et al., 2005 ; Durston, 2003 ; Gustafsson et al., 2000 ; Kelly et al., 2007 ; Lou et al., 1984 ; Lou et al., 1989 ; Lou et al., 1990 ; Lou et al., 1998 ; Mitterschiffthaler et al., 2006 ; Pliszka et al., 2006 ; Rubia et al., 1999 ; Rubia et al., 2005 ; Shaw et al., 2007).

Fonctions cognitives. Le déficit mis en évidence se situerait au niveau des fonctions exécutives, qui comprennent la manière dont vont être planifiés les actes de résolution d'un problème, la capacité de résolution des problèmes, la mémoire de travail, l'inhibition des actes inappropriés et la possibilité de les remplacer par d'autres appropriés (voir par exemple (Castellanos et al., 2006 ; Nichols et Waschbusch, 2004).

Implications générales et applications cliniques. Différents troubles cognitifs ont été corrélés à une modulation de l'activité cérébrale. Ainsi, l'anomalie décrite au niveau des aires sensitives primaires (Shaw et al., 2007) pourrait être reliée à un hyperfonctionnement des processus sensitifs. Le déficit au niveau cingulaire serait, lui, plus particulièrement lié au déficit d'attention, de motivation, à l'inhibition et à la prise de décision (Bush et al., 1999). Plusieurs études se sont intéressées au contrôle de l'inhibition chez les patients TDAH (Pliszka et al., 2006 ; Rubia et al., 2005). Par exemple, chez les patients ayant un TDAH, il y a un défaut d'activation du cortex cingulaire antérieur et du cortex préfrontal ventrolatéral gauche, après un échec d'inhibition (Pliszka et al., 2006). De plus, chez des patients TDAH exempts de tout traitement pharmacologique, une diminution d'activation du cortex préfrontal inférieur droit surviendrait lorsque l'inhibition motrice est un succès et surviendrait au niveau du cortex cingulaire postérieur et du précuneus lorsque l'inhibition est un échec (Rubia et al., 2005). Ces études nous montrent que les patients TDAH auraient de moins bonnes réponses à l'erreur et au conflit.

Par ailleurs, d'un point de vue étiopathogénique, le TDAH serait divisé en un trouble neurodéveloppemental lié à un déficit au niveau du lobe frontal et en un trouble cognitivo-moteur lié à des anomalies temporales, cérébelleuses et sous-corticales (Gustafsson et al., 2000).

Conclusion

Bien que réservée longtemps à la recherche, l'imagerie cérébrale pourrait bientôt prendre une place de plus en plus importante en clinique tant (i) pour l'identification d'endophénotypes permettant de se rapprocher du génotype de certains troubles psychiques que (ii) pour la mise au point diagnostique et (iii) pour la prédiction de réponse à un traitement.

Les méthodes d'imagerie sont nombreuses et permettent, seules ou en association, de mettre l'accent sur la structure du cerveau (résolution structurelle) et / ou sur le fonctionnement des régions cérébrales, ainsi que d'avoir une idée quant au décours temporel des événements neuronaux perturbés (résolution temporelle).

Nous avons illustré brièvement les applications cliniques de la neuroimagerie en présentant cinq maladies psychiatriques fréquentes (le trouble du déficit de l'attention avec hyperactivité, la dépression, le trouble obsessionnel compulsif, le stress post-traumatique et la schizophrénie).

Résumé

La neuroimagerie cérébrale a une place grandissante en psychiatrie. Au départ uniquement structurelle, elle permet une meilleure compréhension de la physiopathologie des troubles psychiatriques par ses applications fonctionnelles. Même si les premières utilisations de l'imagerie en psychiatrie étaient réservées à la recherche scientifique, de nombreux rôles potentiels tant pour le diagnostic que pour le traitement semblent émerger. Nous présentons dans cet article les différents outils d'imagerie cérébrale structurelle et fonctionnelle. Ensuite nous évoquons la place de ces outils en psychiatrie tant pour la recherche que pour la clinique. Enfin, nous décrivons brièvement les régions cérébrales impliquées et quelques illustrations cliniques de la neuroimagerie cérébrale dans cinq maladies psychiatriques fréquentes (le trouble du déficit de l'attention avec hyperactivité, la dépression, le trouble obsessionnel compulsif, le stress post-traumatique et la schizophrénie).

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4.1.2. Function of attention and emotion in visual perception: implications for neurocognitive dysfunctions in depression.

From

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Summary

Interactions between the attentional system, the emotional system and perception are multiple and complex. It is progressively that we will try to approach them. Firstly, we will describe concepts of « bottom-up » (ascending flux of information) and « top-down » mechanisms (descending flux of information), as well as the principle of recurrent network. This will remind us that cognitive functions are organized in modules and hierarchically in the brain. This organization ensures a large capacity of adaptation to the brain architecture. The second part of the paper will focus on the influence of voluntary attention and emotion on perception. Finally, using depression as an example, we will show to what extent good interaction between emotional and attentional processes is crucial for an efficient processing of sensorial information.

Rôle de l'attention et de l'émotion dans la perception visuelle : leurs implications dans les troubles neurocognitifs de la dépression

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Interactions between the attentional system, the emotional system and perception are multiple and complex. It is progressively that we will try to approach them. Firstly, we will describe concepts of « bottom-up » (ascending flux of information) and « top-down » mechanisms (descending flux of information), as well as the principle of recurrent network. This will remind us that cognitive functions are organized in modules and hierarchically in the brain. This organization ensures a large capacity of adaptation to the brain architecture. The second part of the paper will focus on the influence of voluntary attention and emotion on perception. Finally, using depression as an example, we will show to what extent good interaction between emotional and attentional processes is crucial for an efficient processing of sensorial information.

Mécanismes « bottom-up » et « top-down »

Prenez une scène de la vie quotidienne. Typiquement, elle présentera une grande richesse d'informations visuelles comprenant des couleurs, des contrastes de luminance, des formes variées, peut-être du mouvement et des objets divers. Etant donné la capacité de traitement limitée du système visuel, ces différents objets sont en compétition pour une représentation neuronale (Aston-Jones et al., 1999 ; Duncan et al., 1997 ; Duncan, 1998 ; Duncan, 2006 ; Kastner et Ungerleider, 2001 ; Pessoa et al., 2003). Comment cette compétition a-t-elle lieu ? Peut-on l'influencer ? Si, par exemple, vous cherchez un ami dans une foule, vous serez comme aveugle aux inconnus qui pourtant passent devant vos yeux pour ne détecter que votre ami (Levin et al., 2002a ; Levin et al., 2002b ; Simons et al., 2002 ; Varakin et Levin, 2006). Si en revanche un personnage aux allures excentriques apparaissait dans la foule, il est bien possible que votre attention soit automatiquement attirée par cet objet visuel insolite. Cet exemple illustre que la compétition entre les multiples objets dans le cortex visuel peut être biaisée par des mécanismes dits « top-down » (littéralement : « du haut vers le bas ») tels que l'attention volontaire, mais également par des influences dites « bottom-up » (littéralement : « du bas vers le haut ») constituées par la saillance ou l'impact perceptif des informations sensorielles (Corbetta et Shulman, 2002 ; Hopfinger et al., 2000).

Des études en imagerie cérébrale fonctionnelle ont montré que, à la fois en présence et en l'absence de stimulation visuelle, des signaux biaisés dus à l'attention sélective peuvent moduler l'activité neuronale dans le cortex visuel (Tootell et Hadjikhani, 2000 ; Vanduffel et al., 2000). En particulier, bien que la compétition entre les différents stimuli soit résolue *in fine* dans le cortex visuel, la source des effets « top-down » sur l'information visuelle entrante provient d'un réseau de régions corticales frontales et pariétales.

Ainsi, un objet présenté seul dans le champ visuel est plus facilement traité que s'il y a deux objets. A cause des ressources limitées de traitement de données, plusieurs objets présents en même temps dans le champ visuel sont en compétition pour une représentation neuronale.

Pour résumer, deux mécanismes attentionnels sont en constante interaction. Ces deux mécanismes sont le reflet d'une compétition pour la représentation neuronale de différents stimuli sensoriels. Ainsi, les propriétés d'un stimulus externe, telles que sa saillance perceptive, auront une influence « bottom-up » qui viendra interagir avec nos intentions ou nos buts qui eux constituent l'influence « top-down ». L'exemple de la recherche d'un ami dans une foule que nous avons décrit plus haut illustre combien les deux mécanismes sont étroitement liés. Nous verrons qu'ils peuvent agir à différents niveaux de l'organisation fonctionnelle du cerveau.

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Organisation modulaire et hiérarchique du système nerveux central

Le monde externe est dès le départ représenté sous forme de cartes dans le cortex humain. Ainsi, de nombreuses cartes somato-sensibles ou motrices ont été décrites au cours de ces dernières décennies (pensons à l'homunculus de Penfield (Penfield et Rasmussen, 1950). De plus, des cartes rétinotopiques dans le cortex visuel et tonotopiques dans le cortex auditif ont été découvertes chez le primate et chez l'humain (Formisano et al., 2003 ; Guimaraes et al., 1998 ; Sereno, 1998 ; Talavage et al., 2000 ; Van Essen et al., 2001 ; Wandell et al., 2005).

Ainsi, au niveau du cortex visuel, l'influx visuel passe par la rétine, le nerf visuel, décusse dans le chiasma optique, passe ensuite par le corps genouillé latéral se situant à l'arrière du thalamus, puis va dans le cortex visuel d'abord en V1 puis en V2 et, selon les caractéristiques du stimulus, projette dans différentes régions codant pour des attributs spécifiques. Différentes régions sont spécialisées pour le traitement des couleurs (V4 pour « Extrastriate Visual Cortical Area number 4 » ou « Aire visuelle corticale extrastriée numéro 4 »), le mouvement (MT/V5 pour « Medial Temporal » ou « Temporal Médial » et « Extrastriate Visual Cortical Area number 5 » ou « Aire visuelle corticale extrastriée numéro 5 »), les visages (FFA pour « Fusiform Face Area » ou « Aire Fusiforme des Visages »), les lieux (PPA pour « Parietal Place Area » pour « Aire Pariétale des Lieux », etc. (figure I)].

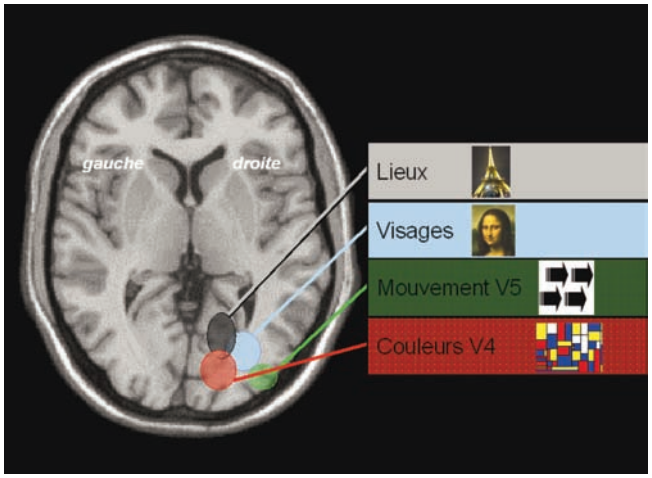
Circuits récurrents

Habituellement, une action (physique ou psychique) se déroule dans le temps comme une séquence de mouvements ou de pensées. Or, toute action ou pensée organisée nécessite une capacité d'adaptation aux contraintes et situations actuelles. Ceci implique une interaction entre des informations passées et des informations nouvelles pour modeler et produire des actions adéquates. L'intégration entre ces différents types d'informations est assurée par des circuits cérébraux récurrents entre des voies ascendantes « bottom-up » et voies descendantes « top-down » (Churchland, 1999).

Les études récentes montrent que le cerveau génère un très grand nombre de projections descendantes entre deux populations neuronales qui sont souvent plus nombreuses que les projections ascendantes.

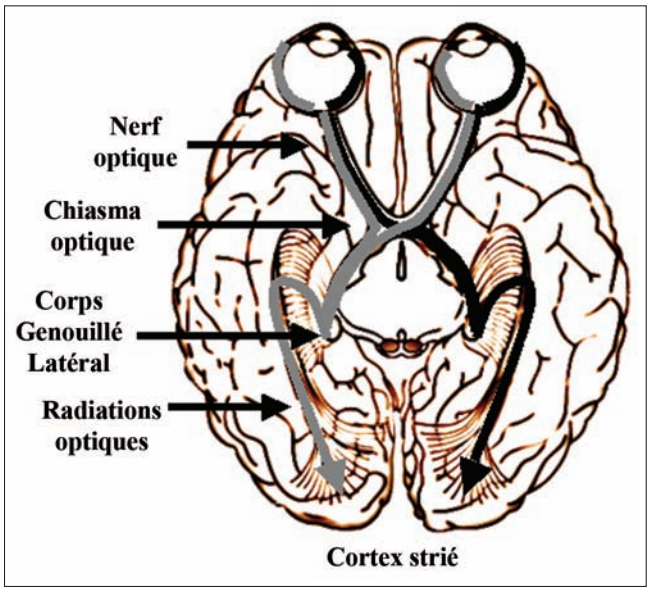
Ainsi, par exemple, le corps genouillé latéral (CGL) projette des axones ascendants vers le cortex visuel primaire (figure II, adapté de Purves et al., 2004). Les neurones du cortex visuel projettent en retour quasiment 10 fois plus d'axones descendants pour établir des connexions synaptiques avec le CGL (Bear et al., 1997). Si l'activité des neurones corticaux est déclenchée par l'activité des neurones du CGL (par les voies ascendantes depuis la rétine), en retour, l'influence des neurones du cortex visuel sur le CGL est fonctionnellement encore plus importante. De la même manière, il existe des connexions ascendantes et descendantes entre différentes régions du cortex visuel (Bullier, 2004).

Figure I



Différentes régions du cortex strié ainsi que de la voie ventrale et de la voie dorsale du cortex visuel sont spécialisées pour le traitement de différents stimuli visuels. Sur la figure sont représentés la région principale du traitement des couleurs (V4), du mouvement (MT/V5), des visages (FFA), des lieux (PPA).

Figure II



L'information visuelle passe par la rétine, le nerf optique, le chiasma optique, le corps genouillé latéral, les radiations optiques et ensuite arrive au cortex visuel primaire.

Mémoire et plasticité cérébrale

L'apprentissage peut être défini comme un processus permettant de conserver des informations acquises, des états affectifs et des impressions capables d'influencer le comportement. Ainsi, la perception comme la mémoire ne sont pas entièrement fidèles et subissent des modifications et des transformations qui résultent du traitement en parallèle de l'information au niveau du cortex. Dans ce contexte, il est intéressant de remarquer que le souvenir de quelque chose n'est pas si différent, au niveau neurobiologique, de sa perception : les deux mettent en jeu un réseau neuronal très similaire (Bear et al., 1997). Ce phénomène observé avait été théorisé par Donald Hebb dans sa *théorie des assemblées cellulaires* de neurones. Selon Hebb, l'engramme représentant une sensation ou une perception particulière (c'est-à-dire la trace mnésique) implique des connexions qui relient plusieurs assemblées de cellules entre elles, celles-la même qui sont associés à cette sensation ou perception (Bear et al., 1997).

Les chercheurs ont mis en évidence au moins quatre facteurs susceptibles de moduler le traitement des informations et leur mémorisation : l'attention, la motivation, l'émotion et le contexte (Bear et al., 1997). Ces facteurs représentent des influences « top-down » sur le traitement de l'information.

1) *Le degré d'attention, de concentration, de vigilance et d'éveil (Gallagher, 2000)*. Ainsi, des troubles de l'attention peuvent diminuer radicalement les performances mnésiques en modulant la perception du monde. Par ailleurs, l'effort conscient de répétition ou d'intégration de l'information améliore les capacités mnésiques.

2) *L'intérêt, la motivation, le besoin ou la nécessité*. Détecter des informations pertinentes et apprendre est plus facile quand le sujet vous passionne. La motivation est donc un facteur qui contribue positivement à la mémoire.

3) *Les valeurs affectives associées aux expériences, l'humeur et le degré d'émotion de l'individu (LaBar, 2003 ; LaBar et Cabeza, 2006 ; McGaugh et al., 2000)*. Beaucoup de gens se rappellent par exemple où ils étaient quand ils ont appris l'attentat du 11 septembre 2001 aux « Twin Towers ». Le traitement immédiat et l'encodage en mémoire des événements chargés d'émotion par le cerveau est facilité.

4) *Le contexte (le lieu, l'éclairage, les odeurs, les bruits, etc.)*. Il accompagne une expérience et s'enregistre avec les données à mémoriser. Nos systèmes mnésiques sont donc contextuels. Par conséquent, si l'on a un trou de mémoire, on peut s'aider en se remémorant le lieu de l'apprentissage ou encore l'endroit où l'on a vu un objet perdu pour la dernière fois. Ces éléments sont appelés des « indices de rappel ».

Emotions

Comme nous venons de le voir, les émotions influencent l'apprentissage et en cela conditionnent l'encodage, la consolidation mnésique et le rappel (LaBar, 2003 ; LaBar et Cabeza, 2006 ; McGaugh et al., 2000).

Une structure cérébrale qui se situe dans les régions limbiques, l'amygdale, joue un rôle central dans le traitement des émotions et dans l'apprentissage (LeDoux, 2000). L'information sensorielle parvient à l'amygdale essentiellement par deux voies. La première vient directement du thalamus sensoriel alors que la seconde passe par les différents cortex sensoriels avant d'atteindre l'amygdale (Bear et al., 1997).

L'*amygdale* est au carrefour de nombreux circuits cérébraux ; des centaines de régions du cerveau sont en relation soit unidirectionnelle soit bidirectionnelle avec le complexe amygdalien (Aggleton et Saunders, 2000).

L'*hippocampe* est l'une de ces régions. Il est impliqué dans le stockage et la remémoration de souvenirs explicites (*mémoire explicite*). Ainsi, ses connexions à l'amygdale peuvent être aux sources d'une émotion déclenchée par un souvenir particulier. Cette région est également spécialisée dans le traitement du contexte d'une situation, c'est-à-dire d'un ensemble de stimuli. Certains ont pu ainsi montrer que l'hippocampe, avec ses connexions avec l'amygdale, jouait un rôle important comme « source » d'anxiété lorsqu'un contexte est associé à un événement traumatisant.

Le *cortex préfrontal* est une autre région fortement connectée à l'amygdale. Ainsi, sa partie médiale serait impliquée dans le processus d'extinction de réponse de peur conditionnée. La phase de décision (« fight or flight ») survenant après une réaction émotive automatique dans un contexte de danger impliquerait également le cortex préfrontal. En complément à un système de réponse rapide et automatique (connexions directes à l'amygdale), le cortex préfrontal influencerait l'activité de l'amygdale, permettant ainsi d'exercer un certain contrôle « conscient » sur notre anxiété. Le revers de ces mécanismes peut être observé en psychopathologie où de l'anxiété peut être éprouvée en imaginant l'échec d'un scénario donné ou même la présence de dangers inexistants.

L'information sensorielle externe arrive à l'amygdale de deux manières différentes : soit par une route courte, rapide mais imprécise, en venant directement du thalamus, soit par une route longue, lente mais plus précise, celle qui passe par le cortex de haut niveau hiérarchique.

La réponse à un danger comporte deux phases. Une première implique la voie rapide du thalamus à l'amygdale et nous alerte de tout ce qui semble représenter un danger. La deuxième phase est celle de la voie plus lente thalamo-cortico-amygdalienne qui affine ou corrige les réponses. Ces deux voies sont donc complémentaires.

Perception

Les conséquences de l'interaction des mécanismes attentionnels, mnésiques et émotionnels sont larges. Des chercheurs ont montrés que les émotions facilitaient la perception et potentialisaient les bénéfices perceptifs de l'attention (Phelps et al., 2006 ; Vuilleumier, 2005). Des dysfonctions amygdaliennes seraient présentes dans de nombreux troubles psychiques et ainsi, il est possible que la perception de stimuli émotionnels soit altérée chez ces patients. Au moins deux hypothèses peuvent rendre compte du lien entre le système émotionnel (notamment l'amygdale) et la perception. Premièrement, des études anatomiques chez le singe ont montré qu'il existait des connexions directes et indirectes de l'amygdale vers le cortex visuel (Amaral et Price, 1984). En second, l'amygdale pourrait modifier la perception via une modification du système attentionnel (Vuilleumier et al., 2001). Ainsi, quel que soit le mécanisme, la détérioration de la perception pourrait contribuer à la survenue et au maintien de dysfonctionnements psychiques.

Altérations des cortex associatifs dans la dépression

Des études de neuroimagerie fonctionnelle réalisées chez des patients *dépressifs* majeurs ont révélé des anomalies de fonctionnement des cortex associatifs polymodaux (préfrontaux et pariétaux) et des régions limbiques et paralimbiques (cortex cingulaire antérieur, amygdale, hippocampe) (Malizia, 2005). Par exemple, au repos, il existe une diminution de la consommation cérébrale de glucose dans les régions préfrontales et pariétales (Drevets et al., 1997). Les études de neuroimagerie fonctionnelle ont également montré un déficit d'activation de ces cortex lorsque le patient est soumis à des tâches cognitives, par rapport à des sujets normaux. Par exemple, il existe une corrélation significative entre l'hypoperfusion frontale et les altérations cognitives chez les déprimés, particulièrement pour les tâches demandant un effort mental (Rogers et al., 1998).

Or, comme on l'a vu plus haut, le système nerveux central s'organise d'une manière modulaire, hiérarchique et récurrente. Ainsi, dans le cadre de la dépression majeure, cette organisation suppose que toute pathologie des cortex de haut niveau (associatifs polymodaux) s'accompagne d'une altération de la modulation de l'activité des cortex sous-jacents, voire des cortex primaires.

Conclusion

Nous avons vu que les systèmes perceptif, attentionnel, mnésique et émotionnels interagissent de manière complexes à différents niveaux. Ainsi, les effets « bottom-up » (par exemple, stimuli sensoriels externes) interagissent perpétuellement avec les influences « top-down » (par exemple, buts personnels). De plus, les informations venant de l'extérieur (« bottom-up ») et les contraintes internes (« top-down ») sont en constante compétition pour leur représentation au niveau cérébral. En tenant compte que le cerveau est organisé de manière modulaire, hiérarchique et récurrente, on a montré qu'une sensation peut être perçue de manière différente en fonction du vécu personnel d'une personne et ce par l'influence rétroactive des perceptions accumulées dans le passé. Nous avons également vu que le système émotionnel a un lien privilégié avec la perception, l'attention et la mémoire. Ainsi, ce modèle propose que des dysfonctions au niveau des structures cérébrales responsables des effets « top-down » peuvent affecter la perception du monde en interférant avec le traitement des informations sensorielles « bottom-up ». La dépression a été prise comme paradigme d'une dysfonction des mécanismes « top-down » affectant le traitement des informations sensorielles, mais ce modèle pourrait être appliqué à de nombreux autres dysfonctionnements psychiques.

Résumé

Les interactions entre le système attentionnel, le système émotionnel et la perception sont complexes et multiples. C'est de manière progressive et par étape que nous allons essayer de les approcher. Tout d'abord, nous décrirons les concepts de mécanismes « bottom-up » (flux ascendant d'informations) et « top-down » (flux descendant d'informations), ainsi que le principe de circuits récurrents. Ceci nous permettra de rappeler que les fonctions cognitives sont organisées de manière modulaire et hiérarchisée dans le cerveau. Cette organisation assure une très grande capacité d'adaptation à l'architecture cérébrale. Le second volet de notre exposé traitera de l'influence de l'attention volontaire et des émotions sur la perception. Finalement, en utilisant la dépression comme exemple, nous montrerons combien une bonne interaction entre processus émotionnels et attentionnels est essentielle à un traitement efficace des informations sensorielles.

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4.2. Functional magnetic resonance imaging studies

4.2.1. Abnormal neural filtering of irrelevant visual information in depression.

From

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Summary

The pathophysiology of major depressive disorder (MDD) includes both affective and cognitive dysfunctions. We aimed to clarify how regions regulating affective processing interact with those involved in attention, and how such interaction impacts perceptual processing within sensory cortices. Based on previous work showing that top-down influences from attention can determine the processing of external inputs within early sensory cortices, we tested with functional magnetic resonance imaging (fMRI) whether MDD alters attentional ("top-down") effects on the neural filtering of irrelevant, nonemotional visual stimuli. The present fMRI study was conducted in 14 nonmedicated patients with a first episode of unipolar MDD and 14 matched controls. During scanning, subjects performed two tasks imposing two different levels of attentional load at fixation (easy or difficult), while irrelevant colored stimuli were presented in the periphery. Analyses of fMRI data revealed thatMDDpatients show (1) an abnormal filtering of irrelevant information in visual cortex, (2) an altered functional connectivity between frontoparietal networks and visual cortices, and (3) a hyperactivity in subgenual cingulate/ medial orbitofrontal cortex that was modulated by attentional load. These results demonstrate that biological abnormalities contribute to the cognitive deficits seen in major depression, and clarify how neural networks implicated in mood regulation influence executive control and perceptual processes. These findings not only improve our understanding of the pathophysiological

mechanisms underlying cognitive dysfunctions in MDD, but also shed new light on the interaction between cognition and mood regulation.

Behavioral/Systems/Cognitive

Abnormal Neural Filtering of Irrelevant Visual Information in Depression

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The pathophysiology of major depressive disorder (MDD) includes both affective and cognitive dysfunctions. We aimed to clarify how regions regulating affective processing interact with those involved in attention, and how such interaction impacts perceptual processing within sensory cortices. Based on previous work showing that top-down influences from attention can determine the processing of external inputs within early sensory cortices, we tested with functional magnetic resonance imaging (fMRI) whether MDD alters attentional ("top-down") effects on the neural filtering of irrelevant, nonemotional visual stimuli. The present fMRI study was conducted in 14 nonmedicated patients with a first episode of unipolar MDD and 14 matched controls. During scanning, subjects performed two tasks imposing two different levels of attentional load at fixation (easy or difficult), while irrelevant colored stimuli were presented in the periphery. Analyses of fMRI data revealed that MDD patients show (1) an abnormal filtering of irrelevant information in visual cortex, (2) an altered functional connectivity between frontoparietal networks and visual cortices, and (3) a hyperactivity in subgenual cingulate/medial orbitofrontal cortex that was modulated by attentional load. These results demonstrate that biological abnormalities contribute to the cognitive deficits seen in major depression, and clarify how neural networks implicated in mood regulation influence executive control and perceptual processes. These findings not only improve our understanding of the pathophysiological mechanisms underlying cognitive dysfunctions in MDD, but also shed new light on the interaction between cognition and mood regulation.

Key words: **depression; attention; sensory processing; affective regulation; vmPFC; subgenual cingulate cortex; medial orbitofrontal; frontoparietal network; functional magnetic resonance imaging; functional connectivity**

Introduction

Major depressive disorder (MDD) is characterized by affective and cognitive dysfunctions (Chamberlain and Sahakian, 2006). Understanding the neurobiology underlying this multifaceted psychiatric disorder emerges as a major health and research challenge (Nestler et al., 2002).

Brain imaging studies in MDD have documented abnormalities in regions involved in affective and cognitive regulation, such as the anterior cingulate cortex and the orbitofrontal cortex (OFC), as well as frontoparietal networks subserving attention and executive functions (Mayberg et al., 1999). In addition, MDD patients may recruit greater prefrontal processing to achieve similar (or poorer) task performance than control subjects, suggesting that a disturbed emotional state intensifies cognitive interference (Harvey et al., 2005). These findings indicate that a dysfunction implicating frontal–limbic circuits might cause both cognitive and emotional disturbances (Mayberg, 1997; Mayberg et al., 1999; Drevets, 2000). A plausible pathophysiological mechanism for MDD would thus involve a disordered neural network with two distinct and interacting components: an enhanced activation within limbic circuits and an altered engagement of prefrontal executive circuits. It is unclear (1) whether a dysfunction within frontal–limbic networks also affects lower-level processing by altering top-down influences (Fales et al., 2008); and (2) to what extent perceptual processes are biased by a dysregulation of affective (limbic) versus cognitive (prefrontal) control circuitry. Yet, impairments in perception secondary to changes in top-down factors can significantly worsen cognitive deficits observed in MDD. The study of functional changes at early levels of perceptual integration is thus required to get a comprehensive model of the neural dysfunctions underlying neuropsychological deficits in MDD and to better understand how affective regulation might impact perceptual processing.

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Table 1. Clinical characteristics of depressed patients and control subjects[a]

MDD group						Control group					
ID	Age (years)	Sex	HDRS	HARS	Education (years)	ID	Age (years)	Sex	HDRS	HARS	Education (years)
1	21	f	21	15	15	1	21	f	0	0	14
2	28	f	33	19	15	2	27	f	1	2	16
3	29	f	32	16	13	3	32	f	1	2	15
4	29	f	34	12	13	4	24	f	3	4	15
5	32	f	37	19	15	5	31	f	2	0	14
6	38	f	30	18	14	6	32	f	0	0	17
7	54	f	20	17	15	7	56	f	2	0	12
8	19	m	30	22	14	8	20	m	1	0	12
9	19	m	30	10	13	9	19	m	1	0	13
10	36	m	21	14	13	10	34	m	1	0	13
11	39	m	27	14	13	11	35	m	6	7	13
12	38	m	24	18	12	12	34	m	0	0	16
13	40	m	26	17	14	13	36	m	3	3	17
14	42	m	25	15	14	14	39	m	1	0	14
Mean[b]	33.1 ± 9.84	7:7	27.86 ± 5.27	16.14 ± 3.11	13.78 ± 0.97		31.4 ± 9.51[c]	7:7	1.57 ± 1.60[d]	1.29 ± 2.13[d]	14.35 ± 1.69[c]

[a]Patients were selected by a team of psychiatrists with extensive experience in depression. All subjects were Caucasian and right handed; they were off medication for 3 months prior to the experimental day.

[b]Data are given as mean ± SD. For the Sex column, data are the ratio of male to female.

[c]Two-sample *t* test testing for group differences, degrees of freedom (df) = 26; NS.

[d]Two-sample *t* test testing for group differences, df = 26; $p < 0.001$.

Previous neuroimaging studies in healthy and brain-damaged participants demonstrated that top-down influences from emotion or attention can determine the processing of external inputs within early sensory cortices by enhancing attended information while suppressing unattended information. Recently, we showed that high attentional load at fixation can lead to a suppression of functional magnetic resonance imaging (fMRI) response to irrelevant peripheral stimulation in visual cortex (Schwartz et al., 2005). These findings provided a neural foundation for Lavie's theory of attention (Lavie, 2005), which predicts that increasing processing load of a relevant task determines the extent to which irrelevant distractors are processed.

Based on these previous findings, here we tested with fMRI whether changing attentional demands of a central task would affect the processing of task-irrelevant colored visual stimuli presented in the periphery. By modulating attentional load at central fixation without changing sensory inputs, we hypothesized that mood changes would interfere with top-down control of activity in visual regions. A second main aim of the study was to directly assess distant effects of frontoparietal executive networks on the processing of irrelevant stimuli in visual cortices by applying functional connectivity analyses. By implementing an affective neuroscience approach to depression, our fMRI study constitutes a useful test of the relevance of biological abnormalities to the cognitive deficits seen in major depression. More generally, our study provides new insights into the functional interaction between neural networks implicated in mood regulation and those involved in executive control and perceptual processes.

Materials and Methods

Subjects

Over a 2 year period, we recruited unmedicated subjects who presented with a first episode of major unipolar depression and agreed to perform an fMRI experiment. Sixteen patients could complete the whole MRI protocol; age- and education-matched healthy controls were also scanned. The inclusion criteria for the MDD and control groups were age between 18 and 56 years, willingness to participate, and ability to provide signed informed consent. The protocol was approved by the research ethics committee of the Faculty of Medicine of the University of Liège. The exclusion criteria were current or past cardiovascular or neurological disorder (e.g., Parkinson's disease). Subjects were excluded if they were pregnant, lactating, or had conditions for which an MRI would be contraindicated (e.g., metallic implants).

Depressed subjects were recruited through the psychiatric outpatients consultation of the Liege University Hospital by a team of trained psychiatrists who performed a medical examination and conducted the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-IV) (Spitzer et al., 1994). Sixteen subjects with a first lifetime episode of unipolar major depressive disorder, with no prior antidepressant or antipsychotic treatment, were included in the experimental protocol. Two patients could not maintain reliable central visual fixation (as monitored by eye tracking, see below). Data from these two patients were excluded from further analysis, and 14 subjects were thus included in the final analyses (seven males, drug-free, Hamilton Depression Rating Scale ≥17) (Table 1).

Healthy control subjects were recruited through advertisements. They were selected to match the MDD patients for gender, age, and sociocultural background. None of them reported any severe medical problem or any neurological or psychiatric history. After providing informed consent, they were screened using the Axis I SCID-IV and the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The exclusion criteria for the control subjects were an HDRS score >6, a history of mood disorders, or any other DSM-IV Axis I mental illness. Fourteen controls matching the final selection of patients were included in the analyses.

Procedure

During the main fMRI experiment, the participants performed a detection task on a rapid successive visual presentation (RSVP) of colored letters (one letter every 750 ms; 500 ms duration each, plus 250 ms blank) that was shown on a fixed central location at fixation (Fig. 1*A*). This RSVP stream consisted of T-shaped stimuli displayed with two possible orientations (upright or upside-down) and eight different colors in a pseudorandom order. Blocks of 20 s with Mondrian-like stimuli formed by a 20 × 20 grid of colored rectangles, presented bilaterally at 6° of visual angle from fixation (subtending 6° × 10°), alternated with blocks without peripheral stimuli (Fig. 1*B*). To enhance stimulation of visual cortex, Mondrian-like displays changed colors randomly every 500 ms during blocks with peripheral stimulation (Tong et al., 2006). All visual stimuli were projected on a screen and seen through a mirror mounted on the MRI headcoil (total display size 22° × 16°, 60 Hz refresh rate) and generated using a MATLAB Toolbox, allowing visual presentation and response recording with precise timing (Cogent, www.vislab.ucl.ac.uk/Cogent/).

During scanning, the participants performed either a low-load or a high-load task, or were required to only fixate the central RSVP (40 s

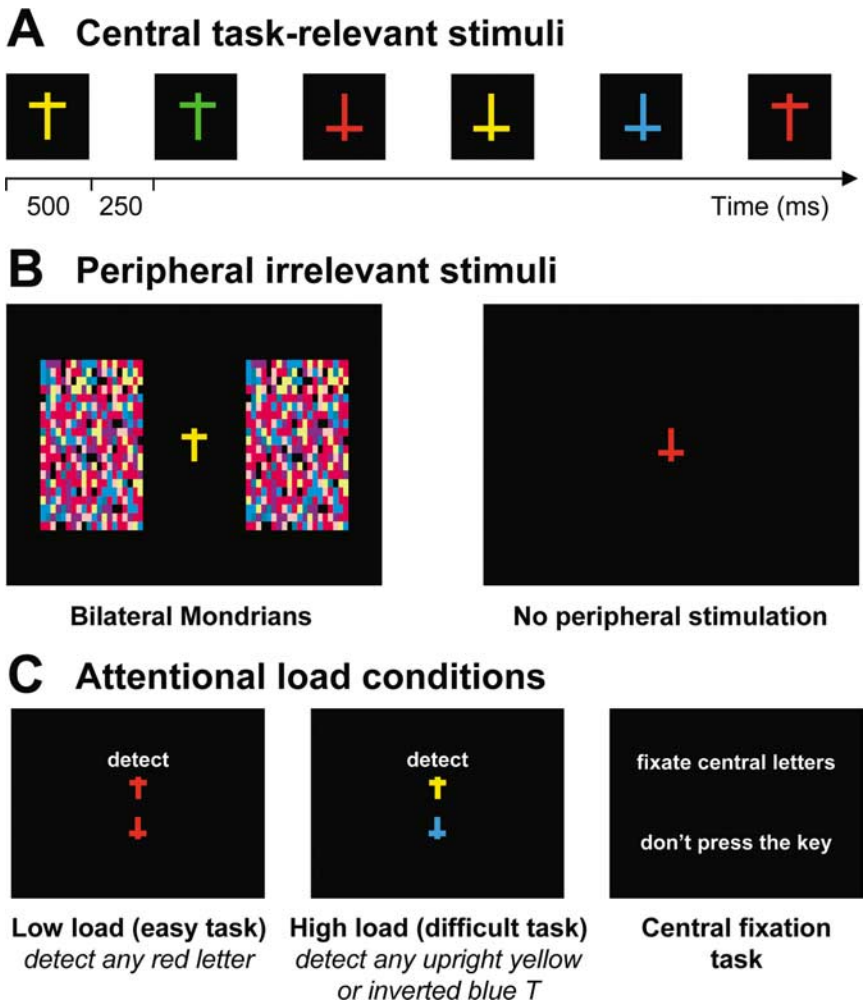

Figure 1. Stimuli and design in the attentional load experiment. ***A***, A rapid continuous stream of colored "T" shapes appeared at central fixation during all blocks (500 ms duration each, 250 ms interval). ***B***, Irrelevant peripheral stimulation included 20 s blocks with bilateral colored, "Mondrian-like" stimuli, alternating with blocks without any peripheral stimulation. ***C***, Two main attentional load conditions required the subjects to either detect any red T regardless of its orientation (low load), or to detect all upright yellow T shapes and upside-down blue T shapes. Additional blocks of central fixation (baseline) were also included. The central visual stream remained identical in each task condition, only the task instructions differed.

period each, separated by 3 s instruction panel) (Fig. 1*C*). Low-load, high-load, and baseline fixation periods alternated in a pseudorandom order (randomized across participants) during one single continuous scanning session. The low-load task (easy, pop-out) (Treisman and Gormican, 1988; Wojciulik and Kanwisher, 1999) required a key press for any red T regardless of its orientation. The high-load task (difficult, conjunction) required a key press for any upright yellow T or upside-down blue T (both types of conjunction targets had to be monitored for throughout this task). The baseline fixation task required passive fixation of the letter stream but no key press. Importantly, the exact same stream of 684 central stimuli was presented during all task conditions. In both high- and low-load conditions, items that required a button-press response appeared on average every 15 stimuli (6.7% of the total number of central stimuli), and items that were targets in one condition also appeared with the same frequency as task-irrelevant stimuli in the other condition (i.e., high-load targets appeared as distractors under low-load instructions, and vice versa). Therefore, only the task instructions distinguished the high-load and low-load conditions for the central task. The peripheral Mondrian-like stimuli were always irrelevant to the central task, and the participants were instructed to ignore them.

MRI data acquisition

Data were acquired with a 3T head-only MR scanner (Allegra, Siemens) using a gradient echoplanar imaging (EPI) sequence [32 transverse slices with 30% gap, repetition time (TR): 2130 ms, echo time (TE): 40 ms, flip angle: 90°, field of view (FOV): 220 × 220 mm, matrix size: 64 × 64 × 32, voxel size: 3.4 × 3.4 × 3 mm]. Functional volumes ($n = 255$) were acquired during one single continuous scanning run. The first three volumes were discarded to account for T1 saturation effects. A structural MR scan was acquired at the end of the experimental session (T1-weighted 3D magnetization-prepared rapid-acquisition gradient echo sequence, TR: 1960 ms, TE: 4.43 ms, inversion time: 1100 ms, FOV: 230 × 173 mm, matrix size: 256 × 192 × 176, voxel size: 0.9 × 0.9 × 0.9 mm). During scanning, eye movements and pupillary size were measured continuously using an infrared eye tracking system (LRO5000, Applied Science Laboratories, sampling rate: 60 Hz). Eye tracking data were used to ensure that all subjects included in the analyses maintained good central fixation during the whole scanning session.

fMRI data analysis

Functional MRI data were analyzed using SPM2 (http://www.fil.ion.ucl.ac.uk) implemented in MATLAB (The MathWorks). Functional scans were realigned, normalized to the MNI EPI template (2D spline, voxel size: 2 × 2 × 2 mm) and spatially smoothed with a Gaussian kernel with full-width at half maximum (FWHM) of 8 mm.

Standard block design analyses. Data were analyzed using a two-step procedure taking into account the intraindividual and interindividual variance. At the individual level, brain responses were modeled at each voxel, using the general linear model with six trial types convolved with the canonical hemodynamic response function (HRF): baseline fixation with color in periphery, baseline fixation with no peripheral stimuli, low load with color in periphery, low load with no peripheral stimuli, high load with color in periphery, high load with no peripheral stimuli. Because missed targets and false alarms [including responses with reaction times (RTs) > 750 ms] involved incorrect motor responses (absence of key presses during misses; inappropriate key presses during false alarms), we included all actual motor responses in the fMRI design as an additional regressor of no interest to capture any spurious brain activation attributable to group differences in motor behavior (i.e., misses and false alarms). Six movement parameters from spatial realignment were included as additional regressors of no interest to account for residual motion artifacts. High-pass filtering was performed using a cutoff period of 128 s to remove low-frequency drifts from the time series. Linear contrasts between regressors of interest tested for the main effects of attentional load (high load vs low load and low load vs high load). Using within-subject contrasts between the activity for two different levels of attentional load as main variables for the second-level whole-brain group analyses, as in the present study, would also minimize effects related to general differences in effective difficulty (if any). The summary statistical images were spatially smoothed with a Gaussian kernel of 6 mm FWHM and entered into a second-level one-way ANOVA implemented in SPM2 to assess random-effects group comparisons. The resulting SPM maps were thresholded at $p < 0.001$ (uncorrected). Common group effects were assessed using conjunction analysis to preserve only voxels that were significant in the contributing SPM maps of both control and MDD populations based on the conjunction null hypothesis (Friston et al., 2005). Direct statistical group comparisons were obtained using exclusive masking to reveal the voxels that

Table 2. Behavioral performance during scanning

	MDD group[a]		Control group[a]		Statistics[b]		
Measure	Low load	High load	Low load	High load	Effect of group	Effect of load	Group-by-load interaction
RT (ms) on correct responses	492.98 ± 61.56	553.20 ± 41.75	489.85 ± 38.80	566.60 ± 36.32	$F_{(1,26)} = 0.107$ $p = 0.745$	$F_{(1,26)} = 89.65$ $p < 0.001$	$F_{(1,26)} = 1.306$ $p = 0.263$
Hits (%)	91.00 ± 12.84	73.64 ± 18.61	97.22 ± 5.07	85.61 ± 9.39	$F_{(1,26)} = 4.485$ $p < 0.05$	$F_{(1,26)} = 54.16$ $p < 0.001$	$F_{(1,26)} = 2.13$ $p = 0.156$
False alarms[c]	7.54 ± 8.8	29.05 ± 15.33	6.65 ± 1.53	18.29 ± 8.96	$F_{(1,26)} = 2.87$ $p = 0.101$	$F_{(1,26)} = 66.67$ $p < 0.001$	$F_{(1,26)} = 5.92$ $p < 0.05$

[a]Data are given as mean ± SD.

[b]ANOVA with load as within-subject factor and group as between-subject factor.

[c]False alarms correspond to the percentage of key presses recorded outside an interval of 750 ms after the presentation of a target.

showed increased response in one population in the absence of such effect in the other population. The SPM constituting the exclusive mask was thresholded at $p < 0.05$, whereas the contrast to be masked was thresholded at $p < 0.001$. Note that the more liberal the threshold of an exclusive mask, the more conservative is the masking procedure. Note also that the use of conservative whole-brain random-effects group comparisons (Holmes and Friston, 1998) together with the relatively broad age range of the studied populations (MDD: 19–54; matched controls: 19–56 years) ensures that any statistically significant group difference reflects a robust result that can be generalized to a larger population.

Functional connectivity analyses. A second set of analyses aimed to assess condition-dependent changes in the functional coupling between brain regions. This was done using psychophysiological interaction (PPI) analyses, which explain the activity in one part of the brain in terms of the interaction between an experimental manipulation (psychological factor) and the activity in another brain region (physiological factor) (Friston et al., 1997). PPI analyses were computed to test the hypothesis that functional connectivity between brain regions would differ between the two populations as a function of the current attentional context. We extracted time series from regions of interest revealed by the main contrasts in each individual, averaging activity within a 10-mm-radius sphere, centered at the peak of the activation. This physiological signal was deconvolved using the HRF to estimate the underlying neuronal signal, multiplied with the psychological variable (low vs high load), and convolved again with the HRF to obtain the expected blood oxygenation level-dependent (BOLD) response for the PPI (Gitelman et al., 2003). The two main effects (physiological and psychological factors) and the critical PPI were entered in new fixed-effects analyses, together with movement parameters. Any significant psychophysiological interaction ($p < 0.001$) indicated a change in the regression coefficients between any reported brain area and the reference region, related to attentional load manipulation. Individual PPI regression estimations were then included in random-effects group ANOVAs (inferences reported at $p < 0.001$, uncorrected). Note that the interaction effect is orthogonal to the main effects of task and that the inclusion of both main effects of task in the analysis ensures that any activation associated with the PPI cannot be explained by any of these main effects (e.g., overall effect of low- vs high-load conditions).

Results

Clinical characteristics

Sixteen patients and their matched controls completed the study, but two patients were excluded because they did not maintain reliable central visual fixation. The 14 remaining MDD patients and their 14 healthy matched controls were included in the final analyses. Table 1 reports the main demographic and clinical characteristics of the study population. Differences between the groups were statistically significant for both depression and anxiety measures (HDRS, HARS; two-sample t test, $p < 0.001$ for both measures). Depression scores correlated with anxiety scores in controls but not in MDD patients ($r = 0.87$, $r^2 = 0.76$, $p < 0.001$; $r = 0.078$, $r^2 = 0.006$, $p = 0.79$; respectively). In the MDD group, the duration of episodes reported during the SCID-IV interviews ranged from 1 to 5 months (mean, 3.2 months). All 14 patients were experiencing their first MDD episode, and none had been prescribed an antidepressant. Their education level (assessed in years) ranged from 12 to 15 years (mean, 13.78 ± 0.97 years).

Behavioral results

Performance on the central RSVP (Fig. 1) during scanning was assessed by analyzing RTs and hit rates on target trials, as well as false alarms (including responses with an RT > 750 ms) using ANOVAs with attentional load (high, low) as within-subjects factor (repeated measures) and group as between-subjects factor (Table 2). There was a main effect of attentional load for all measures (all $p < 0.001$), with slower RTs, reduced hit rates, and more false alarms during the high- compared with the low-load condition, indicating that the instructions successfully modulated task difficulty in both groups. Importantly, there was no group difference in reaction times, which suggests that task difficulty was mostly comparable for patients and controls, and that both populations were equally vigilant and attentive during the task. There was a group effect for hit rates due to the patients missing slightly more targets (hits, 91% in low load and 73.64% in high load) than their controls (hits, 97.22% in low load and 85.61% in high load) and a group-by-attentional load interaction for false alarms due to the patients making more such errors during the high-load condition. Indeed, planned t tests on hits and false alarms revealed that patients and controls differed during high attentional load (hits: $p = 0.041$; false alarms: $p = 0.031$) but not during low attentional load (hits: $p = 0.103$; false alarms: $p = 0.773$). However, activity change in regions showing critical group effect [i.e., V4 and subgenual anterior cingulate cortex (SgAcc)/ventral medial prefrontal cortex (vmPFC), see below] did not correlate with hits or false alarms (Table 3), thus ruling out that differences in performance accounted for the reported fMRI group differences.

During scanning, eye movements were measured continuously using an infrared eye tracking system. ANOVAs conducted on eye movement data revealed no significant group difference, neither for the absolute distance from fixation nor for horizontal deviations ($F_{(1,26)} = 1.20$, $p = 0.28$; $F_{(1,26)} = 4.12$, $p = 0.43$, respectively). These results suggest that both populations fixated the central stream of letters equally well. We also found no group difference in pupil diameter, suggesting similar levels of central arousal and attention in both groups (e.g., Siegle et al., 2003; Sterpenich et al., 2006), which is consistent with previous results in depressed subjects (e.g., Johnstone et al., 2007).

fMRI results

For clarity, rather than separate main effects within each group, we first describe effects found in both patients and controls using conjunction analyses to preserve only voxels that were significant

Table 3. Correlations between attention-related activity change regions of interest (V4, SgACC/vmPFC) and hits and false alarm (FA), separately in MDD and control groups

	V4 (*x*, *y*, *z*: 20, −68, −8)		SgACC/vmPFC (*x*, *y*, *z*: 25, −6, 30)	
	Hits (high)	FA (high)	Hits (high)	FA (high)
MDD group				
r^2	0.0016	0.0463	0.0278	0.0327
$F_{(1,13)}$	0.0189	0.5830	0.3432	0.4062
p	0.8928	0.4599	0.5688	0.5359
Control group				
r^2	0.0056	0.0280	0.0577	0.2429
$F_{(1,13)}$	0.0678	0.3456	0.7347	3.8493
p	0.7990	0.5675	0.4082	0.0734

Table 4. Brain regions showing main effects of high minus low attentional load (group conjunction: MDD patients and controls for the high > low load contrast)

			MNI coordinates				
Brain areas	L/R	BA	*x*	*y*	*z*	*t* value[a]	Cluster size (voxels)[b]
Inf. frontal gyrus/operculum	L	44/48	−44	4	28	6.18	781
Inf. frontal gyrus/operculum	R	44/48	48	10	32	5.82	367
Sup. parietal/IPS	L	7	−20	−64	56	5.29	1294
Sup. parietal/IPS	R	7	34	−58	48	4.98	737
Insula	R	47	32	24	−2	4.78	92
Inf. occipital/VWFA	L	19	−44	−68	−10	4.75	115
Precentral/Mid. frontal	L	6	−32	−2	54	4.4	302
SMA	L	6/32	−8	12	52	4.3	225
Sup. frontal	R	8	32	10	64	4.25	40
Inf. occipital	R	19	50	−72	−10	3.73	33
Mid. frontal	R	45/48	40	34	20	3.62	8
Inf. parietal	R	40	48	−42	50	3.52	6

Inf., Inferior; IPS, Intraparietal sulcus; Mid., middle; SMA, supplementary motor area; Sup., superior; L, left; R, right; BA, Brodmann's area.

[a]All $p < 0.001$ uncorrected (random-effect analysis).

[b]Threshold cluster size of 5 voxels.

in the contributing SPM maps of both populations (Friston et al., 2005). We then report between-group comparisons whenever they yielded statistically significant results.

Effects of high attentional load

We first tested for effects of increased attentional load by comparing fMRI activity during the high- versus the low-attentional-load conditions using linear contrasts of parameter estimates in the context of ANOVA models, as described in Materials and Methods. A conjunction of the SPM maps from the patients and from the controls for this comparison showed that both populations strongly engaged inferior frontal and superior parietal regions during increased attentional load at fixation (Table 4, Fig. 2), consistent with the recruitment of a distributed attentional network subtending top-down influence under higher-load condition in all participants (Schwartz et al., 2005). Another region in inferior occipital cortex showed increased activation during the high-load condition (*x*, *y*, *z*: −44, −68, −10) (Fig. 2). Because this region lies close to an area known as the visual word form area (VWFA) (Vinckier et al., 2007), increased activation of the VWFA probably reflects letter identification specifically during the high-load condition, which imperatively requires distinguishing between upright and upside-down "T" shapes (whereas processing of the shape of the central targets was not relevant during the low-load task).

Effects of low attentional load

We then tested for regions more activated during low compared with high attentional demands (low > high load). Based on Lavie's theory of attentional load (Lavie, 1995, 2005) and on our previous fMRI results in normal controls (Schwartz et al., 2005), we predicted increased activity in visual regions due to less filtering of the peripheral colored stimuli during the low-load condition. The group conjunction analysis revealed that only bilateral medial OFC survived the statistical threshold (Table 5). In contrast, when we directly compared controls to MDD patients for this same contrast, we found increased response in visual cortices, including the primary visual cortex (calcarine sulcus) and a region previously found to be maximally modulated by such central load manipulation (Schwartz et al., 2005) and corresponding to the color-responsive area V4 (Talairach coordinates: *x*, *y*, *z*: 20, −66, −4; MNI coordinates: *x*, *y*, *z*: 20, −68, −8) (Table 5, Fig. 3*A*) (Zeki et al., 1991; Bartels and Zeki, 2000). The latter activation was specifically driven by enhanced response to peripheral colored stimuli during the low-load compared with the high-load condition in the controls (Fig. 3*B*). For the same contrast (low > high load), MDD patients showed a significant attenuation of BOLD response in bilateral vmPFC region during high attentional load, encompassing the medial OFC and rostral anterior cingulate cortex/SgAcc (Fig. 3*C*). This modulation of brain response in the patients was driven by the attentional task, independently of the presence or absence of peripheral stimuli (Fig. 3*D*).

Functional connectivity

To further investigate the load-related top-down modulations of brain activity, we used dedicated functional connectivity analyses. Specifically, using a whole-brain approach we tested for changes in connectivity as a function of task load between regions of interest (i.e., regions driving top-down influences) and any other region of the brain. We performed such connectivity analyses for two different seed regions, the right parietal and frontal peaks revealed by the main conjunction analysis for the high- versus low-load contrast (Fig. 2, Table 4), ipsilateral to the main effect of load in visual cortex (V4). We found that functional connectivity was increased between the right IPS and V4, as well as between the right frontal cortex and V4 ($p < 0.001$), selectively in the context of low attentional load in controls but not in patients.

Finally we tested whether activity in our main regions of interest (i.e., V4 and vmPFC/SgAcc) correlated with the severity of depression, as assessed by the HDRS, but we did not find any significant correlation, neither in the MDD group nor in the control group. This finding indicates that the observed functional changes, which pertain to the pathophysiology of MDD, are mostly independent of the clinical severity of depression.

Discussion

A reliable observation in neuropsychological studies of major depression is an impairment across several domains of attention implicating sustained attention (Porter et al., 2003; Hill et al., 2004; Weiland-Fiedler et al., 2004), resistance to interference (Lemelin et al., 1997), response selection (Azorin et al., 1995), and

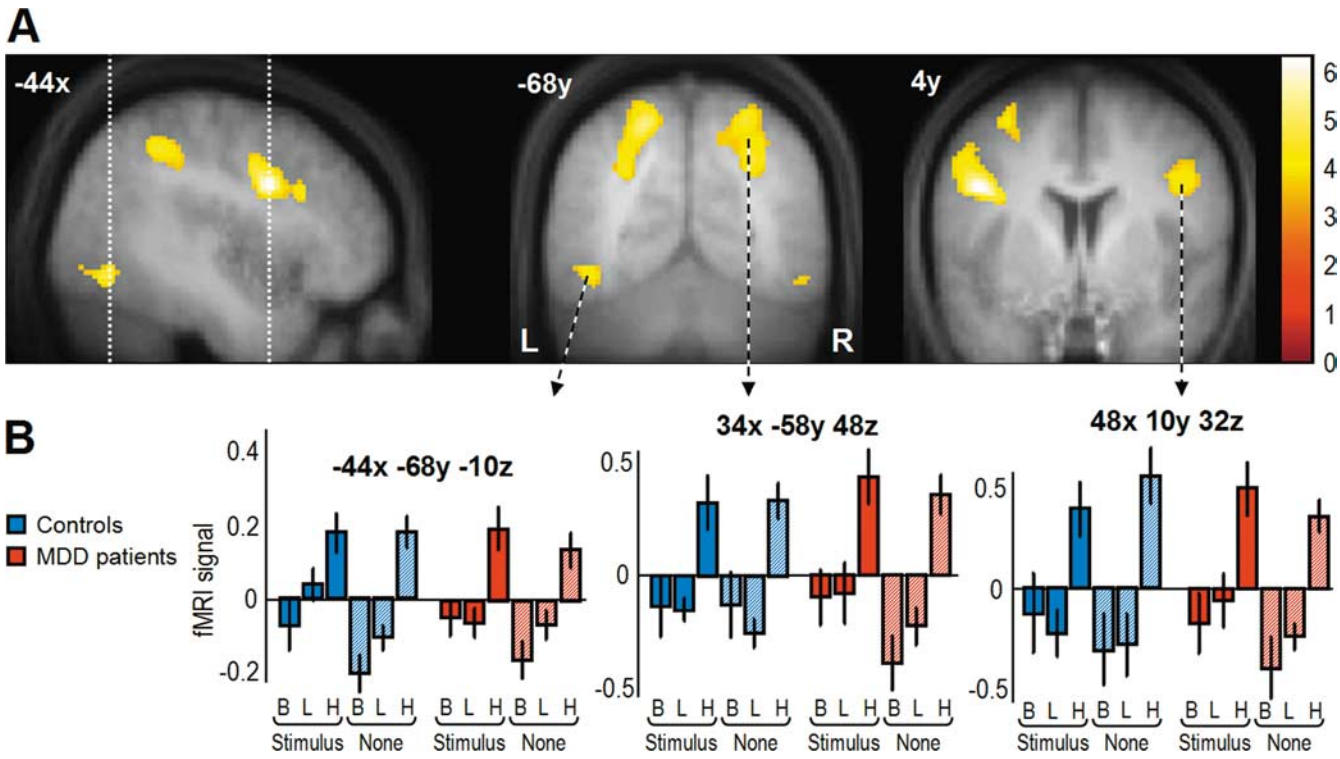

Figure 2. Main effect of high attentional load. ***A***, Statistical maps from the group conjunction analysis showing increased activation in lateral occipital (*x*, *y*, *z*: −44, −68, −10; visual word form area) (Vinckier et al., 2007), superior parietal and inferior frontal regions in both MDD patients and controls. Maps are overlaid on average T1 structural scan, thresholded at $p < 0.001$ uncorrected. Color bar on the right indicates *t* values. ***B***, Parameter estimates extracted from the statistical peaks demonstrate selective activation during the high-load task across all conditions of peripheral stimulation and in both populations. B, Baseline fixation; L, low attentional load; H, high attentional load.

Table 5. Brain regions showing main effects of low minus high attentional load

Brain areas	L/R	BA	MNI coordinates			*t* value[a]	Cluster size (voxels)[b]
			x	*y*	*z*		
Group conjunction: MDD patients and controls for the low > high load contrast							
OFC (medial orbital)	L	11	−16	38	−16	4.52	98
OFC (medial orbital)	R	11	8	40	−22	4.03	21
Group comparison: controls masked by MDD patients for the low > high load contrast							
Early visual (calcarine)	R	17/18	12	−86	0	5.88	1401
V4	R	18	22	−74	−8	5.73	[c]
Early visual (calcarine)	R	17/18	2	−82	20	4.63	[c]
Precentral gyrus	L	6	−34	0	−40	4.78	52
Ant. lingual gyrus	R	17	22	−54	6	3.81	35
Ant. lingual gyrus	R	18	12	−50	4	3.48	[c]
OFC lateral	L	11	−24	38	−18	3.81	11
Group comparison: MDD patients masked by controls for the low > high load contrast							
OFC (medial orbital)	L	11	−16	44	−18	3.38	14
OFC (medial orbital)	R	11	16	40	−20	3.38	13
OFC (rectus)	R	11	4	38	−14	3.35	68
Ant. cingulate (rostral subgenual)	L	25	−6	30	−8	3.32	[c]

Ant, Anterior; OFC, orbitofrontal cortex; L, left; R, right; BA, Brodmann's area.

[a] All $p \leq 0.001$ uncorrected (random-effect analysis).

[b] Threshold cluster size of 5 voxels.

[c] Belongs to the same cluster as row above.

biased attention and processing for negative emotional information (Erickson et al., 2005; Goeleven et al., 2006; Waters et al., 2006; Leyman et al., 2007). The neural substrates that link internal affective states, attentional processes, and sensory representations of stimuli remain unclear, despite the central importance of such relationships in the phenomenology of mood disorders and mood regulation. Our fMRI study aimed to clarify these associations by providing a first investigation of "pure" top-down, task-related modulation in brain activity triggered by simple, nonemotional visual stimuli.

By selectively manipulating top-down attentional influences on the neural processing of irrelevant visual stimulation, we found that unmedicated MDD patients show an abnormal filtering of irrelevant information in visual cortex, together with an alteration of the functional connectivity between frontoparietal networks and visual cortices. Our results also suggest that in-

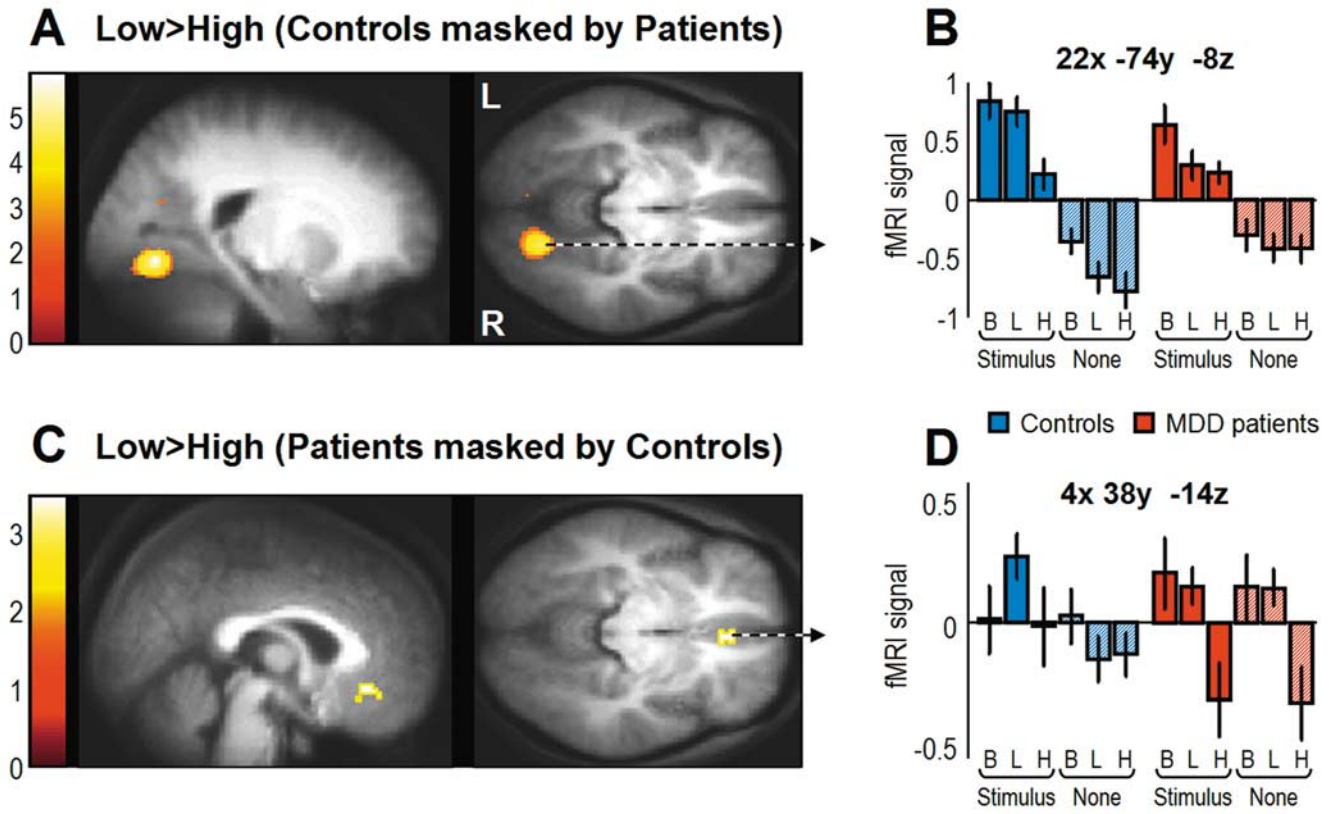

Figure 3. Main effects of low attentional load. ***A***, Increased response during the low- minus the high-load condition in V4 for controls relative to MDD patients. ***B***, Parameter estimates extracted from V4 peak show decreased activity during low versus high load in controls. Note that decreases from baseline to low load in response to peripheral colored stimuli was significant in patients ($t = 2.36, p = 0.013$) but not in controls ($t = 0.98, p = 0.16$). ***C***, Decreased subgenual cingulate response during the high-load condition in MDD patients compared with controls. ***D***, Parameter estimates showed decreased fMRI signal during high attentional load in patients but not in controls. For visualization purposes, statistical parametric maps are overlaid on average T1 structural scan and thresholded at $p < 0.005$ uncorrected. Color bars on the left indicate *t* values. B, Baseline fixation; L, low attentional load; H, high attentional load.

creased attentional involvement in a cognitive task causes a powerful decrease in subgenual cingulate cortex activity in the patients' population. Hereafter we detail the key findings of this study and how they might improve our understanding of the links between affective and cognitive dysfunctions. We also discuss their potential implications for therapeutic approaches to mood disorders.

Neural filtering of irrelevant stimuli

The present fMRI data provide whole-brain measures of signal change during two main tasks performed at the center of screen, differing only in the amount of attention that they require, while irrelevant colored stimulations were presented in the periphery. Increased top-down cognitive demands during the high-attentional-load condition was indicated by slower reaction times and increased activity in frontoparietal regions in both controls and MDD patients, replicating our previous results in controls (Schwartz et al., 2005). The pattern of brain regions more activated when increasing task demands largely overlapped in controls and patients. Hence, depression might not primarily interfere with the recruitment of the classical neural networks subserving voluntary goal-directed attention, consistent with previous findings using working memory tasks (Barch et al., 2003). In contrast, major between-group differences arose when testing for brain regions more activated during the low-load condition (i.e., reflecting less filtering or reduced suppression of processing in those regions). Based on Lavie's theory that the processing of irrelevant distractors depends on the current attentional load (Lavie, 2005), we predicted enhanced fMRI signal in visual regions for the low- versus high-load contrast. Increased activity in the color-responsive area V4 in controls during low load confirmed the hypothesis that higher task demands at fixation reduce the processing of irrelevant peripheral stimulation in healthy subjects. Similar results were found in our previous study using high-contrast checkerboards and in the motion-sensitive region V5 in another fMRI study in which displays with irrelevant moving dots were used (Rees et al., 1997; Schwartz et al., 2005). Critically, we did not observe such activity increase in V4 during low attentional load (compared with high load) in MDD patients, who showed a decrease of V4 activity during both the low- and high-load tasks (when compared with baseline activity) (Fig. 3*B*). These fMRI results demonstrate that depression may involve a shift in task-dependent modulation of V4 activity, with MDD patients showing a sharp reduction of distractors processing at lower levels of attentional load compared with healthy controls. This finding may be interpreted as a first indication that depressed patients engage important cognitive resources even in a simple pop-out task, which consequently restricts the processing of peripheral distractors and might reduce the spatial spanning of attention (Posner and Petersen, 1990).

Disrupted functional connectivity in depression

An important finding of the present study is that while both depressed patients and controls showed similar frontoparietal activity changes when increasing task load, the neural processing of irrelevant stimuli in V4 was differentially affected by task load

in each population. To reconcile these results and better characterize the mechanisms underlying load-specific modulation of V4, we directly assessed the functional connectivity between frontoparietal regions and the V4 area. This analysis revealed an increase in functional connectivity between V4 and both IPS and inferior frontal peaks, selectively in the context of low attentional load in controls but not in patients. These results are consistent with Lavie's hypothesis that reduced attention to the task leaves more resources available for the processing of concurrent information coming from periphery (here the colored Mondrian-like stimuli), which would in turn call for more top-down control to be exerted (here on V4) to avoid automatic orienting of attention toward distracting information (Lavie, 1995, 2005). In contrast, increased attentional engagement in the central task would consume more attentional resources and thus limit the processing of the irrelevant distractors. While our attentional load manipulation powerfully modulated this "push-pull" mechanism of selective attention in the controls (Pinsk et al., 2004), MDD patients did not show any load-related increased coupling of activity between parietal or frontal regions and visual cortices. This result might again reflect that the low-load condition was potentially quite demanding for the patients, which would be consistent with a reduction of V4 activity even during the low-load condition.

Load-related reduction of subgenual cingulate activity

Another major finding of the present study is a suppression of subgenual cingulate cortex (SgAcc, Brodmann's area 25) and medial OFC activity during high-attentional-load condition (compared with low load) in the depressed subjects, which was independent of the peripheral stimulation. These regions of the vmPFC are known to be involved in emotion and motivation regulation (Mayberg et al., 1999; Elliott et al., 2000; Liotti et al., 2000; Lewis et al., 2005; Morgane et al., 2005), as well as in emotional disorders [see recent reviews (Drevets, 2007; Ressler and Mayberg, 2007)]. SgAcc was found to be overactive in acute sadness and in treatment-resistant depressed patients (Mayberg et al., 1999, 2005). Moreover, antidepressant therapeutic effects in MDD have been linked to SgAcc activity, i.e., mainly a decrease of activity after pharmacological antidepressant treatments (Mayberg et al., 2000; Davidson et al., 2003; Walsh et al., 2007), after electroconvulsive therapy (Nobler et al., 2001), or during deep brain stimulation (Mayberg et al., 2005). Moreover, predictive measures of response to cognitive behavior therapy were also found to be linked to activation levels in this brain area (Siegle et al., 2006; Kennedy et al., 2007).

Load-related suppression of activity in vmPFC regions would be consistent with the recent model of emotion regulation proposed by Phillips et al. (2008), according to which dorsal PFC regions, subtending voluntary emotion regulation, are in functional reciprocal relationship with ventral PFC regions (including SgAcc), subtending automatic emotion regulation. The pathophysiology of mood disorders in which emotions are dysregulated may involve disturbances within this network of interacting brain regions (Keedwell et al., 2005; Phillips et al., 2008). Increased activity of vmPFC/SgAcc in MDD patients during the low-attentional-load condition, as found here, could be thus due to abnormalities in automatic emotion regulation, and reduction of this activity by cognitive effort may reflect the impact of the dorsal prefrontal system (strongly activated during high load in the present study) on the ventral prefrontal system.

To our knowledge, the present data provide the first evidence of a transient reduction of SgAcc/vmPFC activity caused by a cognitive manipulation in a population of unmedicated, nonelderly patients with a first episode of major unipolar depression. By shedding new light on the neural dynamic of subgenual activity in MDD, this result may have several possible functional and clinical implications. In particular, the reduction of SgAcc/vmPFC activity has been found to be critically involved in antidepressant effects in MDD (see above). Elevated cognitive load could thus directly impact a critical node in the functional anatomy of mood regulation.

Restoring top-down influences onto emotional–limbic circuits

The reduction of SgAcc/vmPFC activity during the high-attentional-load condition in MDD may involve the disengagement from self-focused attention toward an external task (Gusnard et al., 2001; Nagai et al., 2004). Increased focused attention (due to task instructions) may thus act as a "circuit breaker" by targeting a region that, in MDD, is dysfunctional at resting baseline and more strongly connected to a distributed limbic and paralimbic neural network (Greicius et al., 2007). Reduced SgAcc activity may therefore alleviate depressive symptoms by preventing the generation of intrusive thoughts within cortical–limbic networks, such as self-focused thoughts and ruminations. This hypothesis would also fit the recent suggestion of Drevets (2007) that cognitive–behavioral strategies for managing depressive symptoms may reinstate the system's adaptive modulation of emotional behavior and experience by restoring top-down influences (from vmPFC) onto emotional–limbic circuits (Davidson et al., 2002). The present neuroimaging findings provide important, new support for this hypothesis by showing that cognitive effort may potentially impact cortical–limbic networks involved in mood regulation by suppressing SgAcc activity in MDD patients. To what extend increasing attentional demands could also momentarily normalize responses to emotional stimuli in MDD and alleviate dysphoria is a clinically relevant question raised by the current study.

In conclusion, the present study reveals distinct effects of task-demands on activity in unimodal sensory and limbic regions. Task-related top-down influences from frontoparietal networks were altered in depressed subjects, leading to an abnormal neural filtering of irrelevant, nonemotional information in visual cortices and a modulation of limbic activity. These findings provide new insights into the functional connections between brain networks subserving cognition and affective regulation.

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4.2.2. Neurobiological bases of suicidality in major depression.

From

Desseilles M, Schwartz S, Dang-Vu TT, Sterpenich V, Darsaud A, Vandewalle G, Albouy G, Schmidt C, Balteau E, Degueldre C, Phillips C, Luxen A, Ansseau M, Maquet P. Neurobiological Bases of Suicidality in Major Depression. (in preparation)

Summary

Suicide is a major public health problem that typically occurs in the context of a depression. We used functional magnetic resonance imaging to reveal the neurobiological correlates of suicidality in depressed patients. The present 3 Tesla fMRI study was conducted in 14 non-medicated patients with a first episode of unipolar MDD and 14 matched controls. During scanning, subjects performed two tasks imposing two different levels of attentional load at fixation (easy or difficult, i.e. low or high attentional load), while irrelevant stimuli (i.e. faces) were presented in the periphery. To obtain an unbiased measure of suicidality from the Hamilton Rating Scale for Depression (HRSD) scores, we computed their singular value decomposition, a mathematical procedure related to principal component analysis. Functional MRI data were analyzed using a two-step procedure taking into account the intra-individual and inter-individual variance. The summary statistics images of the individual level were entered into a second-level one-way ANOVA implemented in SPM2 (http://www.fil.ion.ucl.ac.uk) to assess random-effects group comparisons. We performed additional whole-brain second-level correlation analyses for the main contrasts of interest using a component of the HDRS as covariates with singular value decomposition of the scale. When asked to engage attention in a cognitive task (high > low attentional load) depressed patients activated noradrenergic locus coeruleus, serotonergic raphé nuclei and amygdala in proportion of their suicidality. No such correlation was observed in healthy participants, whose suicidality scores were within normal ranges. In animals, activity in the mesopontine reticular formation and amygdala can promote rapid behavioral shifts in response to cognitive challenges by facilitating the functional reorganization of cortical networks. Our results suggest that, in the context of high attentional demands, depressed patients may be prone to impulsive shifts in behavioral states that could be prevented by a better control over amygdalar activity and its modulation by aminergic neuromodulators.

Neurobiological Bases of Suicidality in Major Depression

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We used functional magnetic resonance imaging (fMRI) to reveal the neurobiological correlates of suicidality in depressed patients. When asked to engage attention in a cognitive task depressed patients recruited mesopontine tegmental regions (including noradrenergic locus coeruleus and serotonergic raphé nuclei) and the amygdala in proportion to their suicidality. By facilitating the functional reorganization of cortical networks, these activations are likely to make them prone to impulsive shifts in behavioral states.

Suicide is a major public health problem with about one million fatalities and ten millions attempts registered worldwide every year. Suicidal behavior typically occurs in the context of a psychiatric disorder such as depression[1]. Postmortem studies suggest that aminergic neuromodulation by the serotonergic raphé nuclei and noradrenergic locus coeruleus (LC) from the mesopontine reticular formation are implicated in impulsivity and increased suicide risk[2]. Yet, the neural mechanisms underlying elevated suicidality in patients with depression remain elusive and, despite its major clinical importance, no physiological measure of suicide risk is currently available.

Here, we aimed at characterizing the neural correlates of suicidality in depressed patients using functional magnetic resonance imaging (fMRI). Because high attention investment worsens adverse effects of impulsivity[3], we developed a behavioral task including two levels of attentional load to test whether brain responses to increased attentional challenge may covary with suicidality in regions mediating aminergic neuromodulation. We measured regional fMRI signal changes in 14 unmedicated subjects who presented with a first episode of major unipolar depression and 14 controls matched for age, sex, and socio-cultural level (age: 19-54y; median: 34y). During the attention paradigm, participants performed two versions of a central letter detection task involving either low or high attentional demands while irrelevant stimuli (i.e., neutral faces) were presented in the periphery of the display[4, 5],. The 'easy' or low attentional load task required a key-press for any red T irrespective of its orientation. The 'difficult' or high load task (conjunction) required a key-press for any upright yellow T or upside-down blue T.

Whole-brain functional MRI data were analyzed voxelwise by statistical parametric mapping (SPM2, http://www.fil.ion.ucl.ac.uk), using a two-step procedure taking into account the intra-individual and inter-individual variance (Supplementary Methods). We first looked for commonalities in the differential effect of attentional load for both depressed patients and normal controls using a conjunction analysis[6] (Supplementary Table S3). As expected from previous fMRI studies using similar paradigms[4, 5], the difficult task condition, relative to the easy condition activated a distributed fronto-parietal network known to subserve attentional mechanisms[7]. To directly compare the two groups for attention-related effects, we computed an interaction (attentional load by group), which did not reveal any significant activation. These findings suggest that the depressed patients were actually engaged in the task and recruited the relevant brain areas to the same extent as the normal subjects. Consequently, any difference in activation related to suicidality, as found below, could not be attributed to a general difference in task-related engagement between depressed patients and healthy controls.

To selectively identify brain regions in which attention-related responses were proportional to individual levels of suicidality, we conducted regression analyses within the depressed patients' group. In a first step, individual scores for the suicide item of the Hamilton Rating Scales for Depression (HRSD) was regressed against the effect of attention (high > low attentional load). The left mesopontine tegmentum showed a trend for a regression (MRF : 2, -36, -32mm, Z = 2.78, p_{SVC} = 0.076). The weakness of this approach is that the different items of the HRSD are known to be partially correlated[8]. Because suicidality involves a

constellation of symptoms[2, 9], we reasoned that the complexity of suicidality would be best characterized by a response profile that would span over several HRSD items. To obtain such a complex and unbiased measure of suicidality from the HRSD scores, we computed their singular value decomposition, a mathematical procedure related to principal component analysis. The second eigenvector, which accounted for 10% of total HRSD variance, characterized suicidality across its various items (see Supplementary Material). The corresponding eigenvariate, a scalar summary of the degree to which each patient expressed suicidality, was used as independent variable in a voxelwise regression analysis. We found that responses induced by attention in the left amygdala and the dorsal mesopontine tegmentum, an area compatible with locus coeruleus and raphé nuclei, increased linearly and significantly with suicidality (Fig. 1). No such correlation was observed in healthy participants, whose suicidality scores were within normal ranges.

Activity in the mesopontine reticular formation (especially the LC) and amygdala can promote rapid behavioral shifts in response to cognitive challenges by facilitating the functional reorganization of cortical networks[10]. In the context of augmented attentional demands, depressed patients recruit the amygdala and mesopontine reticular formation in proportion to their suicidality making them prone to abrupt, potentially spurious, shifts in behavioral states. These brain mechanisms might thus lead to increased impulsivity and exacerbate suicidal behavior. By demonstrating that elevated suicidality levels are associated with an augmented fMRI response to attentional challenges in the serotonergic raphé nuclei and noradrenergic locus coeruleus, our results provide a neural foundation for the increased risk of suicidal behavior during the first weeks of antidepressant treatments[11], which are known to increase aminergic drive. Finally, the observation that the amygdala was over-responsive to cognitive stress in depressed patients more prone to suicide may also have important implications for public health management. Because emotional regulation processes can modulate amygdala activity [12, 13] and decision making [14], future work should establish whether efficient suicide prevention can be achieved by developing behavioral (as well as pharmacological) strategies that may potentiate the control over amygdala activity.

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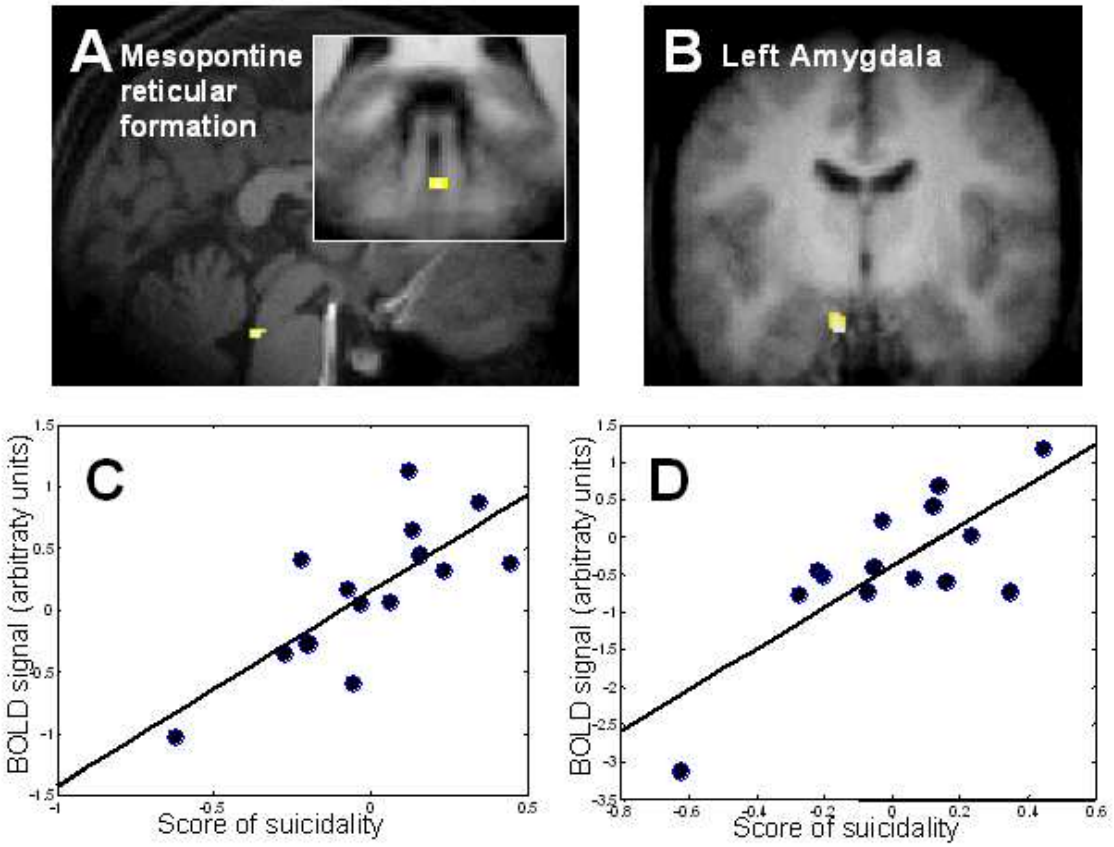
Figure 1. Regression between suicidality and responses to high attentional demands in depressed patients. (a) Whole-brain regression analysis showing significant effect in the mesopontine reticular formation [MNI coordinates: 2x -38y -30z mm; Z=3.96], anb **(b)** in the left amygdala [-10x -10y -28z; Z=4.45]. **(c)** Regressions between individual suicidality levels as assessed by single value decomposition and regional brain responses elicited by high (vs low) attention in the mesopontine reticular formation and **(d)** the amygdala of depressed patients. All $P < 0.05$, corrected for multiple comparisons.



Neurobiological Bases of Suicidality in Major Depression

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SUPPLEMENTARY METHODS

POPULATION

Depressed subjects were recruited through the psychiatric outpatients consultation of the Liege University Hospital by a team of trained psychiatrists who performed a medical examination and assessed the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-IV) [1]. Over a two-year period, sixteen subjects with a first lifetime episode of unipolar major depressive disorder (MDD), with no prior antidepressant or antipsychotic treatment, were included in the experimental protocol. Sixteen healthy controls also participated to the experiment; they were selected to match each MDD patients for gender, age, and socio-cultural background. Exclusion criteria for the control subjects were any severe medical problem, any neurological history, as well as any psychiatric history, a Hamilton Depression score [2] greater than 6, or any other DSM-IV Axis I mental illness. Additional exclusion criteria for both the MDD and control groups were current or past cardiovascular or neurological disorder (e.g., Parkinson disease). Subjects were excluded if they were pregnant or lactating, or had conditions for which an MRI would be contraindicated (e.g., metallic implants). Inclusion criteria for both groups were age between 18 and 56 years, willingness to participate, and ability to provide signed

informed consent. The protocol was approved by the research ethics committee of the Faculty of Medicine of the University of Liège.

Two patients could not maintain reliable central visual fixation (as monitored by eyetracking). Data from these 2 patients and for the corresponding controls were excluded from further analysis. Thus, the final analyses included 14 MDD patients (7 males, drug-free, Hamilton Depression Rating Scale ≥ 17; Supplementary Table S1) and their corresponding 14 matched controls.

FUNCTIONAL MRI ACQUISITION

Data were acquired with a 3T head-only MR scanner (Allegra, Siemens, Erlangen) using a gradient echo EPI sequence (32 transverse slices with 30 % gap, TR: 2130 ms, TE: 40 ms, FA: 90°, FOV: 220 x 220 mm, matrix size: 64 x 64 x 32, voxel size: 3.4 x 3.4 x 3 mm). Functional volumes were acquired during two continuous scanning runs (255 volumes each). The first three volumes were discarded to account for T1 saturation effects. A structural MR scan was acquired at the end of the experimental session (T1-weighted 3D MP-RAGE sequence, TR: 1960 ms, TE: 4.43 ms, TI: 1100 ms, FOV: 230 x 173 mm, matrix size: 256 x 192 x 176, voxel size: 0.9 x 0.9 x 0.9 mm). During scanning, eye movements and pupillary size were measured continuously using an infrared eye tracking system (LRO5000, Applied Science Laboratories, Bedford, MA, sampling rate = 60 Hz). Eye tracking data were used to ensure that all subjects included in the analyses maintained good central fixation during the whole scanning session.

FUNCTIONAL MRI ANALYSIS

Functional MRI data were analyzed using SPM2 (http://www.fil.ion.ucl.ac.uk) implemented in MATLAB (Mathworks Inc., Sherbom, MA). Functional scans were realigned, normalized to the MNI EPI template (2D spline, voxel size: 2 x 2 x 2 mm) and spatially smoothed with a Gaussian kernel with full-width at half maximum (FWHM) of 8 mm.

Conventional SPM Approach

Whole-brain fMRI data were analyzed using a two-step procedure taking into account the intra-individual and inter-individual variance. At the individual level, brain responses were modelled at each voxel, using the general linear model with 4 trial types convolved with the canonical hemodynamic response function: low load with face stimuli in the periphery, low load with no peripheral stimuli, high load with faces in the periphery, high load with no peripheral stimuli. Seven additional regressors of no interest were included in the analyses: trials with motor response (target detection and false alarms), plus 6 movement parameters from spatial realignment to account for residual motion artifacts. High-pass filtering was performed using a cut-off period of 128 s to remove low frequency drifts from the time series. Linear contrasts between regressors of interest tested for the main effects of attentional load (high versus low load; low versus high load). The summary statistics images were spatially smoothed with a Gaussian kernel of 6 mm FWHM and entered into a second-level one-way ANOVA implemented in SPM2 to assess random-effects group comparisons, with the contrast (high > low attention) as within-subject factor, and group (MDD, controls) as between-subjects factor. The resulting SPM maps were thresholded at $p < 0.001$ uncorrected. Note that using within-subject contrasts as main variables for second-level whole-brain group analyses, as in the present study, also minimizes effects related to group difference in task difficulty (if any). Note also that the use of conservative whole-brain random-effects group comparisons [3] together with the relatively broad age-range of the studied populations (MDD: 19-54; matched controls: 19-56 years) ensures that any statistically-significant group difference reflects a robust result that can be generalized to a larger population.

Common group effects were assessed using conjunction analysis to preserve only voxels that were significant in the contributing SPM maps of both control and MDD populations based on the conjunction null hypothesis [4]. Direct statistical group comparisons were obtained using the main interaction of 'attentional load' by 'group'. Statistical inferences were performed at a threshold of $p < 0.05$ after correction for multiple comparisons over small spherical volumes (8 mm radius) around a priori locations of interest [5].

Regression Analyses

To assess whether individual clinical characteristics could explain attentional modulation of regional brain responses, we performed additional whole-brain second-level regression analyses for the main contrasts of interest using scores from the Hamilton Depression Rating Scale (HDRS, [2] as covariates. Analyses were conducted separately for each population to discard effects trivially due to the overall difference between controls and MDD patients on both these clinical measures. The main goal of this analyze was to assess whether some of the group differences in load-modulation of brain activity might also be observed within groups when individual differences in suicide levels of the HDRS were taken into account.

We then computed a singular value decomposition[6] to extract the main factors ('psychometric constructs') characterizing the population's variance over the 17 items of the HDRS. Singular value decomposition is an extension of Principal Component Analysis (PCA) to rectangular matrices. The results of a PCA are typically discussed in terms of component scores (factors explaining the distribution of the population's variance over the variables included in the analysis) and loadings (contributions of the different variables to each factor)[6]. Singular value decomposition was performed on a matrix constituted by the 17 items of the HDRS in the 14 depressed patients (matrix of 17 x 14). This multivariate analysis identified a first component explaining 42 % of the variance and a second main component explaining 10 % of the residual variance.

The first component showed a major loading of items 1, 7, and 10, corresponding respectively to 'depressed mood', 'work and activities', and 'psychological anxiety', which captures well a main 'depression' compound (Figure S1). Whole-brain correlation analysis using this first component as regressor revealed a positive correlation of depression level and response to high attentional demands in sensory/visual areas. The second component showed a major loading of item 3 'suicide' and negative loadings of items 11 and 15 respectively 'somatic anxiety' and 'hypochondriasis' (Figure S2). The

result of the whole-brain correlation analysis using this second component as regressor (reported in the main manuscript) revealed that responses induced by attention in the left amygdala and the dorsal mesopontine tegmentum, an area compatible with locus coeruleus and raphé nuclei, increased linearly and significantly with suicidality.

SUPPLEMENTARY RESULTS

CLINICAL CHARACTERISTICS

Sixteen patients and their matched controls completed the study but 2 patients were excluded because they could not maintain reliable central visual fixation. The 14 remaining MDD patients and their 14 healthy matched controls were included in the final analyses. Supplementary Table S1 gives the main demographic and clinical characteristics of the study population. Differences between the groups were statistically significant for both depression and anxiety measures (HDRS, HARS; two-sample t-test, $p < 0.001$ for both measures). MDD patients and controls did not differ on any other variable reported in Table S1. Their education level (assessed in years) ranged from 12 to 15 years (mean, 13.78 ± 0.97 years).

BEHAVIOURAL RESULTS

Performance on the central attentional load task during scanning was assessed by analyzing the reaction times (RT) and hit rates on target trials, as well as the number of false alarms using ANOVAs with Attentional Load (High, Low) as within-subjects factor (repeated measures) and Group (MDD, controls) as between-subjects factor (Supplementary Table S2). There was a main effect of Attentional Load for all measures, with slower RT, lower hit rate, and more false alarms during the high compared to the low load condition (all $p < 0.05$), indicating that the instructions successfully modulated

task difficulty in both groups. There was a main effect of Group for hit rates due to the patients missing slightly more targets (hits, 92.57% in low load and 87.12% in high load) than the controls (hits, 96.43% in low load and 95.64% in high load), but no Group by Attentional Load interaction. No other effect of Group or interaction was found for any other measure.

SPM RESULTS

For clarity, rather than separate main effects within each group, we first describe whole-brain effects commonly found in both MDD patients and controls using conjunction analyses (Supplementary Methods). We then report between-group comparisons whenever they yielded statistically significant results.

Effects of High Attentional Load

We first tested for effects of increased attentional load by comparing fMRI activity during the difficult and the easy tasks (high > low attentional load) using linear contrasts of parameter estimates in the context of ANOVA models (Supplementary Methods). A conjunction of the SPM maps from the patients and from the controls for the high > low load contrast revealed that both populations strongly engaged inferior frontal and superior parietal regions during increased attentional load at fixation (Table S3), consistent with the recruitment of a distributed attentional network subtending top-down influence under higher-load condition in all participants [7, 8].

Effects of Low Attentional Load

We then tested for regions more activated during low as compared to high attentional demands (low > high load). Based on Lavie's theory of attentional load [9, 10] and on our previous fMRI results in normal controls [11], we predicted increased activity in visual regions due to less filtering of the peripheral stimuli during the low load condition. The

group conjunction analysis (low > high load) revealed that left frontal, anterior and posterior cingulate, and occipital regions survived the statistical threshold (Table S3).

Between-group comparisons

The attentional load by group interaction did not reveal any significant activation. These findings suggest that the patients were actually engaged in the attention task and recruited the relevant brain areas to the same extent as the normal subjects.

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Table S1: Clinical characteristics of the depressed patients and their matched controls [a]

	MDD Group					Control Group				
	Age (years)	Sex	Education (years)	HDRS	HARS	Age (years)	Sex	Education (years)	HDRS	HARS
1	21	f	15	21	15	21	f	14	0	0
2	28	f	15	33	19	27	f	16	1	2
3	29	f	13	32	16	32	f	15	1	2
4	29	f	13	34	12	24	f	15	3	4
5	32	f	15	37	19	31	f	14	2	0
6	38	f	14	30	18	32	f	17	0	0
7	54	f	15	20	17	56	f	12	2	0
8	19	m	14	30	22	20	m	12	1	0
9	19	m	13	30	10	19	m	13	1	0
10	36	m	13	21	14	34	m	13	1	0
11	39	m	13	27	14	35	m	13	6	7
12	38	m	12	24	18	34	m	16	0	0
13	40	m	14	26	17	36	m	17	3	3
14	42	m	14	25	15	39	m	14	1	0
Mean [b]	33.1 ± 9.84	7:7	13.78 ± 0.97	27.86 ± 5.27	16.14 ± 3.11	31.4 ± 9.51 [c]	7:7	14.35 ± 1.69 [c]	1.57 ± 1.60 [d]	1.29 ± 2.13 [d]

Abbreviations: MDD, major depressive disorder; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale.

[a] Patients were selected by a team of psychiatrists with extensive experience in depression. All subjects were Caucasian and right handed; they suffered from a first episode of unipolar depression and were all unmedicated.

[b] Data are given as mean ± SD

[c] Two-sample t-test testing for Group differences, d.f.26; NS

[d] Two-sample t-test testing for Group differences, d.f.26; $p < 0.001$

Table S2: Behavioural performance during scanning [a]

Measure	**MDD Group**		**Control Group**		**Statistics** [b]		
	Low load	**High load**	**Low load**	**High load**	**Effect of Group**	**Effect of Load**	**Interaction Group by Load**
RT on hits (ms)	516.04 ± 70.49	610.34 ± 64.26	511.99 ± 57.02	607.92 ± 60.82	$F_{1,26}$=0.02; p =0.88	$F_{1,26}$=250.5; p < 0.001	$F_{1,26}$=0.01; p =0.893
Hits (%)	92.57 ± 12.21	87.12 ± 13.96	96.43 ± 3.64	95.64 ± 4.80	$F_{1,26}$=4.27; p =0.049	$F_{1,26}$=6.93; p = 0.014	$F_{1,26}$=3.86; p=0.06
False alarms (%)	6.20 ± 12.40	15.08 ± 14.06	3.23 ± 4.83	8.58 ± 7.02	$F_{1,26}$=2.55; p =0.12	$F_{1,26}$=38.64; p < 0.001	$F_{1,26}$=2.38; p =0.13

Abbreviation: MDD, major depressive disorder; RT, reaction times.

[a] Data are given as mean ± SD unless otherwise indicated.

[b] ANOVA with Load as within-subject factor and Group as between-subject factor.

Table S3. Brain regions showing main effects of attentional load in both group (conjunction; see Supplementary Methods)

Brain Areas	L/R	BA	MNI coordinates X Y Z			Z value [a]	Cluster Size (voxels) [b]
Common brain activations in MDD patients and controls for High > Low Attention							
Inf. frontal gyrus / Operculum	L	44/48	-46	4	28	5.12	362
Inf. parietal	L	40	-44	-38	44	5.09	840
Inf. parietal	R	40	42	-40	40	4.22	276
Sup. parietal / IPS	L	7	-20	-64	54	4.24	206
Sup. parietal / IPS	R	7	36	-60	64	3.37	14
Sup. parietal / IPS	R	7	22	-66	60	3.30	26
Precentral/Mid. frontal	R	6	30	0	50	4.18	181
Precentral/Mid. frontal	L	6	-34	-2	62	4.90	620
SMA	L	6	-8	8	54	4.69	431
SMA	R	6	12	8	58	3.58	17
Mid. occipital	L	19	-28	-70	32	3.36	11
Common brain activations in MDD patients and controls for Low > High Attention							
Inf. Frontal / orbital	L	47	-36	34	-14	3.58	58
Sup. frontal	L	8/9	-20	34	54	3.67	103
Ant. Cingulate	L	25/11	-4	28	-20	3.57	178
Ant. Cingulate	L	11	-8	46	-4	3.29	23
Ant. Cingulate	R	32	10	52	16	3.47	70
Post. Cingulate	R	23	2	-48	32	3.26	19
Mid. temporal	L	21	-52	-10	-26	3.57	52
Mid. temporal	L	21	-58	-16	-24	3.47	[c]
Angular	L	39	-50	-72	38	3.82	223
Precuneus	L	23	-10	-64	26	3.32	22
Lingual / V4	R	18	20	-72	-6	4.31	639
Sup. occipital	L	17	-14	-94	6	4.15	569
Calcarine	L	17	-18	-56	12	4.08	90

Abbreviations: Inf, Inferior; IPS, Intra Parietal Sulcus; Mid, Middle; SMA, Supplementary Motor Area; Sup, Superior; VWFA, Visual Word Form Area

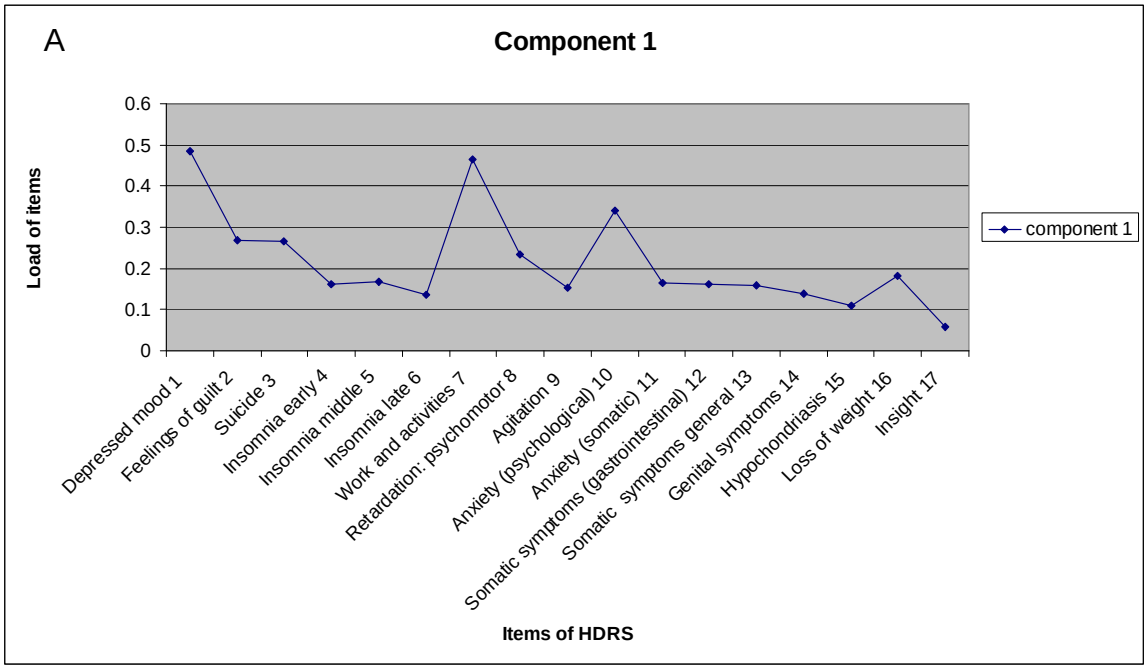
[a] All $p < 0.001$ uncorrected (random-effect analysis).

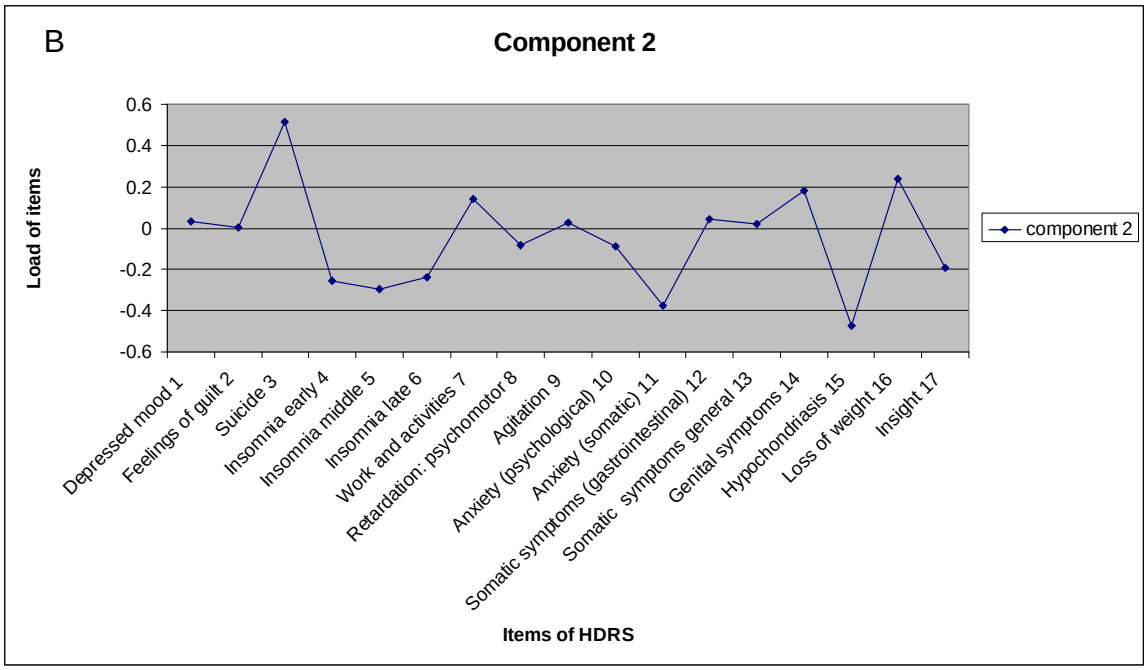
[b] Threshold cluster size of 5 voxels

[c] Belongs to the same cluster as row above

Figure S1. Two first components resulting from the singular value decomposition of the Hamilton Depression Rating Scale

Figure displays items of the HDRS (x axis) and the loadings of each items (y axis) in the contribution of the component (or eigenvector) score. **(a)** First component showing a major loading of items 1, 7, and 10, respectively 'depressed mood', 'work and activities', and 'psychological anxiety'. **(b)** Second component showing a major loading of item 3 'suicide' and negative loadings of items 11 and 15, respectively 'somatic anxiety' and 'hypochondriasis'.




B
Component 2
Load of items
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
Depressed mood 1
Feelings of guilt 2
Suicide 3
Insomnia early 4
Insomnia middle 5
Insomnia late 6
Work and activities 7
Retardation: psychomotor 8
Agitation 9
Anxiety (psychological) 10
Anxiety (somatic) 11
Somatic symptoms (gastrointestinal) 12
Somatic symptoms general 13
Genital symptoms 14
Hypochondriasis 15
Loss of weight 16
Insight 17
Items of HDRS
component 2

5. Conclusions and perspectives

5.1. Construction of an original attentional paradigm

We reviewed the interactions between attentional top-down and bottom-up mechanisms and we proposed that these interactions might be disrupted in pathological conditions, such as depression.

We developed an original attentional paradigm allowing us to explore these attentional mechanisms in healthy subjects and in patients suffering from depression. Our paradigm has two tasks imposing two different levels of attentional load at fixation (easy or difficult), while irrelevant colored stimuli are presented in the periphery. It allows us to evaluate behavioural responses in low attentional load or in high attentional load.

We adapted our attentional paradigm in order to use it simultaneously with fMRI data acquisition.

5.2. Contribution of our results to the pathophysiology of depression

Using fMRI we showed functional abnormalities within visual cortices, suggesting altered processing at early stages of information processing in patients with depression. We clarified how regions regulating affective processing interacted with those involved in attention, and how this interaction impacts perceptual processing within early sensory cortices.

Our fMRI study examined attentional effects on the processing of task irrelevant nonemotional visual stimuli in 14 nonmedicated patients with a first episode of unipolar MDD versus 14 matched controls.

Based on the observation that visual cortical responses to irrelevant stimuli is diminished as task demands increase, our prediction was that this effect would be

impaired in depressed subjects as a consequence of dysfunctions in cortices subtending high attentional demand or top-down processes.
Our study revealed a set of interesting observations that suggested complex effects of depression on attentionally-driven 'filtering':

1) In visual cortex (V4), responses to irrelevant colored stimuli diminished at high attentional load in controls, but were suppressed in depressed patients irrespective of attentional load. This effect corresponded to attention-related impairement in frontal and parietal functional connectivity with V4 in patients.

2) SgACC / vmPFC responses to irrelevant colored stimuli was reduced during high attentional load in controls, but in patients the vmPFC activity was strongly affected by attentional load irrespective of the presence or absence of the stimuli.

These observations are novel and reveal interesting neural effects on low level stimulus processing associated with depression and mediated by cognitive attentional systems. Our results also extend current knowledge about the mechanistic role of the vmPFC, a putative functional substrate for depression.

Our study revealed, for the first time with fMRI, that the pathophysiology of MDD involves impairments in early information processing. Such perceptive disturbance may lead to cognitives dysfunctions (see section 1.1.5) and could be a potential target for future treatments of depression.

Phillips and colleagues recently described a neural model of emotion regulation that includes voluntary and automatic regulatory subprocesses (Phillips, Ladouceur et al. 2008). They highlighted two major neural systems: (1) a feedforward pathway: a medial prefrontal cortical system, including the orbital frontal cortex, SgACC, rostral ACC, hippocampus and parahippocampus, and dorsomedial PFC, and (2) a feedback pathway: a lateral prefrontal cortical system, including dorsolateral PFC and ventrolateral PFC. These authors suggest that the former neural system may be involved in automatic subprocesses, whereas the latter neural system may subserve voluntary subprocesses. These two neural systems may be activated concurrently during regulation of emotional states. SgACC was involved in automatic emotional

processes (e.g. Phelps, Delgado et al. 2004). In addition, SgACC was involved in the default-mode network of MDD (Greicius, Flores et al. 2007) and linked to self-focused thoughts (Sheline, Barch et al. 2009). Our findings suggest that cognitive attentional load may decrease automatic emotional processes and self-focused thoughts. In addition, modulations of the vmPFC might lead to emotional, cognitive, endocrine, autonomic and neurochemical regulations (see section 1.1.8).

Thus, our findings shed new light on the interaction between cognition and mood regulation. While SgACC is thought to be a final common pathway for several treatments in depression (see section 1.1.8), our study suggests that increased cognitive load could have therapeutical effects by decreasing a baseline hyperactive SgACC / vmPFC in MDD patients and consequently acting as a circuit-breaker of depression. Cognitive training or rehabilitation might be proposed to these patients.

3) During high attentional demand, MDD patients activated noradrenergic locus coeruleus, serotonergic raphé nuclei and amygdala in proportion of their suicidality.

This is the first fMRI demonstration of brainstem abnormalities in living MDD patients. To explain the increase of deliberate acts of self-harm in the first month of antidepressant treatment (Jick, Kaye et al. 2004), a mismatch in symptom improvement was first proposed (i.e. physical energy gets better first while resolution of suicidal ideations is slower) (see section 1.1.6). Here, we suggest a novel pathophysiological hypothesis in which the interplay between locus coeruleus (Einhauser, Stout et al. 2008) and amygdala (Bouret and Sara 2005) plays a key role in impulsive shifts in behavioural states, which may in turn precipitate suicidal behaviour.

We propose that a better control over amygdalar activity and its modulation by aminergic neuromodulators might avoid extreme, impulsive reactions. Amygdalar-frontal connectivity was shown in several studies (Phelps, Delgado et al. 2004; Banks, Eddy et al. 2007). For instance, Banks and collaborators (2007) demonstrated that activity in left amygdala covaried with activity in a set of area including the right SgACC during a reappraisal-based strategy to downregulate negative affect (Banks, Eddy et al. 2007). Since, during an effortful affective reappraisal task, a positive

association between vmPFC and amygdala has been shown in MDD patients (Johnstone, van Reekum et al. 2007), as compared to healthy subjects, our attentional cognitive task might be used in order to decrease this counterproductive recruitment of prefrontal-subcortical circuitry (Desseilles, Balteau et al. 2009).

In addition to cognitive therapy and antidepressants (DeRubeis, Siegle et al. 2008), benzodiazepine could be used in order to decrease amygdalar activity (Paulus, Feinstein et al. 2005).

5.3. Perspectives in pathology: top-down dysfunction in mental illnesses

Based on our results, we showed that deficits in top-down modulations in unipolar depression have remote consequences on cerebral functioning, even at early processing levels. According to this model, altered competition between top-down and bottom-up sensory processes might lead to a distorted perception of the world. Depression was taken as a paradigmatic example of a top-down dysfunction, yet this model could be applied to other psychiatric disorders such as bipolar disorders (at the other side of the mood spectrum), anxiety disorders (e.g. obsessive-compulsive disorders) or schizophrenia (Silbersweig and Stern 1996).

In addition, disorders of mood and cognition overlap in the elderly and there is an emerging consensus that both groups of disorders share similar neurobiological substrates (Kumar, Ajilore et al. 2008). For instance, recent brain imaging techniques such as PET-based in vivo protein binding could help elucidate common pathophysiological mechanisms in order to detect patients at risk, to monitor disease and to evaluate new treatments in several neurodegenerative diseases including Alzheimer disease (Appleby, Roy et al. 2007).

As an exemple, we detail hereafter why we should study top-down dysfunctions, using our attentional paradigm, in hallucinations and in obsessive-compulsive disorders. Such research program could verify the generality of our findings in MDD patients.

In our future research, we plan to explore with our paradigm other sensorial modalities. We suggest that top-down and bottom-up processes are involved in other sensorial modalities such as olfactory (e.g. Atanasova, Graux et al. 2008), auditory (e.g. Silbersweig and Stern 1996), somatosensory (e.g. Von Korff and Simon 1996), gustative (e.g. Steiner, Lidar-Lifschitz et al. 1993) modalities.

5.3.1. Top-down dysfunctions in hallucinations

Hallucinations are involuntary perceptions in the absence of external stimuli (Sadock and Sadock 2005). They can occur in any sensory modality (e.g. exteroceptive such as visual, auditory, olfactory, gustatory, or tactile; interoceptive or proprioceptive). More

strictly, hallucinations are perceptions in a conscious and awake state in the absence of external stimuli and they have traits of real perceptions, in that they are vivid, significant, and positioned in external objective space. In that way hallucinations can be distinguished, for instance, from *dreaming* (Dang-Vu, Desseilles et al. 2007); *illusion* (Kitaoka, Gyoba et al. 2006); *imagery* (Bartolomeo 2002).

Hallucinations have been shown in pathological conditions (e.g. neurological disorders, delirium tremens, drug or alcohol use, psychosis, sleep deprivation) (Sadock and Sadock 2005) and in normal populations (Laroi, Marczewski et al. 2004). For instance, hypnagogic hallucinations (occur as one is falling asleep) and hypnopompic hallucinations (occur when one is waking up) are considered normal phenomena. The form and content of hallucinations are particularly prominent and incapacitating in schizophrenia. In this latter condition, normal balance between sensory (bottom-up) and mental (top-down) factors is distorded (Grossberg 2000). Under certain circumstances, top-down factors override or prevail on bottom-up informations in determining the final percept (conscious experiences in the absence of bottom-up information).

Our paradigm explicitly target top-down attentional mechanisms and could be used to explore the neural basis of top-down perceptual processing in hallucinations and particularly in schizophrenia.

5.3.2. Top-down dysfunctions in obsessive-compulsive disorders (OCD)

Functional neuroimaging studies have revealed abnormalities in polymodal associative cortices (prefrontal and parietal) and in limbic and paralimbic areas (anterior cingulate cortex, amygdala, hippocampus, etc.) in OCD (Geuze, Vermetten et al. 2005; Malizia 2005; Friedlander and Desrocher 2006). These findings suggest an alteration of the modulation by higher-level regions of lower stages of information processing, down to that occuring within primary sensory cortices (Desseilles, Ansseau et al. 2008). In addition, functional abnormalities in the striatum have been demonstrated. A metabolic hyperactivity in the cortico-subcortical loop involving striatum has been suggested to be concomitant to the onset of obsessions (Guehl, Benazzouz et al. 2008). Moreover, the alleviation of the OCD symptoms by

pharmacotherapy or psychotherapy is accompanied by a normalization of frontal hyperactivity (orbitofrontal cortex, dorsolateral-prefrontal cortex and anterior cingulate cortex), while posterior brain activity related to action-monitoring function increases (Nakao, Nakagawa et al. 2005).

In these patients, attentional biases (Bannon, Gonsalvez et al. 2002; Clark 2002; Cohen, Lachenmeyer et al. 2003; Chamberlain, Blackwell et al. 2005; Chamberlain and Sahakian 2006) (selection of inadequate information or behaviour as well as inhibition of pertinent information and behaviour) play a major role in the initiation and maintenance of the symptoms (Beck and Clark 1997). Moreover, this process of information selection involves fronto-striatal areas (Passingham 1996; Rotge, Guehl et al. 2009).

Based on the findings reviewed above, we hypothesized that a dysfunction in fronto-striatal networks could underpin not only affective and behavioural characteristics of OCD patients, but also perception and cognitive functioning, because OCD patients process information in a more rigid and less adapted way (Soref, Dar et al. 2008). In addition, we propose that attentional biases linked to the dysfunctional activity within high level regions (« top-down » effect) imply a reorganisation of the functional connectivity, even during the resting state of the brain (Raichle, MacLeod et al. 2001; Raichle and Snyder 2007).

Using the same attentional paradigm (Desseilles, Balteau et al. 2009), we conducted a preliminary study on attentional dysfunctions in 16 obsessive-compulsive patients (age (mean ± SD): 29.62 ± 9.32 y; Y-BOCS: 22.87 ± 6.69) and 16 healthy subjects (age: 29.93 ± 10.13 y) (Figure 18).

Measure	OCD Group		Control Group		Statistics†		
	Low load	High load	Low load	High load	Effect of Group	Effect of Load	Interaction Group by Load
RT (ms) on correct responses	501.83 ± 51.59	607.85 ± 50.41	495.20 ± 55.23	629.56 ± 75.37	$F_{1,30}$=0.22; p =0.646	$F_{1,30}$=84.01; p < 0.001‡	$F_{1,30}$=1.17; p =0.288
Hits (%)	97.10 ± 5.67	87.93 ± 10.21	97.21 ± 4.65	90.39 ± 14.73	$F_{1,30}$=0.31; p =0.583	$F_{1,30}$=10.09; p = 0.003§	$F_{1,30}$=0.22; p=0.644
False alarms (%)	7.30 ± 8.52	25.47 ± 19.32	1.70 ± 3.07	19.84 ± 23.76	$F_{1,30}$=1.67; p =0.206	$F_{1,30}$=25.35; p < 0.001‡	$F_{1,30}$<0.001; p =0.996

Figure 18 : Behavioural performances during scanning. Abbreviation: OCD, obsessive-compulsive disorder. Data are given as mean ± SD unless otherwise indicated. †ANOVA with Load as within-subject factor and Group as between-subject factor. ‡P<0.001; §P<0.01; #P<0.05

Our paradigm recruited the fronto-parietal attentional network in both populations (Figure 19).

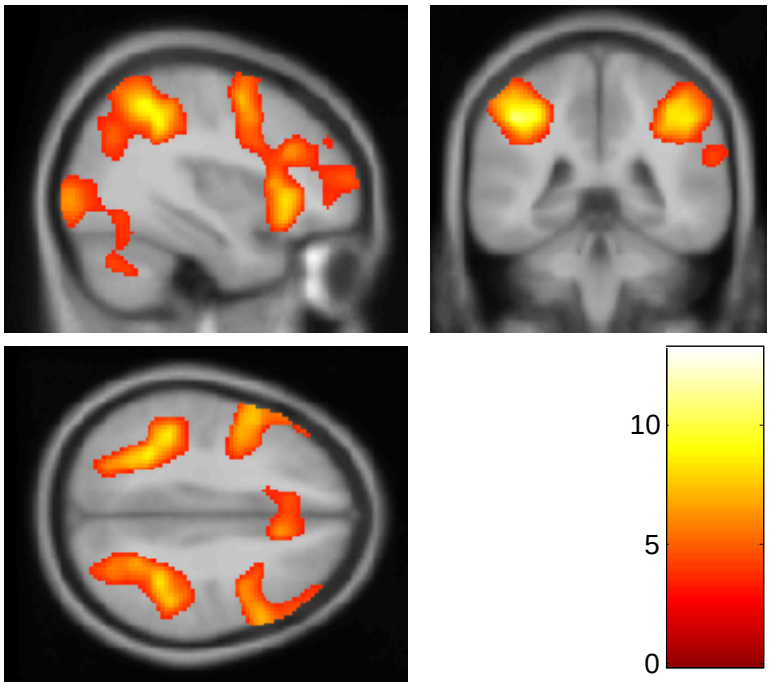


Figure 19 : Main effect of high attentional load. Group conjunction (OCD patients and controls) for the high > low load contrast showing the fronto-parietal attentional network (Corbetta and Shulman 2002).

Control subjects showed, in low > high attentional load, an increased response in the colour responsive region V4a, as compared to OCD patients (Figure 20). These preliminary results not only confirm that our attentional paradigm leads to replicable patterns of brain activity across studies and populations (Desseilles, Balteau et al. 2009), but also suggest an abnormal filtering of irrelevant information in patients with OCD (like we found in depressed patients. We anticipate that further analysis of these data as well as a detailed characterization of the resting-state in OCD patients will provide important new insights into the pathophysiology of OCD.

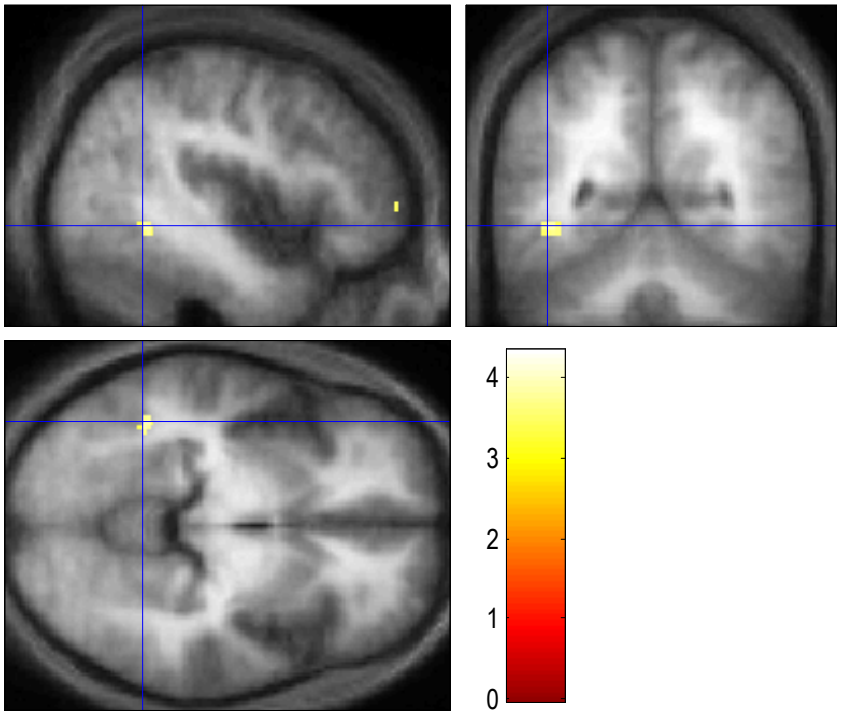


Figure 20 : Main effect of low attentional load. Increased response during the low- minus the high-load condition in V4a for controls relative to OCD patients. xyz = -44,-54,-8, small volume correction (radius 10 mm) based on a priori area from the litterature (Bartels and Zeki 2000). For visualization purposes, statistical parametric maps are overlaid on average T1 structural scan and thresholded at p< 0.005 uncorrected. Color bar indicates t values.

5.4. Perspective in therapy

5.4.1. Cognitive training in top-down regulation

A major issue of neuropsychological experimentation is the development of objective tests aiming at (i) detect the onset, (ii) monitor the course of major depression, and (iii) assess the efficacy of various treatments. In addition, in the context of cognitive therapy, a neuropsychological training could help patients to improve their symptoms. Our task has shown a decrease of subgenual ACC /ventromedial PFC area in high attentional load suggesting that varying attentional load could act as a circuit-breaker in depression.

5.4.2. Evaluation of treatment

We propose that our neuropsychological paradigm could be used in the context of the evaluation of treatment efficacy (in pre- and post- treatment) such as phsychotherapy, pharmacotherapy, including well known drugs or “novel antidepressant” such as ketamine (Maeng and Zarate 2007; Machado-Vieira, Salvadore et al. 2008; Maeng, Zarate et al. 2008) or oxytocine (Arletti and Bertolini 1987) and other somatotherapies of depression (including TMS, ECT, DBS, light therapy, …).

For these treatments, *effectiveness* can be studied by using pre- post- brain imaging comparisons (Figure 21). Our task could thus be very useful to assess functional modulations of brain activity, and to distinguish between activity changes that are independent or dependent of attentional capacities. The comparisons of activity in brain areas, either activation or deactivation, may inform about a potential normalization or compensation. The *prognosis* of response or non-response to a specific therapy can be studied by comparing the cerebral activity between subjects who have responded or not to the treatment. This could potentially provide information on the usefulness of doing a particular type of therapy since this is often a long, costly and grueling work. In addition to the aid in the choice of the best treatment, *target* regions could be pinpointed using neuroimaging at baseline or during cognitive tasks in order to modulate directly the brain activity subtending these

symptoms. In addition to psychotherapy, functional magnetic resonance imaging or electroencephalographic devices could be used in order to train patient to neurofeedback and thus facilitate the normalization of activity in targeted regions.

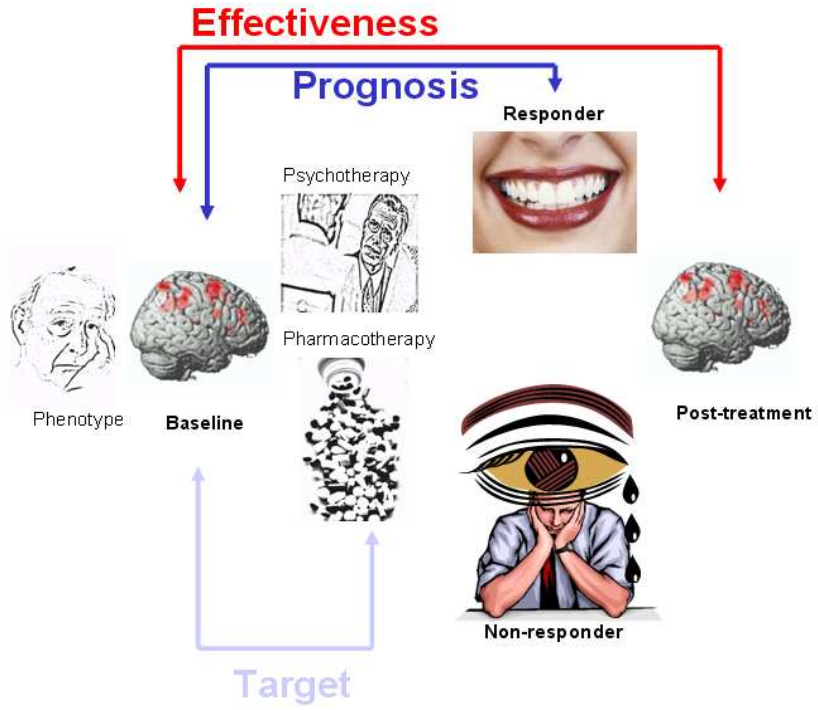


Figure 21 : Evaluation of effectiveness, prognosis and target in therapy of mental illnesses (see the main text for explanations).

5.5. Perspectives in methodology

5.5.1. Integration with other biological measures

Several biological markers of depression have been previously highlighted (see section 1.1.10) and all of them could be associated with brain imaging. For instance, 'gene by environment' interactions, chronotype, and brain biochemistry could be associated with our attentional paradigm.

Gene by environement interactions could be studied by coupling our attentional paradigm with the study of gene polymorphisms including the promoter region of the serotonin transportor (5-HTTLPR) and brain-derived neurotrophic factor (BDNF) (Frodl, Moller et al. 2008). Additionnaly circadian genes have been linked to mental disorders (Lamont, Legault-Coutu et al. 2007) and could be used in genetic imaging protocols.

Chronotype and cognitive performance have been linked and we should study in brain imaging the influence of the time of the day at which testing occurs, in function of the genotype and the psychic disorder (Schmidt, Collette et al. 2007).

Recently, reciprocal interplay between cognitive activity and *brain biochemistry* has been studied using PET scanning (McNab, Varrone et al. 2009). Several neurotransmitters (including monoaminergic system, glutamatergic system or acetylcholine) have been involved in neuropsychiatric disorders (Mann 2005; Pittenger, Sanacora et al. 2007; Belmaker and Agam 2008; Sanacora, Zarate et al. 2008) and cognitive functions (Briand, Gritton et al. 2007). Our original attentional paradigm could be used in order to study the interplay between attentional resources and neurotransmitters.

5.5.2. Voxel-based morphometry

Anatomical volumes could be analyzed using the optimized procedure for voxel-based morphometry (VBM). Compared to other morphometric techniques that involve predefined local brain regions of interest, VBM assesses grey (and white) matter differences across the whole brain after discounting global shape differences. Bet-

ween-group differences will be assessed by contrasting the preprocessed gray matter volumes of the patients and the controls.

5.5.3. Dynamic causal modelling

Dynamic causal modeling or DCM is a modelling procedure of brain effective connectivity. It aims at treating the brain as an input–state–output system. By perturbing the system with known inputs (i.e. our attentional task), measured responses are used to estimate various parameters that govern the evolution of brain states (Friston, Harrison et al. 2003; Kiebel, Garrido et al. 2007; Chen, Kiebel et al. 2008; Marreiros, Kiebel et al. 2008).

As our attentional task can modulate brain activity in a set of known areas, we could model a network using DCM in order to assess effective connectivity in patients with depression as compared to healthy subjects.

5.5.4. Independent component analysis and default network

ICA is a statistical technique that separates a set of signals into independent (uncorrelated and non-Gaussian) spatiotemporal components. When applied to the T2* signal of fMRI, ICA allows not only for the removal of artifacts, but for the isolation of neural networks with a similar time course of activity, during cognitive task or resting-state. Doing this, subsequent correlations could be computed between neuronal activity within these networks and the clinical scores of depression and anxiety.

Subgenual ACC has been involved in the default network of patients presenting depression (Greicius, Flores et al. 2007). In addition, medial prefrontal areas have been involved in the self-focused thoughts (Gusnard, Akbudak et al. 2001; Sheline, Barch et al. 2009). We could analyze our data using ICA (independent component analysis) module of the FSL software (www.fmrib.ox.ac.uk/fsl/melodic2/index.html) in order to link the activity within the default network with the self-focused thoughts such as ruminations.

Below we present our preliminary results of ICA of 14 MDD patients previously described in our main study (Desseilles, Balteau et al. 2009).

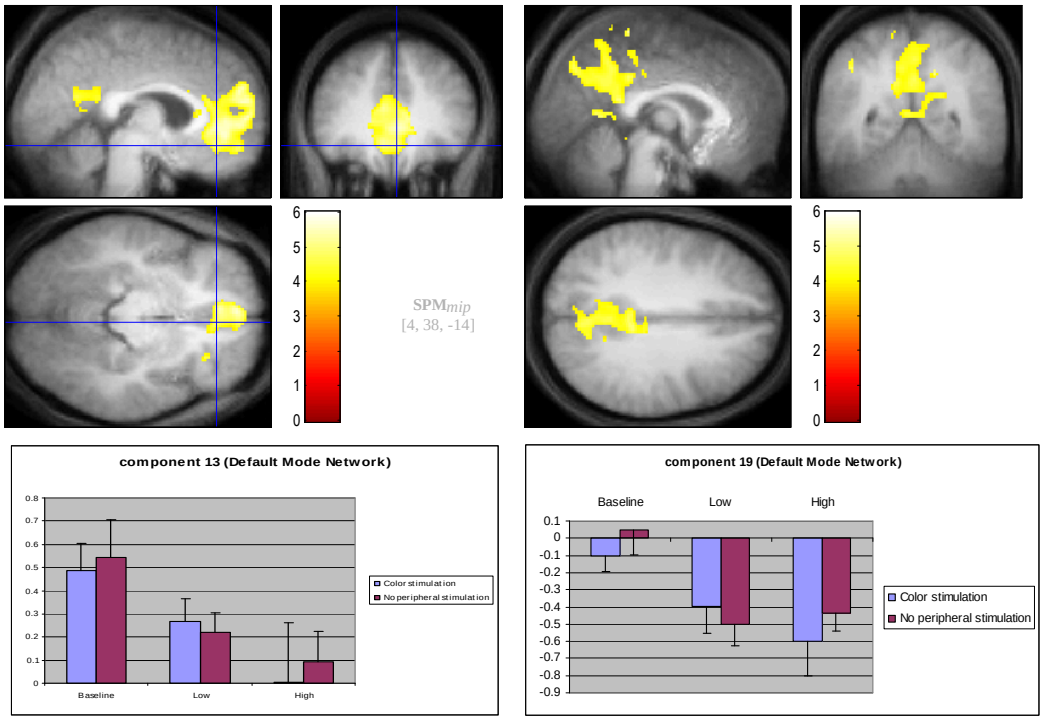


Figure 22 : Default mode network components. SPM maps of the component after ICA analysis of 14 MDD patients. The graphic represent the mean of correlations between regressors (3 attentional conditions: baseline, low and high attentional load; 2 stimulus condition: color stimulation, no peripheral stimulation) and time-course of the component of the ICA analysis.

The SgACC / vmPFC area described in our study (xyz = 4, 38, -14) is in fact in the default-mode network (Figure 22, left panel). These preliminary ICA results are congruent with the hypothesis that SgACC / vmPFC activity is increased at baseline in MDD patients and is diminished by attentional load.

In addition, our results suggest that the correlation between time-course of the ICA components was opposed for the attentional network component (Figure 23) and the default-mode network components (Figure 22). These results suggest a reverse correlation between these two networks. Further analyses will determine how the patients' population and the controls might differ for such large-scale patterns of synchronized brain activity.

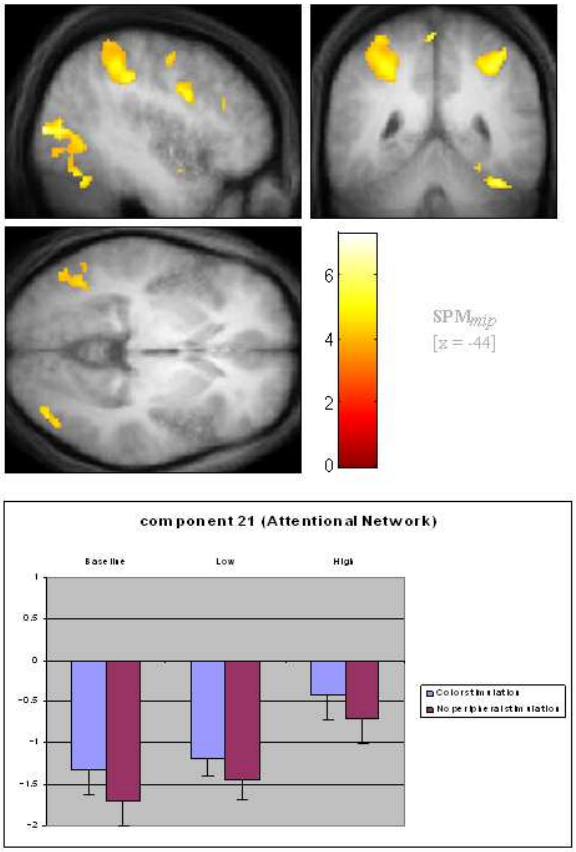


Figure 23 : Attentional network component. SPM maps of the component after ICA analysis of 14 MDD patients. The graphic represent the mean of correlations between regressors (3 attentional conditions: baseline, low and high attentional load; 2 stimulus condition: color stimulation, no peripheral stimulation) and time-course of the component of the ICA analysis.

5.6. Concluding remarks

In the present work, we have clarified how neural networks implicated in mood regulation may influence executive control and perceptual processes. Our findings not only improve our understanding of the pathophysiological mechanisms underlying cognitive dysfunctions in MDD, but also shed new light on the interaction between cognition and mood regulation.

Taken together, our results demonstrate the usefulness of our attentional paradigm in the study of biological abnormalities that contribute to the cognitive deficits observed in various psychiatric disorders. Additionally it provides an original neuropsychological tool aiming at assessing the treatment efficacy for a variety of psychic disorders with top-down dysfunctions.

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7. Supplemental thesis

7.1. Electroconvulsive therapy in depression

7.1.1. The electroconvulsive therapy in 2008

From

Servais S, Ansseau M, Mikolajczak G, Desseilles M. L'électroconvulsivothérapie en 2008. Rev Med Liege,63(5-6), 2008, 404-410

Summary

Electroconvulsive therapy (formerly called sismotherapy, electronarcosis or shock therapy) is a therapeutic tool used in several psychiatric illnesses. It consists in the induction of a generalized convulsive seizure by a transcranial electric stimulation. If it is true that this tool continues to stigmatise the collective imagination in giving rise to dread and suspicion (considered by some people as a barbarian or obsolete therapy), it is however an effective (sometimes irreplaceable) and well tolerated treatment. Over the last decades, ECT has generated renewed interest in psychiatric therapy. It constitutes today the oldest biological therapeutic tool still in use in psychiatry.

L' ÉLECTROCONVULSIVOTHÉRAPIE EN 2008

S. SERVAIS (1), M. ANSSEAU (2), G. MIKOLAJCZAK (3), M. DESSEILLES (4)

RÉSUMÉ : L'électroconvulsivothérapie (anciennement dénommée sismothérapie, électronarcose ou électrochoc) est une technique thérapeutique utilisée dans certaines affections psychiatriques. Elle consiste en la réalisation d'une crise convulsive généralisée induite par le passage d'un courant électrique transcrânien. S'il est vrai que cette méthode continue de stigmatiser l'imaginaire collectif en suscitant effroi et méfiance (modèle de barbarie thérapeutique pour certains, traitement obsolète pour d'autres), elle se révèle, au contraire, être un traitement souvent très efficace, dans certains cas irremplaçable, et dans l'ensemble très bien toléré. Ainsi, ces dernières années ont vu un regain d'intérêt pour l'ECT. Elle constitue, aujourd'hui, la plus ancienne des somathérapies psychiatriques toujours en vigueur.

MOTS-CLÉS : *Psychiatrie - Electroconvulsivothérapie - Dépression - Trouble bipolaire - Schizophrénie*

THE ELECTROCONVULSIVE THERAPY IN 2008

SUMMARY : Electroconvulsive therapy (formerly called sismotherapy, electronarcosis or shock therapy) is a therapeutic tool used in several psychiatric illnesses. It consists in the induction of a generalized convulsive seizure by a transcranial electric stimulation. If it is true that this tool continues to stigmatise the collective imagination in giving rise to dread and suspicion (considered by some people as a barbarian or obsolete therapy), it is however an effective (sometimes irreplaceable) and well tolerated treatment. Over the last decades, ECT has generated renewed interest in psychiatric therapy. It constitutes today the oldest biological therapeutic tool still in use in psychiatry.

KEYWORDS : *Psychiatry - Electroconvulsive therapy - Depression - Bipolar disorder - Schizophrenia*

INTRODUCTION

L'électroconvulsivothérapie (ECT) est une technique thérapeutique ancienne. Elle est utilisée dans certaines indications précises. Après un bref historique, nous aborderons dans cette revue les indications et contre-indications, la prédiction de la réponse au traitement, les aspects pratiques de la technique ainsi que les complications rencontrées. Enfin, nous ferons le point sur les hypothèses anciennes et récentes concernant les mécanismes d'action de l'ECT.

HISTORIQUE

L'histoire de l'ECT (1-4) remonte au début des années 1930 et aux travaux d'un psychiatre hongrois, Lasdislas Joseph Von Meduna (5). Ceux-ci se basaient sur deux observations. La première était le constat (qui s'avèra être erroné par la suite) d'un antagonisme clinique entre schizophrénie et épilepsie. Ainsi, Von Meduna pensait-il avoir noté qu'un épileptique ne pouvait être schizo-phrène, et inversement. La seconde observation était la disparition d'un bon nombre de symptômes chez les malades mentaux qui présentaient une crise convulsive spontanée.

D'abord chimique (camphre, cardiazol), la convulsivothérapie devint ensuite électrique suite aux travaux de Cerletti et de Bini (6).

Utilisée dans un premier temps dans le traitement de troubles psychotiques dont la schizophrénie essentiellement, cette technique montra, par la suite, de meilleurs résultats dans les formes sévères de dépression.

Dans les années 1940, l'ECT connut des progrès importants en termes de confort du patient et de diminution des risques grâce à l'utilisation de l'anesthésie générale et l'introduction de la curarisation. L'anesthésie générale supprime l'anxiété anticipatoire liée au traitement (les malades n'assistent plus aux préparatifs) et permet de franchir sans troubles la phase post-critique. Le curare permet d'atténuer les contractions musculaires et réduit ainsi les complications mécaniques liées aux convulsions (luxations, fractures,…).

La convulsivothérapie a connu une très rapide extension de 1938 à 1960. Malheureusement, certains psychiatres pratiquèrent ce traitement sans se soucier réellement des indications, l'essentiel étant parfois même de maîtriser des malades indisciplinés ou agités. Au cours des années 1960-1970, on assista à une nette diminution de la pratique de la technique en raison de l'apparition de groupes de pression très actifs contre l'électrochoc, mais aussi de la découverte des antidépresseurs et des neuroleptiques. Néan-

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moins, depuis les années 1980 et aujourd'hui encore, l'ECT connaît un nouvel essor.

Indications

Des études contrôlées randomisées ont démontré l'efficacité thérapeutique et la rapidité d'action de l'ECT par rapport aux traitements de référence dans diverses affections psychiatriques telles que la dépression, la manie, la schizophrénie (par exemple, (7)). L'ECT peut être considérée comme un traitement de première intention lorsqu'il existe un risque vital à court terme, lorsque l'état de santé du patient est incompatible avec l'utilisation d'une autre forme de thérapeutique classique, voire, dans une indication appropriée, à la demande du patient. Elle est utilisée en seconde intention lorsque le traitement pharmacologique de référence est mal toléré ou n'est pas efficace. L'ECT peut également être utile dans des cas où le traitement médicamenteux actif en début de cure devient par la suite inefficace. L'électrochoc permet, en effet, dans ces situations, d'obtenir à nouveau une réponse au traitement (8).

Pathologies

Les différentes pathologies pour lesquelles l'ECT s'avère être efficace sont nombreuses (2-4) :

La dépression

L'ECT a une efficacité curative à court terme sur les dépressions majeures. Le taux de rémission après ce traitement est de 70-90%. L'électronarcose se révèle être le meilleur traitement de la dépression mélancolique. Elle est plus efficace que les autres méthodes thérapeutiques (médicaments antidépresseurs, psychothérapies,…). Malgré cela, en raison de sa moindre facilité d'utilisation, l'électrochoc tire ses indications des limites et des échecs de la chimiothérapie antidépressive. En effet, les antidépresseurs n'agissent qu'après un délai de quelques semaines, ce qui peut imposer les chocs face aux cas urgents. L'ECT est donc indiquée en cas de haut risque de suicide, de mélancolie délirante, stuporeuse ou agitée, de refus de nourriture ou de boissons, de résistance ou d'intolérance aux psychotropes. Les patients souffrant d'une dépression bipolaire réagissent tout aussi bien, voire même plus rapidement, que les déprimés unipolaires.

On note en outre une action rapide de l'ECT dans le traitement de la dépression. Par exemple, on observe une disparition rapide des idées suicidaires chez 40% des patients déprimés après une semaine de traitement (trois séances d'électrochocs) (7).

En l'absence de tout traitement ultérieur, la majorité des patients atteints de troubles de l'humeur connaissent une rechute dans les six mois suivant la cure. C'est pourquoi un traitement par antidépresseurs devrait être débuté le plus rapidement possible à l'issue de l'ECT. Une alternative est représentée par la réalisation d'ECT d'entretien chez les patients qui ne réagissent pas assez au traitement de maintenance par psychotropes ou ne tolèrent pas celui-ci.

La manie

Bien que l'ECT se soit révélée efficace chez des patients maniaques, le traitement médicamenteux est préféré en première intention (neuroleptiques et lithium). Par ailleurs, l'ECT est aussi efficace que le lithium comme traitement curatif de l'accès maniaque aigu chez des patients recevant des neuroleptiques et permet d'obtenir une diminution rapide de l'agitation et de l'exaltation. Elle trouve donc son indication dans le traitement d'un épisode maniaque en cas d'épuisement extrême, de manie délirante, confuse ou furieuse, ou tout autre état dans lequel la vie du patient est en danger et exige une réponse rapide ainsi qu'en cas de résistance ou d'intolérance aux psychotropes.

Le nombre de séances nécessaires pour obtenir une réponse dans la manie est souvent inférieur au nombre requis dans la dépression.

La schizophrénie

Le traitement de choix de la schizophrénie est la chimiothérapie neuroleptique. L'ECT est à envisager en seconde intention et toujours en association aux antipsychotiques pour le traitement des psychoses chimiorésistantes. Elle peut également être utilisée dans les troubles schizo-affectifs, avec un soulagement rapide des exacerbations symptomatiques schizophréniques. Elle est également efficace dans les syndromes paranoïdes aigus lorsque l'intensité de l'angoisse ou la thématique délirante font courir un risque de passage à l'acte et dans la catatonie, lorsque la symptomatologie thymique est au premier plan.

L'impression clinique est que la schizophrénie exige un nombre de séances plus important que les troubles dépressifs.

Le risque de rechutes après la cure est important. Dès lors, un traitement par antipsychotiques s'impose à l'issue de l'ECT.

LA CATATONIE

Il s'agit d'une inhibition psychomotrice qui se caractérise par un négativisme important et un ensemble de troubles moteurs tels que : inertie, mutisme, rigidité musculaire, des paroles et des gestes bizarres et stéréotypés. Bien que généralement rattachée aux troubles schizophréniques, la catatonie se manifeste également chez des patients souffrant de troubles thymiques. La catatonie réagit presque toujours favorablement à l'ECT. Néanmoins, un traitement par benzodiazépines doit d'abord être tenté avant d'opter pour l'électrochoc.

AUTRES AFFECTIONS

L'ECT s'avère efficace, mais ne constitue pas le traitement de premier choix dans de nombreuses affections telles que le Syndrome Neuroleptique Malin, le délirium, la maladie de Parkinson (efficacité transitoire sur les symptômes moteurs), l'épilepsie sévère, certains syndromes algiques (douleurs neuropathiques, fantômes,…), certains troubles moteurs tardifs (dyskinésie tardive,…) (9).

Affections psychiatriques ne constituant pas une indication pour l'ECT

L'ECT n'est pas indiquée dans certaines pathologies telles que, par exemple, les troubles liés à une substance, les troubles des conduites alimentaires, les troubles du contrôle des impulsions ainsi que les troubles de personnalité. L'ECT est également inefficace dans les démences et les troubles mnésiques purs. Une nuance doit néanmoins être apportée en ce qui concerne ce que l'on appelle les états de pseudo-démence dans lesquels les patients présentent un syndrome dépressif caractérisé se manifestant par une symptomatologie d'allure démentielle. Dans ce cas, l'ECT s'avère être efficace pour traiter la pathologie psychiatrique de fond et, donc, les différents symptômes qui en découlent. L'ECT constitue dans ce cas un traitement d'épreuve (10).

GROUPES PARTICULIERS

Trois populations particulières sont constituées par les enfants et les adolescents, les femmes enceintes et les personnes âgées (2-4).

ENFANTS ET ADOLESCENTS

Le recours à l'ECT chez les jeunes est exceptionnel. Les indications sont les mêmes que celles posées chez l'adulte, mais l'ECT n'est utilisée qu'en dernière intention, après échec des autres thérapeutiques disponibles. La technique doit évidemment être adaptée au seuil épileptogène généralement plus faible chez les enfants. On ne dispose actuellement pas encore de données scientifiques sur les effets secondaires potentiels, en particulier cognitifs, de l'ECT sur le cerveau en développement de l'enfant.

GROSSESSE

L'ECT peut être utilisée chez la femme enceinte et s'avère parfois être une thérapeutique de choix en raison de l'effet tératogène démontré de certains psychotropes. Une consultation gynécologique et un avis pré-anesthésie sont conseillés avant la réalisation de la cure. A partir du deuxième trimestre, une surveillance du fœtus (rythme cardiaque fœtal) est réalisée lors de chaque séance. En cas de grossesse à risque ou à l'approche du terme, la présence d'un obstétricien est souhaitable.

PERSONNES ÂGÉES

Les recommandations sont identiques à celles posées pour les adultes. Certains médicaments antidépresseurs sont moins bien tolérés chez les personnes âgées et l'ECT s'avère être une alternative thérapeutique efficace. L'intensité du stimulus doit être adaptée en raison d'une augmentation du seuil épileptogène avec l'âge. Les limitations dans l'utilisation de l'électrochoc pour cette population résident dans le fait qu'il y aurait un risque accru d'effets secondaires cognitifs.

PRÉDICTION DE LA RÉPONSE AU TRAITEMENT PAR ECT

Plusieurs échelles permettent de prévoir, en fonction de la symptomatologie que présente le patient, l'efficacité potentielle de la sismothérapie dans un syndrome dépressif caractérisé. Une d'entre elles, élaborée par Carney et coll. (1965), est encore utilisée en pratique clinique (11). Elle permet de calculer un score prédictif de réponse à l'ECT. Ainsi, une perte de poids importante, un réveil précoce, un morphotype pycnique dans la terminologie de Kretschmer (8), des idées délirantes somatiques, paranoïdes ou de référence sont des éléments de bon pronostic de réponse à l'électrochoc. Par contre l'anxiété, l'aggravation vespérale de la symptomatologie, l'apitoiement sur soi-même, l'hypochondrie et des traits de caractère hystériques sont prédictifs d'une réponse moins favorable à l'ECT.

Contre-indications

Il importe de distinguer, d'une part, les contre-indications liées au choc proprement dit et, d'autre part, celles liées à l'anesthésie ou à la curarisation (2-4).

Contre-indications liées au choc

Il n'existe aucune contre-indication absolue à l'ECT. Les contre-indications relatives les plus fréquentes concernent certaines affections cardio-vasculaires et neurologiques. Parmi les affections cardio-vasculaires, on trouve l'infarctus myocardique récent et l'insuffisance coronarienne sévère (risque d'aggravation), les anévrismes et les malformations vasculaires (risque de rupture et d'hémorragie), les maladies emboligènes telles que la phlébite aiguë et les arythmies (risque d'embolisation). Parmi les affections neurologiques, l'hypertension intracrânienne, l'AVC récent ischémique, mais surtout hémorragique, et les lésions expansives cérébrales peuvent être des contre-indications. Mentionnons toutefois que, récemment, une équipe de médecins a réalisé des électrochocs chez un patient présentant une dépression caractérisée résistante au traitement et un astrocytome anaplasique temporal gauche accompagné d'un oedème cérébral, avec dans ce cas, un traitement préalable par dexaméthasone parentérale (12).

D'autres affections s'associent à un certain risque et l'appréciation du rapport bénéfices / risques est ici judicieux : l'existence d'antécédents épileptiques (possibilité de déclenchement de crises après les chocs et dans certains cas, d'états de mal épileptique), les états déficitaires démentiels (confusion post-critique plus fréquente dans ces cas), le phéochromocytome (augmentation du risque de troubles graves du rythme et de la pression artérielle lors de l'ECT), l'hyperthyroïdie (induction possible d'une crise hyperthyroïdienne par l'ECT), le diabète (effet hyperglycémiant probable de la convulsion). Il existe également certaines contre-indications d'ordre médicamenteux (par exemple : les anticoagulants).

Contre-indications liées à l'anesthésie et à la curarisation

On y retrouve les risques classiques inhérents à l'anesthésie, d'ordre cardio-circulatoire, respiratoire et allergique. La myasthénie doit rendre la curarisation prudente.

Pratique de l'ECT

La pratique de l'ECT se décompose en plusieurs temps : les préalables, puis la technique proprement dite (2).

Préalables

Le patient doit être informé des raisons pour lesquelles on préconise l'électrochoc, des objectifs thérapeutiques et des risques iatrogènes. L'ECT ne peut être réalisée qu'à condition que le patient ait donné son consentement éclairé. En pratique, ce consentement éclairé ne peut pas toujours être obtenu (patients délirants, par exemple). Il convient alors de rencontrer la famille et d'exposer tant la problématique du malade que les risques et avantages de la technique proposée en vue d'obtenir leur consentement. Le bilan pré-thérapeutique comporte une anamnèse, un examen clinique, un examen biologique et un électrocardiogramme. Cela permet de détecter d'éventuelles affections existantes et d'évaluer les risques liés à l'anesthésie générale et aux convulsions. D'autres examens tels que l'EEG et le scanner cérébral semblent être superflus (sauf pour préciser une anomalie décelée lors de l'anamnèse ou de l'examen clinique).

Technique

En un premier temps, on procède à l'anesthésie générale et à la curarisation. Une fois celles-ci obtenues, l'électrochoc peut être délivré. Les seuls appareils d'ECT admis de nos jours sont ceux à courant bref pulsé, couplé à un enregistrement EEG. Les appareils anciens à courant sinusoïdal ne sont plus acceptables, car le type de stimulus qu'ils génèrent est clairement associé à un risque accru de troubles cognitifs secondaires et s'avère être moins efficace pour induire une crise. Il existe divers positionnements possibles des électrodes sur le crâne. Longtemps, l'application bitemporale a été préférée en raison de son efficacité. Néanmoins, les effets secondaires (essentiellement cognitifs) ne sont pas rares. Aujourd'hui, plusieurs études démontrent que l'électrochoc unilatéral, qui consiste en la stimulation de l'hémisphère non dominant, entraîne moins d'effets indésirables cognitifs et reste aussi efficace que le choc bitemporal lorsqu'on a recours à un stimulus d'une intensité légèrement supérieure. De même, avec une stimulation adéquate, une ECT bifrontale est aussi efficace qu'une ECT bitemporale. L'ECT bitemporale reste néanmoins indiquée en cas de trouble sévère ou mettant en danger la vie du patient, quand une rémission rapide prime sur le risque d'effet secondaire.

Le monitorage de la crise est essentiel. Il permet de juger de l'efficacité d'une ECT. Les convulsions doivent être généralisées bilatéralement, tant sur le plan moteur qu'EEG (d'où l'importance du monitorage des caractéristiques motrices et électroencéphalographiques de la crise). Une crise comitiale inférieure à 15 secondes s'avèrerait inefficace. Outre la durée de la crise, il importe de prendre en compte ses caractéristiques telles que l'amplitude, l'arrêt brutal de la crise,… L'absence de crise caractérisée (simple absence ou crise avortée) entraîne souvent une angoisse et une confusion importantes après la séance. Elle est souvent liée à une décharge insuffisante et il paraît préférable de réitérer aussitôt la stimulation.

On préconise en général deux séances par semaine, parfois trois en cas de troubles sévères ou lorsqu'une action rapide s'impose. Le nombre total de séances dépend du diagnostic et de la sévérité du trouble. En cas de dépression, une rémission est attendue après une moyenne de huit séances d'ECT bilatérale (13). Dans tous les cas, le traitement doit être poursuivi jusqu'à une rémission complète ou l'apparition d'un plateau dans le processus de rémission et l'absence de toute amélioration durant les trois dernières séances. Lorsque la rémission est obtenue, le traitement peut être interrompu, car le risque de récidive n'est aucunement réduit par des séances supplémentaires.

On peut noter la potentialisation pharmacologique de l'ECT par certains médicaments. Ainsi, la combinaison de l'ECT à des antidépresseurs ou à des antipsychotiques augmenterait l'efficacité clinique de l'ECT. Par contre, chez un patient candidat à une ECT, les anti-épileptiques et les benzodiazépines sont contre-indiqués à cause de leur activité anti-convulsivante.

Effets indésirables et complications

L'ECT est une thérapeutique fiable et les complications sont aujourd'hui très rares (2-4).

- Le risque vital est minime, comparable à celui de l'anesthésie générale et, par ailleurs, très inférieur au risque vital des états dépressifs avant les chocs.

- Au cours de la séance, les risques sont dus aux changements physiologiques induits par le stimulus électrique et la crise convulsive qui s'ensuit. Les effets cardio-circulatoires et cérébraux sont les plus importants. Au niveau cardio-vasculaire, le stimulus provoque, durant son administration et immédiatement après, une forte réponse parasympathique qui induit une bradycardie (voire, une asystolie) et une hypotension. Par contre, au moment où la crise se déclenche, cette réponse est suivie d'une stimulation orthosympathique responsable d'une tachycardie, d'une hypertension artérielle et, donc, d'une augmentation de la consommation myocardique en oxygène. Pendant ces deux phases, le patient risque d'être exposé à des arythmies passagères : troubles de conduction, bradyarythmies, asystolie durant la réponse parasympathique; tachycardie ventriculaire et supra-ventriculaire, extrasystoles ventriculaires, altérations des phases terminales et sous-décalage du segment ST pendant la crise orthosympathique. Ces anomalies s'observent presque uniquement chez des patients qui souffrent déjà d'affection cardio-circulatoire. Au niveau cérébral, le stimulus provoque une vasoconstriction de courte durée, suivie d'une augmentation de la vascularisation cérébrale et, donc, de la pression intra-crânienne. Cette élévation passagère de la pression intra-crânienne peut précipiter un engagement chez les patients atteints d'un processus expansif intra-crânien.

- Des crises comitiales prolongées, des états de mal épileptique ou des crises convulsives tardives (survenant parfois plusieurs heures après le choc) ont été rapportés, mais sont rares. On les observe essentiellement en cas d'abaissement du seuil épileptogène suite à différents facteurs tels que des médicaments (lithium, antidépresseurs,…) ou des troubles organiques (épilepsie, sevrage,…).

- Des troubles subjectifs banals peuvent s'observer après les chocs, comme des céphalées, des douleurs musculaires, des nausées.

- Les accidents psychiatriques sont essentiellement représentés par des états confusionnels apparaissant immédiatement après le choc. Ainsi, «l'agitation post-ictale» se manifeste-t-elle par une agitation motrice, une désorientation, un manque de réactivité. Le syndrome est généralement bénin et bref, mais il peut aussi, dans certains cas, évoluer vers le «délire post-ictal». Celui-ci correspond à un état de confusion extrême avec une baisse du niveau de conscience et une forte agitation motrice (dont des stéréotypies), un comportement agressif, voire des symptômes psychotiques tels que des idées délirantes et des hallucinations (2). Ces deux états s'accompagnent souvent d'une amnésie lacunaire. Généralement, ils se résolvent en 5 à 60 minutes. Il est rare qu'ils persistent plusieurs jours, voire quelques semaines, ce qui doit faire suspendre la cure. Parmi les autres complications psychiatriques, certains auteurs mentionnent des épisodes de manie (ou d'hypomanie) post-ictale. Le trouble se manifeste généralement dans les 24

heures qui suivent la séance d'ECT et dure en moyenne entre 2 et 4 jours.

- Les troubles secondaires cognitifs représentent l'inconvénient majeur des électrochocs. Ils sont essentiellement constitués de troubles mnésiques. Au moins 1 patient sur 3 se plaint de troubles subjectifs de la mémoire. Ces troubles sont de nature variable, de type amnésie antéro- et/ou rétrograde, mais sont le plus souvent transitoires. La mémoire antérograde semble plus touchée dans les jours qui suivent les chocs, mais le trouble disparaît en général. L'amnésie rétrograde peut être durable chez certains patients. La sévérité des troubles est liée au nombre total et à la fréquence des séances d'ECT, au positionnement des électrodes (sévérité plus marquée en cas de position bilatérale), au type de courant utilisé (courant sinusoïdal plus à risque) et à son intensité. On note, par ailleurs, que l'amélioration de l'état dépressif par la cure d'ECT s'accompagne d'une amélioration subjective de la mémoire.

Mécanisme d'action : hypothèses

Le mode d'action des électrochocs reste toujours mal connu et est l'objet de nombreuses recherches.

Plusieurs hypothèses explicatives se sont succédé au cours des décennies (14-16). Parmi celles-ci, on peut citer la théorie de «dissolution-reconstruction de la conscience» proposée dans les années 1940-1950, alors que l'ECT était en plein essor. Elle se fondait sur les principes jacksoniens (H. Jackson, neurologue anglais du 19ème siècle). Selon ceux-ci, les différentes fonctions du système nerveux, surtout celles qui touchent au psychisme, résulteraient d'un lent processus de construction progressive grâce auquel se créeraient des associations entre des territoires cérébraux et une véritable hiérarchisation des fonctions. Sous l'influence de causes pathologiques diverses, les fonctions cérébrales les plus labiles (que sont les fonctions les plus complexes et les plus récemment acquises) se désagrégeraient les premières, tandis que d'autres (les plus automatiques) résisteraient. Ainsi, selon ces théories, émergeraient les pathologies mentales. L'électrochoc, en ramenant momentanément à zéro le psychisme du malade, réaliserait une dissolution des fonctions mentales, comparable à l'écroulement d'une maison réduite à des moellons épars. Lorsque cesse le «coma», survient une reconstruction de l'édifice mental avec parfois un retour à une organisation normale.

Aujourd'hui, sans doute suite au changement de paradigme dans la conception des pathologies mentales avec l'émergence des théories neuro-biochimiques, les recherches s'intéressent principalement aux modifications biologiques observées au cours des électrochocs (1). Il a été mis en évidence que l'ECT agit sur différents neurotransmetteurs dont la noradrénaline, la sérotonine, la dopamine et l'acétylcholine mais également sur l'activité opioïde et l'activité GABA (acide gamma-aminobutyrique). Durant la crise généralisée, on observe une augmentation des taux plasmatiques de prolactine, d'hormone adrénocorticotrope (ACTH), de cortisol, d'ocytocine, de vasopressine, de bêta-endorphine et, de manière moins consistante, d'hormone de croissance.

Des études par tomographie à émission de positons ont produit des résultats équivoques. Cependant, une diminution du métabolisme dans les régions frontale, préfrontale et pariétale a été mise en évidence à plusieurs reprises (1). Récemment, une étude en imagerie par résonance magnétique fonctionnelle a montré que l'ECT diminuait l'activité dans la région subgénuale du cortex cingulaire antérieur gauche chez les patients déprimés (17). Cette région constitue une région clé dans le circuit cérébral de la dépression. De plus, une repousse des fibres moussues de l'hippocampe a également été observée (1).

Par ailleurs, il ne faut pas négliger les facteurs de régression physique et psychique qu'entraîne l'utilisation de l'ECT (anesthésie, ...) et le rôle des soignants. Ces éléments peuvent parfois intervenir dans le succès thérapeutique de la technique.

Conclusion

L'électroconvulsivothérapie est une technique applicable en première ou en seconde intention dans de nombreux troubles psychiatriques ou neurologiques. Elle se fait actuellement sous sédation et curarisation afin de limiter les risques inhérents à l'induction de la crise d'épilepsie lors du passage du courant électrique transcrânien. Les contre-indications de l'ECT ne sont que relatives. Cependant, le risque classique inhérent à l'anesthésie est à prendre en considération. Le peu de complications, la fiabilité et une connaissance (tant au niveau de la technique qu'au niveau des mécanismes biologiques impliqués) de plus en plus précise en font un outil thérapeutique à ne pas négliger.

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7.1.2. Therapy for Depression in a Patient With an Intracranial Arachnoid Cyst.

From

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Summary

Electroconvulsive therapy (ECT) has been frequently considered relatively contraindicated in patients with space-occupying lesions in the brain. After the 7 cases available in the literature, we describe the safe use of ECT in a depressive patient with arachnoid cyst. We provide a comprehensive review on this clinical association, and we conclude that even if the few data available are reassuring, careful neurological evaluation before the ECT treatment is indicated.

Electroconvulsive Therapy for Depression in a Patient With an Intracranial Arachnoid Cyst

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Abstract: Electroconvulsive therapy (ECT) has been frequently considered relatively contraindicated in patients with space-occupying lesions in the brain. After the 7 cases available in the literature, we describe the safe use of ECT in a depressive patient with arachnoid cyst. We provide a comprehensive review on this clinical association, and we conclude that even if the few data available are reassuring, careful neurological evaluation before the ECT treatment is indicated.

Key Words: electroconvulsive therapy, arachnoid cyst, intracranial lesion

(*J ECT* 2008;00:00–00)

Electroconvulsive therapy (ECT) is a psychiatric treatment in which seizures are induced with electricity for therapeutic effect. Today, ECT is most often used as a treatment for severe major depression which has not responded to other treatments. Although it is a relative contraindication, the possibility of increased intracranial pressure must be carefully assessed.

After the early case of a patient with an intracranial arachnoid cyst who was successfully treated with ECT[1] and the recent case series of ECT in patients with arachnoid cysts,[2] we report here an additional case and summarize the state of knowledge on this topic.

We describe a man with a major depression and an asymptomatic arachnoid cyst of the right anterior temporal and the right lateral prefrontal lobes who was successfully treated with ECT. Structural brain magnetic resonance imaging (MRI) carried out twice (at 1-year interval) before the ECT did not reveal any evolution in the cyst and allowed the use of ECT.

CASE REPORT

M.A. was a 58-year-old man admitted in the Department of Psychiatry with a diagnosis of recurrent major depression, according to the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision*, of 4-month duration that had been unresponsive to antidepressant medication. The patient's general medical examination was normal, and a detailed neurological examination was nonfocal.

He had experienced his first depressive episode 20 years before admission and was successfully treated with clomipramine. Clomipramine was retried again recently for approximately 3 months, with no effect at all. The patient was eager to undergo ECT.

Previous structural brain MRI performed for depression assessment revealed an asymptomatic arachnoid cyst of the right anterior temporal and the right lateral prefrontal (dimension, 7.6 × 4.1 × 8.1 cm) (Fig. 1). Moreover, MRI was carried out twice (at 1-year interval) before the ECT and did not reveal any evolution in the cyst and allowed the use of ECT.

On admission, the patient exhibited a profoundly sad mood with diurnal variation. He had morbid ideas, feelings of hopelessness and helplessness. Moreover, psychomotor retardation, social withdrawal, decreased libido, and anorexia with a 10-lb weight loss were present. He woke up early in the morning, and his sleeping time was decreased. His score on the Folstein Mini-Mental Status Examination was 30. His score on the Hamilton Depression Scale was 27.

After providing informed consent, M.A. underwent a course of 7 brief pulse bilateral (temporal) ECT treatments, administered 3 times a week in a specialized treatment suite (pulse width, 1 millisecond; frequency, 60 Hz; duration, 3 seconds; current, 800 mA; charge, 288 mC).

Anesthesia included 100% oxygen by mask, 2 mg/kg propofol 1%, 4 mL lidocaine 1%, and 1 mg/kg succinylcholine chloride 5%.

M.A. tolerated the ECT treatment and did not experience any major systemic side effects. He typically achieved complete recovery of his pretreatment orientation within 1 hour of the ECT treatment and denied any persistent memory disturbance. After 3 ECT treatments, the depressive symptoms improved and fully remitted after 5 ECT treatments.

DISCUSSION

Arachnoid cysts are described as benign, congenital, intra-arachnoidal space–occupying lesions that are filled with clear cerebrospinal fluid.[3] Not communicating with the ventricular system and modeled on surrounding structures, they are common and represent 1% of all intracranial masses.[3] The incidence tends to be higher in men. Most arachnoid cysts are supratentorial and approximately half are found in the middle cranial fossa, anterior to the temporal lobes.

Intriguingly, the precise mechanism for the formation of arachnoid cysts is not yet known. Some hypotheses have been proposed: "splitting" or diverticulum of the developing arachnoid, active fluid secretion by the cyst wall, trauma, mastoiditis, meningitis, and subarachnoid hemorrhage.[3]

Of major concern for our clinical issue, arachnoid cysts seem to be generally stable over time. However, there have

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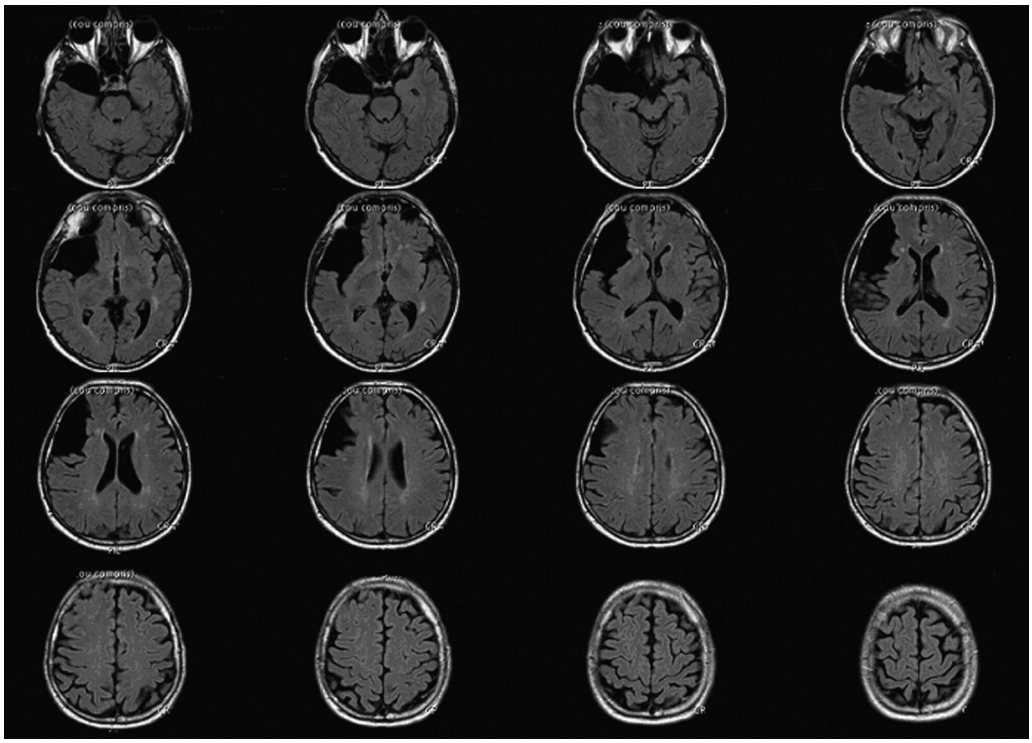

FIGURE 1. Structural MRI showing an arachnoid cyst of the right anterior temporal and the right lateral prefrontal cortex (dimension, 7.6 × 4.1 cm in the axial plane and 8.1 cm in the coronal axis).

been reported cases with sudden or progressive enlargement, as well as spontaneous resolution.[3] Moreover, the size of the cyst is sometimes small and not preoccupying or sometimes compresses the underlying brain.[3]

According to Osborn and Preece,[3] "The best diagnostic clue for arachnoid cyst is a sharply demarcated extra-axial cyst that can displace or deform the adjacent brain. Scalloping of the adjacent calvarium is often seen. The classic arachnoid cyst has no identifiable internal architecture and does not enhance. The cyst typically has the same signal intensity as cerebrospinal fluid at all sequences. Occasionally, however, hemorrhage, high protein content, or lack of flow within the cyst may complicate the MR appearance. Arachnoid cysts have an increased prevalence of coexisting subdural hematomas, especially when they occur in the middle cranial fossa."

In addition to the pathophysiology of arachnoid cysts, this case report raises several considerations not only about pathophysiological mechanisms of depression but also about the action and side effects of ECT.

First, to what extent is the arachnoid cyst involved in the pathophysiology of depression? Data on this topic are scarce, and a general conclusion cannot be proposed. Second, to date, there is no consensus about whether there is a hemisphere lateralization in primary and secondary depression. Indeed, as Mayberg[4] stated for depression in lesion-deficit studies, there is no clear consensus as to whether the left or right hemisphere is dominant in the expression of depressive symptoms. She observed in reports of patients with traumatic frontal lobe injury a high correlation between affective disturbances and right hemisphere pathology. In addition, studies in stroke suggest that left-sided lesions of both frontal cortex and the basal ganglia are more likely to result in depressive symptoms than right lesions.[4] Moreover, as for idiopathic depression: "Unlike the lesion-deficit literature, most of the studies report bilateral rather than left-lateralized abnormalities, although asymmetries have been reported."[4] Third, our patient had an arachnoid cyst of the right anterior temporal and right lateral prefrontal cortex. These regions are involved in the pathophysiological network of depression.[4] Thus, it can be hypothesized that alteration of these areas can change the mood.

Second, because the conduction of electrical current from the ECT device may be sensitive to an alteration in brain structure, as in this patient, it may logically be hypothesized that the efficacy of the therapy may be diminished. Nevertheless, congruent with previous results,[1,2] ECT was clinically effective in this patient, as has been described in other patients with organic brain disease.[5]

Third, the side effects of ECT in patients with space-occupying lesions are a long-standing debate because intracranial pressure increases during the treatment. Space-occupying lesions within the brain are classically considered as relative contraindications to ECT.[6] Nevertheless, several clinical reports suggest that ECT may be safely given to patients with these lesions so long as intracranial pressure is not increased. In fact, the contention that ECT is contraindicated for patients who have a space-occupying lesion derives from several observations that the increase in intracranial pressure occurring during ECT treatment is amplified by the space-occupying lesion. In consequence, noncardiogenic pulmonary edema, cerebral edema, brain

hemorrhage, and neurological deterioration and death might be precipitated.[5] Maltbie et al[7] confirmed that ECT was contraindicated in patients with intracranial tumor, but it may be permissible in patients with space-occupying lesions if the treatment is strongly indicated.[5] For Abrams,[8] numerous successful prospective administrations of ECT to patients with known brain tumors (mostly meningiomas) largely demonstrate the safety of this procedure when it is performed cautiously and with foreknowledge.

The literature insists on the imperative necessity to check for the presence of increased intracranial pressure and absence of evolution of brain lesions. Intriguingly, the majority of prospective administrations of ECT to patients with brain tumor (mostly meningiomas) were unlikely to have caused increased intracranial pressure.[8] Moreover, administration of ECT in the presence of a brain tumor, accompanied by increased intracranial pressure, has been shown to be safe and effective after 1-week treatment with parenteral dexamethasone.[9]

Our patient underwent MRI twice, and the results did not show any sign of evolution or displacement of midline structures. Moreover, he did not show any disorientation or short-term memory performance decline after ECT treatment. Congruent with the findings of Escalona et al,[1] our findings show that our patient was not at increased risk for adverse cognitive effects from ECT.

In conclusion, this is an additional case of ECT for depression in a patient with an arachnoid cyst. Despite reassuring data of the 8 cases available in the literature, more systematic research is needed to establish more clearly the risk of ECT in this rare population. Moreover, systematic structural brain imaging before ECT could probably reveal some neurological abnormalities that would have been ignored otherwise.

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7.2. A prominent role for amygdaloid complexes in the Variability in Heart Rate (VHR) during Rapid Eye Movement (REM) sleep relative to wakefulness.

From

Desseilles M, Dang-Vu T, Laureys S, Peigneux P, Degueldre C, Phillips C, Maquet P. A prominent role for amygdaloid complexes in the Variability in Heart Rate (VHR) during Rapid Eye Movement (REM) sleep relative to wakefulness; Neuroimage, 32(3), 2006, 1008-1015

Summary

Rapid eye movement sleep (REMS) is associated with intense neuronal activity, rapid eye movements, muscular atonia and dreaming. Another important feature in REMS is the instability in autonomic, especially in cardiovascular regulation. The neural mechanisms underpinning the variability in heart rate (VHR) during REMS are not known in detail, especially in humans. During wakefulness, the right insula has frequently been reported as involved in cardiovascular regulation but this might not be the case during REMS. We aimed at characterizing the neural correlates of VHR during REMS as compared to wakefulness and to slow wave sleep (SWS), the other main component of human sleep, in normal young adults, based on the statistical analysis of a set of H2 15O positron emission tomography (PET) sleep data acquired during SWS, REMS and wakefulness. The results showed that VHR correlated more tightly during REMS than during wakefulness with the rCBF in the right amygdaloid complex. Moreover, we assessed whether functional relationships between amygdala and any brain area changed depending the state of vigilance. Only the activity within in the insula was found to covary with the amygdala, significantly more tightly during wakefulness than during REMS in relation to the VHR. The functional connectivity between the amygdala and the insular cortex, two brain areas involved in cardiovascular regulation, differs significantly in REMS as compared to wakefulness. This suggests a functional reorganization of central cardiovascular regulation during REMS.

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A prominent role for amygdaloid complexes in the Variability in Heart Rate (VHR) during Rapid Eye Movement (REM) sleep relative to wakefulness

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Rapid eye movement sleep (REMS) is associated with intense neuronal activity, rapid eye movements, muscular atonia and dreaming. Another important feature in REMS is the instability in autonomic, especially in cardiovascular regulation. The neural mechanisms underpinning the variability in heart rate (VHR) during REMS are not known in detail, especially in humans. During wakefulness, the right insula has frequently been reported as involved in cardiovascular regulation but this might not be the case during REMS. We aimed at characterizing the neural correlates of VHR during REMS as compared to wakefulness and to slow wave sleep (SWS), the other main component of human sleep, in normal young adults, based on the statistical analysis of a set of $H_2{}^{15}O$ positron emission tomography (PET) sleep data acquired during SWS, REMS and wakefulness. The results showed that VHR correlated more tightly during REMS than during wakefulness with the rCBF in the right amygdaloid complex. Moreover, we assessed whether functional relationships between amygdala and any brain area changed depending the state of vigilance. Only the activity within in the insula was found to covary with the amygdala, significantly more tightly during wakefulness than during REMS in relation to the VHR. The functional connectivity between the amygdala and the insular cortex, two brain areas involved in cardiovascular regulation, differs significantly in REMS as compared to wakefulness. This suggests a functional reorganization of central cardiovascular regulation during REMS.

Keywords: REM sleep; Heart rate; Functional neuroimaging; Positron emission tomography; Functional connectivity; Amygdala; Insula

Introduction

Rapid eye movement sleep (REMS) is characterized by low-amplitude, relatively high-frequency electroencephalographic (EEG) rhythms, rapid eye movements and a complete muscular atonia interrupted by short muscular twitches. In addition, during REMS, neurovegetative regulation exhibits distinct features that are observed neither during wakefulness nor during non-REM sleep (NREMS). A striking example concerns thermoregulation. During REMS, a warm thermal load does not induce skin vasodilatation whereas a cold thermal load does not elicit any cutaneous vasoconstriction (Parmeggiani, 1980). These findings suggest that REMS is characterized by an "open-loop" mode of regulation, which does not rely on homeostatic feedback loops as strictly as during wakefulness or NREMS (Parmeggiani, 1985). During these 2 states, "closed-loop operations of automatic control mechanisms […] warrant an efficient and steady regulation of [autonomic] functions" (Parmeggiani, 1985). These rules presumably apply also to other neurovegetative systems. Accordingly, respiratory and heart rates are known to be much more variable during REMS than during NREMS or wakefulness (Orem and Keeling, 1980).

Although cardiovascular regulation is understood in detail, the cerebral correlates of VHR have been characterized only recently, and exclusively during wakefulness. In humans, VHR has primarily been related to the activity in the insular cortex. Intraoperative electrical stimulation of the insula elicits changes in heart rate and blood pressure (Oppenheimer et al., 1992). In normal subjects, functional neuroimaging studies showed that in response to physical exercise (Williamson et al., 1997, 1999) and mental stressor tasks (Critchley et al., 2000), both associated with significantly increased heart rate, the activity in both insula covaried with heart rate.

Heart rate regulation changes during sleep and has also been related to forebrain activity, as assessed by EEG recordings. For

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instance, EEG power spectral density relates to VHR indices (Otzenberger et al., 1997, 1998; Ehrhart et al., 2000; Brandenberger et al., 2001; Ako et al., 2003). However, the cerebral correlates of VHR during sleep needs to be further characterized, anatomically refined and described separately for NREMS and REMS. Indeed, heart rate regulation differs between these 2 types of sleep due to predominant parasympathetic and sympathetic drives, respectively (Brandenberger, 2005). In this paper, we were particularly interested in characterizing the cerebral correlates of VHR during REMS because of the intriguing autonomic control described in this stage of sleep. We hypothesized that during REMS, heart rate regulation involves the amygdala. This structure is one of the most active brain areas during REMS in man (Maquet et al., 1996). Due to its anatomical connectivity, it is in good position to influence key regions involved in cardiovascular regulation like the hypothalamus and the parabrachial complex in the brainstem (Hopkins and Holstege, 1978). The paraventricular nucleus of the hypothalamus is a key site for regulating autonomic activities such as blood pressure and heart rate (Coote, 1995; Xia and Krukoff, 2003). The parabrachial complex is known to be implied in the regulation of sympathetic activity and heart rate (Henderson et al., 2002).

We examined the cerebral correlates of VHR in REMS, as compared to wakefulness and SWS, in humans, using positron emission tomography (PET). To do so, we conducted a retrospective analysis on a set of PET scans acquired in 13 non-sleep deprived normal participants during SWS, REMS or wakefulness with simultaneous electroencephalographic and electrocardiographic recordings. We determined the brain areas where the regional blood flow (CBF) was more tightly related to the VHR during REMS than during wakefulness, during SWS than during wakefulness or during SWS than during REMS. We focused on a set of target areas identified as critical in autonomous regulation during wakefulness: the insula (Cechetto and Saper, 1987; Oppenheimer et al., 1992; Oppenheimer, 1994; Corfield et al., 1995; Oppenheimer et al., 1996; Williamson et al., 1997; Critchley et al., 2000), the amygdala (Orem and Keeling, 1980; Sei and Morita, 1996; Critchley et al., 2000), the hypothalamus (paraventricular nucleus) (Hopkins and Holstege, 1978; Coote, 1995; Xia and Krukoff, 2003) and the midbrain (Herbert et al., 1990; Chamberlin and Saper, 1992; Henderson et al., 2002). Other areas more occasionally implicated in heart rate regulation were also considered as potential regions of interest: the hippocampus (Rowe et al., 1999; Ribeiro et al., 2002; Pedemonte et al., 2003), the anterior cingulate cortex (Buchanan et al., 1985; Neafsey, 1990), the ventromedial prefrontal cortex (Buchanan et al., 1985; Neafsey, 1990), the motor cortex (Critchley et al., 2000), the neostriatum (Delgado, 1960; Bradley et al., 1987, 1991; Lin and Yang, 1994; Critchley et al., 2000), the cerebellum (Delgado, 1960; Bradley et al., 1987, 1991; Lin and Yang, 1994; Critchley et al., 2000) and the brainstem areas of the pons and medulla (Willette et al., 1984; Allen and Cechetto, 1992; Critchley et al., 2000).

Methods

Subjects and experimental protocol

Data were obtained from previous sleep studies conducted in our center using the $H_2{}^{15}O$ infusion method (Maquet et al., 2000; Peigneux et al., 2003). All subjects were young, healthy, right-handed and male volunteers ($n=13$; age range 20–30 years) who gave their informed consent to participate in studies approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. All had normal sinus rhythm and regular sleep–wake habits. None had any medical, surgical or psychiatric history; none was taking medication. Each subject spent three consecutive nights in the PET scanner at usual sleep time. Polysomnography monitoring during the first two nights allowed us to check for any abnormality in sleep (insomnia, sleep fragmentation, REMS onset, etc.) and accustomed participants to the experimental setting. Participants were selected for the third night if they could maintain 20 min of continuous stage 2, stages 3–4 of NREMS and REMS on both habituation nights. During the third night, PET scans were performed both during various stages of sleep when polysomnography showed steady characteristic sleep patterns and during waking at rest with eyes closed in complete darkness. During waking scans, the subjects had to stay still, eyes closed.

At least two waking, two stage 2, two stages 3–4 and two REMS scans were obtained in all subjects. In the present manuscript, we used 97 PET scans (30 during W, 29 during SWS and 38 during REMS) from 13 subjects who all had high-quality electrocardiographic (EKG) recordings in all the 3 main states of vigilance (wakefulness, NREMS, REMS). The same subjects were used for the delta analysis published by Dang-Vu et al. (2005).

Sleep analysis

Polysomnography was performed with a Synamp (Neuroscan, NeuroSoft Inc.K, Sterling, Virginia) system at 500 Hz or 1000 Hz, with a band width of 0.15–100 Hz. EEG on (at least) C3–A2 and C4–A1 derivations were recorded. In all cases, vertical and horizontal electrooculograms, chin electromyographic derivation and chest electrocardiogram were recorded on bipolar montage. Sleep scoring followed standard international criteria (Rechtschaffen and Kales, 1968).

Heart rate analysis

The analysis was performed on the 90-s recordings obtained during each PET scan. The EKG was visually checked in order to discard any period containing movement, muscle or breathing artefact. A template of the QRS complex was generated by averaging the QRS complexes over the whole 90 s of recording. A coefficient of correlation was computed at each time point between the template and the actual recording using a sliding window. Correlation coefficient above 0.80 was shown to reliably identify the occurrence of a QRS complex. This threshold was used to detect R events. RR intervals, from these tagged events were then computed, generating a new time series covering the whole 90-s scanning period. The variability in heart rate (VHR) was simply estimated as the standard deviation of the duration of RR intervals, as it has been described as a valid measure of the VHR (Malik, 1996).

PET data acquisitions

PET data were acquired on a Siemens CTI 951 R 16/31 scanner in three-dimensional mode. The head of the subjects was stabilized by a thermoplastic face mask secured to the head holder (Truscan Imaging, Annapolis, Maryland), and a venous catheter was inserted in a left antebrachial vein. First, a 20-min transmission scan was acquired for attenuation correction using three rotating

sources of 68-Ge. Then, when polysomnography showed stable characteristic patterns, rCBF, taken as a marker of local neuronal activity (Jueptner and Weiller, 1995), was qualitatively estimated during a maximum of 12 emission scans per subject using the $H_2{}^{15}O$ technique. Each scan consisted of two frames: a 30-s background frame and a 90-s acquisition frame. The slow intravenous water ($H_2{}^{15}O$) infusion began 10 s before the second frame. Six millicuries (mCi) equivalent to 222 megaBecquerel (MBq) was injected for each scan, in 5 cubic centimeters (cc) saline, over a period of 20 s, starting 10 s before the onsets of the active frame. The infusion was totally automated in order not to disturb the subject during the scanning period. Data were reconstructed using a Hanning filter (cutoff frequency: 0.5 cycle/pixel) and corrected for attenuation and background activity.

Brain imaging data analysis

PET data were analyzed using Statistical Parametric Mapping (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB® (The MathWorks, Inc., Natick, Massachusetts). For each subject, all scans were realigned to the first scan. PET images were then normalized to a standard template within the Montreal Neurological Institute (MNI) space (Frackowiak et al., 1997). Finally, normalized PET images were smoothed using a Gaussian Kernel of 16 millimeters full width at half maximum.

Data were analyzed using a general linear model, in a single step conforming to a fixed effects analysis. This analysis does not allow to partition variance in within- and between-subject components. The results therefore do not pertain to the population at large but only to the studied sample.

The design matrix included 2 regressors: the main effect of the condition (state of vigilance: REMS, SWS or Wakefulness) and the condition (state of vigilance) by VHR interaction.

Global flow adjustment was performed by proportional scaling. Areas of significant changes were determined using linear contrasts. The contrast of interest estimated the condition and VHR effects, as well as the interactions between the condition and VHR (REMS versus SWS; SWS versus wakefulness; REMS versus wakefulness). Each of these contrasts identified the brain areas where the regional activity is more tightly related to VHR during the first than the second state of vigilance.

A psychophysiological interaction was also analyzed. This analysis assessed whether the relationship between the activity in the reference region identified (i.e., the amygdala, see Results section) and other distant areas depends on the state of vigilance (Wakefulness or REMS) (Friston et al., 1997). A new linear model was constructed using three regressors. The first regressor was the condition effect (REMS versus wakefulness). The second regressor was the activity in the reference area (amygdala, coordinates: 36, 8, −20 mm). The third regressor represented the interaction of interest between the first (psychological) and second (physiological) regressor.

In both analyses, the resulting set of voxel values for the contrast of interest constituted a map of the t statistic {SPM(T)}, thresholded at $p<0.001$ ($Z\geq3.09$). Corrections for multiple comparisons were then performed at the voxel level over the entire brain volume or over small volumes (Small Volume Correction {SVC} with spheres of 10 mm) centered on coordinates previously published in the literature (Critchley et al., 2002a, 2002b; see also introduction).

Results

Statistical data

A repeated measure ANOVA was conduced with stage of vigilance (SWS versus REMS versus wakefulness) as within-subject factor and VHR as dependent variable. Results showed a trend for a difference between conditions ($F(2,24)=2{,}4006$, $p=0.1121$). Planned comparisons compared REMS with SWS, SWS with wakefulness and REMS with wakefulness. VHR tended to differ between REMS and SWS ($p=0.1043$), as well as between SWS and wakefulness ($p=0.958025$). The only significant difference was detected between REMS and wakefulness ($p=0.03371$).

Imaging data

Difference in the distribution of cerebral activity between wakefulness and REMS

The main effect of condition (state of vigilance: wakefulness or REMS) is reported to establish the consistency of the present findings with previous studies (Maquet et al., 1996; Braun et al., 1997; Maquet, 2000; Maquet et al., 2000; Peigneux et al., 2003, 2004) and will not be discussed further.

Regional CBF was significantly larger during REMS than during wakefulness in the occipital area, in the lateral and mesiotemporal regions, in the anterior cingulate and in the precentral cortex (Table 1). Conversely, higher activity during wakefulness (versus REMS) was found bilaterally in the dorsolateral prefrontal and parietal cortices and in the posterior cingulate cortex (Table 2).

Difference in the distribution of cerebral activity between wakefulness and SWS

The main effect of condition (state of vigilance: wakefulness or SWS) is reported to establish the consistency of the present findings with previous studies (see, for instance, Maquet, 2000) and will not be discussed further.

Table 1
Increased brain activity during REMS compared to wakefulness

Area	x	y	z	Z score	P
Left lingual gyrus	−28	−64	−2	7.25	<0.001
Right lingual gyrus	28	−62	0	6.98	<0.001
Left cuneus	−16	−90	20	6.19	<0.001
Right cuneus	6	−82	16	6.12	<0.001
Left precuneus	−20	−48	54	6.54	<0.001
Right anterior cingulate cortex	6	−2	40	6.34	<0.001
Left anterior cingulate cortex	−12	−10	42	5.39	0.001
Right medial temporal gyrus	66	−14	−2	5.75	<0.001
Right superior temporal gyrus	−62	−16	2	5.65	<0.001
Right precentral gyrus	38	−20	54	5.28	0.001
Left amygdala	−30	−2	−18	4.50	0.042

Localization and statistical results concerning the local maxima of the brain areas where the activity is larger during REMS as compared to wakefulness. Coordinates are defined in the stereotatic MNI space, relative to anterior commissure. x represents the lateral distance from midline (positive, right); y is the anteroposterior distance from anterior commissure (positive: anterior); z represents the rostrocaudal distance from the bicommissural plane (positive: rostral). These results survive a correction for multiple comparisons over the entire brain volume at a threshold of corrected $P<0.05$.

Table 2
Increased brain activity during Wakefulness compared to REMS

Area	x	y	z	Z score	P
Right medial frontal gyrus	44	50	−2	>10	<0.001
Right superior frontal gyrus	42	52	8	>10	<0.001
Right inferior frontal gyrus	54	16	14	7.01	<0.001
Right precentral gyrus	54	12	46	6.51	<0.001
Left medial frontal gyrus	−46	50	4	>10	<0.001
Left inferior parietal gyrus	−44	−56	38	6.14	<0.001
Left cingulate gyrus	−2	−34	26	6.85	<0.001

Localization and statistical results concerning the local maxima of the brain areas where the activity is larger during wakefulness as compared to REMS. Coordinates and inferences are determined as in Table 1.

Regional CBF was significantly deactivated during SWS than during wakefulness in the thalami, orbital frontal cortex, precuneus and in the parietal cortex (Table 3).

Effect of VHR on CBF

We did not identify any area where the regional CBF was significantly related to the VHR irrespective of the state of vigilance (wakefulness or REMS or SWS).

Condition (REMS versus Wakefulness) by VHR interaction

The activity in the lateral aspect of the right amygdala (coordinates: 36, 8, −20) was shown to be related to VHR more tightly during REMS than in wakefulness (Z=3.11, p_{SVC}=0.028, reference coordinates taken in Critchley et al., 2002a, 2002b; Fig. 2). Due to the poor spatial resolution of PET scanning, it is not possible to further specify this area that probably encompasses part of the extended amygdala (Alheid and Heimer, 1988) (Fig. 1).

Psychophysiological interaction

Psychophysiological interaction assessed whether functional relationships between amygdala and any brain area were modulated by the state of vigilance. The psychophysiological interaction using the amygdala as reference region (x=36, y=8, z=−20) identified a single area in the anterior insular cortex (Fig. 2A). This result indicates that the anterior insula is connected more tightly with the amygdala during wakefulness than during the REMS (Z=3.11, p_{SVC}=0.028, reference coordinates taken in Critchley et al., 2000) (Fig. 2B).

Insular cortex is involved in central processing of various sensory modalities. It is why we chose specifically for the small volume correction of our interest region the coordinates of a paper that investigates specifically the cardiovascular regulation to insure that the region is implicated in this physiological function (Critchley et al., 2000).

Table 3
Decreased brain activity during SWS compared to wakefulness

Area	x	y	z	Z score	P
Orbital frontal cortex	26	38	−28	>10	<0.001
Orbital frontal cortex	−22	40	−26	>10	<0.001
Left thalamus	−8	10	−2	>10	<0.001
Parietal cortex	42	−76	48	6.23	<0.001
Parietal cortex	−46	−62	48	7.48	<0.001
Precuneus	−2	−82	52	6.92	<0.001

Localization and statistical results concerning the local maxima of the brain areas where the activity is smaller during SWS as compared to wakefulness. Coordinates and inferences are determined as in Table 1.

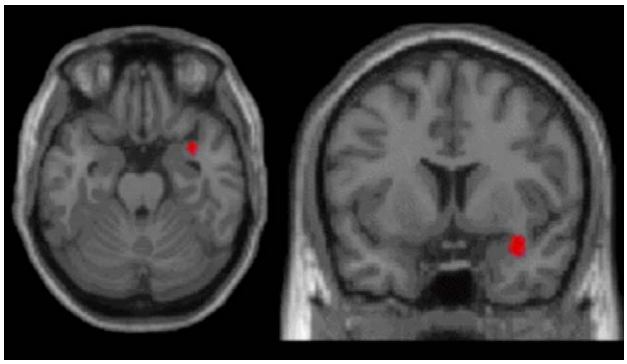

Fig. 1. The activity in the lateral aspect of the right amygdala (coordinates: 36, 8, −20) is more tightly related to VHR during REMS than during wakefulness (Z=3.11, p_{SVC}=0.028). The functional results are displayed over an individual MRI scan normalized to the MNI space in transverse (left panel), frontal (right panel) and sagittal planes. The functional results are displayed at p<0.001, uncorrected.

Condition (SWS versus wakefulness) by VHR interaction, condition (wakefulness versus SWS) by VHR interaction, condition (REMS versus SWS) by VHR interaction and condition (SWS versus REMS) by VHR interaction

These analyses did not identify a single significant change in regional cerebral blood flow ($p_{uncorrected}$=0.001).

Discussion

Methodological issues

We used the standard deviation of heart rate as a measure of VHR during the 90-s duration of each PET scan. This parameter has been proposed as a valid estimation of VHR (Malik, 1996).

Alternatively, VHR can be estimated in the frequency domain. Two components can be isolated in a spectrum calculated from short-term recording: low-frequency (LF) and high-frequency (HF) components. The distribution of the power and the central frequency of LF and HF may vary in relation to changes in autonomous modulations of heart period (Malik, 1996). HF power would reflect parasympathetic activity, whereas LF power would primarily reflect a mixed sympathetic and parasympathetic influence (Malik, 1996). Due to methodological constraints of PET measurements, the time series recorded during the 90-s scans were too short to obtain reliable heart rate power spectra. Recordings of approximately 1 min are needed to assess the high-frequency peak whereas at least 2 min recording are needed to reliably assess the low-frequency component (Akselrod et al., 1981; Malik, 1996; Otzenberger et al., 1997, 1998; Brennan et al., 2002).

Consequently, we conservatively assessed VHR using the standard deviation of the heart rate. This measure is relatively more sensitive to high-frequency variations in heart rate (Malik, 1996).

It should be noted that a circadian effect is not likely to confound our results. The acquisition times for wakefulness, REMS and NREMS largely overlapped. Furthermore, a circadian factor is probably minor because VHR is highly sleep stage dependent (Zemaityte et al., 1984; Raetz et al., 1991; Vanoli et al., 1995; Pivik et al., 1996; Brandenberger et al., 2001; Viola et al., 2002). For instance, individual profiles revealed abrupt HR increases in each transition from deeper sleep to lighter sleep or awakening (Viola et al., 2002). The standard deviation of normal RR intervals and LF:

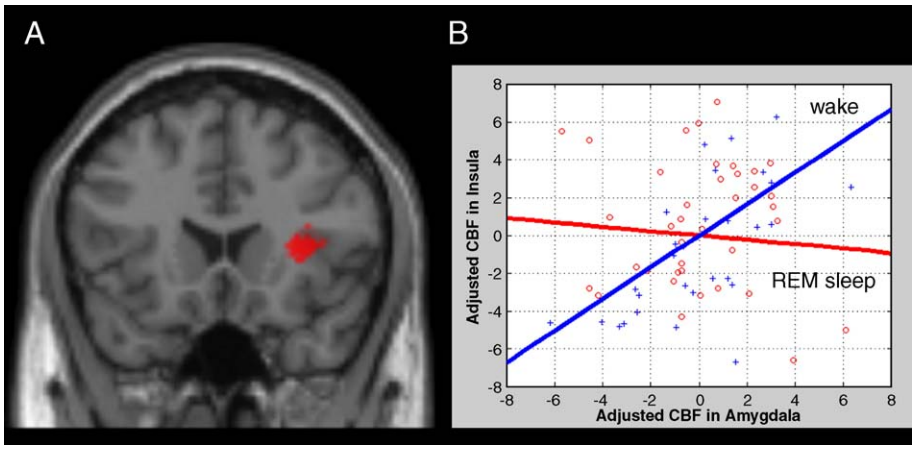

Fig. 2. (A) Psychophysiological interaction using the amygdala rCBF as reference region ($x=36$, $y=8$, $z=-20$) and the state of vigilance (REMS versus wakefulness) as condition identified a single area in the right anterior insular cortex. The functional result is displayed over an individual MRI scan normalized to the MNI space in transverse, frontal and sagittal planes. The functional results are displayed at $p<0.001$, uncorrected. (B) Regression of insular on amygdalar activity during REMS and in wakefulness. This result indicates that the right anterior insula is connected more tightly with the amygdala during wakefulness than during the REMS ($Z=3.11$, $p_{SVC}=0.028$, reference coordinates taken in Critchley et al., 2000). The straight lines correspond to the regression, in wakefulness and REMS, respectively. The dots correspond to the adjusted rCBF observed in the 2 regions (red dots: REMS, blue cross: wakefulness).

(LF+HF) ratio decreases during SWS and significantly increases during REMS and during intrasleep awakening (Viola et al., 2002). However, the circadian factor cannot be totally ruled out. Although sympathetic nervous system activity is mostly influenced by sleep states, parasympathetic nervous system activity has been shown to be under circadian regulation (Burgess et al., 1997).

Dreams are known to occur frequently during REMS. One might argue that dream content would partly explain the variability in heart rate that ever report. As no dream reports were obtained from the subjects after each scan, we are in a position neither to confirm or falsify such a conclusion.

Amygdala in the regulation of heart rate variability during REMS

Central regulation of heart rate probably involves distributed networks encompassing cortical, hypothalamic and brainstem structures. At the cortical level, no significant effect of VHR was observed. This suggests that the functional neuroanatomy of central cardiovascular regulation varies between wakefulness, SWS and REMS. This hypothesis is further supported by the condition by VHR interaction.

The latter shows that the amygdala is the only area where the rCBF covaries with VHR differentially during REMS than during wakefulness. In particular, the activity in the amygdala is more tightly related to VHR during REMS than during wakefulness. No significant difference was observed between REMS and SWS and between SWS and wakefulness in terms of brain areas where the regional blood flow is related to VHR. Given results did not show any significant difference in VHR between SWS and wakefulness nor between SWS and REMS, we cannot argue that the modulatory influence of the amygdala is specific to REM sleep. However, we can suggest that the neural correlates of VHR differ between wakefulness and REM sleep. At present, no definite conclusion can be reached for SWS during which the cerebral correlates of VHR differed neither from wakefulness nor from REMS.

The coordinates of the significant changes in blood flow point to the lateral aspect of the amygdala. Although the poor spatial resolution of the PET cannot precisely describe the location of the amygdala response, it should be noted that these coordinates were reported in studies involving the right amygdala in cardiovascular regulation during wakefulness (Critchley et al., 2002a, 2002b).

The amygdala is intimately implicated in several basic features of REMS. In humans, the amygdala is particularly active in REMS (Maquet et al., 1996). In cats, cholinergic activation of the central amygdaloid nucleus produces a long-term facilitation of REMS occurrence (Calvo et al., 1996). Similarly, pharmacological stimulation (by vasointestinal peptide) of the amygdala induces increased amounts of REMS and ponto-geniculo-occipital waves (Simon-Arceo et al., 2003). Likewise, the rebound of REMS induced by microinjections of GABA agonist into the periaqueductal grey matter elicited a significant increase in c-*fos* labeling in the amygdala (Sastre et al., 2000).

Moreover, amygdala is in good position to influence critical regions for the cardiovascular regulation (Hopkins and Holstege, 1978), like the hypothalamus (Coote, 1995; Shannahoff-Khalsa and Yates, 2000; Xia and Krukoff, 2003) and parabrachial complex (Henderson et al., 2002).

The psychophysiological interaction also shows that the functional connectivity between amygdala and insula is different during REMS as compared to wakefulness. The functional relationship between the amygdalar and the insular cortices seems tighter during wakefulness than during REMS. During wakefulness, the insula plays a major role in cardiovascular regulation (Oppenheimer et al., 1992; Critchley et al., 2000). In normal humans, rCBF in the right insula covaries with heart rate (Critchley et al., 2000). Functional magnetic resonance imaging (fMRI) recently confirmed the functional links between the insular cortex and the modulation of heart rate (Williamson et al., 1997, 1999; Critchley et al., 2000). The activity in the left insula increases during dynamic exercise (cycling) but not passive exercise (cycling movement induced by moving pedals independently) (Williamson et al., 1997, 1999). Likewise, increased rCBF in right insula covaried with HR during isometric exercise and

mental stressor tasks like arithmetic (Critchley et al., 2000). Moreover, the observations of brain damaged patients confirm the pivotal influence of the insular cortex in cardiovascular regulation (Oppenheimer, 1994; Oppenheimer et al., 1996; Tokgozoglu et al., 1999). The insular cortex is implicated in the generation of cardiac arrhythmias following hemispheric stroke (Oppenheimer, 1994). Accordingly, strokes in the region of insula (especially on the right side) leads to decrease VHR and to increased the incidence of sudden death (Tokgozoglu et al., 1999). Similarly, left-sided acute insular stroke "increase basal cardiac sympathetic tone and was associated with a decrease in randomness of heart rate variability" (Oppenheimer et al., 1996). In epileptic patients, electrical stimulations within the insula elicit changes in heart rate (Cechetto and Saper, 1987; Oppenheimer et al., 1992; Cechetto, 1994). Finally, it is known that the insula is anatomically and functionally connected with autonomic centers involved in heart rate regulation such as the amygdala and the hypothalamus (Augustine, 1996).

In contrast to what happens during wakefulness, our findings suggest that the amygdala largely influences heart rate during REMS. Moreover, our results suggest that this change in cardiovascular regulation is accompanied with a change in functional connectivity between the amygdala and the insula.

During REMS relative to wakefulness, the insula is less likely to modulate cardiovascular regulation, through its projections toward the amygdala. In this respect, the amygdala seems to take a prominent role in cardiovascular regulation during REMS in contrast to wakefulness. As amygdala is an integral part of the cerebral networks which generate and maintain REMS (Datta et al., 1998), the participation of the amygdala in VHR explains why the latter is an intrinsic characteristic of this sleep stage.

The modified cardiovascular regulation during REMS relative to wakefulness might have some bearing on important clinical issues. Many studies have demonstrated that the incidence of adverse cardiovascular events like sudden deaths or arrhythmias (Verrier et al., 1996) peak in the early morning hours (Muller et al., 1985, 1987; Tofler et al., 1987; Willich et al., 1987; Maron et al., 1994; Venditti et al., 1996; Elliott, 1998, 2001), and particularly during REMS (Schafer et al., 1997; Viola et al., 2002, 2004). Future research will have to assess the role of the amygdala and the change in its connectivity with the insular cortex in these life-threatening events.

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7.3. Neuroimaging insights into the pathophysiology of sleep disorders.

From

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Summary

Neuroimaging methods can be used to investigate whether sleep disorders are associated with specific changes in brain structure or regional activity. However, it is still unclear how these new data might improve our understanding of the pathophysiology underlying adult sleep disorders. Here we review functional brain imaging findings in major intrinsic sleep disorders (i.e., idiopathic insomnia, narcolepsy, and obstructive sleep apnea) and in abnormal motor behavior during sleep (i.e., periodic limb movement disorder and REM sleep behavior disorder). The studies reviewed include neuroanatomical assessments (voxel-based morphometry, magnetic resonance spectroscopy), metabolic/functional investigations (positron emission tomography, single photon emission computed tomography, functional magnetic resonance imaging), and ligand marker measurements. Based on the current state of the research, we suggest that brain imaging is a useful approach to assess the structural and functional correlates of sleep impairments as well as better understand the cerebral consequences of various therapeutic approaches. Modern neuroimaging techniques therefore provide a valuable tool to gain insight into possible pathophysiological mechanisms of sleep disorders in adult humans.

Neuroimaging Insights into the Pathophysiology of Sleep Disorders

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Neuroimaging methods can be used to investigate whether sleep disorders are associated with specific changes in brain structure or regional activity. However, it is still unclear how these new data might improve our understanding of the pathophysiology underlying adult sleep disorders. Here we review functional brain imaging findings in major intrinsic sleep disorders (i.e., idiopathic insomnia, narcolepsy, and obstructive sleep apnea) and in abnormal motor behavior during sleep (i.e., periodic limb movement disorder and REM sleep behavior disorder). The studies reviewed include neuroanatomical assessments (voxel-based morphometry, magnetic resonance spectroscopy), metabolic/functional investigations (positron emission tomography, single photon emission computed tomography, functional magnetic resonance imaging), and ligand marker measurements. Based on the current state of the research, we suggest that brain imaging is a useful approach to assess the structural and functional correlates of sleep impairments as well as better understand the cerebral consequences of various therapeutic approaches. Modern neuroimaging techniques therefore provide a valuable tool to gain insight into possible pathophysiological mechanisms of sleep disorders in adult humans.

Keywords: PET, SPECT, fMRI, insomnia, depression, narcolepsy, obstructive sleep apnea syndrome, restless legs syndrome, REM sleep behavior disorders.

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OVER THE LAST COUPLE OF DECADES, SEVERAL STUDIES HAVE USED FUNCTIONAL NEUROIMAGING TECHNIQUES TO INVESTIGATE THE CEREBRAL correlates and consequences of primary sleep disorders in adult humans. By revealing the regional patterns of activation associated with specific sleep disorders, the data from positron emission tomography (PET) and magnetic resonance imaging (MRI) techniques complement and extend previous findings mainly based on electroencephalography (EEG) and brain-damaged patients. Here we review recent functional neuroimaging data gained from adult patients having sleep disorders. Our goal is to assess how these new data might improve our knowledge of the neural mechanisms involved in the pathophysiology of some major sleep disorders. Critical EEG results are also considered, but a comprehensive integration of electrical neuroimaging with metabolic and hemodynamic findings is beyond the scope of the current review.

We first report functional imaging studies in intrinsic sleep disorders such as idiopathic insomnia, narcolepsy and obstructive sleep apnea. We then focus on neuroimaging findings in abnormal motor behavior during sleep (i.e., periodic limb movement disorder and REM sleep behavior disorder). We also consider brain functions in sleep disorders related to specific psychiatric disorders. Rare sleep disorders and case reports are not reviewed here.

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Each sleep disorder section starts with an introduction to the disorder, including possible pathophysiological brain mechanisms, followed by a detailed review of the structural and functional neuroimaging findings, and ends with a summary of the main findings.

IDIOPATHIC INSOMNIA

Insomnia is characterized by complaints of difficulty in initiating or maintaining sleep or of nonrestorative sleep, which cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.[1] Insomnia therefore presents with subjective symptoms. Insomnia might arise directly from sleep/wake regulatory dysfunction or indirectly from comorbid behavioral, psychiatric, neurological, immune, or endocrine disorders, including disturbances secondary to the use of drugs. Insomnia appears to be a 24-h disorder because it is not restricted to sleep complaints alone but can affect several aspects of daytime functioning as well. Importantly, insomnia is a common disorder in our society, with 10% to 20% of the general population reporting insomnia complaints and related impairment of daytime functioning.[2]

Depression is often associated with insomnia.[3] In this section, we also review the data pointing to some common underlying neurophysiological mechanisms for both sleep and mood regulation.

Hyperarousal Hypothesis in Insomnia

According to the *International Classification of Sleep Disorders* (ICSD-2), idiopathic insomnia "is a lifelong inability to obtain adequate sleep that is presumably due to an abnormality of the neurological control of the sleep-wake system."[4] Idiopathic insomnia is thought to reflect an imbalance between arousal and sleep promoting systems, which results in a global cortical hyper-

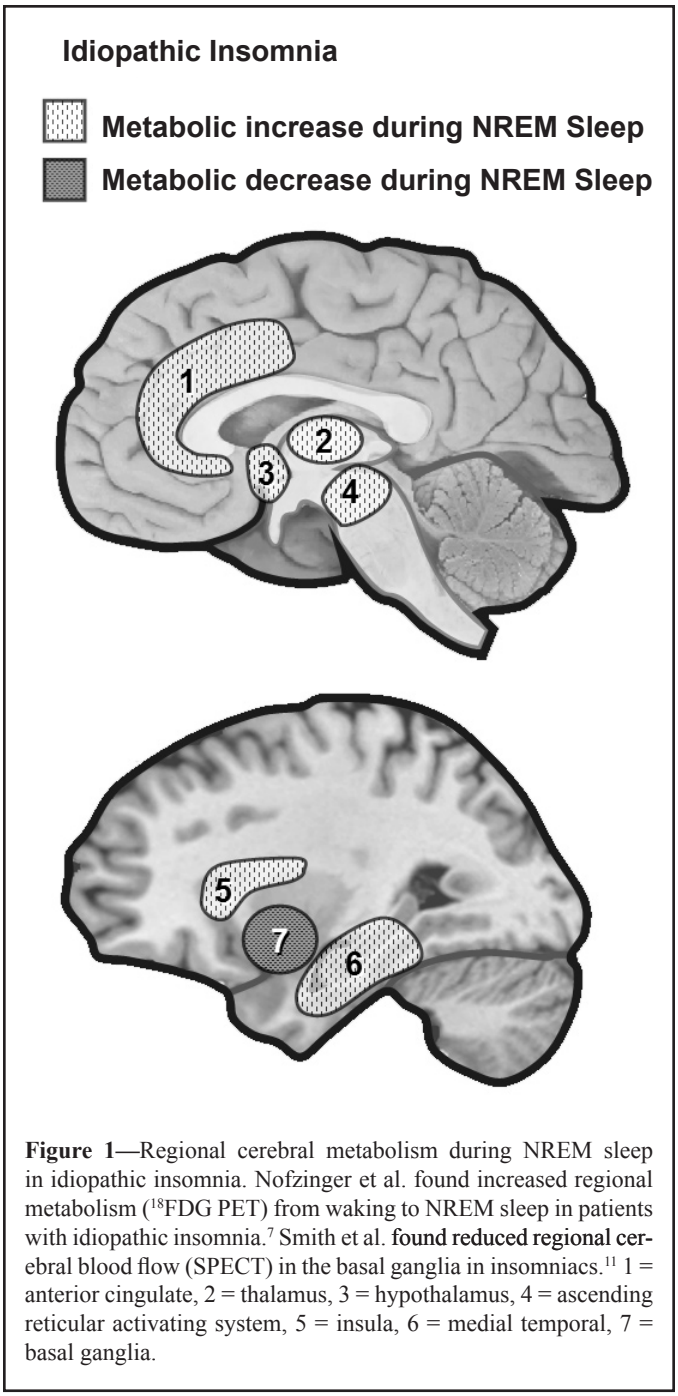

Figure 1—Regional cerebral metabolism during NREM sleep in idiopathic insomnia. Nofzinger et al. found increased regional metabolism (^{18}FDG PET) from waking to NREM sleep in patients with idiopathic insomnia.[7] Smith et al. found reduced regional cerebral blood flow (SPECT) in the basal ganglia in insomniacs.[11] 1 = anterior cingulate, 2 = thalamus, 3 = hypothalamus, 4 = ascending reticular activating system, 5 = insula, 6 = medial temporal, 7 = basal ganglia.

activity as evidenced by EEG studies (see below). In line with the elevated arousal levels, several studies have reported increased alertness using the multiple sleep latency test as well as increased tension and anxiety during wakefulness, associated with a reduction of total sleep duration.[5] Poor sleep may also have important consequences on daytime functioning such as altered mood and motivation, decreased attention and vigilance, low levels of energy and concentration, and increased daytime fatigue.[5] In addition, insomnia increases the risk of major depression.[3]

Quantitative EEG recordings have confirmed an overall cortical hyperarousal in primary insomnia, characterized by an increase in beta/gamma activity at sleep onset and during NREM sleep.[6] Insomnia would therefore result from a conditioned state of central nervous system (CNS) arousal, which enhances a variety of sensory and cognitive phenomena that are normally suppressed or at least diminished at sleep onset. Uncommon high-frequency activity associated with sleep onset might thus contribute to the frequent misperception of insomniacs of not being asleep while objective EEG parameters indicate otherwise.[6]

Functional Imaging in Insomnia

To our knowledge, only a few studies have assessed the functional neuroanatomy of idiopathic (or primary) insomnia disorder by recording brain activity during NREM sleep. Nofzinger et al. used ^{18}fluorodeoxyglucose (^{18}FDG) PET to measure regional brain metabolism (indexed by glucose consumption, CMRglu) in 7 patients with idiopathic insomnia and 20 healthy age-matched and gender-matched subjects during waking and NREM sleep.[7] Insomnia patients showed increased global CMRglu during the transition from waking to sleep onset as compared to healthy subjects, suggesting that there is an overall cortical hyperarousal in insomnia. Moreover, insomniac patients exhibited less reduction of relative CMRglu from waking to NREM sleep in the ascending reticular activating system, hypothalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices, as illustrated in Figure 1. Increased metabolism was also observed in the thalamus, which might reflect persistent sensory processing as well as subsequent shallower sleep. In contrast, during wakefulness decreased metabolism was found in subcortical (thalamus, hypothalamus, and brainstem reticular formation) as well as in cortical regions (prefrontal cortex bilaterally, left superior temporal, parietal, and occipital cortices). These findings suggest that insomnia might involve abnormally high regional brain activity during sleeping states, associated with reduced brain metabolism during waking. The observed reduction in prefrontal cortex activity during wakefulness is consistent with reduced attentional abilities and impaired cognitive flexibility resulting from inefficient sleep and is consistent with a chronic state of sleep deprivation.[8-10]

Another preliminary study by Smith et al.,[11] which compared 5 insomniacs with 4 normal sleepers using single photon emission computed tomography (SPECT), found no significant regional increase during NREM sleep but reduced regional cerebral blood flow (rCBF) in frontal medial, occipital, and parietal cortices, as well as in the basal ganglia (Figure 1). Interestingly, in Nofzinger's study, decreases in activity in these same regions were also found in insomniacs, but during wakefulness. However, some of the methodological limitations in the Smith's study need to be considered. Firstly, the blood flow was only sampled during the first NREM cycle. Therefore, the observed decreased metabolism in insomniacs might reflect cortical hypoarousal during the initial phases of NREM sleep following sleep onset, while it remains possible that the patients were more aroused over later NREM sleep cycles, which would be more consistent with higher beta activity later at night (see above). Secondly, the blood flow was measured after a longer duration of NREM sleep in insomnia patients than in healthy subjects, leading to a possible underestimation of activity in the patients because blood flow decreases over long NREM periods. Because of such methodological limitations, these preliminary results cannot rule out the hyperarousal hypothesis of primary insomnia.

Four of the insomnia patients from the Smith's study were rescanned after they had been treated by cognitive behavioral

therapy (which included sleep restriction and stimulus control[12]). After treatment, sleep latency was reduced by at least 43%, and there was a global 24% increase in CBF with significant increases in the basal ganglia. The authors proposed that such increase in brain activity might reflect the normalization of sleep homeostatic processes. These interesting initial results will inspire further investigation on the effects of psychotherapy on brain functioning in insomnia.

Depression and Insomnia

Depression is the most common primary diagnosis in patients suffering from insomnia.[13] Of all psychiatric conditions associated with insomnia, depression (in particular unipolar depression) is the most frequently diagnosed one.[3] Depressed patients frequently report increased daytime fatigue and tend to compensate with daytime napping. Patients with bipolar disorder, on the other hand, report insomnia while depressed, but also hypersomnia, with extended nocturnal sleep periods, difficulty in awakening, and excessive daytime sleepiness.[13] Thus, sleep disturbances appear to vary even across depression subtypes. In addition, depression is associated with other sleep disorders like OSAS (see OSAS section).[14] Here, we only focus on the links between depression and insomnia. Indications of hyperarousal in both conditions suggest shared neurophysiological mechanisms underlying both sleep and mood regulation.[15]

Hyperarousal Hypothesis in Depression

In depressed patients, modifications of the sleep architecture is characterized by reduced slow wave sleep (SWS), early onset of the first episode of REM sleep, and increased phasic REM sleep.[16] Gillin et al.[17] postulated that depression is closely linked to an abnormal increase in some aspects of physiological arousal. Consistent with this hypothesis, total scores on the Hamilton Depression Rating Scale (HDRS) as well as sleep disturbance in depression, a distinct symptom cluster included in the HDRS, have been found to correlate with increased metabolism and regional cerebral blood flow during wakefulness in a large set of cerebral areas including limbic structures, anterior cingulate, thalamus, and basal ganglia.[18]

Intriguingly, total sleep deprivation is the only known therapeutic intervention in depression that has proven antidepressant effects within 24 hours. Sleep deprivation has rapid beneficial effects, but unfortunately only for about half of the depressive population, with depressive symptoms reappearing after 1 night of recovery sleep.[3] One hypothesis is that sleep deprivation can transiently counteract global hyperarousal in the responder population.[19]

Since hyperarousal has also been described in insomnia, this may be a common pathway underpinning the close relationship between sleep and mood disorders. Evidence for reciprocal relationship between sleep and depression is twofold: sleep disturbances often accompany depression whereas chronic insomnia is a risk factor for the development of depression.[20] Subclinical sleep EEG alterations may persist in patients at risk for a depressive episode, thus offering further evidence of a close link between sleep and mood regulation.

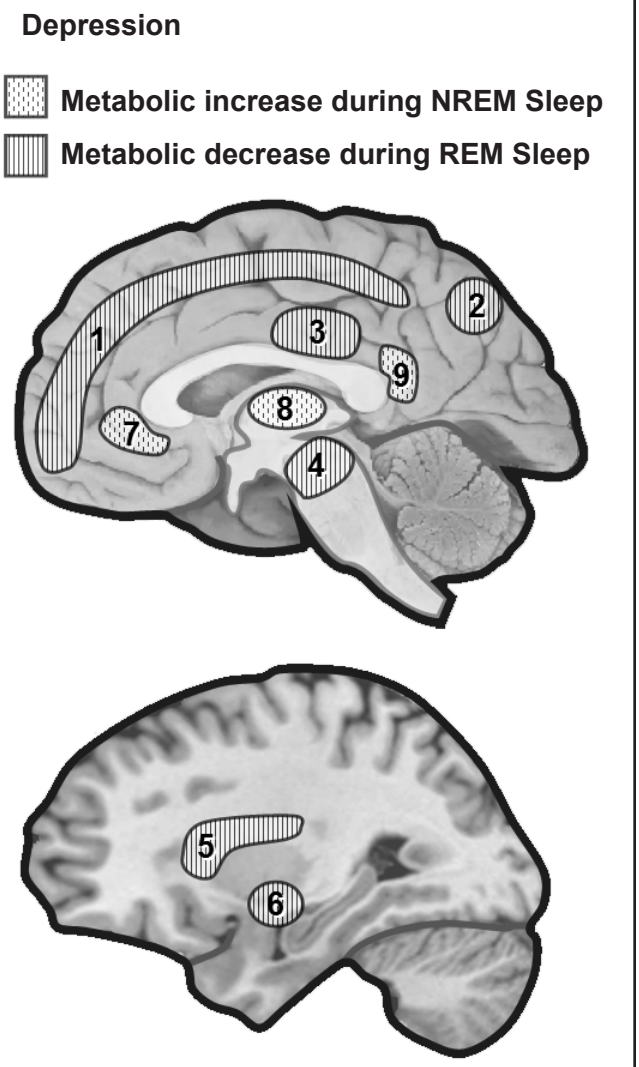

Figure 2—Metabolic changes during REM and NREM sleep in depression. During NREM[23] and REM,[24] depressed patients show "elevated" activity measured by CMRglu across several cortical and subcortical regions sleep compared to presleep wakefulness.[23,24] 1 = frontoparietal, 2 = posterior parietal, 3 = supplementary motor area, 4 = ascending reticular activating system, 5 = insula, 6 = ventral pallidum, 7 = medial prefrontal, 8 = thalamus, 9 = posterior cingulate.

Neuroimaging of Sleep in Depression

A pioneering study by Ho et al. examined NREM using PET in 10 patients with depression and 12 controls.[21] The depressed patients showed higher CMRglu during NREM sleep in the pons, posterior cingulate, amygdala, hippocampus, and occipital and temporal cortices. There was a significant reduction of relative CMRglu in medial-orbital frontal and anterior cingulate cortices, caudate nucleus, and medial thalamus. These early findings support the hypothesis that hyperarousal in depression affects a network of limbic and posterior cortical regions, but also that the decreased medial frontal and striatal metabolism may be a hallmark of depression.[22] More recent studies have confirmed that depressed patients have relatively persistent "elevated" activity measured by CMRglu across many brain

regions during sleep compared to presleep wakefulness (REM: 24 depressed patients compared to 14 controls;[23] NREM: 12 depressed patients compared to 13 controls,[24] see Figure 2). Regions more activated during REM sleep included frontal, parietal, premotor, and sensorimotor cortices, as well as the insula, the ventral pallidum, and the midbrain reticular formation.[23] Regions more activated during NREM sleep included the temporal and occipital cortices, as well as the insula, posterior cingulate, cerebellum, and thalamus.[24] However, increased metabolism was also found in prefrontal cortex (unlike[21]). These results are again consistent with a general hyperactivation of arousal systems in depression that may underlie both sleep disturbances such as insomnia as well as nonrestorative sleep complaints in depressed patients.

Increased rapid eye movement density (number of REMs per minute of REM sleep) was found to correlate with depression severity and clinical outcomes.[25] In humans, REMs bursts are classically thought to reflect ponto-geniculo-occipital (PGO) waves, possibly associated with orienting responses and arousal processes during sleep.[26,27] An ^{18}FDG PET study assessed cerebral glucose consumption in a group of 13 medication-free depressed patients during REM sleep.[28] The average REM count (an automated analog of REM density) was found to positively correlate with the metabolism in a network of regions involved in emotional regulation and emotion-induced arousal (medial and ventrolateral prefrontal cortex) as well as in regions linking emotion and attention systems (striate cortex, precuneus, and posterior parietal cortex).[29] Whether increased activity in these regions may drive hyperarousal during REM sleep remains unclear. These results might not be specific to depression because no control data were provided in that study and because the observed activation pattern overlapped with results of healthy controls from other studies.[26,30]

Summary

Because currently available data are limited and not perfectly consistent, any conclusion about the cerebral correlates of insomnia during NREM sleep has to remain tentative. Whilst there is some evidence for decreased activity in cortical areas during early NREM sleep as well as during wakefulness, several subcortical regions involved in sleep/wake regulation, including limbic and paralimbic regions, were found to be more active during the transition from waking to sleep states. The available data generally support the hyperarousal theory of insomnia with increased neuronal activity during NREM sleep being a possible key factor contributing to sleep misperception and disturbances in insomnia.

Depression is often associated with insomnia, as well as with hyperarousal characterized by persistent "elevated" activity across many brain regions during NREM sleep. Strong evidence for hyperarousal in both idiopathic insomnia and depression, together with persistent alterations in sleep architecture in remitted depression, corroborate common neurophysiological mechanisms underlying sleep and mood regulation.

Changes in brain functions after insomnia treatments have to be assessed more carefully in future neuroimaging studies. Indeed, functional imaging could be coupled with pharmacological or psychotherapeutic treatments in order to assess the neurophysiological response to such interventions, and thus allow a better understanding of the neural mechanisms underlying the recovery from primary insomnia.

NARCOLEPSY

Narcolepsy is a sleep/wake disorder characterized by the clinical tetrad of excessive daytime sleepiness, sudden loss of muscle tone (cataplexy), sleep paralysis, and hypnagogic hallucinations. Nocturnal sleep disruption is typical in narcolepsy. Almost all patients with narcolepsy (with cataplexy subgroup) are positive for the human leukocyte antigen (HLA) subtype DQB1*0602; this HLA subtype is much less frequent in the general population.[31] Additional biological markers include sleep-onset REM periods (SOREMPs) on multiple sleep latency tests (MSLT) and low level of cerebrospinal fluid (CSF) hypocretin-1 (orexin A).

Lately, narcolepsy has been linked to a loss of hypothalamic neurons producing hypocretin (also called orexin), a neuropeptide implicated in arousal systems.[32] Hypocretin neurons are localized in the lateral hypothalamus and have widespread projections throughout the brain. Hypocretin neurons receive inputs from excitatory (glutaminergic) and inhibitory (noradrenergic, serotonergic and GABAergic) neurons.[32] Hypocretin neurons have been found to be implicated in maintaining wakefulness, as well as in the regulation of motor functions (locomotion, muscle tone), energy expenditure, and sympathetic activity.[32] Postmortem autopsy studies showed a loss of hypocretin messenger ribonucleic acid (mRNA) and a reduction or loss of hypocretin peptides. Low CSF hypocretin-1 levels is an usual finding in narcolepsy with definite cataplexy.[31] In contrast, in most patients with narcolepsy without cataplexy and in other primary sleep-wake disorders (such as insomnia or restless legs syndrome), CSF hypocretin-1 levels are normal. However, low CSF hypocretin-1 levels can also be found in several neurological disorders irrespective of sleep habits.

Over the past decade, brain imaging studies have provided major insights into the functional neuroanatomy of normal human waking state, REM sleep or SWS. Yet, only a few studies looked at how brain activity might be altered in narcoleptic patients. Moreover, the neural correlates of other characteristic symptoms in narcoleptic patients such as cataplexy, hypnopompic/hypnagogic hallucinations or sleep paralysis remain largely unknown.

Structural Abnormalities in Narcolepsy

Because it controls transitions between sleep states, the pontine tegmentum was first proposed as a possible main site of anatomical or functional impairments in narcolepsy. While Plazzi and coworkers[33] had reported pontine tegmentum abnormalities (T2 hyperintensity) in 3 patients with narcolepsy using MRI, 2 other structural MRI studies[34,35] found no pontine abnormalities in idiopathic narcolepsy (except in 2 out of 12 patients who had longstanding hypertension[35]). However, the MRI abnormalities found in the study of Plazzi and colleagues could reflect nonspecific age-related pontine vascular changes rather than a narcolepsy-related phenomenon, as they were indistinguishable from ischemic changes and were associated with similar anomalies in the hemispheres.

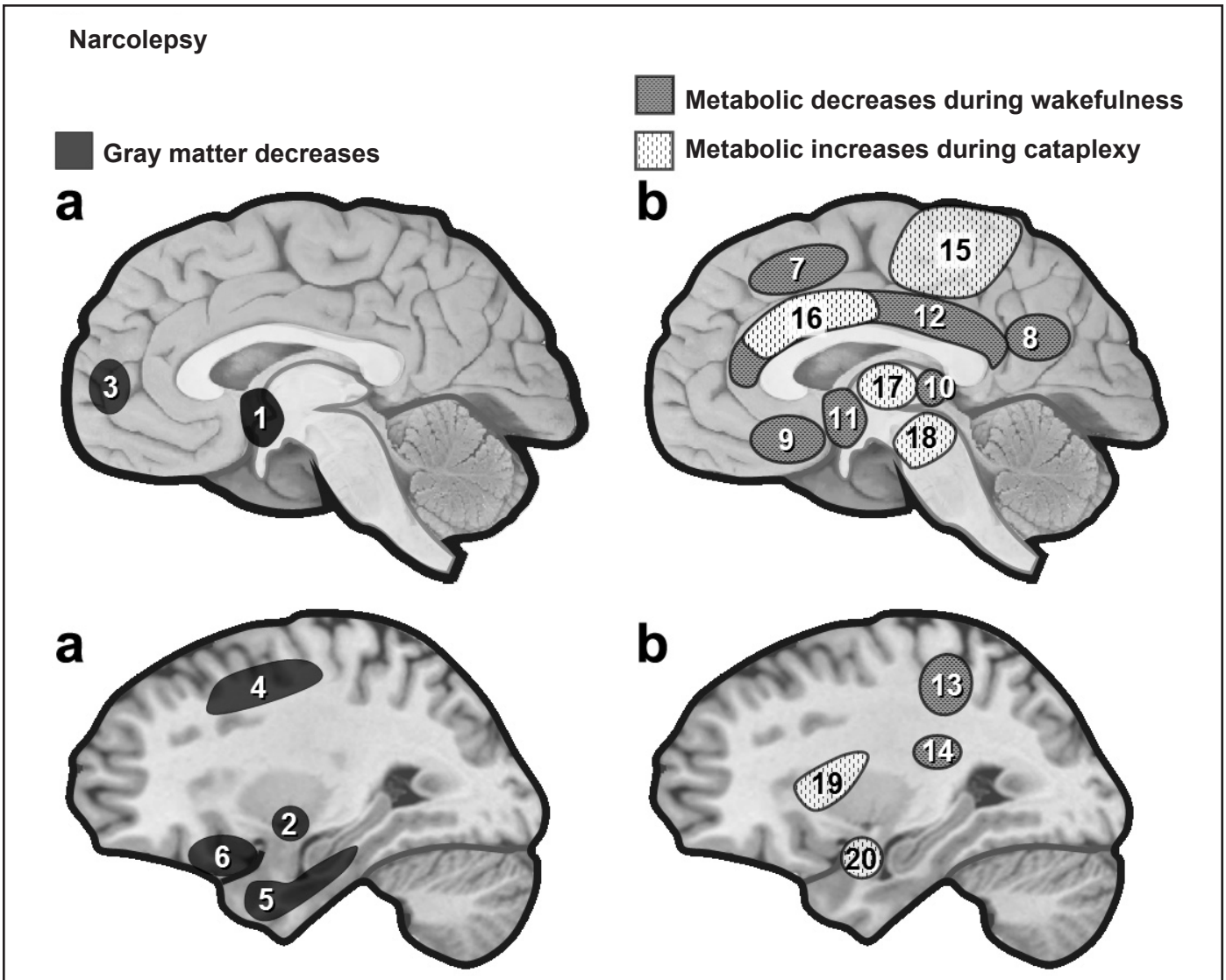

Figure 3—(a) Anatomical brain changes in narcoleptic patients assessed by VBM. In narcoleptic patients, cortical gray matter loss was found to affect frontal brain regions,[37] temporal regions,[38] as well as hypothalamus, cerebellum (vermis) and ventral striatum[39] (see also[40]). However, hypothalamus damage is not systematically found in VBM studies.[36] (b) Functional brain changes in narcolepsy. Narcoleptic patients show reduced baseline activity during wakefulness (^{18}FDG PET, SPECT) in several regions including the hypothalamus and mediodorsal thalamic nuclei.[45,46] During cataplexy, one SPECT study reported hyperperfusion in several brain regions including limbic area, brainstem and motor regions[51] (but see also[52]). 1 = hypothalamus, 2 = nucleus accumbens (right), 3 = frontomesial, 4 = prefrontal (right), 5 = inferior temporal, 6 = inferior frontal, 7 = superior frontal, 8 = inferior parietal lobule, 9 = rectal/subcallosal gyrus, 10 = dorsal thalamus, 11 = hypothalamus, 12 = cingulate, 13 = post central/supramarginal, 14 = caudate, 15 = premotor and motor cortex, 16 = cingulate, 17 = thalamus, 18 = brainstem, 19 = insula (right), 20 = amygdala (right).

Differences in brain morphology that are not identifiable by routine inspection of individual structural MRI can be investigated using voxel-based morphometry (VBM). VBM allows between-group, statistical comparisons of tissue composition (gray and white matter) across all brain regions, based on high-resolution scans. To date, VBM studies reported equivocal results in narcoleptic patients. An early study found no structural change in brains of patients with hypocretin-deficient narcolepsy,[36] suggesting that functional abnormalities of hypocretin neurons could either be associated with microscopic alterations undetectable by VBM or not be associated with any structural changes whatsoever. Two subsequent studies did find cortical gray matter reduction in patients with narcolepsy, predominantly in frontal brain regions[37] as well as in inferior temporal regions[38] (Figure 3). Relative global gray matter loss was independent of disease duration or medication history and there were no significant subcortical gray matter alterations.[38] Significant gray matter concentration decreases were found in the hypothalamus, cerebellum (vermis), superior temporal gyrus and right nucleus accumbens in 29 narcoleptic patients relative to unaffected healthy controls.[39] Given the major projection sites of hypocretin-1 (the hypothalamus among others) and hypocretin-2 (the nucleus accumbens among others), the decreases in gray matter could reflect secondary neuronal losses due to the destruction of specific hypocretin projections. A recent VBM study corroborated sig-

nificant reduction in hypothalamic gray matter volume in 19 patients compared with 16 controls.[40]

Proton magnetic resonance spectroscopy (^{1}H-MRS) was also used to assess the N-acetylaspartate (NAA) and creatinine plus phosphocreatinine (Cr+PCr) content in the hypothalamus of narcoleptic patients. An analysis of spectral peak area ratios revealed a decrease in the NAA/Cr+PCr ratio in the hypothalamus of 23 narcoleptic patients compared with 10 control subjects.[41] An earlier study found similar NAA/Cr+PCr ratios in the ventral pontine areas of 12 narcoleptic patients compared to 12 controls.[42] Reduced NAA/Cr+PCr ratio indicates reduced neuronal function which could reflect neuronal loss (i.e., fewer neurons), but could also be due to reduced activity of existing neurons. Decreased NAA concentration is typically seen in neurodegenerative, inflammatory, or vascular disorders.[43] The partial reversibility of NAA deficit during recovery from acute brain pathology[44] suggests that reduced brain NAA may be not only related to neuronal loss, but also to neuronal dysfunction.

Several factors can explain inconsistencies across both VBM and spectroscopy studies such as inhomogeneous patient groups, history of treatment or, for VBM, pre-statistical image processing and limited sensitivity of this technique (which means that large sample sizes are needed to obtain reliable results). VBM studies with larger samples of drug-naive patients are required to identify reliably structural abnormalities in narcolepsy.

Functional Imaging in Narcolepsy

Baseline activity during wakefulness was assessed with ^{18}FDG PET by measuring CMRGlu in 24 narcoleptic patients and 24 normal controls.[45] Narcoleptic patients had reduced CMRGlu in bilateral precuneus, bilateral posterior hypothalami and mediodorsal thalamic nuclei[45] (see Figure 3). A subsequent SPECT study showed hypoperfusion in bilateral anterior hypothalami.[46] These two studies indicate lower waking baseline activity in narcolepsy.

Other studies have compared regional brain activity during wakefulness and sleep states. An early study using ^{133}Xe inhalation showed that during wakefulness, brainstem and cerebellar blood flow was lower in narcoleptic patients than in normal subjects.[47] In contrast, rCBF increased in all areas after sleep onset as compared to wakefulness, in particular in temporo-parietal regions, possibly related to visual dreaming or hypnagogic hallucinations. More recently, a ^{99}mTC-HMPAO (technetium ^{99}m-hexamethylpropyleneamine oxime) SPECT study in 6 narcoleptic patients found no difference between waking state and REM sleep suggesting similar overall cortical activity across these two states.[48] However, the lack of control data significantly limits the interpretation of this result. Further studies are needed to confirm these findings on a larger narcoleptic population including systematic comparisons with matched controls.

Brain responses to visual and auditory stimuli were studied in 12 narcoleptic patients and 12 control subjects using functional MRI (fMRI).[49] There was no group difference in spatial extent of cortical activation between control and narcoleptic subjects.

Finally, based on the clinical observation that cataplexy episodes are often triggered by positive emotions (e.g., hearing or telling jokes), a recent event-related fMRI study was performed on 12 narcoleptic patients and 12 controls while they watched sequences of humorous pictures. Both patients and controls were similar in humor appreciation and activated regions known to contribute to humor processing, including limbic and striatal regions. A direct statistical comparison between patients and controls revealed that humorous pictures elicited reduced hypothalamic response together with enhanced amygdala response in the patients. These results suggest that hypothalamic HCRT activity physiologically modulates the processing of emotional inputs within the amygdala, and that suprapontine mechanisms of cataplexy might involve a dysfunction of hypothalamic–amygdala interactions triggered by positive emotions.[50]

Neural Correlates of Cataplexy

There are very few data describing the neural correlates of cataplexy in narcoleptic patients. One study reported preliminary SPECT data on 2 patients during a cataplexy episode compared to REM sleep or baseline wakefulness.[51] During cataplexy, perfusion increased in limbic areas (including amygdala, insula and cingulate gyri) and basal ganglia, thalami, premotor cortices, sensorimotor cortices and brainstem, whereas perfusion decreased in prefrontal cortex and occipital lobe (Figure 3). Increased cingulate and amygdala activity may relate to concomitant emotional processing that is usually reported as a powerful trigger of cataplexy. However, such hyperperfusion in the pons, thalami and amygdaloid complexes was not found in a recent single case report,[52] which revealed increased activity in several cortical areas including cingulate cortex, orbitofrontal cortex and right putamen during an episode of cataplexy (here, during status cataplecticus). Future studies using well-designed fMRI protocols on larger samples of patients would be particularly suited to better characterize this complex symptom.[50]

Neurotransmission in Narcolepsy: Ligand Neuroimaging Studies

Given the role of acetylcholine as an important neurotransmitter in the generation of REM sleep, it was hypothesized that narcolepsy might also involve disturbances within the cholinergic system. However at present, this hypothesis is not supported by the available PET data which could not show any change in muscarinic cholinergic receptors in narcoleptic patients.[53] Recently, the release of endogenous serotonin was measured during wakefulness and sleep in human brain using a serotonin antagonist as PET ligand (^{18}FMPPF in 14 narcoleptic patients).[54] Serotonin receptor availability increased in sleep compared to wakefulness in narcoleptic patients. Unfortunately, as there was no control group, these results can only support the fact that serotonin release promotes wakefulness and suppresses REM sleep, as suggested by previous animal data.[55]

Likewise, the dopamine system has been probed by PET in narcoleptic patients because increased dopamine D2 (dopamine receptor 2) binding was shown in the brain of deceased narcoleptic patients.[56,57] One SPECT study found D2-receptor binding in the striatal dopaminergic system correlated with the frequency of cataplectic episodes and sleep attacks in 7 patients with narcolepsy.[58] However, this finding was not confirmed by other PET[59,60] or SPECT studies.[61,62] Interestingly, although binding levels of IBZM (iodobenzamide, dopamine D2 recep-

tor ligand) might be similar in narcoleptic patients and normal controls, treatment by stimulants and/or antidepressants for 3 months have been shown to significantly increase the ligand uptake in 4 out of 5 patients as compared to pretreatment scans.[62] Therefore, a potential explanation for discrepancies with the postmortem studies might be related to the drug treatment of narcoleptic patients. Consistent with this hypothesis, Rinne et al.[63] found no evidence of altered striatal dopamine transporter availability in 10 drug-free narcoleptics (without any treatment in the past) compared to 15 healthy controls with PET using a dopamine transporter ligand (^{11}C-CFT). Collectively, these neuroimaging results suggest that the reported postmortem increase in dopamine binding might be due to long-term effects of prior treatment rather than intrinsic modifications due to the pathophysiology of narcolepsy.

Neural Consequences of Treatment in Narcolepsy

Madras et al. studied the neurochemical substrate of modafinil, a stimulant drug used in the treatment of narcolepsy, in vivo (in rhesus monkey) and in vitro (in human embryonic kidney cells).[64] They found that modafinil occupies striatal dopamine transporter sites and thalamic norepinephrine transporter sites in vivo and modulates transporters of both catecholamines as well as serotonin in vitro. These results suggest that the therapeutic action of modafinil is mediated by the modulation of catecholamine receptors.

Moreover, the effects of stimulant drugs on cerebral function in narcoleptic patients were assessed by 2 fMRI studies. The first one tested the effect of modafinil on 8 narcoleptic patients and 8 control subjects while they were presented with multiplexed visual and auditory stimulation.[49] Modafinil administration efficiently increased self-reported levels of alertness in 7 of 8 narcoleptic subjects but did not modify the average level of activation in either controls or narcoleptics. Another fMRI study assessed the effects of amphetamines in 2 patients with narcolepsy and 3 healthy controls.[65] Whereas the extent of the brain response to auditory and visual stimulation decreased after amphetamine administration in controls, the reverse pattern was observed in narcoleptic patients, with increased response in primary and association sensory cortices. This latter finding suggests that the beneficial effects of amphetamine may be mediated by some enhancement of sensory processing in arousal-deficient subjects. These early neuroimaging results on the effects of stimulant drugs still need to be replicated over larger samples of patients.

One EEG study used advanced methods of distributed source localization (based on intracerebral current density estimates, LORETA[66]) to analyze waking EEG recordings in 15 narcoleptic patients before and after 3 weeks of modafinil or placebo.[67] Cognitive performance (calculation task) was significantly better after modafinil and correlated with a decrease in prefrontal delta, theta, and alpha-1 power, suggesting that modafinil might influence medial prefrontal processes. Interestingly, Thomas and Kwong[68] showed that modafinil can counteract the negative effects of a single night of sleep deprivation on working memory, but only when the difficulty of the task remains moderate (2-back task). This was associated with the recruitment of areas in the executive network including prefrontal and parietal regions.

Summary

Although human narcolepsy is associated with hypothalamic hypocretin/orexin dysfunction, no clear evidence for hypothalamic or pontine tegmentum abnormalities emerges from the structural imaging studies reviewed here, including MRI and spectroscopy data. By contrast, the few available functional imaging studies have consistently found hypoactivity in the hypothalamus. These findings suggest that narcolepsy is associated with abnormal hypothalamic function in the absence of consistent structural alterations detectable by current imaging methods. Higher-field MRI scanners with improved signal and spatial resolution might provide a more refined picture of the structural changes in narcolepsy. Neuroimaging data of narcolepsy during active tasks testing specific brain circuits,[50] as well as during different sleep states are very promising.

One of the cardinal symptoms of narcolepsy, i.e., cataplexy, has been found to be associated with increased activity in areas involved in emotion and reward processing. These data collected on a total of 3 patients still need confirmation.

In addition to a hypocretin/orexin dysfunction, it has been suggested that the dopamine system might also be involved in pathophysiology of narcolepsy, based on postmortem studies showing an increase in striatal dopamine binding. However, the available neuroimaging results on living patients indicate that increases in dopamine activity might be due to long-term effects of prior treatment rather than intrinsic modifications due to the pathophysiology of narcolepsy.

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of upper airway obstruction that occur during sleep and are usually associated with a reduction in blood oxygen saturation. These nocturnal respiratory disturbances result in brief arousals from sleep (i.e., sleep fragmentation) that considerably disturb sleep architecture and may lead to an almost complete deprivation of REM sleep and stages 3 and 4 of NREM sleep. Both sleep disturbances and hypoxemia contribute to excessive daytime sleepiness, a common symptom of the syndrome. OSAS is associated with significant morbidity, such as hypertension, cardiovascular disease, stroke and also motor vehicle accidents. Large epidemiologic studies revealed that OSAS affects 2% of women and 4% of men of the general adult population[69] and up to 25% of the elderly (i.e., over 60 years).[70]

The pathophysiology of OSAS is complex and not yet completely understood. Several studies suggest that OSAS in all age groups is due to a combination of both anatomic airway narrowing and alterations in upper airway neuromuscular tone.[71] The pathophysiology of OSAS also includes enhanced chemoreflex sensitivity and an exaggerated ventilatory response during hypoxemic episodes.[72]

Alterations of cognitive processes, behavior and interpersonal relations are commonly observed in OSAS patients. Both hypoxemia and fragmented sleep are proposed as the main factors leading to neurocognitive impairments during wakefulness. Several studies emphasized the deterioration of executive functions in OSAS patients, including the inability to initiate new mental processes, as well as deficits in work-

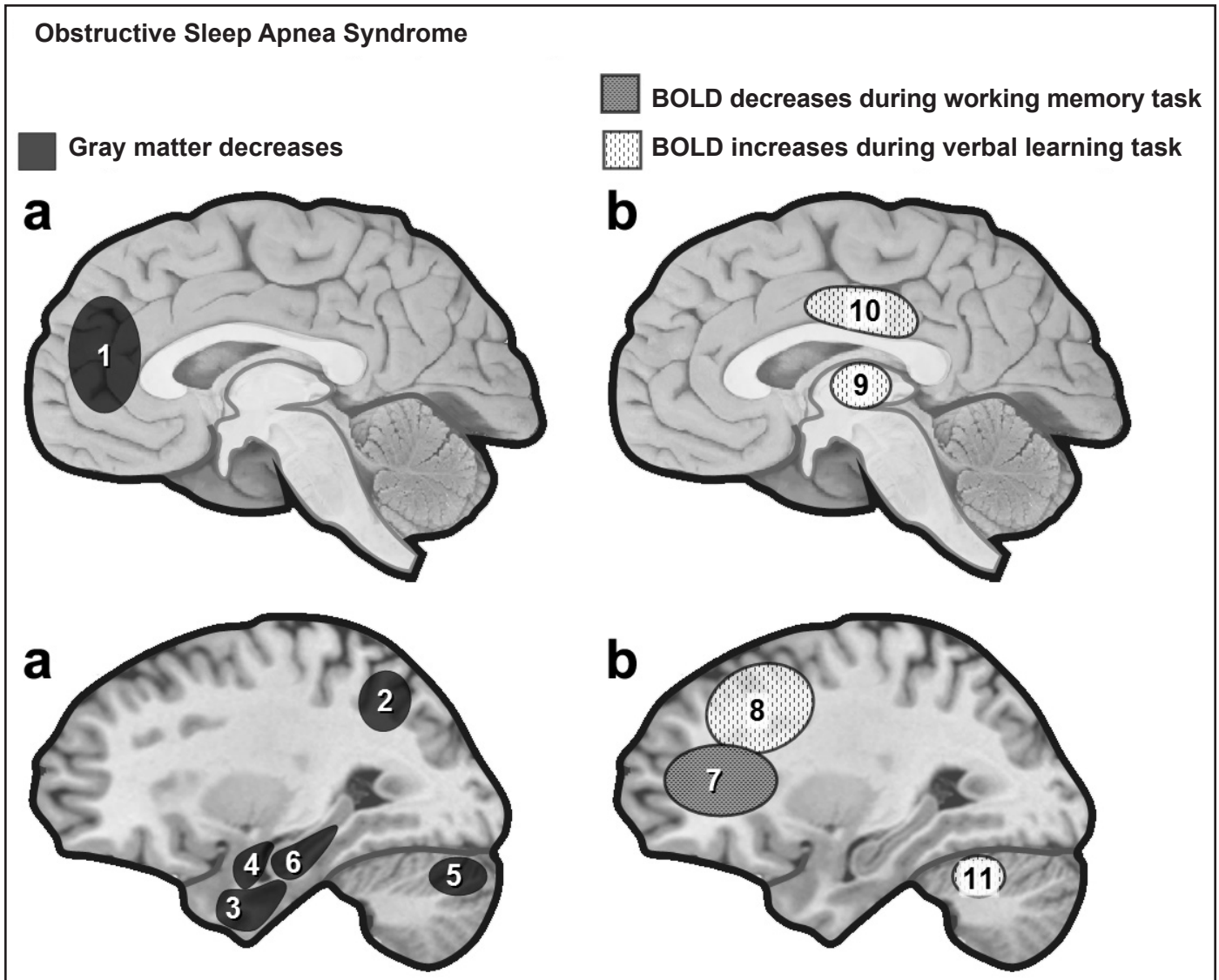

Figure 4—(a) Regional gray matter loss in OSAS patients. VBM results in OSAS patients revealed gray matter loss limited to the left hippocampus[80] or extending to regions involved in cognitive functions and motor regulation of the upper airway.[79] (b) Task-related activation in OSAS patients. Functional MRI in OSAS patients during a 2-back working memory task was associated with reduced dorsolateral prefrontal activity,[87] while verbal learning was associated with increases in frontal cortex, thalamus and cerebellum.[88] 1 = left anterior cingulate cortex, 2 = posterior lateral parietal cortex, 3 = inferior temporal gyrus, 4 = parahippocampal gyrus, 5 = right quadrangular lobule, 6 = left hippocampus, 7 = dorsolateral prefrontal cortex, 8 = inferior/middle frontal, 9 = thalamus, 10 = cingulate gyrus, 11 = cerebellum.

ing memory, selective attention and continuous attention.[73] A recent meta-analysis showed that untreated patients with OSAS had negligible deficits in intellectual and verbal functioning but a substantial impairment of vigilance and executive functioning.[74] 'Cognitive reserve' might protect against OSAS-related cognitive decline.[75]

It is still unclear whether the cognitive consequences of OSAS are reversible or not.[76,77] Structural alterations may indicate irreversible cerebral changes that would underpin permanent cognitive impairments, although this proposal remains a matter of debate in the literature.[78]

Structural Changes in OSAS

Several studies used voxel-based morphometry (VBM) on high-resolution MRI scans to assess structural brain changes in patients with OSAS. An early study found regional gray matter loss in OSAS patients (n = 21) compared to healthy controls (n = 21) in regions involved in various cognitive functions and motor regulation of the upper airway, including frontal, temporal, and parietal regions, anterior cingulate, hippocampus, and cerebellum[79] (see Figure 4). By contrast, another VBM study showed lower gray matter concentration limited to the left hippocampus in 7 OSAS patients compared to 7 controls, with no difference in total gray matter volume between the two groups.[80] A more recent study on 25 OSAS patients and 23 controls found neither gray matter volume deficits nor focal structural changes in severe OSAS patients.[81] Comparing both neuropathological and neuropsychological effects of hypoxia in patients with either carbon monoxide poisoning or OSAS, Gale and Hopkins[82] reported hippocampal atrophy in both groups. Importantly, hippocampal volume correlated with performance on nonver-

bal tasks (Wechsler Adult Intelligence Scale–Revised Block Design) in both groups. There was no significant correlation between hippocampal volume and global memory performance but in the OSAS group only, there was a linear relationship between hippocampal volume and a subset of memory tests (e.g., delayed recall on the Rey-Osterrieth Complex Figure Design, Trial 6 of the Rey Auditory Verbal Learning Test). This suggests a link between hippocampus damage and some memory performance in OSAS.

Single voxel proton magnetic resonance spectroscopy (^{1}H-MRS) has also been used to assess whether OSAS can induce axonal loss or dysfunction, or myelin metabolism impairment. An early study using ^{1}H-MRS in 23 OSAS patients showed that the N-acetylaspartate/choline ratio (NAA/Cr) in cerebral white matter was significantly lower in patients with moderate to severe OSAS than in patients with mild OSAS and healthy subjects.[83] In a more recent study, magnetic resonance spectra were obtained from prefrontal cortex, parieto-occipital, and frontal periventricular white matter. The NAA/Cr and choline/creatine (Cho/Cr) ratios as well as absolute concentrations of NAA and Cho were significantly lower in the frontal white matter of OSAS patients when compared to controls.[84] These findings may explain some of the deficits in executive function associated with OSAS, but it is still unclear whether hypoxia or sleep fragmentation is the primary cause of such dysfunction.

Consistent with the VBM results above, decreases in absolute creatine-containing compounds in the left hippocampal area correlated with increased OSAS severity and worse neurocognitive performance.[85] Interestingly, a recent study of Halbower et al.[86] showed decreased NAA/Cho ratio in the left hippocampus and in the right frontal cortex using the same technique in a pediatric population with OSAS.

Taken together these VBM and spectroscopy studies point to an atrophy and/or dysfunction of hippocampal regions in OSAS.

Brain Imaging of Cognitive Functions in OSAS

Cognition in OSAS patients has been extensively studied, yet little is known about associated functional cerebral changes. Thomas et al.[87] used fMRI to study 16 OSAS patients (8 of them were rescanned after treatment with positive airway pressure) and 16 healthy controls during a 2-back verbal working memory task. Both performance on the task and dorsolateral prefrontal activity were reduced in the patients' population, regardless of nocturnal hypoxia (Figure 4). After treatment, resolution of subjective sleepiness and the partial recovery of posterior parietal activation contrasted with persistent performance deficits and lack of prefrontal activation. Another fMRI study examined the cerebral correlates of learning and memory in 12 nontreated OSAS patients and 12 matched healthy controls.[88] Verbal learning performance was similar for both groups, but OSAS patients showed increased brain activation in different regions, including bilateral inferior frontal and middle frontal gyri, cingulate gyrus, thalamus, and cerebellum. The recruitment of additional brain areas during the task in OSAS patients reflect an adaptive compensatory recruitment response.[88] This hypothesis is consistent with increased brain activity seen after sleep deprivation in healthy subjects which has been thought to reflect dynamic, compensatory changes in cerebral activation during a task after sleep deprivation.[89]

Cognitive performance may improve with nasal continuous positive airway pressure (nCPAP) treatment, but evidence suggests that some cognitive impairments may be permanent. For instance, improved attention and vigilance is commonly reported after nCPAP treatment in OSAS patients, but no such improvement is found for constructional abilities or psychomotor functioning.[76] Intrinsic neural dysfunction may explain the neuropsychological deterioration in OSAS patients.[90] In addition, several studies have linked OSAS and depression.[14] Overlaps of structural and functional deficits in the hippocampus, anterior cingulate, and frontal cortex (areas consistently showing abnormal structure or function in the depression literature[91]) provide several potential biological links between OSAS and mood disorders. Regardless of the mechanism, nCPAP therapy in OSAS patients can decrease depression scores and overall psychopathology, thus providing further evidence for a relationship between both these pathologies.[92]

Neural Correlates of Autonomic Dysfunction and Impaired Ventilatory Control

The apneas in OSAS patients have considerable hemodynamic consequences, involving a complex cascade of physiological events. Repetitive episodes of apnea trigger marked fluctuations in both blood pressure and heart rate and affect cardiovascular regulation. Several important regulatory mechanisms in cardiovascular homeostasis seem to be impaired in OSAS patients—for instance, the ventilatory response to carbon dioxide is elevated in OSAS patients.[72] This may be associated with an altered autonomic balance and result in the subsequent development of cardiovascular diseases in patients with OSAS.

Several fMRI studies have been conducted to characterize the response to sympathetic challenge or respiratory stress in OSAS patients. Based on the observation that OSAS patients exhibit altered sympathetic outflow, Harper et al.[93] used fMRI to assess changes in brain activity during a forehead cold pressor challenge, which typically elicits respiratory slowing, bradycardia, and enhanced sympathetic outflow. Compared with 16 control subjects, 10 OSAS patients exhibited signal increases in cingulate and cerebellar and frontal cortex; whereas fMRI signal decreased in medullary, midbrain areas, and cerebellar nuclei, as well as in ventral thalamus, hippocampus, and insula (with such signal modulation often paralleling changes in breathing and heart rate). In another study conducted in 8 drug-free OSAS patients (compared with 15 controls), the fMRI response to Valsalva maneuver revealed reduced brain response in parietal, temporal, and posterior insular cortex, as well as in the cerebellum and hippocampus; while activity was enhanced in the lateral precentral gyrus, anterior cingulate, and superior frontal cortex in OSAS.[94] These findings suggest that OSAS impacts on cerebellar, limbic, and motor areas involved in the control of airway muscles that mediate a compensatory response to the Valsalva maneuver. Another fMRI study investigated brain activity changes during baseline and expiratory loading conditions in 9 OSAS and 16 controls.[95] Both groups developed similar expiratory loading pressures, but OSAS patients failed to show the appropriate autonomic cerebral

responses. Indeed, OSAS patients had reduced activation within the frontal cortex, anterior cingulate, cerebellar dentate nucleus, dorsal pons, anterior insula, and lentiform nuclei, together with increased activation in the ventral pons, midbrain, quadrangular cerebellar lobule, and hippocampus. Moreover, activity in the fastigial nuclei of the cerebellum and the amygdala showed substantial variability increase in OSAS subjects. A more recent fMRI study evaluated brain activity changes during baseline and inspiratory loading in 7 patients with OSAS and 11 controls.[96] A number of cortical and subcortical areas mediating sensory, motor, and autonomic processes were affected in OSAS patients, with abnormal activation in primary sensory thalamus and sensory cortex, supplementary motor cortex, cerebellar cortex and deep nuclei, cingulate, medial temporal, and insular cortices, right hippocampus, and midbrain.[96] Taken together, these fMRI results indicate abnormal brain responses to experimentally induced respiratory and cardiovascular stresses in OSAS, most frequently affecting the cerebellum, insula, cingulate, and motor cortices. This altered pattern of brain activity in OSAS patients during physiologic stress also suggests that similar brain dysfunctions may occur during pathological apneas in sleep, which could lead to permanent neural changes over time. Interestingly, an fMRI study showed significant signal increases in hippocampus, frontal cortex, precentral gyrus, frontal cortex, mediodorsal thalamus, and cerebellar cortex and decreases in the anterior cingulate cortex and postcentral gyrus, coincident with apnea during Cheyne-Stokes breathing (characterized by repeated episodes of apnea followed by increasing and declining respiratory efforts during sleep) in 2 patients.[97]

Neural Consequences of Treatment in OSAS

A few studies have assessed the long-term neural consequences of nasal continuous positive airway pressure (nCPAP) treatment in OSAS. In an early ^{99}mTC-HMPAO SPECT study in 14 adult OSAS patients, tracer injections were performed between 02:00 and 04:00 during stage 2 sleep, when numerous episodes of obstructive apnea were observed.[98] Reduced perfusion in the left parietal region was found, which was completely reversed under effective nCPAP therapy, suggesting that some deleterious effects of OSAS on brain activity might be reversible.[87] In another study using ^{1}H-MRS in 14 OSAS patients, NAA in the parietal-occipital cortex was significantly reduced more in OSAS patients than in controls but, unlike the SPECT study above, this reduction persisted after nCPAP therapy despite clinical, neuropsychological, and neurophysiological normalization.[99]

The effect of mandibular advancement (a frequent treatment of OSAS) was studied in 12 healthy subjects using fMRI during respiratory stress induced by resistive inspiratory loading.[100] This treatment led to decreased fMRI response in the left cingulate gyrus and bilateral prefrontal cortices. Together with these objective results, the subjective effects of the treatment assessed by a visual analog scale confirmed the successful reduction of respiratory stress.

Based on the available data, it remains unresolved whether cerebral dysfunctions in OSAS can be alleviated by efficient treatment of nocturnal apnea.

Summary

The reviewed studies suggest that neuropsychological impairments in OSAS are attributable to functional alterations in prefrontal, anterior cingulate, hippocampal, and parietal cortices. Even if abnormal brain activations are sometimes reversible under nCPAP, persistent structural brain changes have been reported in OSAS patients. Consistent with such findings, several studies have suggested that not all neuropsychological impairments disappear after nCPAP treatment. Although the basic mechanisms underlying OSAS are not completely understood, a dysregulation in autonomic functions might contribute to the neural pathophysiology of OSAS. However, it is important to note that some of the deficits observed in OSAS patients may also be attributable to other concomitant factors such as age, elevated body mass index, or depression.

ABNORMAL MOTOR BEHAVIOR (1): PERIODIC LIMB MOVEMENTS AND RESTLESS LEGS SYNDROME

Periodic limb movements in sleep (PLMS) and restless legs syndrome (RLS) are distinct but overlapping syndromes. PLMS is characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep (mainly NREM sleep).[4,101] To date, the largest epidemiological study evaluating the simultaneous presence of PLMS and sleep complaints reported a 3.9% prevalence in 18,980 subjects from the general population between 15 and 100 years of age.[102]

The diagnosis of PLMS requires the presence of PLMS on polysomnography as well as an associated sleep complaint such as "unrefreshing sleep." Partial arousal or even awakening frequently accompanies movements, but the patient is usually unaware of these movements or sleep disruption. Periodic limb movements are themselves nonspecific, occurring during *sleep*—(PLMS) with RLS and with other sleep disorders (e.g., narcolepsy, sleep apnea syndrome, REM sleep behavior disorder)—or during *wakefulness* (PLMW) and also in healthy subjects.[103] Thus, the diagnosis of PLMS requires the exclusion of other potential causes for the associated sleep complaint.

Restless legs syndrome (RLS) is a disorder characterized by uncomfortable leg sensations, usually prior to sleep onset or during the night, which cause an almost irresistible urge to move the legs.[4,101] The prevalence of RLS is estimated at 5% to 20%.[101] The diagnosis of RLS, by contrast to PLMS, is essentially made on clinical grounds. In addition, most of the patients who suffer from RLS also have PLMS. Psychiatric illnesses such as depression and anxiety have been associated with chronic sleep loss[20,104] and appear to be more prevalent in those with RLS and PLMS than with normal controls.[105,106] Interestingly, several genetic variants associated with susceptibility to PLMS[107] and RLS[108] were discovered recently. As RLS and PLMS are not always distinguished in the literature, our review below will cover both RLS and PLMS together.

Structural Abnormalities

Recently structural cerebral abnormalities have been reported in patients with idiopathic RLS. High-resolution T1-weighted MRI of 51 patients compared with 51 controls using VBM re-

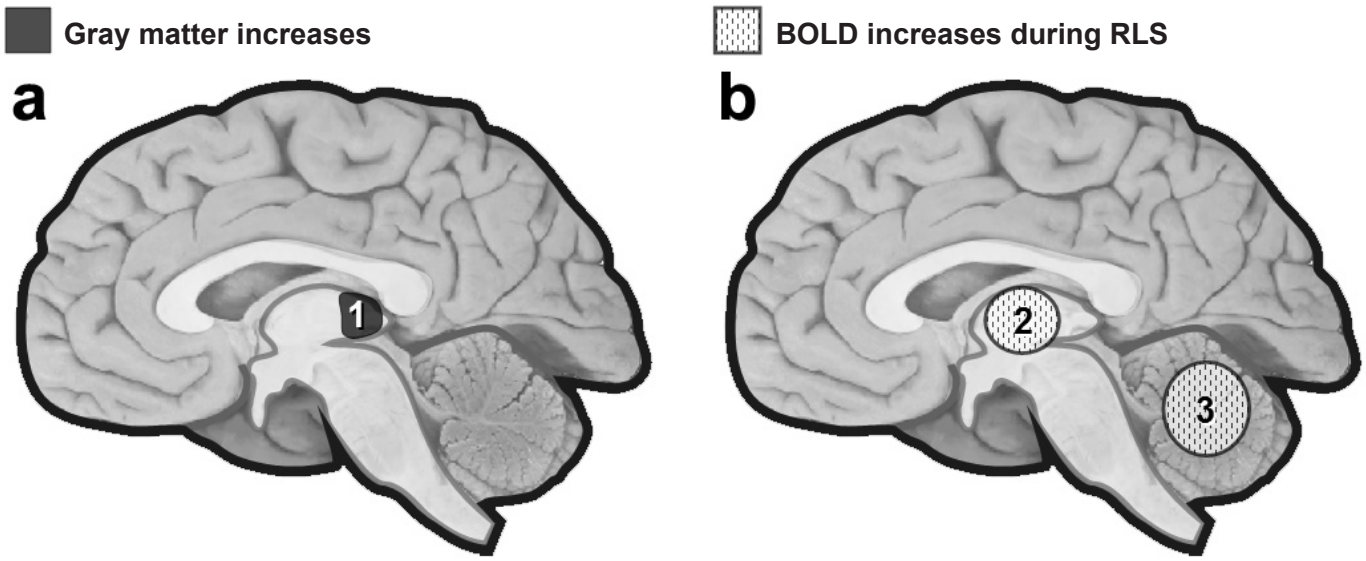

Figure 5—(a) Cortical gray matter changes in RLS. VBM in RLS patients revealed bilateral gray matter increase in the pulvinar.[109] (b) BOLD increases during RLS. Cerebellum and thalamus are more activated (fMRI) when RLS patients experience leg discomfort.[110] 1 = pulvinar, 2 = thalamus, 3 = cerebellum.

vealed a bilateral gray matter increase in the pulvinar (Figure 5).[109] The authors suggested that changes in thalamic structures could be directly involved in the pathogenesis of RLS or may instead reflect a consequence of dopaminergic therapy or of a chronic increase in afferent input due to sensory leg discomfort.

Functional Imaging

Functional neuroimaging has also attempted to localize some cerebral generators of leg discomfort and periodic limb movements in RLS. An fMRI study (19 patients) performed during wakefulness showed bilateral activation of the cerebellum and contralateral activation of the thalamus when patients with RLS experienced leg discomfort.[110] This is partially consistent with the VBM study reported above.[109] During a second condition combining periodic limb movements and sensory leg discomfort, patients also showed activity in the cerebellum and thalamus, with additional activation in the red nuclei and brainstem close to the reticular formation. In neither condition was any cortical activation found. However, when subjects were asked to voluntarily imitate PLMS, there was no activation in the brainstem, but rather additional activation in the globus pallidus and motor cortex. These results are in agreement with those of an EEG study showing no cortical potentials prior to periodic leg movements during the daytime.[111] Together, these results support an involuntary mechanism of induction and a subcortical origin for RLS, as also suggested by a transcranial magnetic stimulation study.[112]

Neurotransmission Abnormalities

A suprasegmental release of inhibition from descending inhibitory pathways implicating dopaminergic, adrenergic, and opiate systems is thought to be involved in RLS/PLMS pathogenesis.

Dopaminergic System

RLS becomes worse when dopamine antagonists are given, whereas dopaminergic drugs have been shown to relieve RLS.[113] Studies using SPECT or PET examined both presynaptic DA transporter and postsynaptic D2-receptor binding in the striatum to better characterize the neurophysiological mechanisms underlying the deficit.

Presynaptic DA transporter reflects the number of DA neurons in the substantia nigra and was shown to be similar[114-116] or moderately hypofunctional[117,118] between patients with RLS (accompanied or not by PLMS) and controls. Two studies used a ligand marker binding dopamine transporter to evaluate striatal presynaptic DA status in RLS-PLMS patients and controls and found no difference between the 2 populations.[115,116] In another study, presynaptic striatal dopamine activity correlated negatively with the number of PLMS in 11 patients with idiopathic Parkinson disease (PD) and periodic leg movements during sleep, suggesting that striatal dopaminergic nerve cell loss might cause PLMS in PD.[119]

For postsynaptic D2-receptor binding, the results are more equivocal. On the one hand, several SPECT studies[114,120] comparing RLS (with or without PLMS) patients to age-matched controls failed to find any significant difference. In one of these studies,[120] 14 patients with idiopathic RLS and PLMS successfully treated by dopaminergic (e.g., ropinirole) and nondopaminergic (e.g., gabapentin) treatment were investigated while off medication and compared to 10 healthy controls. The patients presented sleep disturbances, severe PLMS, and severe RLS symptoms during scanning but did not show any signifi-

cant differences in striatum/frontal D2 receptors binding ratio. These findings suggest that the dopaminergic system might be affected elsewhere, possibly in the diencephalo-spinal part of the dopaminergic system.

On the other hand, Staedt et al. have tested the hypothesis of a decrease in dopaminergic activity in PLMS patients across a series of SPECT studies[121-123] and consistently reported decreased IBZM (postsynaptic) striatal uptake, indicating lower D2 receptor occupancy in PLMS patients. Treating patients with dopamine replacement therapy increased IBZM binding and improved the sleep quality in these patients.[122] In line with these results, another SPECT study reported a small but statistically significant decrease in D2-receptor binding in 10 drug-naive patients suffering from both RLS and PLMS compared with 10 age-matched controls.[116] Consistent with this observation, a PET study showed a decrease in striatal D2-receptor binding (postsynaptic) for raclopride (an in vivo marker of dopamine D2/D3 receptor binding) in 13 patients with RLS compared with controls.[118] No relationship was observed, however, between D2-receptor binding and either RLS severity or PLMS indices.[116,118]

A recent study investigated both striatal and extrastriatal dopamine activity in 16 RLS patients naïve to dopaminergic drugs and 16 matched controls.[124] The results confirmed augmented dopamine activity in the striatum, but also in the thalamus, insula, and anterior cingulate cortex. The latter is part of the medial nociceptive system, which is thought to regulate the affective and motivational component of pain. This pattern of results is thus consistent with the hypothesis of RLS as a disorder of somatosensory processing.

Overall, presynaptic DA transporter binding appears normal in patients with RLS, contrary to what is typically found in early Parkinson disease, suggesting that these two conditions do not share a common pathophysiology. However, postsynaptic D2-receptor binding may be decreased indicating a possible dysfunction of D2-receptors or down-regulation due to increased levels of site occupancy by endogenous DA resulting from an increase in DA release. In addition, extrastriatal (i.e., thalamus and anterior cingulate cortex) as well as striatal brain areas seem to be involved in DA dysfunctions and these extrastriatal areas may subtend a possible pathway for sensory symptoms of RLS.

Iron Metabolism Abnormalities

Some recent studies implicated the cerebral metabolism of iron in the physiopathology of RLS-PLMS.[125] Importantly, iron and dopaminergic systems are linked since iron is an important cofactor for tyrosine hydroxylase, the step-limiting enzyme in DA synthesis, and also plays a major role in the functioning of post-synaptic D2 receptors.[126]

A neuropathologic study (7 RLS brain and 5 normal brains) showed a marked decrease of H-ferritin (ferritin heavy chain) and iron staining in RLS substantia nigra.[127] Using a special MRI measurement (R_2*), Allen et al.[128] found decreased regional iron concentrations in the substantia nigra and in the putamen of 5 patients with RLS (compared to 5 controls), both in proportion to RLS severity, consistent with regional iron insufficiency in RLS patients. In a more recent study, the same team found diminished iron concentration across 10 brain regions in early-onset RLS (beginning of RLS symptoms before 45 years, n = 22), but not in late-onset RLS (n = 19) when compared to controls (n = 39).[129] These convergent observations suggest that RLS may be associated with impaired iron metabolism (i.e., impaired regulation of transferring receptors), which might indirectly affect the dopamine system as well.

Opiate System

Opioid receptor agonists, acting predominantly on the pain system, have been found to significantly improve RLS symptoms.[130] Nevertheless, available data suggest that this effect may be mediated by dopamine and may thus not be related to specific deficiencies of the endogenous opioid system.[131] Using PET and ^{11}C-diprenorphine (a nonselective opioid receptor radioligand), von Spiczak et al.[132] found no difference in opioid receptor binding between 15 RLS patients and 12 controls. However, in this study, negative regional correlations between ligand binding and RLS severity was found in the pain system (medial thalamus, amygdala, caudate nucleus, anterior cingulate gyrus, insula, and orbitofrontal cortex). Moreover, pain scores correlated inversely with endogenous opioids binding in orbitofrontal cortex and anterior cingulate gyrus. Therefore, the most likely interpretation of decreased opioid binding (i.e., availability) may be an increase in endogenous opioid release consecutive to pain or dysesthesia.[132]

Summary

PMLS/RLS still appears as a complex and multifarious movement disorder which implicates many brain areas and most probably a variety of pathophysiological mechanisms. However, the recent findings from anatomical, functional, and ligand neuroimaging studies converge to suggest a critical involvement of mostly subcortical regions (brainstem, thalamus, cerebellum) and of the dopamine system in the control and generation of leg movements. However, because presynaptic dopamine function is normal in PMLS/RLS disorders, the underlying pathophysiological mechanisms must differ from Parkinson disease. In addition, several observations suggest that RLS may be associated with impaired iron metabolism that will indirectly affect the dopamine system. Finally, consistent with PMLS/RLS being related to major somatosensory disturbances, abnormal dopamine and opioid activity was found in regions belonging to the medial pain system (e.g., thalamus, anterior cingulate, insula) which mediate the unpleasant component of pain.[133] It is noteworthy that there are no data available during sleep itself, probably given methodological difficulties such as the unpredictability of occurrence of leg movements, as well as scanning artifact due to movements.

ABNORMAL MOTOR BEHAVIOR (2): REM SLEEP BEHAVIOR DISORDER

REM sleep behavior disorder (RDB) is characterized by brisk movements of the body associated with dream mentation that usually disturb sleep continuity.[134] This parasomnia has a prevalence estimated at 0.5% of the population,[135] mainly affecting men older than 50 years of age. During the night, patients be-

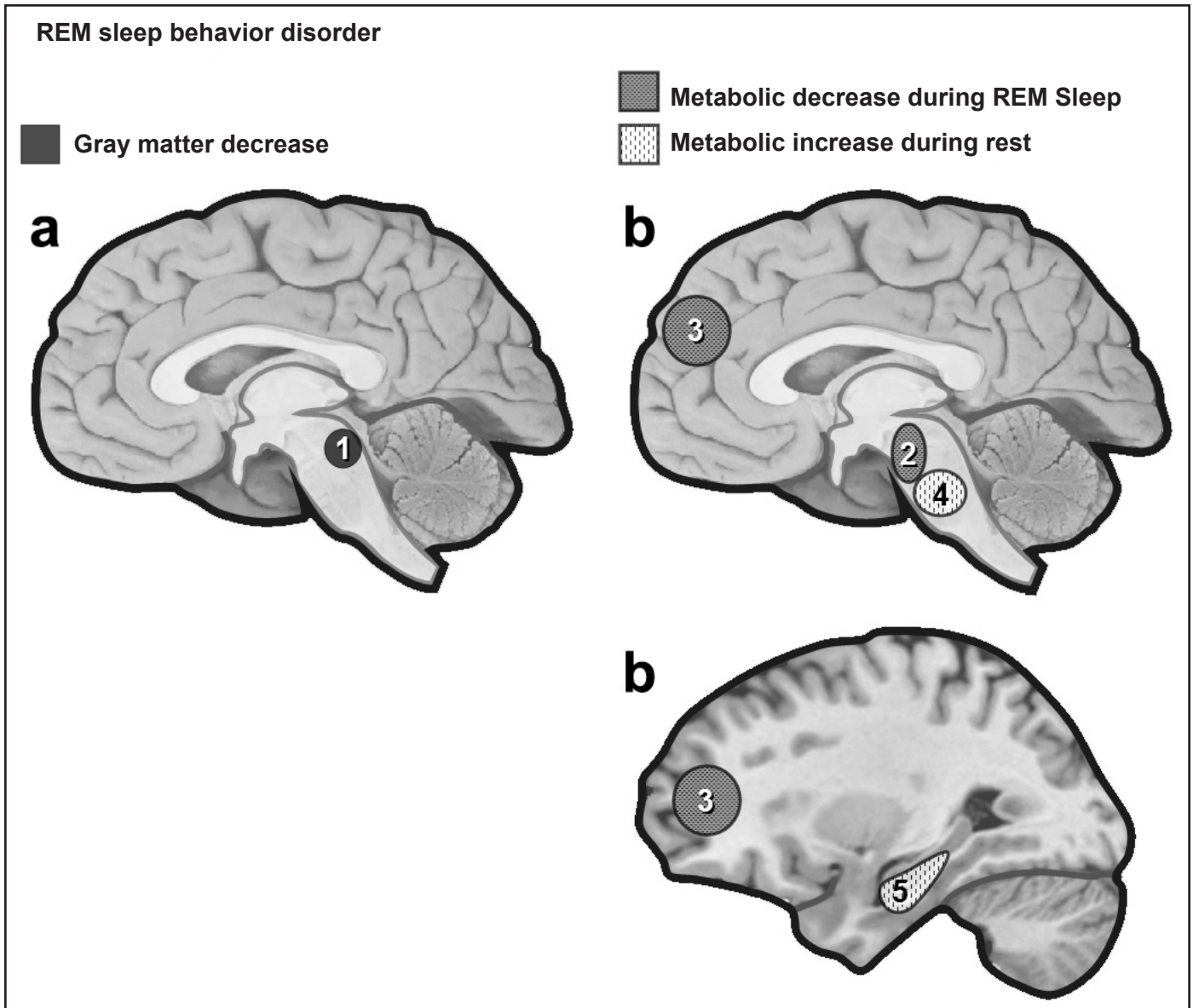

Figure 6—(a) Brain lesions in RDB. Patients with RDB have lesions affecting the dorsal mesopontine tegmentum.[142] (b) Metabolic changes during REM sleep, patients with RBD show decreased blood flow (SPECT) in the pons and superior frontal regions,[143] and increased activity in the pons, putamen and hippocampus during rest at wake.[144] 1 = mesopontine tegmentum, 2 = pons, 3 = superior frontal lobe, 4 = pons, 5 = right hippocampus.

have as if they were acting out their dreams. The disease may be idiopathic (up to 60%) or associated with other neurological disorders. A sizeable proportion of patients with RBD will develop extrapyramidal disorders,[136,137] Lewy body dementia,[138] or multiple system atrophy.[139,140] Critically, signs of RBD may often precede the clinical onset of neurodegenerative diseases such as Parkinson disease or Lewy body dementia.[136,138] Any evidence for RBD should thus be considered with great care as this may have major clinical implications.

Structural and Functional Abnormalities

An early experimental model of RBD in the cat showed that lesions in the mesopontine tegmentum can lead to the disappearance of muscle atonia during REM sleep and the appearance of dream-enactment behavior.[141] A magnetic resonance imaging (MRI) study confirmed this hypothesis in man, showing that 3 of 6 patients with RDB had lesions affecting the dorsal mesopontine tegmentum (Figure 6).[142] A study combining anatomical MRI and ^{123}I-IMP SPECT measurements during REM sleep in 20 patients with RBD reported significantly decreased blood flow in the pons and superior frontal regions in patients with RBD, in comparison with 7 normal elderly subjects.[143] Decreased blood flow in the frontal lobe of patients with RBD did not correlate with frontal lobe atrophy. Another SPECT study in 8 RBD patients during waking rest confirmed decreased activity in frontal and temporoparietal cortices and found increased activity in the pons, putamen, and right hippocampus.[144] Similarly, "acting out" of oneiric behaviors was associated with significantly lower cerebral metabolic rate for glucose in a set of

brain areas (parietal, temporal, and cingulate cortices) in both Alzheimer and dementia with Lewy body disease.[145]

Increased Cho/Cr ratio in the brainstem suggesting local neural dysfunction was revealed by proton magnetic resonance spectroscopy (^{1}H-MRS) in a 69-year-old man with idiopathic RBD.[146] However, another ^{1}H-MRS study in a large group of patients with idiopathic RBD (n = 15) compared to matched controls (n = 15) did not reveal any difference in NAA/Cr, Cho/Cr, and myoinositol/Cr ratios in the pontine tegmentum and the midbrain.[147] Mesopontine neuronal loss or ^{1}H-MRS detectable metabolic disturbances in idiopathic RBD therefore remain hypothetical. Future ^{1}H-MRS may provide a noninvasive metabolic evaluation of brainstem neuronal function in RBD and may usefully contribute to the differentiation of secondary RBD with neurodegenerative disorders from idiopathic disorders.[148]

Neurotransmission Abnormalities

Using SPECT, the binding of ligands of striatal presynaptic dopamine transporters in RBD patients (n = 5) during wakefulness was found to be lower than in normal controls but higher than in Parkinson patients (n = 14).[149,150] This result suggests that the number of presynaptic dopamine transporters decreases in both Parkinson and RBD patients. Moreover, such findings provide evidence for a continuum of striatal presynaptic dopaminergic dysfunction in patients with subclinical RBD (i.e., individuals who have REM sleep without atonia but without behavioral manifestations), clinical RBD, and Parkinson disease.[150] No such differences were found for a marker of postsynaptic D2 receptor density in RDB patients.[149]

The same conclusions were reached by another study that probed the density of striatal dopaminergic terminals using PET and 11C-dihydrotetrabenazine (11C-DTBZ, an in vivo marker for dopamine nerve terminals) in 6 elderly subjects with chronic idiopathic RBD compared to 19 age-matched controls.[151] Significant reductions in striatal ^{11}C-DTBZ binding were found in all striatal nuclei, with the greatest reduction in the posterior putamen. The striatal vesicular monoamine transporter density is actually considered to be a direct function of the number of DA neurons in the substantia nigra, therefore suggesting a loss of DA midbrain neurons in chronic RBD.

Recently, one SPECT study using a radiomarker of the presynaptic dopamine transporter in 11 RBD patients (mostly with narcolepsy) and controls revealed that 2 "idiopathic" RBD patients with severe olfactory dysfunction (anosmia) had degeneration of presynaptic nigrostriatal neurons, as determined by reduced dopamine transporter binding.[152] The authors suggested that the discrepancies between studies may be related to RBD symptoms duration, since patients who had reduced (2 patients) or pathologically asymmetrical (1 patient with mild hyposmia) dopamine transporter binding had by far the longest duration of RBD symptoms (14, 16, and 38 years).

It remains to be shown whether these alterations (mainly dysfunction in mesopontine tegmentum and DA neurotransmission impairments) play a causal role in the pathophysiology of RBD, or reflect functional consequences or adaptations to the pathological condition. Although there is evidence that some Parkinson patients do show excessive nocturnal movements,[119,153] only a small percentage of Parkinson patients develop full-blown RBD. RBD has been found to also occur in patients with voltage-gated potassium channel antibody-associated limbic encephalitis.[154] These observations suggest that modifications involving other systems of neurotransmission and/or other regions (e.g., frontal lobe, limbic system) are probably necessary for full-blown RBD to occur.

Summary

Dream-enactment behavior during REM sleep, which characterizes RBD, may in some cases be idiopathic but is predominantly associated with neurodegenerative diseases. Results from proton magnetic resonance spectroscopy may usefully contribute to the differentiation of idiopathic versus secondary RBD associated with neurodegenerative disorders. Neuroimaging studies have revealed that RDB may affect several levels of cerebral organization, from neurotransmission (presynaptic striatal DA) to neuroanatomical integrity (lesions in mesopontine tegmentum) and brain function (frontal, temporoparietal and cingulate cortex dysfunctions). Whether these cerebral anomalies play a causal role in the pathophysiology of RBD or mainly reflect pharmacological consequences or adaptations to the pathological condition is still unclear.

CONCLUSIONS

Modern functional neuroimaging techniques provide unprecedented possibilities to explore brain functions during normal and pathological sleep. This review demonstrates that a functional brain imaging approach may address a wide range of issues pertaining to the treatment and underlying pathophysiology of sleep disorders.

One line of research aims to characterize the neural consequences of sleep disruption due to intrinsic sleep disorders or to extrinsic environmental or medical causes. Functional neuroimaging can also be used to assess the effects of hypnotic drugs on regional brain function. A second, more fundamental challenge for a neuroimaging approach is to determine to what extent cerebral dysfunctions at wake as well as during sleep contribute to the primary physiological mechanisms of sleep disorders.

Although this review shows that neuroimaging can be used to achieve these goals, the approach is hampered by several factors: (a) Scanning patients or controls during their sleep or during pathological manifestations requires specialized equipment (e.g., EEG) and many adjustments in the scanning parameters (especially for fMRI studies). In addition, it is never guaranteed that the participant will sleep during data acquisition. Clinical manifestations of sleep disorders are often unpredictable and transient (e.g., sleepwalking, RBD); thus one cannot predict if the pathological event will occur during the scanning period. Moreover, clinical manifestations are often associated with large body movements that may interfere with image acquisition and create artifacts. In this respect, SPECT is probably the most appropriate procedure because the radiotracer can be administered during the clinical events, well before the brain images are acquired. An excellent example of such a study pertains to sleepwalking.[155] (b) Assessing short- or long-term effects of treatments remains complicated, since neuroimaging data col-

lected at different time points cannot be straightforwardly compared because of unavoidable fluctuations in signal (e.g., fMRI), and more importantly because treatments may have nonspecific influences across a distributed network of areas (e.g., dopamine system). Moreover, as suggested by the present review, it is difficult to find large and homogeneous groups of patients. (c) Last but not least, the theoretical framework necessary for designing an efficient clinical neuroimaging protocol is only available for a few sleep disorders. One such example is narcolepsy; the discovery of the hypocretin system and its role in narcolepsy in the late 90s[156] has indubitably changed the main goal and target systems (and thus the experimental designs) of neuroimaging studies in narcoleptic patients.[39,50]

Neuroimaging studies may usefully contribute to the establishment or refinement of a nosography of sleep disorders. For instance, neuroimaging could help classify different subtypes of insomnia in terms of their underlying characteristic patterns of regional brain activity, an approach that may prove complementary to standard clinical observation.

Although substantial methodological progress has been achieved, much effort is still needed to better characterize neurophysiological mechanisms involved in sleep disorders, especially in teasing apart those mechanisms which have a causal role in the pathophysiology from those which are secondary consequences. Future brain imaging will undoubtedly provide new and valuable information about the functional and structural consequences of long-term sleep disruption. Ultimately, neuroimaging will help with clinical diagnosis and prognosis of sleep pathologies at an individual level. These considerations argue for closer collaboration and partnership between basic and imaging neuroscientists, sleep researchers, and sleep clinicians for designing and conducting multimodal assessments of sleep disorders.

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7.4. Obsessive-compulsive disorders

From

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Summary

Obsessive-compulsive disorder is a frequent and debilitating illness characterised by obsessions and/or compulsions. It causes a major distress for the patients and their families. Evaluation scales can complete the diagnosis which is mainly clinic. The physiopathology of OCD is not yet fully understood although several etiological hypotheses have been proposed and despite the existence of various treatment approaches. This review aimed at summarizing the last progress made in the understanding of the OCD physiopathology.

Les troubles obsessionnels-compulsifs

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Obsessive-compulsive disorder is a frequent and debilitating illness characterised by obsessions and/or compulsions. It causes a major distress for the patients and their families. Evaluation scales can complete the diagnosis which is mainly clinic. The physiopathology of OCD is not yet fully understood although several etiological hypotheses have been proposed and despite the existence of various treatment approaches. This review aimed at summarizing the last progress made in the understanding of the OCD physiopathology.

Key words : Psychiatry, Anxiety Disorders, Obsessive-Compulsive Disorder, Physiopathology

Introduction

Le Trouble obsessionnel-compulsif (TOC) est une maladie fréquente classée dans les « troubles anxieux » du manuel diagnostique et statistique des troubles mentaux (DSM-IV-TR) (American Psychiatric Association, 2000). Nous verrons dans cette revue que le TOC présente des différences avec les autres troubles anxieux (Bartz et Hollander, 2006) tant au point de vue épidémiologique, étiologique que de la comorbidité. De plus, le TOC appartiendrait à un ensemble plus large de troubles comprenant des symptômes obsessionnels ou compulsifs (Castle et Phillips, 2006).

Epidémiologie

La prévalence à 12 mois du TOC chez les *adultes* varie entre 0,1 % et 2,3 % selon une méta-analyse récente faite à partir de 21 études européennes (Wittchen et Jacobi, 2005). De plus, il semble que le TOC soit présent dans de nombreux pays à travers le monde avec une prévalence quasi identique dans les différents pays où s'est déroulée l'étude à l'exception de Taiwan qui présentait une prévalence particulièrement basse (0,4 %) (Weissman et al., 1994). Chez les adultes, la prévalence du TOC serait globalement répartie de façon équivalente entre les hommes et les femmes (Sasson et al., 2001). La prévalence sur la vie est de l'ordre de 2 % (Ansseau et al., 1999).

Chez les *adolescents*, la répartition « homme-femme » du TOC est plus discutée. Ainsi, une étude indique que la prévalence chez les adolescents (moyenne d'âge de 16,6 ans) est de 0,53 % en moyenne mais serait environ deux fois plus élevée pour les garçons que pour les filles (Lewinsohn et al., 1993). Cependant, une autre étude sur un plus petit échantillon montre une prévalence de 4 % avec un ratio homme : femme de 0,7 : 1 (Douglass et al., 1995).

Chez les *enfants* entre 5 et 15 ans, une étude portant sur un large échantillon a montré une prévalence de 0,25 % (Heyman et al., 2003).

L'impact économique du TOC est très important et serait en partie dû au fait que la maladie est sous-diagnostiquée, et donc traitée trop tardivement, ce qui entraînerait des perturbations personnelles et professionnelles entre autres (Stein et al., 1996).

Description clinique

Le TOC (Figure 1) ne s'apparente que de loin à la névrose obsessionnelle (Figure 2) dans la mesure où la névrose obsessionnelle fait appel à la notion de structure psychique et fait appel à des mécanismes psychodynamiques particuliers qui ne sont pas pris en compte dans l'approche catégorielle du DSM-IV-TR. De plus, le TOC a peu à voir avec le « trouble de personnalité obsessionnel-compulsif » (Figure 3) ou la personnalité obsessionnelle (Figure 4). Il est considéré comme une entité psychopathologique à part entière par le courant psychiatrique qui s'inspire de l'approche prônée par le DSM (« Diagnostic and Statistical Manual of Mental Disorders », Manuel Diagnostic et Statistique des troubles mentaux). Selon le DSM-IV-TR (American Psychiatric Association, 2000) (Figure 1), le TOC se caractérise par la récurrence d'obsessions et de compulsions, ce qui entraîne une souffrance importante du sujet mais aussi de sa famille. Les *obsessions* sont des pensées intrusives, dérangeantes, génératrices d'anxiété. Le sujet reconnaît que ses pensées sont issues de lui-même, et non imposées de l'extérieur comme c'est le cas chez certains patients psychotiques présentant des idées de référence. Les *compulsions* sont des actes ou des pensées exécutées en réponse aux obsessions, afin de les neutraliser et de diminuer

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Figure 1

Diagnostic DSM-IV-TR du Trouble Obsessionnel-Compulsif

Existence soit d'obsessions soit de compulsions.

Obsessions définies par :

(1) Pensées, impulsions ou représentations récurrentes et persistantes qui, à certains moments de l'affection, sont ressenties comme intrusives et inappropriées et qui entraînent une anxiété ou une détresse importante.

(2) Les pensées, impulsions ou représentations ne sont pas simplement des préoccupations excessives concernant les problèmes de la vie réelle.

(3) Le sujet fait des efforts pour ignorer ou réprimer ces pensées, impulsions ou représentations ou pour neutraliser celles-ci par d'autres pensées ou actions.

(4) Le sujet reconnaît que les pensées, impulsions ou représentations obsédantes proviennent de sa propre activité mentale (elles ne sont pas imposées de l'extérieur comme dans le cas des pensées imposées).

Compulsions définies par :

(1) Comportements répétitifs (p. ex., lavage des mains, ordonner, vérifier) ou actes mentaux (p. ex., prier, compter, répéter des mots silencieusement) que le sujet se sent poussé à accomplir en réponse à une obsession ou selon certaines règles qui doivent être appliquées de manière inflexible.

(2) Les comportements ou les actes mentaux sont destinés à neutraliser ou à diminuer le sentiment de détresse ou à empêcher un événement ou une situation redoutés ; cependant, ces comportements ou ces actes mentaux sont soit sans relation réaliste avec ce qu'ils se proposent de neutraliser ou de prévenir, soit manifestement excessifs.

A un moment durant l'évolution du trouble, le sujet a reconnu que les obsessions ou les compulsions étaient excessives ou irraisonnées. N.B. : Ceci ne s'applique pas aux enfants.

Les obsessions ou compulsions sont à l'origine de sentiments marqués de détresse, d'une perte de temps considérable (prenant plus d'une heure par jour) ou interfèrent de façon significative avec les activités habituelles du sujet, son fonctionnement professionnel (ou scolaire) ou ses activités ou relations sociales habituelles.

Si un autre Trouble de l'Axe I est aussi présent, le thème des obsessions ou des compulsions n'est pas limité à ce dernier (p. ex., préoccupation liée à la nourriture quand il s'agit d'un Trouble des conduites alimentaires ; au fait de s'arracher les cheveux en cas de Trichotillomanie ; inquiétude concernant l'apparence en cas de Peur d'une dysmorphie corporelle ; préoccupation à propos de drogues quand il s'agit d'un Trouble lié à l'utilisation d'une substance ; crainte d'avoir une maladie sévère en cas d'Hypocondie ; préoccupation à propos de besoins sexuels impulsifs ou de fantasmes en cas de Paraphilie ; ou ruminations de culpabilité quand il s'agit d'un Trouble dépressif majeur).

La perturbation ne résulte pas des effets physiologiques directs d'une substance (p. ex. : une substance donnant lieu à abus, un médicament) ni d'une affection médicale générale.

Spécifier si :

Avec peu de prise de conscience : si la plupart du temps durant l'épisode actuel, le sujet ne reconnaît pas que les obsessions et les compulsions sont excessives ou irraisonnées.

Figure 2

Description de la névrose obsessionnelle selon la nosographie française

La névrose obsessionnelle est définie par la survenue d'obsessions et de compulsions.

(1) Les **obsessions** sont des contenus psychiques qui assiègent littéralement l'esprit et sont incoercibles malgré la lutte anxieuse mise en œuvre pour tenter en vain de les chasser. Les contenus de pensée pouvant donner lieu à des obsessions sont très nombreux. Nous retiendrons entre autres, les obsessions **phobiques** (crainte spécifique qui existe en dehors de l'objet phobogène, ce qui la différencie des phobies spécifiques), les obsessions **idéatives** (ruminations obsédantes concrètes – mots, objets, chiffres, ... – ou abstraites – la vie, la mort, ... – ; débats de conscience interminables sur des vérifications, des omissions, des erreurs, ...), les obsessions **impulsives** ou « phobies d'impulsion » (crainte d'être amené de façon irrésistible à commettre un acte nuisible voire criminel).

(2) Les **compulsions** sont des actes auxquels le sujet se sent contraint de manière répétitive, tout comme un rite, tout en reconnaissant leur caractère absurde, ridicule et embarrassant. Les plus fréquentes sont les rites de **lavage**, les rites de **vérifications**, les manies du **retour en arrière**, rites concernant l'habillement et la **toilette**, **arithmomanie** (calculs mentaux réalisés avant toute action), **onomatomanie** (recherche obsédante de la signification d'un mot, crainte de prononcer des mots tabous, rituels de mots conjuratoires).

Figure 3

Diagnostic DSM-IV-TR du Trouble de Personnalité Obsessionnel-Compulsif

Mode général de préoccupation pour l'ordre, le perfectionnisme et le contrôle mental et interpersonnel, aux dépens d'une souplesse, d'une ouverture et de l'efficacité, qui apparaît au début de l'âge adulte et est présent dans des contextes divers, comme en témoignent au moins quatre des manifestations suivantes :

(1) Préoccupations pour les détails, les règles, les inventaires, l'organisation ou les plans au point que le but principal de l'activité est perdu de vue.

(2) Perfectionnisme qui entrave l'achèvement des tâches (p. ex. : incapacité d'achever un projet parce que des exigences personnelles trop strictes ne sont pas remplies).

(3) Dévotion excessive pour le travail et la productivité à l'exclusion des loisirs et des amitiés (sans que cela soit expliqué par des impératifs économiques évidents).

(4) Est trop consciencieux, scrupuleux et rigide sur des questions de morale, d'éthique ou de valeurs (sans que cela soit expliqué par une appartenance religieuse ou culturelle).

(5) Incapacité de jeter des objets usés ou sans utilité même si ceux-ci n'ont pas de valeur sentimentale.

(6) Réticence à déléguer des tâches ou à travailler avec autrui à moins que les autres se soumettent exactement à sa manière de faire les choses.

(7) Se montre avare avec l'argent pour soi-même et les autres ; l'argent est perçu comme quelque chose qui doit être thésaurisé en vue de catastrophes futures.

(8) Se montre rigide et têtu.

Figure 4

Description de la personnalité obsessionnelle selon la nosographie française

Caractère bien structuré associant :

(1) Un souci constant de l'ordre et de la propreté, une grande méticulosité, une ponctualité rigoureuse, un perfectionnisme. S'ensuivent différentes attitudes comme la fidélité aux engagements, le sens du devoir, l'attitude scrupuleuse dans les obligations, ...

(2) Le sens de l'économie pouvant aller jusqu'à l'avarice en passant par la mesquinerie. Ces personnes ont des difficultés à partager et à donner ce qui va de pair avec le plaisir de possession et qui conduit fréquemment à amasser (collections, ...).

(3) L'entêtement obstiné rend compte de la ténacité et de la persévérance de ces personnes. Elles sont souvent peu influençables et autoritaires.

Ces personnes cherchent fréquemment le mot exact et s'expriment avec concision. Elles sont froides et impassibles. Elles intellectualisent et ne laissent pas affleurer les affects qui pourraient les faire souffrir. La vie psychique de ces personnes paraît faite de souvenirs et de sentiments juxtaposés sans liens entre eux (mécanisme de défense : l'isolation). Un autre mécanisme de défense est fréquemment à l'œuvre : la formation réactionnelle ; c'est une attitude qui s'oppose à un désir refoulé et qui se constitue en réaction contre celui-ci. C'est donc d'abord un refoulement, puis un contre-investissement dans un élément conscient de force égale. Ainsi, la propreté excessive est une formation réactionnelle contre le goût de la saleté. De même, la soumission et la politesse exagérées sont des formations réactionnelles contre l'agressivité inconsciente intense.

ainsi l'anxiété. Au *début* de la maladie, l'individu peut tenter de résister aux compulsions, ce qui crée une grande anxiété. Au fur et à mesure de l'*évolution* et après plusieurs échecs de résistance, le sujet n'essayerait plus de combattre ses compulsions et se laisserait aller à elles, les intégrant dans ses activités quotidiennes.

Sous-types

Les TOC forment un groupe hétérogène. Afin d'améliorer la prise en charge des patients, des phénotypes plus homogènes sont recherchés. En plus d'une description phénotypique, des endophénotypes (phénotypes étendus) basés sur des paradigmes neurophysiologiques, génétiques, immunologiques, neuropsychologiques ou neuroanatomiques (imagerie cérébrale) sont recherchés (de Mathis et al., 2006).

Il existe différentes manières de subdiviser les patients présentant un TOC : classifications **catégorielles** (catégories exclusives basées soit sur la présence de tics, soit sur l'âge de début, soit sur des antécédents d'infection streptococcique), classifications **dimensionnelles** (dimensions biologiques et comportementales non exclusives déterminées principalement à partir d'analyses factorielles) et extension du phénotype des TOC (trouble du spectre obsessionnel-compulsif) (de Mathis et al., 2006).

En plus de l'âge d'apparition du TOC (Delorme et al., 2005), l'évolution (chronique ou épisodique) (Perugi et al., 1998), le degré d'insight (bon ou mauvais) (Aigner et al., 2005; De Berardis et al., 2005; Eisen et al., 2004; Matsunaga et al., 2002; Ravi Kishore et al., 2004) ainsi que l'origine des obsessions (obsessions autogènes ou réactives à un stimulus extérieur spécifique) (Lee et Kwon, 2003) permettent également de classer les patients. De plus, différents groupes symptomatiques ont été mis en évidence par des analyses factorielles à partir d'échelles cliniques du TOC (Baer, 1994; Leckman et al., 1997; Summerfeldt et al., 1999). Ces différentes catégories de symptômes sont corrélées à des comorbidités psychiatriques spécifiques (Hasler et al., 2005).

Dans la présente synthèse, nous avons choisi de présenter quelques grandes classes de la subdivision par symptômes car cette subdivision est la plus fréquemment utilisée en clinique:

1) **Contamination** : crainte persistante d'être contaminé par des objets ou par d'autres personnes, ou de contaminer soi-même d'autres personnes, entraînant des compulsions de lavage.
2) **Vérification** : vérifications compulsives en réponse à des obsessions de doute (« ai-je bien fermé la porte, le gaz… ? »).
3) **Accumulation** : accumulation excessive d'objets multiples (voire de déchets) qui n'ont aucune utilité objective, en réponse à des obsessions concernant la peur de jeter quelque chose d'important ou qui pourrait servir.
4) **Agressivité/Sexualité** : pensées obsédantes concernant le fait d'avoir blessé ou tué quelqu'un et/ou images à contenu sexuel ou agressif venant sans cesse à l'esprit. Ces craintes peuvent parfois s'appliquer au patient lui-même. Cette classe de symptômes est aussi appelée « phobie d'impulsion ».

Diagnostic

Age de début et évolution

Selon une étude prospective (Skoog et Skoog, 1999) s'étant déroulée sur une période de 40 ans, il semble que le TOC apparaisse le plus souvent au début de l'âge adulte (40 %), avec néanmoins une proportion significative (29 %) d'individus ayant débuté la maladie avant l'âge de 20 ans. Toujours selon cette étude, un début précoce (avant 20 ans) est plus fréquent chez les garçons (44 %) que chez les filles (22 %) et un début tardif (dès 40 ans) ne se retrouve que chez 4 % des sujets.

Dans au moins 50 % des cas, le TOC débuterait dans l'enfance ou l'adolescence (Sasson et al., 2001). Mais, malgré cette haute fréquence de début précoce et probablement en raison de la honte qu'ils éprouvent à parler de leurs symptômes, les patients seraient généralement pris en charge bien plus tard dans leur vie (Hollander et al., 1996).

Notons que la présence d'obsessions et de compulsions fait partie du développement normal de l'enfant ; ainsi il faudra être

prudent afin de ne pas poser un diagnostic trop hâtif de TOC et se référer à la clinique qui inclut une évaluation des contextes personnel, développemental, familial et scolaire entre autres (Sahuc, 2006).

Chez la plupart des individus, le TOC semble s'améliorer naturellement avec le temps, bien que certains symptômes puissent persister (Skoog et Skoog, 1999). Le TOC a le plus souvent une évolution chronique, mais une évolution épisodique se verrait chez certains patients (Perugi et al., 1998), avec possibilité de « chronicisation » ultérieure (Sasson et al., 1997 ; Skoog et Skoog, 1999). L'évolution épisodique semble être associée plus fréquemment à un trouble de l'humeur de type bipolaire (Tukel et al., 2007) et être de meilleur pronostic (Skoog et Skoog, 1999).

Le contenu des obsessions pourrait être lié à l'évolution du trouble étant donné les comorbidités spécifiques des différentes obsessions (Hasler et al., 2005).

D'une manière générale on peut distinguer différents facteurs (Sasson et al., 2001) de mauvais pronostic (la « soumission » aux compulsions, le début dans l'enfance, des compulsions « bizarres », la nécessité d'une hospitalisation, la coexistence d'un trouble dépressif caractérisé, et la présence d'un trouble de personnalité) et différents facteurs de bon pronostic (une bonne adaptation sociale et occupationnelle, la présence de facteurs précipitants – par exemple : grossesse, perte, traumatisme, une évolution épisodique des symptômes).

Spectre des troubles apparentés au TOC

De nombreuses autres maladies psychiatriques ou neurologiques présentent des comportements compulsifs ou impulsifs. C'est ainsi que des auteurs ont proposé un classement en termes de « spectre des troubles apparentés au TOC » selon une perspective dimensionnelle ou spectrale (Bouvard, 2006 ; Hollander et al., 2007). Un continuum dimensionnel a également été proposé (Hollander, 1993). Deux pôles sont présents, le pôle « compulsions » à une extrémité et un pôle « impulsions » à l'autre. Différentes pathologies sont situées sur cette dimension avec au pôle de compulsion, le TOC, et au pôle d'impulsion, le trouble de personnalité antisociale.

De plus, le spectre des troubles apparentés au TOC peut être divisé en trois groupes (Bouvard, 2006) :

1) Troubles se distinguant par la présence d'obsessions et de comportements répétitifs (pôle « compulsions ») : TOC, trouble dysmorphophobique, hypocondrie, dépersonnalisation, auxquels nous pourrions ajouter la schizophrénie (Kayahan et al., 2005) et les troubles du comportement alimentaire (Jimenez-Murcia et al., 2007) avec présence de TOC.
2) Troubles avec comportements impulsifs : kleptomanie, jeu pathologique, compulsions sexuelles, trichotillomanie, trouble de personnalité borderline et antisociale.
3) Maladies neurologiques avec symptômes obsessionnels-compulsifs : syndrome de Gilles de la Tourette, maladie de Huntington, maladie de Parkinson, chorée de Sydenham (atteinte due au streptocoque bêta-hémolytique, SBH), autisme, syndrome d'Asperger, ADHD (Attention Deficit Hyperactivity Disorder), torticolis spasmodique, auquel nous pourrions ajouter les troubles dus à des lésions cérébrales (incluant les accidents vasculaires cérébraux et les tumeurs cérébrales, les infections cérébrales et les accidents traumatiques du cerveau) (Coetzer, 2004).

Examens complémentaires

Lorsque nous sommes face à des symptômes obsessionnels-compulsifs, il nous semble important de déterminer avant tout à quelle entité ils appartiennent : TOC idiopathique ou TOC secondaire à une autre maladie psychiatrique ou neurologique.

Habituellement, pour ce qui est du TOC idiopathique et du TOC associé à une autre maladie psychiatrique, l'examen psychique seul devrait suffire au diagnostic. L'examen clinique sera normal, si ce n'est parfois la présence d'atteintes cutanées dues aux lavages intempestifs.

Les examens physiques complémentaires seront le plus souvent indiqués lorsqu'il y a, suite à l'examen clinique, suspicion d'une maladie organique (neurologique ou infectieuse) sous-jacente. Par exemple, on réalisera des examens en électroencéphalographie et en imagerie cérébrale à la recherche d'une tumeur ou d'une maladie vasculaire cérébrale. De même, la recherche d'anticorps antistreptococciques ainsi que le frottis de gorge se fera si l'on suspecte une infection à streptocoques bêta-hémolytiques du groupe A.

Echelles d'évaluation

Il existe plusieurs échelles d'évaluation qui explorent différents aspects des obsessions-compulsions. Bien qu'elles soient non indispensables en pratique clinique, elles se montrent généralement très importantes pour la recherche, notamment afin d'accéder au sous-typage de TOC selon les différents types d'obsessions ou de compulsions. Nous présentons ici trois échelles fréquemment utilisées en recherche :

1. L'échelle d'obsessions-compulsions de Yale Brown (Yale-Brown Obsessive Compulsive Scale, Y-BOCS) (Goodman et al., 1989a ; Goodman et al., 1989b) détecte pour chaque sujet pris individuellement ses trois principales obsessions-compulsions, et les évalue ensuite de façon globale selon cinq dimensions : durée, gêne, anxiété, degré de résistance, degré de contrôle.
2. L'inventaire de Padoue révisé (Padua Inventory – Revised, PI-R) (Sanavio, 1988 ; Van Oppen et al., 1995) est un auto-questionnaire subdivisé en sous-échelles représentant différents sous-types d'obsessions-compulsions obtenus par analyse factorielle : impulsion, comportement de lavage, comportement de vérification, rumination, précision.
3. L'inventaire d'accumulation (Saving Inventory – Revised, SI-R) (Frost et al., 2004) n'étudie que le comportement d'accumulation compulsive.

Comorbidité

Le TOC est associé à une comorbidité importante (Bouvard, 2006 ; Rasmussen et Eisen, 1990 ; Sasson et al., 2001). Les troubles associés les plus fréquemment observés sont : le syndrome dépressif, la phobie simple ou la phobie sociale, les troubles de l'alimentation et l'alcoolisme mais également les tics, les troubles de personnalité et la schizophrénie.

Les différents sous-groupes symptomatiques auraient des comorbidités psychiatriques spécifiques (Hasler et al., 2005). Ainsi les patients présentant principalement des obsessions agressives, sexuelles, religieuses ou somatiques et des compulsions de vérification auraient plus de troubles anxieux et de troubles dépressifs. Les patients ayant des obsessions de contamination et des compulsions de nettoyage auraient plus de troubles alimentaires. Les patients ayant des obsessions de symétrie et des compulsions de rangement, répétition et comptage auraient plus de troubles bipolaires et de troubles paniques.

La consommation d'alcool et d'autres substances (par exemple des anxiolytiques) semble être pour le sujet un moyen d'augmenter sa résistance aux obsessions-compulsions. L'humeur dépressive fréquemment associée est probablement due à la souffrance psychique et à la perte de temps qu'occasionne la maladie.

Trouble de personnalité obsessionnelle-compulsive (TPOC)

Le trouble de personnalité obsessionnelle-compulsive est considéré comme une entité psychopathologique à part entière par le courant psychiatrique qui s'inspire de l'approche prônée par le DSM-IV-TR. Le TPOC (Figure 3) ne s'apparente que de loin avec la personnalité obsessionnelle décrite dans la nosologie psychiatrique française (Figure 4).

Le trouble de personnalité obsessionnelle-compulsive est un des dix troubles de la personnalité décrits par le DSM-IV-TR (American Psychiatric Association, 2000). Il fait partie du groupe C des troubles de la personnalité, c'est-à-dire le groupe des personnalités anxieuses et craintives. Contrairement au courant analytique décrivant un continuum entre le normal et le pathologique (Gabbard, 2005), le DSM-IV-TR établit un seuil de pathologies et des catégories. Il faudra donc un certain nombre de critères pour poser un diagnostic de type binaire, « normal » versus « pathologique ». Cependant, les nouvelles classifications du DSM-V (Trull et al., 2007) devraient être plus dimensionnelles, rétablissant ainsi un continuum.

La distinction entre une aptitude personnelle (tendant vers la précision, la méticulosité et le contrôle, valorisée par la société actuelle), une pathologie de la personnalité (source d'une souffrance ou d'une altération du fonctionnement) et un TOC caractérisé est parfois difficile et une approche dimensionnelle permettrait donc de résoudre en partie ce problème.

Diagnostic différentiel

La présence des seules obsessions ou compulsions est suffisante pour poser le diagnostic de TOC selon le DSM-IV-TR (American Psychiatric Association, 2000). Cependant, les seules obsessions sous la forme de ruminations congruentes à l'humeur et s'améliorant parallèlement au syndrome dépressif ne permettent pas à elles seules de poser le diagnostic de TOC (American Psychiatric Association, 2000). Il en va de même pour les troubles alimentaires ou les autres troubles associés présents dans le spectre des troubles obsessionnels-compulsifs ainsi que pour l'hypocondrie ou le trouble anxieux généralisé (Bouvard, 2006).

Etiopathogénie

L'étiopathogénie du TOC semble être psychique et biologique. D'un point de vue psychique, divers modèles se sont succédés au cours du temps (Bouvard, 2006) (Figure 5). D'un point de vue biologique, le TOC semble être une entité hétérogène impliquant probablement des facteurs génétiques, des facteurs cérébraux structurels et fonctionnels, les systèmes de neurotransmission et le système immunitaire. Cependant, en ce qui concerne le rôle respectif précis de tous ces facteurs, les études n'en sont encore qu'au début et des recherches plus poussées sont en cours.

Figure 5

Modèles étiopathogéniques classiques et récents du TOC

Pour le détail des différents modèles, se référer à Bouvard, 2006.

- Classiques
  - Le modèle de la **psychasthénie** de Janet insistant sur le niveau de tension psychologique.
  - Le modèle de **névrose obsessionnelle** de Freud insistant sur les mécanismes de défense du Moi contre des conflits inconscients réprimés par le Surmoi (isolation, déplacement, formation réactionnelle, inhibition, ...).
  - Le modèle **comportemental** de Beech et Perrigault insistant sur l'habituation et celui de Mowrer insistant sur l'évitement de la réponse fournissent une explication au maintien des symptômes.
- Récents
  - Le modèle **cognitif**
  - Le modèle **biologique** et neuropsychologique repose sur 4 aspects :
    - L'imagerie fonctionnelle montrant des dysfonctions des circuits frontaux sous-corticaux
    - Les troubles neurologiques accompagnés de TOC
    - L'importance du cortex frontal dans l'inhibition cognitive et comportementale
    - L'importance du système sérotoninergique dans le TOC
  - Le modèle **intégratif** propose deux aspects :
    - Le spectre des TOC proposé par Hollander
    - Le modèle de l'impulsivité perçue et de la compulsivité compensatoire de Cottraux.

Génétique

Beaucoup de recherches ont utilisé les études sur jumeaux monozygotes et dizygotes afin d'essayer de déterminer la part des facteurs génétiques et environnementaux d'une pathologie psychiatrique. Ainsi, si le taux de concordance pour une pathologie donnée est de 100 % pour les jumeaux monozygotes, on peut conclure que cette pathologie est le plus probablement purement génétique.

Les études de jumeaux montrent une concordance beaucoup plus importante chez les monozygotes (87 %) par rapport aux dizygotes (47 %), suggérant une composante génétique du TOC (Carey et Gottesman, 1981 ; Sasson et al., 2001).

Dans les études familiales, les parents du premier degré de sujets atteints de TOC sont eux-mêmes plus souvent atteints que les sujets contrôles (Kim et Kim, 2006), mais on ne peut pas exclure dans ces études l'influence de l'environnement familial.

Les études de screening génétique réalisées jusqu'à présent dévoilent la probable implication des gènes relatifs aux systèmes de neurotransmission, notamment sérotoninergique et dopaminergique (Kim et Kim, 2006).

Corrélats neuroanatomiques

Imagerie anatomique

Les images réalisées par scanner ou résonance magnétique nucléaire montrent des différences structurales au niveau de certaines régions du cerveau des sujets atteints de TOC (Malizia, 2005) : le striatum, la substance blanche corticale, la substance grise du cortex fronto-orbitaire et l'amygdale. Les résultats de différentes études sont équivoques. Il s'agit de différences de volume allant soit vers l'augmentation, soit vers la diminution. Par ailleurs, certaines études n'observent pas de différences entre les patients et les contrôles (voir (Malizia, 2005) pour une revue détaillée). Chez l'enfant, on a retrouvé une augmentation des fibres myélinisées du corps calleux et une diminution du volume thalamique.

Imagerie fonctionnelle

Les études en imagerie fonctionnelle au repos montrent l'existence dans le TOC d'un dysfonctionnement, dans le sens d'une hyperactivité, au niveau de certaines structures cérébrales (Malizia, 2005) : entre autres, les lobes frontaux (surtout le cortex fronto-orbitaire), les ganglions de la base (surtout les noyaux caudés) et le gyrus cingulaire antérieur. Globalement, il s'agirait d'un dysfonctionnement du circuit reliant le cortex frontal, le thalamus et les ganglions de la base. Cependant, d'autres études n'ont pas montré d'anomalie fonctionnelle au repos ou bien ont révélé un hypométabolisme plutôt qu'une hyperactivité (voir (Malizia, 2005) pour une revue détaillée).

Neurotransmission

C'est l'efficacité des inhibiteurs de la recapture de la sérotonine (Cartwright et Hollander, 1998) dans le traitement du TOC qui a conduit les chercheurs à s'intéresser au système de neurotransmission sérotoninergique comme étant probablement impliqué dans ce trouble. Les études réalisées jusqu'à présent montrent que non seulement le métabolisme sérotoninergique (Cartwright et Hollander, 1998), mais aussi d'autres systèmes de neurotransmission comme la voie dopaminergique (Marazziti et al., 1992), jouent probablement un rôle dans le TOC.

Auto-immunité

On retrouve des manifestations obsessionnelles-compulsives chez 70 % des enfants présentant une chorée de Sydenham (Swedo et al., 1994), celle-ci étant due à une infection par le streptocoque bêta-hémolytique du groupe A (SBHA). Dans ce cas, les manifestations obsessionnelles-compulsives seraient liées aux anticorps contre le SBHA qui s'attaqueraient aussi aux ganglions de la base, et le TOC appartiendrait alors au groupe d'entités cliniques nommé « maladies neuropsychiatriques auto-immunes associées aux infections à streptocoque » (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections, PANDAS) (Swedo et al., 2004).

Traitement

Pour les TOC primaires (Bouvard, 2006), les guidelines préconisent généralement l'association psychothérapie-pharmacothérapie (Cottraux et al., 1990). De nouvelles techniques comme la stimulation magnétique transcrânienne et la stimulation des noyaux gris de la base semblent prometteuses dans les cas difficiles à traiter. La chirurgie est utilisée de manière exceptionnelle.

Pour les TOC secondaires, le traitement est celui de la pathologie primaire. Par exemple, pour le TOC dans la chorée de Syndenham, le traitement par immunoglobulines intraveineuses et par plasmaphérèse s'est montré efficace (Swedo et al., 2004).

Psychothérapie

Quelle que soit l'orientation (cognitivo-comportementale, psychanalytique, systémique) de la psychothérapie, des entretiens préliminaires sont fortement indiqués. Lors de ces entretiens préliminaires, une évaluation clinique précautionneuse aura lieu afin de pouvoir examiner le contexte de survenue du symptôme. L'indication d'une thérapie individuelle, de couple, de famille ou de groupe ou l'absence d'indication d'une thérapie devra être évaluée. De même, l'orientation la plus appropriée à la demande et à la situation du patient devrait être discutée lors des premiers entretiens.

Cognitivo-comportementale

La psychothérapie cognitivo-comportementale (TCC) considère le symptôme du patient comme extérieur à lui et son but est de faire disparaître le symptôme. La TCC est fortement indiquée dans le TOC en raison de ses bons résultats pour faire

disparaître le symptôme obsessionnel-compulsif (Bouvard, 2006). La stratégie comportementale consiste en une prévention de la réponse compulsive lorsque le sujet est exposé graduellement aux stimuli déclencheurs des obsessions-compulsions. Elle est combinée à une thérapie cognitive destinée à modifier les fausses croyances liées aux obsessions.

Ainsi, une TCC basée sur l'exposition (en imagination ou dans la réalité) au stimulus anxiogène et la prévention des réponses ritualisées suite à cette exposition sera proposée aux patients voulant se débarrasser de leurs symptômes sans forcément vouloir analyser la raison historique de la survenue de ces symptômes.

Psychanalytique

La psychothérapie d'orientation analytique considère le symptôme du patient comme faisant partie de lui et son but est de mettre à jour le contenu latent de ce que manifeste le symptôme. L'analyse du sens que prend le symptôme et de la place qu'il va occuper dans l'économie psychique du sujet ainsi que dans la dynamique interpersonnelle sera au centre des consultations.

Systémique

La psychothérapie systémique considère le symptôme comme étant un révélateur de dysfonctions relationnelles (de couple, de famille, de groupe, soit de « système »). Ainsi, un patient présentant un TOC peut être un patient cible, révélateur d'un problème familial, de couple, parental, etc.

Pharmacothérapie

Antidépresseurs

Les antidépresseurs inhibant la recapture de la sérotonine sont efficaces dans le TOC (Bouvard, 2006). La première molécule a avoir montré son efficacité est la clomipramine, ensuite sont apparus les SSRI (Inhibiteurs Sélectifs de la Recapture de la Sérotonine - Selective Serotonin Reuptake Inhibitors). Ces derniers, bien que légèrement inférieurs en terme d'efficacité par rapport à la clomipramine, sont actuellement indiqués en première ligne en raison de leur meilleur profil de sécurité.

Stahl décrit quelques caractéristiques essentielles du traitement par SSRI dans le TOC (Stahl, 2000). Tout d'abord, la dose de départ est la même que dans la dépression mais la dose d'entretien est plus élevée parce que les effets thérapeutiques sont moindres chez les patients présentant un TOC que chez les patients dépressifs. Ensuite, la réponse clinique est d'environ 50 %, ce qui est moins que dans la dépression. Le début de cette réponse clinique est plus tardif que dans la dépression et il est recommandé d'attendre entre 12 et 26 semaines pour déterminer si on observe une réponse clinique ou pas. Enfin, certains patients répondent mieux à un SSRI qu'à un autre.

D'autres suggèrent de choisir les SSRI en fonction de leur pharmacocinétique (Bouvard, 2006). Ainsi, par exemple, le citalopram et la sertraline, n'induisant presque pas d'inhibition des enzymes hépatiques à cytochromes P450, interagiront moins avec des co-médications. La fluoxétine a une demi-vie longue et est ainsi intéressante pour les patients présentant une faible compliance au traitement pharmacologique. Cependant, elle ne serait pas le meilleur choix pour les patients agités ou ayant des antécédents de troubles de l'humeur maniaques ou hypomaniaques (Bouvard, 2006).

Les doses utilisées seront donc en tous cas plus importantes que dans la dépression. Plusieurs SSRI devront parfois être essayés, sur une période suffisamment longue, afin de trouver celui auquel le patient répond le mieux. Après plusieurs essais successifs et sans résultat de trois SSRI prescrits aux doses maximales, on peut donner de la clomipramine. Cependant, il faudra rester attentif au risque de syndrome sérotoninergique et s'assurer que les SSRI ont eu le temps d'être éliminés de l'organisme avant de débuter le traitement à la clomipramine.

Si la clomipramine par voie orale ne donne toujours pas de résultat satisfaisant, il est possible de l'administrer par perfusion intraveineuse sous forme de cure.

Augmentation

Bien que les SSRI soient la base du traitement, de nombreux patients sont réfractaires à ce seul traitement pharmacologique ou leur réponse clinique est incomplète. L'augmentation consiste à ajouter une autre médication jouant sur le système sérotoninergique, une substance intervenant au niveau d'un autre système ou bien une intervention non pharmacologique. Ainsi, par exemple, l'ajout d'un neuroleptique atypique en cas de non-réponse ou de réponse partielle au traitement antidépresseur semble efficace (Skapinakis et al., 2007). Les neuroleptiques sont plus particulièrement indiqués lors de la présence de tics et /ou de symptômes psychotiques associés ainsi qu'en présence d'un syndrome de Gilles de la Tourette.

Stimulation magnétique transcrânienne répétitive

Il s'agit d'une technique non invasive. A travers le crâne, un courant électrique produit par un champ magnétique est délivré au niveau de régions stratégiques du cerveau. L'utilisation de cette technique étant assez récente, les résultats cliniques qui en découlent sont encore assez équivoques et d'autres études doivent être réalisées (Martin et al., 2003).

Electroconvulsivothérapie

L'électroconvulsivothérapie (ECT) est une technique médicale consistant à délivrer un choc électrique au niveau du crâne, ce qui engendre une crise convulsive généralisée accompagnée d'une perte de conscience. L'ECT est utilisée sous narcose afin que le patient n'ait pas les effets secondaires de la crise d'épilepsie induite par le traitement.

Cette technique n'est pas utilisée en première intention dans le TOC. Elle présenterait un intérêt en cas de syndrome dépressif caractérisé associé au TOC (Thomas et Kellner,

2003), dans les cas réfractaires (Maletzky et al., 1994) au traitement psychothérapeutique et pharmacologique ou dans les cas de TOC associés à un syndrome de Gilles de la Tourette (Strassnig et al., 2004).

Stimulation des noyaux gris de la base (DBS = Deep Brain Stimulation)

Ce traitement n'est proposé que dans les cas de TOC résistants et suite à la décision d'un collège d'experts (Bouvard, 2006). En effet, il s'agit là d'un traitement assez invasif qui ne devrait donc être utilisé qu'en dernier recours.

Le placement d'électrodes au niveau des régions profondes du cerveau est au départ une technique utilisée chez les sujets parkinsoniens réfractaires. On a remarqué que lorsque des symptômes obsessionnels-compulsifs étaient présents, ceux-ci s'amélioraient également après la mise en place des électrodes, ce qui suggère l'utilisation de cette technique dans le TOC.

Les électrodes agiraient en inhibant les circuits hyperfonctionnels retrouvés dans le TOC (en fait, l'hyperstimulation générée par les électrodes au niveau de ces circuits aurait comme conséquence de les inhiber).

Psychochirurgie

Les procédures consistent à sectionner les fibres nerveuses des circuits hyperactifs entre le cortex et les ganglions de la base (Bouvard, 2006). Quatre type d'interventions ont été développés : la cingulotomie, la tractomie subcaudée, la leucotomie limbique (combinant la tractomie subcaudée et des lésions au niveau du cingulum) et la capsulotomie.

Ces interventions ne donnent pas d'amélioration clinique dans tous les cas et, de plus, elles ne sont pas dépourvues d'effets secondaires irréversibles tels que des crises d'épilepsie sur cicatrice gliale ou des infections cérébrales. C'est pourquoi la psychochirurgie n'est utilisée qu'en dernier recours dans certains hôpitaux seulement, et après décision d'un comité d'experts.

Conclusion

Le TOC est une maladie fréquente et hétérogène. Des sous-typages cliniques ont été proposés en vue de diminuer l'hétérogénéité de ce trouble. D'un point de vue étiologique, la tendance actuelle est de l'inclure dans un spectre faisant partie d'autres troubles psychiatriques et/ou neurologiques ayant en commun la présence d'obsessions ou de compulsions. Le traitement proposé actuellement doit être au minimum composé d'une psychothérapie. Si une prise en charge pharmacothérapeutique s'avère nécessaire, les antidépresseurs sérotoninergiques semblent être les plus indiqués en première ligne.

Résumé

Le trouble obsessionnel-compulsif (TOC) est une maladie fréquente et débilitante caractérisée par la présence d'obsessions et/ou de compulsions. Ce trouble entraîne une détresse importante tant pour la personne qui en souffre que pour son entourage. Le diagnostic, avant tout clinique, peut s'appuyer sur différentes échelles d'évaluation. Bien que plusieurs hypothèses étiopathogéniques existent et que différents traitements soient proposés, la physiopathologie de ce trouble reste encore largement incomprise. Le but de cette revue est de synthétiser les dernières avancées en matière de physiopathologie du TOC.

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7.5. Aripiprazole diminishes cannabis use in schizophrenia.

From

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Summary

Aripiprazole is the first partial agonist dopaminergic D2 with clear antipsychotic effect. Many schizophrenic patients will develop comorbid substance abuse. Cannabis consumption may worsen psychotic symptoms of schizophrenic patients.1 We describe the case of a schizophrenic patient whose use of cannabis and related problems disappeared after treatment with aripiprazole.

sant medications are preferred to benzodiazepines as a first-line of treatment for anxiety disorders in the elderly.[6] Psychotherapy, particularly cognitive behavior therapy, is often effective in these disorders as well.[6]

We reviewed symptoms of three cases in which onset of anxiety symptoms developed after age 60 as a result of having a medical procedure. They were highly functioning individuals and anxiety symptoms led to impairment of their social and occupational life. They were all successfully treated with selective serotonin reuptake inhibitor medications without any side effects and achieved the overall level of functioning.

The first case was a 61-year-old male who worked in graphic art. He developed severe neck pains and a magnetic resonance imaging scan (MRI) of cervical spines was recommended. After having the MRI, he developed recurrent unexpected panic attacks and anxiety about being in a closed place. Commuting to work caused marked distress and he subsequently avoided traveling in a bus, train, or car, and his daily activities were restricted. He initially refused to consider any medications that might limit his creativity. He agreed to a trial of sertraline, 50 mg/day, which was increased gradually to 100 mg. He noted significant improvement in intensity and frequency of his panic attacks and regained the ability to use the public transportation without any fear.

The second case involved a 61-year-old female who was a medical technician.

She suffered gastrointestinal reflux disease and underwent diagnostic upper endoscopy. Since then, she had been feeling anxious, and had poor concentration, frequent unpredicted panic attacks, and anxiety about being in a crowd. She could not resume her work and preferred to stay home to avoid situations that might provoke her anxiety. She was prescribed sertraline and was maintained on 150 mg/day. She reported lower anxiety level, became comfortable in public, and decided to look for a part-time job.

The third case was a 75-year-old male. He was a retired photographer and developed minor neurological deficits. Computed tomography scan (CT) of the head was conducted. After the image study, he started to have periods of intense fear and excessive worry cued by his presence in places from which escape might be difficult. He isolated himself at home, stopped going to church services and the senior citizen center, and suffered depression. He showed significant symptom response on paroxetine, 40 mg/day.

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Aripiprazole Diminishes Cannabis Use in Schizophrenia

To the Editor: Aripiprazole is the first partial agonist dopaminergic D_2 with clear antipsychotic effect. Many schizophrenic patients will develop comorbid substance abuse. Cannabis consumption may worsen psychotic symptoms of schizophrenic patients.[1] We describe the case of a schizophrenic patient whose use of cannabis and related problems disappeared after treatment with aripiprazole.

Mr. A, a 33-year-old Caucasian patient with schizophrenia, has since his mid-20s been treated with olanzapine, 20 mg/day, and escitalopram, 10 mg/day. He did reasonably well with this regimen but was apragmatic. He frequently used cannabis every day (urine screen for tetrahydrocannabinol [THC] was positive). He was moderately obese (BMI: 28) but had no other medical problems. He lived in a community house, in which nurses ensured that he was compliant with treatment. His Brief Psychiatric Rating Scale (BPRS) score was 52. Before his mid-20s, the patient was treated successively for different classic antipsychotic conditions (i.e., haloperidol, bromperidol, and pimozide) and he reported increased cannabis abuse concomitant with these regimens.

Aripiprazole, 15 mg/day, was added to his treatment regimen. After 1 week, the olanzapine dose was decreased to 10 mg. One week later, olanzapine was discontinued. After 5 weeks, escitalopram treatment was discontinued because the pa-

tient was euthymic. Three months later, the patient signaled he felt very good and did not need cannabis anymore. After 12 months of treatment with aripiprazole the patient had not relapsed and did not use cannabis at all (urine screen did not reveal any THC). Moreover, his BMI was 24 and BPRS score decreased to 40.

This case report highlights different proposals about mechanism of action and side effects.

First, the concurrence of the diminution of cannabis consumption with the patient's treatment with aripiprazole suggests that aripiprazole contributed to the occurrence of this diminution. Different mechanisms may have played a part, such as aripirazole's partial agonism at dopamine D_2 receptors.[2] A similar observation was made with cocaine dependence.[3] Dopamine stimulation in the nucleus accumbens has been suggested to cause addictive behavior and aripiprazole's partial dopamine agonist effect in this area may reduce this behavior.[4] In addition, aripiprazole has a number of serotonergic actions that are not related to dopamine potentially modulating the response to THC.[5,6] Other mechanisms may be involved and Mr. A's rapid cessation of cannabis use after starting aripiprazole suggests the need to verify these mechanisms systematically and to plan controlled trials.

Second, several factors have to be considered when regarding why there may be a concomitant increase in substance abuse with the older antipsychotics. It was suggested that a strong antagonist effect at the dopamine D_2 receptors in the nucleus accumbens was involved in concomitant increase in substance abuse with old antipsychotics.[7] Moreover, unrelated to dopaminergic mechanisms, the use of certain antipsychotics with substantial side effects by schizophrenia patients may actually contribute to greater substance use in an effort to self-medicate the side effects.[8,9]

Finally, there could be at least two explanations for the weight loss. The reduction of cannabis use may have contributed to a reduction in eating,[10] and the switch in the antipsychotic to aripiprazole may have been instrumental in such a significant weight reduction, since aripiprazole is weight neutral and olanzapine is known to facilitate weight gain in patients.

To our knowledge, this is the first reported case of aripirpazole's effect on cannabis use. More research is needed to establish the benefits of aripiprazole in regard to cannabis. Some dual diagnosis patients may benefit from aripiprazole, which may reduce craving for and use of cannabis.

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Clinical Correlates of Personality Changes Associated With Traumatic Brain Injury

To the Editor: Traumatic brain injury (TBI) is frequently complicated by alterations in temperament and character that have adverse consequences for day-to-day living, manifesting as poor decision-making, interpersonal problems, communication problems, and often overall poor quality of life.[1] Max et al.[2] have reported extensively on the correlates and predictors of personality changes after traumatic brain injury in children, but there is scant mention in the literature on adults. In this report, we describe the results of a preliminary study of the clinical correlates of personality change following traumatic brain injury in adults.

Analysis

Data are from a retrospective chart review of 54 subjects with closed head injury enrolled in an outpatient neuropsychiatry brain injury clinic. Patients with depressed skull fractures were excluded.

Every patient was evaluated and followed by a clinic psychiatrist. The assignment of personality change due to a general medical condition (TBI) diagnosis was based

7.6. Achalasia may mimic anorexia nervosa, compulsive eating disorder, and obesity problems.

From

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Summary

In the past, physicians did exhaustive medical evaluation in the pursuit of organic pathology for patients with eating disorders. Judging from the literature, the incidence of anorexia nervosa increased over the past century until the 1970s, and now, physicians have an increased awareness of it and find it easier to diagnose. The consequence is the increasing failure to notice organic pathology in patients who have a history of eating disorders. We report the case of a young man referred for evaluation of anorexia nervosa, who, after investigation, turned out to be suffering from achalasia.

tention to the possible benefits of anticonvulsants and dopamine-antagonists.

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Achalasia May Mimic Anorexia Nervosa, Compulsive Eating Disorder, and Obesity Problems

TO THE EDITOR: In the past, physicians did exhaustive medical evaluation in the pursuit of organic pathology for patients with eating disorders.[1] Judging from the literature, the incidence of anorexia nervosa increased over the past century until the 1970s,[2] and now, physicians have an increased awareness of it and find it easier to diagnose. The consequence is the increasing failure to notice organic pathology in patients who have a history of eating disorders.[3] We report the case of a young man referred for evaluation of anorexia nervosa, who, after investigation, turned out to be suffering from achalasia.

Case Report

Mr. A, a 24-year-old Caucasian patient, had a history of vomiting and a 60-kg weight loss over the preceding 7 months (Body Mass Index [BMI] at admission: 17.6). He had suffered from asthma since his childhood. When he was 18, his weight was 96 kg, and he described, from the age of 18 to age 23, compulsive eating behavior with binging, but not purging, and use of laxatives or diuretics. Six months before the beginning of symptoms mimicking anorexia nervosa, his best friend had died in an automobile accident. At this time, he was 120 kg (BMI: 37). He is still very affected by this accident.

When he was admitted, his clinical evaluation was normal except for a low potassium level (2.7 mmol/liter) and frequent complaints about "a lump in the throat." His parents believed that he practiced self-induced vomiting, although he denied this. Frequently, the parents would force him to eat and wait with him during some time after meals to make sure that he did not vomit, because the boy had uncontrollable vomiting after every meal. The early symptoms were heartburn and dysphagia. The patient stated that he often had chest pain after food or liquid intake. Body-image distortions were absent, but the intention to lose weight was present at the early stage. He denied self-induced vomiting, but did note that vomiting improved his symptoms and that he was preoccupied by food, without any rituals. The patient did not use laxatives or diuretics.

Family history revealed that the mother had been diagnosed as having morbid obesity and had had bariatric surgery. She was currently receiving psychotherapy for depression.

For his general practitioner, the conflict about food and autonomy between Mr. A and his parents was thought to have contributed to the illness.

An upper gastrointestinal radiographic series revealed a grossly dilated esophagus and a tight esophageal sphincter compatible with the diagnosis of achalasia. Pneumatic dilatation of the lower esophageal sphincter was successful, and the patient has gained weight since that time. He is still under psychotherapeutic treatment for his family and behavioral problems.

Discussion

Dysphagia is the initial and main clinical feature of achalasia. Often, several years elapse before the disease is diagnosed, and, during this time, other symptoms, such as vomiting and weight loss, are common.[4] During this period, achalasia can be mistaken for anorexia nervosa. Moreover, previous obesity of the patient is of interest, since an association between morbid obesity and achalasia has been described.[5] This, along with episodes of asthma,[6] leads us to believe that the patient probably had his achalasia before his symptoms of dysphagia.

Nevertheless, differential diagnosis between achalasia and anorexia nervosa is not always obvious. First, it has been reported that esophageal motor disorders are common in patients with a diagnosis of primary anorexia nervosa.[7] For example, patients with eating disorders frequently have gastric emptying abnormalities causing bloating, postprandial fullness, and vomiting. These symptoms usually improve with refeeding, but sometimes promotility agents may be necessary.[8] Second, willful avoidance of food and spontaneous or self-induced vomiting have been reported in patients with achalasia.[9–11] Thus, gastrointestinal disorders are common in eating-disorder patients, and many gastrointestinal diseases sometimes present like eating disorders. But, for Rosenzweig and Traube,[12] errors in diagnosis are related to delay in obtaining appropriate investigations or misinterpretation of their results. Abell and Werkman[13] suggest that a careful clinical history can localize gastrointestinal motility disorders,

and they suggest appropriate diagnostic tests.[13] They differentiate between two groups of symptoms: first, dysphagia, odynophagia, heartburn, and reflux have esophageal origins and occur in achalasia. The appropriate diagnostic tests in this case are barium-swallow endoscopy[10] and esophageal motility studies (esophageal manometry or scintigraphy). The second group of symptoms includes nausea, vomiting, anorexia, bloating, and abdominal pain, which are symptoms of motor disorders of the stomach and small intestine.

In summary, the exclusion of organic disease must be a priority, even if a psychotherapeutic intervention may be needed in the global care of this group of patients.

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Postconcussional Symptoms Not a Syndrome

TO THE EDITOR: Taber's Cyclopedic Medical Dictionary defines syndrome as "a group of symptoms, signs, laboratory findings, and physiological disturbances that are linked by a common anatomical, biochemical, or pathological history." It is my view that symptoms typically attributed to post-concussion are so nonspecific and are associated with such a wide variety of other conditions that they do not meet the definition of a syndrome. Iverson and McCracken[1] showed that postconcussive-like symptoms are not unique to the sequelae of mild traumatic brain injury and can also be seen in conditions of chronic pain. Gouvier et al.[2] compared undergraduate students and their families with a group of head-injury patients. They concluded that there were "no significant differences found between the brain-damaged individuals and normals on items assessing self-reported memory problems, problems becoming interested in things, frequent loss of temper, irritability, fatigue, or impatience."[2]

Lees-Haley et al.[3] compared 50 control subjects against 170 personal-injury claimants. The injury claimants had no history of brain injury or toxic exposure. In spite of this, they reported very high rates of complaints generally associated with the so-called "post-concussion syndrome."

Chan[4] studied base rates of symptoms in patients who had not suffered a head injury. The study showed that a high proportion of participants reported symptoms similar to those with so-called post-concussion syndromes.

Rees[5] opined that "published observational work on the nature and etiology of "persistent post-concussive syndrome" and, more particularly, its cognitive sequelae, have been characterized by an unfortunate lack of data, errors in sampling, and insecure methodology."[5]

McAllister and Arciniegas[6] pointed out that the term "post-concussive syndrome" is used inconsistently in the literature, that the symptoms have high base rates in the general population, and that they are nonspecific in nature.

In summary, the so-called symptoms of post-concussional syndrome are notable in that: 1) they are present in a significant number of the normal population, and 2) they are present in very significant numbers of patients who have suffered trauma not involving concussion or brain injury.

Therefore, I conclude there is inadequate evidence that these symptoms meet the definition of a "syndrome."

It is unfortunate that Dr. Hall and colleagues have not referenced these controversies in their otherwise excellent review article. [7]

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