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Genetic influence on the working memory circuitry: Behavior, structure, function and extensions to illness

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Abstract

Working memory is a highly heritable complex cognitive trait that is critical for a number of higher-level functions. However, the neural substrates of this behavioral phenotype are intricate and it is unknown through what precise biological mechanism variation in working memory is transmitted. In this review we explore different functional and structural components of the working memory circuitry, and the degree to which each of them is contributed to by genetic factors. Specifically, we consider dopaminergic function, glutamatergic function, white matter integrity and gray matter structure all of which provide potential mechanisms for the inheritance of working memory deficits. In addition to discussing the overall heritability of these measures we also address specific genes that may play a role. Each of these heritable components has the potential to uniquely contribute to the working memory deficits observed in genetic disorders, including 22q deletion syndrome, fragile X syndrome, phenylketonuria (PKU), and schizophrenia. By observing the individual contributions of disruptions in different components of the working memory circuitry to behavioral performance, we highlight the concept that there may be many routes to a working memory deficit; even though the same cognitive measure may be a valid endophenotype across different disorders, the underlying cause of, and treatment for, the deficit may differ. This has implications for our understanding of the transmission of working memory deficits in both healthy and disordered populations.

Keywords

Working memory; Genetics; Heritability; Neuroimaging; Behavior

1. Introduction

Our ability to interact successfully with our environment relies heavily on our capacity to keep information active and available for reference from one moment to the next. We

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operationalize this capacity as working memory (WMem), a dynamic, short-term storage of information to be actively used or manipulated. Information held in WMem may be applied to a current situation, used as a step in solving a problem, or used as a probe for long-term memory. Intact verbal WMem is critical for activities such as reading, writing, problem solving, planning, and coherent verbal communication. These skills are called upon constantly in daily life, and their impairment could lead to severe disruption in an individual's day-to-day functioning. Accordingly, from an evolutionary standpoint it is clearly advantageous for WMem to be a highly heritable trait, and a great deal of evidence indicates that this is the case.

However, although WMem performance is heritable [1,2], the biological mechanism through which WMem ability is transmitted is unknown. As WMem relies on a distributed network, genes that influence WMem may influence neuronal functioning within specific brain regions or, alternatively, the coordination of activity in these regions. The flexible nature of WMem testing allows for testing across animal models and humans, both healthy and disordered. The breadth of this research has provided a number of potential mechanisms by which a WMem deficit may arise, from the cellular level up to the temporally precise coordination of large-scale cortical regions.

In this review, we will explore various biological mechanisms associated with variation in WMem performance, including cellular signaling mechanisms, structural connectivity of white matter tracts, and integrity of gray matter in key brain regions. For each of these we will also consider individual genes that have been implicated in WMem function, and genetic mutations with disruptions in the mechanisms of interest that also are associated with WMem deficits, such as phenylketonuria, fragile X syndrome and 22q11.2 deletion syndrome. Finally, we will discuss schizophrenia as an example of a complex disorder with a WMem phenotype that is likely the result of a convergence of these underlying mechanisms.

2. Working memory overview

2.1. Working memory models

WMem tasks typically consist of a brief encoding period, followed by a period of maintenance and/or processing in the absence of the original stimuli, and a retrieval period. One key characteristic of WMem tasks is that the memory is stored transiently, to be successful the subject must remember the target stimuli across the delay, and then discard it. Retaining stimuli across multiple trials will actually result in decreased performance due to interference in this type of task.

A predominant model of WMem in cognitive psychology is the three component model of Baddeley [3,4], which includes a visuospatial sketchpad that maintains spatial information, a phonological loop that maintains verbal information and a central executive component that directs attention, integrates information, and coordinates the other two components (see Fig. 1). The phonological loop may be subdivided into a passive phonological store, which represents information using a phonological code that decays with time, and an active rehearsal process that refreshes the decaying representation of the phonological store [3]. This has recently been updated to include a fourth component known as the episodic buffer, which is able to bind together representations from the phonological loop, visuospatial sketchpad, and long term memory [5].

2.2. Working memory assessment

WMem can be measured across species in humans, non-human primates, and rodents. One commonly used animal paradigm is the delayed response task (DRT) in which the animal is

shown the location of a reward, must retain that location across a delay, and then use the retained information to select the location associated with the reward [6] (1997). Also frequently applied is the oculomotor DRT (ODR) and the related delayed anti-saccade task (DAS) [7]. These tasks all require the maintenance of information across a delay followed by a response based on that information, and have been successfully used in many studies to assess neural underpinnings of WMem.

In humans, the available approaches represent a combination of standardized neuropsychological tests often employed clinically, and controlled experimental tasks designed to test theoretical models of cognitive function. Neuropsychological tasks, such as the Wisconsin card sort task (WCST) and span tasks (e.g. Corsi Blocks), have the benefit of being standardized, and thus comparable across study groups and populations, but often are limited to more general constructs. Experimental tasks can probe more refined questions about components of memory function, but vary considerably across sites or studies [8].

Two common examples of experimental tasks are the Sternberg Item Recognition Paradigm [9], a type of DRT, and variants of the N-back Task. In Sternberg style tasks the subject retain a set of items (e.g. letters, digits, or spatial locations) over a delay, and then when presented with a cue, indicate whether or not it was a part of the initial target set. In an n-back design, a continuous string of stimuli (letters, digits, images, etc.) is serially displayed. Subjects monitor the stimuli and report when the current target matches a target that was shown a designated number of presentations ago [i.e. matches the previous target (1-back), or the one two items back (2-back)]. Load is manipulated by increasing the number of items back that the subject must remember. Both tasks allow parametric variation of load, and are amenable to a variety of types of stimuli, and both have been associated with activation in regions associated with WMem. However, N-backs have some limitations, in that there are multiple components: the information must be monitored, updated, temporally tagged, and responses to intervening stimuli must be inhibited [10,11].

2.3. Working memory circuitry

Information held in WMem is largely transitory; information retained over extended periods of time is supported by different, long-term memory processes. To maintain this brief trace, neurons in the prefrontal cortex remain active even when information they code for is no longer present, and subsets of neurons differentially fire as a function of the phase of a WMem task (cue, delay, or response) [12–14]. The orchestration of activity in these cells may rely on dopaminergic input to both the primary pyramidal neurons and to inhibitory interneurons that form the underlying frontal circuitry [14].

While there is certainly involvement of a broader network, a core fronto-parietal network has been predominantly implicated in WMem. Cooling or lesioning the prefrontal cortex interferes with delay task performance [15,6]. Moreover, more precise, single-unit recording studies have found that the dorsolateral prefrontal cortex (DLPFC) might be a specific location for the cells that remain active across the delay periods [16]. Functional neuroimaging can provide more detailed information about activity during WMem tasks in intact human brains. Imaging studies further bolster the localization of WMem to a frontal-parietal circuitry [17–19], a result supported by the finding that during WMem frontal and parietal neurons show similar firing patterns [20,21].

Coordinated fronto-parietal activity is likely supported by the Superior Longitudinal Fasciculus (III), a white matter tract which in part connects Brodmann's Areas 9/46 with the supramarginal gyrus (BA 40) [22]. There is evidence that pure storage mechanisms (either spatial or phonological) are linked to the posterior parietal lobe [18–20], while rehearsal and executive processes are localized to the frontal lobe [18,19,23]. This differentiation has been

hypothesized, at least for verbal memory, to represent cognitive distinctions between the active rehearsal component of the phonological loop and a passive storage component [24], that are included in Baddeley's model.

3. Cellular signaling dysfunction

3.1. Dopamine

The role of dopamine in WMem has been long established, in large part based on the seminal body of work by Goldman-Rakic [25]. Dopamine is a modulatory neurotransmitter with five receptor subtypes (D1–D5). D1 (and D1 like) receptors are proportionately more represented in the cortex than D2 receptors, which are more heavily localized to the striatum [26,27]. There is evidence that D1 receptors have a specific modulatory role in WMem [28,29]. For instance, it has been shown that depleting dopamine in rhesus monkeys in the regions analogous to the DLPFC impaired performance on a WMem task as profoundly as did ablating the same area [30], an effect replicated in rats [31]. Through work using D1 receptor agonists and antagonists, it has been further observed that the effect of D1 stimulation follows an inverted U pattern, such that low levels (as associated with aging or Parkinson's Disease) are associated with lower performance [32–34]; however, high levels (as associated with stress or amphetamine psychosis) are also impairing. Thus, it would appear that there is an intermediate level of D1 stimulation associated with optimal performance [35], when levels of D1 stimulation are low, a DA agonist may improve performance, while when levels are too high an antagonist may improve performance (for review see Ref. [36]).

The interrelationship between the roles of D1 and D2 receptors in WMem is complex, and remains to be fully characterized. D1 receptor stimulation clearly has a role in WMem performance across species. The role of D2 receptors is less clear; blocking D2 receptors does not appear to compromise WMem performance [29]. However, there is some evidence that D2 agonists may impair WMem [37,38]. One proposal is that D1 receptors are involved in maintenance of information, while D2 receptors are involved with cognitive flexibility and updating functions, and it is the balance and interactions between these receptor subtypes that results in the complex patterns observed (for in depth review see Refs. [36,39,40]).

There are a number of mechanisms by which genetic changes can influence dopamine levels and subsequently impact WMem. There are genes that code for the catabolism of dopamine (COMT), for the transporter that removes dopamine from the synapse (DAT1), for the D2 receptor (DRD2), and there are genetic disorders that result in dopaminergic changes, like phenylketonuria (PKU), and schizophrenia (see Fig. 2).

3.1.1. COMT—Possibly the most frequently studied gene in relation to WMem is catechol-O-methyl transferase, an enzyme that degrades catecholamines such as dopamine and is coded for by the COMT gene. Of special interest for WMem, while monoamine oxidase (MAO) is thought catabolize the majority of catecholamines, COMT appears to be particularly involved with dopamine breakdown in the pre-frontal cortex [41]. There is an evolutionarily recent functional single nucleotide polymorphism (SNP), known as the Val158Met polymorphism [42], with the Met form of COMT having lower activity at body temperature [43] and the Val form having higher activity [42]. Evidence for the impact of COMT genotype on WMem performance has been mixed. There is evidence that COMT does influence the degree of frontal lobe activation, as measured by fMRI, with Val allele carriers showing prefrontal hypoactivity or inefficiency [44,45]. These findings have now been extended to show a significant effect of COMT genotype on working memory performance (assayed by the n-back task) for patients with schizophrenia, their healthy

siblings, and controls [46], as well as differential response to amphetamine as a function of COMT genotype, supporting the notion of a characteristic inverted-"U" functional-response curve to increasing prefrontal dopamine signaling [47]. However, not all studies have found these effects on functional activation to be borne out in terms of performance differences. While there is some evidence for an effect of COMT on WMem performance [48,49], a recent meta-analysis revealed no significant effect of the Val158Met SNP on a battery of frontal tasks, including WMem [50]. In addition, the effect of this variant in the general population can only account for a very small percentage of the variance in working memory function [51]. While a meta-analysis of case control studies found a significant but weak effect of the COMT Val/Met polymorphism in European samples [52], there may be additional functional sites in COMT [53]; thus, inconsistent findings across genetic association studies may be due to different combinations of alleles at these functional loci in different samples [54]. In addition, there is evidence for epistatic effects, in which COMT interacts with other genes, such as DRD2 [55,56], which may indicate that COMT variation is just one component of a larger disruption in dopaminergic signaling that leads to WMem deficits. Given the complexities involved in detecting modest effects of these genetic variants in general population samples, it may be more informative to examine individuals with more extreme variation in genotype, where the magnitude of the genetic effect on dopaminergic neurotransmission is potentially much greater.

3.1.2. DRD2—The D_2 dopamine receptor is encoded by the DRD2 gene. As described above, it has previously been demonstrated that administration of DRD2 agonists [57–59] and antagonists [37,60] modulates WMem performance [61]. Accordingly, DRD2 polymorphisms (rs#1800497, rs#6277, rs#2283265) have been associated with changes in WMem capacity, and interestingly, the effects found are modulated by genetic variation in the gene coding for the alpha4 subunit of the nicotinic receptor [62]. In addition, a different SNP (rs1076560) has been associated with differences in prefrontal activity as measured by fMRI during WMem [63]. Together, this indicates that in addition to its epistatic effects with COMT [55,56] DRD2 variation may have independent effects on WMem function.

3.1.3. Disease status—There are a number of diseases that are associated with changes in dopaminergic function. One such a disease is phenylketonuria, a metabolic disorder relatively restricted to the dopamine signaling system. The disorder results from a mutation in the phenylalanine hydroxylase gene (PAH, located in the q22–q24.1 region of chromosome 12), which normally converts phenylalanine into tyrosine, the precursor for dopamine [64]. Decreased PAH activity leads to an increase in phenylalanine levels, and a decrease in tyrosine [65]. In addition to the devastating effects of the increase in phenylalanine, which cause the developmental abnormalities that are the primary symptoms of the disorder, the decrease in tyrosine has an independent impact on cognitive function. Decreasing phenylalanine intake through dietary interventions is a standard treatment, but only addresses the phenylalanine excess, not the tyrosine deficit. While the decrease in tyrosine is not necessarily large, because of the high dopamine turnover, the frontal cortex is particularly sensitive to a lack of tyrosine, which is necessary for dopamine synthesis [66,67]. Thus, children who have been treated for PKU may be otherwise normal, but still have a deficit in prefrontal dopamine [65]. Accordingly, subsequent testing has revealed executive function deficits, particularly WMem and response inhibition deficits, even when the primary symptoms of the disorder are successfully treated [68–70]. The lingering deficits are likely attributable to the low dopamine levels.

Another disorder related to changes in the dopamine signaling system is the 22q11.2 deletion syndrome (22qDS), also known as DiGeorge or velocardiofacial syndrome which results from a hemizygous deletion on chromosome 22 and is characterized by an unique behavioral phenotype involving particular deficits in working memory and attention, as well

as elevated rates of ADHD and psychotic disorder [71]. Because the COMT gene maps to the deleted region, the characteristic behavioral manifestations of this syndrome may be related to dopamine dysregulation resulting from COMT haploinsufficiency [72]. Some studies in children with 22qDS have found the COMT Met allele to be associated with better performance on measures of prefrontal cognitive function, as compared to Val allele carriers [71,73]; but see Ref. [74]. Val genotype was also associated with a more than 4-fold increase in risk for clinically significant behavior problems in children with this syndrome [75]. These data are consistent with previous findings in healthy individuals indicating increased psychopathology associated with Val genotype, suggesting that this SNP may influence both prefrontal cognition and behavior in individuals with COMT haploinsufficiency. However, there is additional evidence suggesting developmental changes in the effect of COMT genotype on both cognition and neuroanatomy: in a longitudinal study of adolescents with 22qDS, Gothelf et al. [76], found that the Met allele was a risk factor for a reduction in prefrontal volume, cognitive function, and the development of psychotic symptoms in adolescence. Thus, while COMT genotype does appear to play a role in the neurocognitive and neuroanatomic expression of the syndrome [77], findings vary considerably across studies, which may be partially attributable to developmental factors that require longitudinal studies for proper elucidation [78].

A mouse model missing the orthologues of the 1.5Mb human 22q11.2 locus, referred to as the Df(16)A+/− strain of mice [79], has shown particular promise in linking molecular, anatomical, and neurofuctional aspects of cognitive impairment. Histologically, this model shows evidence of impaired development of dendrites, dendritic spines, and excitatory synapses in the hippocampus [79], as well as abnormal transcription of proteins related to synapse formation in prefrontal and hippocampal tissue [80]. These mice also display deficits in spatial WMem performance [81], much like patients with 22qDS do [71]. Critically, Sigurdsson et al. [81] recently demonstrated that these behavioral WMem impairments are associated with abnormal, long-range synchronization in a fronto-temporal learning and memory circuit. Specifically, in Df(16)A+/− mice, theta-band EEG oscillations (4–12 Hz) recorded in the hippocampus fail to modulate the firing rate (and also the magnitude of gamma band oscillations, >30 Hz) of prefrontal neurons, despite normal short-range synchronization within the prefrontal cortex and the hippocampus. Wild-type mice, in contrast, show strong prefrontal-hippocampal synchronization, which correlates directly with WMem performance.

3.2. Glutamate and GABA

In addition to the factors discussed above, successful WMem requires an exquisite balance of the excitatory and inhibitory circuitry in the prefrontal cortex that includes the glutamatergic pyramidal neurons as well as GABAergic inhibitory interneurons [82]. Neurons in the prefrontal cortex have been shown to fire persistently during the maintenance phase of WMem tasks [12]. It is thought that this activity is maintained via local recurrent excitatory connections [83], and that it is the balance between the inhibitory and excitatory neurons that allows for the specificity of the WMem trace, with the synchronization of pyramidal cell activity provided by the interneurons being critical for accurate spatial tuning [84,85]. Importantly, this system does not exist in isolation, rather the responses of the pyramidal neurons are modulated by dopaminergic inputs to the frontal lobe [86]. Disruptions in GABAergic, and glutamatergic, functioning in the prefrontal cortex can have a profound impact on WMem performance. Much work in this realm has focused on the role of interneurons, specifically parvalbumin positive GABA neurons, in the synchronization of neuronal firing into oscillatory activity in the gamma-band range. Given that gamma-band oscillations have been shown to increase during WMem performance and in proportion to

memory load [87], it is thought that a disruption in gamma-band oscillations might lead to WMem deficits (for further review, see [85]).

3.2.1. Dysbindin—One example of a gene that influences glutamate signaling is dystrobrevin binding protein-1 (dysbindin, or DTNBP1), which has recently become a focus of genetic investigations in schizophrenia. Dysbindin is expressed in axon terminals of glutamatergic pyramidal neurons [88] and influences glutamatergic function, likely through interactions with vesicular trafficking proteins. Because it is expressed within cortical neurons, including pyramidal neurons [88], it may be well-positioned to modulate functions that depend on the cortical excitatory tone [89,90] such as WMem. Dysbindin over-expression is associated with increased glutamate release and correspondingly higher extracellular glutamate [90], with dysbindin reductions leading to decreases in glutamate release [90,91]. This effect appears to be mediated by interactions between dysbindin and Synaptosomal-associated protein 25 (SNAP25) and synapsin [90], most likely via its binding partner, snapin [92]. It appears that dysbindin has multiple effects on neural transmission that may affect efficacy of glutamatergic release, including slowing kinetics of quantal release, decreasing the overall likelihood of release (indicated by a decrease in excitatory postsynaptic current (mEPSCs)), a decrease in the density of vesicles held in the reserve pool for release, decreased amplitude and frequency of EPSCs and decreased paired-pulse facilitation [89,91], although the mechanisms are not yet fully understood.

Consistent with its glutamatergic effects, dysbindin has been associated with cognitive changes. Recently we found that dysbindin mutant mice show deficits in WMem performance [91,93], and moreover, that the degree of WMem performance is directly related to expression of NR1, the obligatory subunit of the glutamatergic N-methyl-D-aspartic acid (NMDA) receptor. In humans dysbindin, and its location on chromosome 6, has also been associated with general cognitive ability [94,95], spatial WMem [96] and measures of prefrontal cortex function in healthy subjects [97,98].

3.2.2. Extensions to disease—A core hypothesis for the deficits associated with schizophrenia implicates a prominent role for glutamatergic dysfunction, as discussed below. In addition, other genetic disorders have been associates with WMem deficits that may have their roots in GABAergic and glutamatergic changes.

Fragile X syndrome represents one example of such a disorder. Fragile X is caused by a repeat in the FMR1 gene, which produces FMRP (fragile X mental retardation protein). The result of the repeat is a failure to express FMRP, and this deficit is associated with morphological changes, autistic behaviors, and cognitive deficits [99]. Patients with Fragile X show specific deficits in executive functions and WMem [100–104], and the WMem impairment appears to be more pronounced in phonological WMem tasks. These deficits are present even in asymptomatic premutation individuals (those with an abnormally high levels of repeats, but not a high enough number to reach the syndromal threshold), and the number of repeats directly correlates with the degree of the executive function deficit [102]. In addition, patients demonstrate reductions in functional activation during WMem [100,105]. Interestingly, and in support of the findings that the number of repeats influences cognitive function, the level of FMRP protein expression has been directly related to fMRI activation during a WMem task, such that those subjects with lower levels of expression show lower activation [106]. At a cellular level, one consequence of the FMR1 mutation is loss of repression of, and subsequent excessive signaling by, mGluR5 (metabotropic glutamate receptor 5) [107] leading to increased long term depression (LTD) [108]. This may play an important role in disrupting neural development and synaptogenesis, and it has been proposed that drugs that inhibit mGluR may offer hope for treatment of the disorder [109]. While the NMDA receptors affected by dysbindin mutations do not appear to be impacted in

Fragile X [109] in terms of effects on hippocampal LTD, the Group I metabotropic glutamate receptors, of which mGluR5 is a member, have been found to interact with NMDA receptors [110] by potentiating the duration of NMDA receptor-dependent excitatory postsynaptic potentials [111]. However, acute stimulation of mGluR5 has also been associated with increased WMem in healthy volunteers [112]. In general, more research is needed to understand the precise mechanisms of the prominent WMem deficits in this disorder.

4. Morphological changes

4.1. White matter

White matter volume [113,114] and microstructure [115–118] are significantly heritable. The first evidence for a role of genetics in white matter is in the heritability of many disorders affecting white matter, broadly known as the leukoencephalopathies [119]. These diseases can cause either dysmyelination (an abnormal development of myelin) or demyelination (the progressive loss of myelin) [120] and affect lipid storage, protein levels, and cellular metabolism, all of which can interfere with myelin, and cause gross changes visible not only at autopsy, but on standard MRI scans. One heritable abnormality of the white matter which is easily detectable using traditional MRI is the presence of white matter hyperintensities [121,122]. These hyperintense regions are often thought to be due to small ischemic events, something common in normal aging. However, it is possible that the heritability of this measure, in particular the volume of the hyperintense regions, is in part due to the shared cardiovascular risk factor of higher arterial pressure [118]. Despite high heritability, some imaging studies have observed white matter in the later-developing frontal lobes to be less highly correlated within twin pairs ($r = .83$, as compared to .98 for whole volume white matter) [123], indicating the potential for environmental influence across development, particularly in regions that are later to mature.

With the advent of diffusion tensor imaging (DTI), it has become possible to assess not just the global white matter volume, but also the integrity of the white matter microstructure and tract level measures. The basis of the DTI signal is the Brownian motion of the water molecules [124]. Water molecules in the brain move in an environment full of cell membranes, fibers, and other tissue components. Depending on the tissue type, these components limit motion in specific ways. For instance, in white matter tracts, the motion of the molecules is restricted by the long myelinated axons and moves most easily and quickly in the direction parallel to the axon, creating an elongated ellipsoidal pattern of motion known as anisotropic diffusion. If relatively unobstructed (as in CSF) or obstructed but without a directional bias (as in gray matter) the spherical pattern of motion that occurs is known as isotropic diffusion. By measuring the shape of this ellipsoid, we can obtain information such as the degree of myelination, the average fiber diameter, and the similarity in the direction of the fibers within the tract [125]. An index known as fractional anisotropy (FA) summarizes the relative eccentricity of the ellipsoid, and is frequently used as a measure of white matter integrity. Measures obtained using DTI have been shown to be heritable in healthy individuals [115,117,118,126–129]. Furthermore, it appears that changes in white matter across development and aging are heritable [115,121,127,130].

Given the evidence that during WMem performance the frontal and parietal regions show synchronized neural activity and function as an integrated circuit [17,20,21,131] there is interest not just in the cortical regions themselves, but the connections between them such as the SLF, and in particular, to what extent WMem function may be related to the integrity of the underlying white matter. White matter volume has been related to WMem and processing speed [132], and the use of DTI now allows this to be investigated at the level of specific tracts. In particular, SLF integrity has been associated with WMem performance in

healthy controls [133], patients with schizophrenia [133], patients with multiple sclerosis [134,135], and patients with alcoholism [136].

To assess whether the heritability of WMem and white matter might be related, a recent study in a large family sample measured gray matter in the frontal and parietal lobes, white matter in 5 tracts associated with WMem regions, and performance on a variety of frontal-based cognitive tasks. Interestingly, while all the factors were heritable individually, only FA of the SLF and performance on a basic Sternberg style spatial WMem task showed a pattern consistent with pleiotropy, or shared genetic influence. This suggests that inheritance of white matter structure is one of the mechanisms by which WMem deficits may be genetically transmitted [126].

4.1.1. Neuregulin—Some specific genes have also been associated with white matter integrity. One gene of interest is neuregulin (NRG1), which is strongly associated with development. Its role in development includes facilitation of neuronal migration, neurite formation and outgrowth via protein kinase C and mitogen-activated protein kinase pathways, and myelination [137–139]. Additionally, NRG1 is crucial for oligodendrocyte development and proliferation [140–142]. Individuals with the schizophrenia risk-associated neuregulin 1 genotype have white matter abnormalities in fronto-thalamic connections as assessed by MRI and DTI [143]. Closely related to neuregulin is its receptor, ErbB4 and the family of ErbB tyrosine kinase receptors, which also have important implications for development and connectivity. ErbB4 genotype has been associated with changes in structural connectivity as measured by DTI in humans [144,145]. In addition, mice with altered erbB signaling in oligodendrocytes (the cells that make up the myelin sheath in the central nervous system), showed decreased myelination, lower numbers of oligodendrocytes with abnormal morphology, and correspondingly slower conduction velocity in the axons [146]. The evidence for an effect of neuregulin on WMem is mixed, for instance one study found no effect on performance, but an effect on functional activation [147], with other studies also failing to find a WMem association [148] and humans. However, a specific ablation of ErbB4 in parvalbumin positive interneurons resulted in WMem deficits. This may indicate that while NRG and ErbB4 impact white matter integrity, the pattern of the effects does not necessarily result in a specific WMem deficit, and that the deficit seen in disorders like schizophrenia, that are associated with both WMem impairment and NRG1 changes may be the result of epistatic effects, of interactions with other contributing factors, or of a specificity to the disruption in NRG1 that is not replicated in healthy variation or standard knock out mice.

4.2. Gray matter

With advances in MRI analysis and technology, it is possible to get a number of indices of gray matter integrity. Gray matter density (GMD), which can be, for instance, calculated as the proportion of gray matter in a fixed sized sphere centered on cortical surface points, is often used as a proxy of gray matter thickness and, when all things are kept equal, the GMD may represent thickness, although in the face of substantial differences in gyrification or brain shape, the relationship between the two becomes more complex. Calculating gray matter thickness directly is more computationally intensive, as it involves the estimation of the location of the pia mater and of the interface between gray and white matter, and the calculation of their distance across the cortical mantle. There is a substantial body of evidence that gray matter measures are heritable [149–153]. Ref. [149] investigated differences in gray matter density in healthy MZ and DZ twins using three-dimensional cortical mapping techniques that allowed the quantification of the relative genetic influence at all points on the cortex. It was found that frontal, sensorimotor, and anterior temporal regions were under the highest level of genetic control, followed by middle frontal regions

(BA9, BA 46), and then by other frontal and sensorimotor regions. The finding of the high heritability of frontal gray matter are consistent with neuropsychological studies [154–156] in which tasks based in the frontal lobe were found to be most heritable. Interestingly, measures of cortical thickness and surface area have been shown to be genetically and phenotypically independent, which may mean that these measures can each contribute unique information to genetic analyses [153].

Given that gray matter volume in the regions associated with WMem function is known to be heritable, it is of interest whether gray matter structure and cognitive function are related. Relatively more work has been done on the relationship of intelligence and cortical measures than WMem specifically. There has been evidence for a relationship of intelligence (or *g*) with gray matter volume [157], cortical thickness in parietal lobes, medial temporal lobes, and occipital and cingulate regions [158], and gray matter density in cortical regions [159]. In addition, Lenroot et al. [160] showed genetic effects on cortical thickness, and that the degree of genetic relative to environmental effects in regions associated with higher level cognition, which also mature later, such as DLPFC and temporal lobes, show increasing genetic control across childhood and adolescence, which is relevant given that IQ also becomes more heritable across development [161].

Only a few studies have investigated the relationship of cortical measures specifically with WMem in healthy individuals. One, by Posthuma et al. [132] found that overall gray matter volume was highly heritable (82%) and that the correlation between gray (and white) matter volume and WMem were completely determined by a genetic factor regulating both of them. However, this paper assessed total gray matter volume, which is not a very specific index. Recently we used variance components methods to assess the genetic correlations between gray matter, white matter, and WMem measures in large extended pedigrees. While all measures were significantly heritable, including gray matter in the frontal and parietal lobes, there was no genetic correlation between gray matter density and WMem performance [126], indicating that there is not a shared genetic influence on these two factors.

In some populations there may be a stronger direct relationship between gray matter and WMem – for instance, in patients with schizophrenia spectrum disorders [162–164], or in aging populations [165,166]. Given that the relationship in healthy individuals is less clear, this might mean that there has to be an interaction with other factors, or with other genes, for the gray matter to be related to WMem performance.

5. Schizophrenia: a convergence of deficits

WMem deficits can arise from a variety of cellular and structural and functional neurobiological changes. Thus far, the disorders and genes that have been discussed have WMem deficits of relatively specific etiology. One primary example of a disorder that crosses these boundaries is schizophrenia. Patients with schizophrenia have alterations in dopamine, glutamate and GABA function, as well as gray and white matter integrity. Further, although schizophrenia's ultimate etiology is unknown, there is reason to believe that these factors may interact, but also have the potential to contribute to patients' WMem impairment independently of each other (see Fig. 3).

At the descriptive level, a great deal of effort has gone into characterizing schizophrenia patients' WMem impairment [167,168]. While schizophrenia patients show performance deficits in most domains of neurocognitive functioning, working memory appears to be more severely affected [169,170]. WMem dysfunction might in fact contribute to performance deficits in other domains such as abstraction, attention, and language, since co-varying measures of the former tends to eliminate patient-control differences on the latter

[171–173]. For instance, within the spatial domain, SZ patients are deficient in identifying locations after a very brief (1 s) or no delay and are marginally-to-significantly more vulnerable to disruption compared with controls after a longer delay, indicating deficits in encoding as well as maintenance [174–177]. Similar patterns of deficit have been reported in clinically unaffected relatives of patients with schizophrenia [178–180], suggesting that working memory deficits may be linked to a genetic vulnerability to the illness.

Empirically, several lines of evidence suggest working memory dysfunction, and DLPFC activity in particular, as a potential locus of dysfunction in the pathophysiology of schizophrenia and associated impairments in functioning. Functional neuroimaging studies also suggest the involvement of prefrontal cortex in the working memory deficits observed in schizophrenia. Schizophrenic patients fail to activate DLPFC to the degree seen in healthy controls when performing the WCST [181,182], the Tower of London [183], the N-back task [184], and the verbal fluency task [185]. In a functional MRI study of MZ twins discordant for schizophrenia, the affected twin exhibited less DLPFC activation during the WCST than their non-ill co-twin [186] indicating that non-genetic, disease-specific influences must be involved.

Structural neuroimaging studies suggest relatively greater reduction in frontal and temporal cortical volumes as compared to posterior cortical volumes [187]. Cannon and colleagues found that after accounting for individual differences in gyral patterning and shape, DLPFC is one of the few cortical regions in which gray matter is reduced in volume in schizophrenic patients compared with their unaffected MZ co-twins. These changes were also correlated with cognitive dysfunction and symptom severity in the patients [188]. In other studies, global and dorsolateral prefrontal volumetric deficits have been found to correlate with performance deficits on tests sensitive to working memory processes (i.e., executive, attention, and context-based recall tests) [189,190].

Dopaminergic and glutamatergic dysfunction are cardinal features of schizophrenia that may be at the core of the positive and negative symptoms. Several lines of evidence support the role of a dopamine imbalance in schizophrenia symptomatology. Positron emission tomography (PET) studies indicate that patients with schizophrenia show increased levels of striatal dopamine [191], which is of special interest because increases in dopamine have been shown to be psychotogenic, for instance in Parkinson’s patients treated with L-Dopa. Consistent with these data, D2 receptors, which are most densely located in the striatum, are necessary targets of effective antipsychotics [192]. However, despite the clear role of elevated striatal dopamine in the positive symptoms, in the frontal lobe levels are actually decreased. In fact, the degree of D1 receptor upregulation (a putative response to lower dopamine levels), is correlated with the degree of WMem impairment [193]. Accordingly, a number of genes that code for dopamine related traits have been implicated in schizophrenia, for instance, COMT and DRD2 (http://www.szgene.org).

However, dopaminergic imbalance can account for some, but not all, of the symptoms of schizophrenia; thus, one dominant neurochemical hypothesis for understanding schizophrenia posits that it is glutamatergic dysfunction that is the core deficit in schizophrenia. This hypothesis is based on findings that hypoglutamatergic states can mimic both the positive and negative symptoms and may thus be a better model of schizophrenia [194]. Furthermore, chronic administration of the NMDA antagonist phencyclidine (PCP) results in reductions in prefrontal dopamine levels and subsequent cognitive impairment [195], as well as decreased frontal lobe blood flow [196,197]. There is evidence that the glutamate changes in schizophrenia may have a genetic basis; for instance, DTNBP1 has been associated with schizophrenia through linkage [198,199] and association studies [88,200–202]. Biologically, proposed risk haplotypes for dysbindin confer low protein

expression; schizophrenia patients show reduced dysbindin mRNA and protein in PFC [203] and hippocampus [88,204]. *DTNBP1* variation in humans has been associated with cognitive impairments [95,96,205]. The relationship between *DTNBP1* variation and cognitive abilities has been further substantiated by basic neuroscience studies, with findings that dysbindin mutant mice exhibit WMem deficits and altered glutamate signaling [91,93].

In addition to glutamate changes, GABAergic alterations have been associated with WMem deficits in schizophrenia. Suggesting a mechanism distinct from but possibly linked to the abnormal long-range synchronization of prefrontal circuits in *Df(16)A*+/− mice performing a demanding WMem task, Cho and colleagues report that schizophrenia patients display reduced frontal EEG gamma band power during the performance of WMem tasks [206]. Moreover, patients' task-sensitive gamma modulation may be "rescued" by subunit-selective modulation of GABA type A receptor neurotransmission [207].

Post-mortem evidence has revealed disturbed myelin pathology in patients with schizophrenia, including alterations in the distribution of the interstitial cells of the WM [208–210] as well as significant reductions in the number of oligodendroglial cells and ultrastructural alterations of myelin sheaths, mainly in the pre-frontal cortex and caudate [211]. DTI studies have demonstrated decreased FA in widespread brain regions. These include prefrontal, temporo-parietal, and parieto-occipital regions [212], with meta-analytic reviews showing particular deficits in left frontal white matter [213] and along the cingulum bundle, arcuate, and uncinate fasciculus [214]. The superior longitudinal fasciculus (SLF) is one fiber tract of particular interest in schizophrenia as it serves as the primary connection between the frontal and parietal lobes [22]. FA reductions along the SLF have been found in schizophrenia patients [215] and been associated with impaired verbal WMem [216], executive functioning [217], and functional outcome [218]. The white matter changes observed in schizophrenia seem to have a genetic component as well. For instance, expression of myelination-related genes is selectively decreased [219]. Furthermore, expression of these myelin-related genes peaks in adolescence, the period most proximal to disease onset [220]. However, although patients with schizophrenia show heritable deficits in spatial WMem as well as in structural integrity in regions associated with WMem, it has been unclear whether these effects are mediated by common genetic factors or the mechanism by which such deficits might be genetically transmitted. Our work in healthy subjects indicates that there are shared genetic factors contributing to WMem performance and white matter integrity in the SLF [126].

6. Conclusions

We have demonstrated that specific deficits in dopamine signaling, glutamate signaling, GABA signaling, white matter integrity, and gray matter integrity all can independently contribute to variation in WMem performance and provide potential mechanisms for the inheritance of deficits. Therefore, WMem deficits across different disorders (for instance, PKU, Fragile X, and schizophrenia) might be phenotypically similar, but be produced by different genetic mechanisms (for instance, see Fig. 4). Thus, while WMem may be a phenotype for multiple disorders, it is important to understand what neural mechanisms underlie the deficit. The construct of WMem may be a valid, useful, and reliable phenotype across multiple disorders, but that does not necessarily imply that the deficit is caused by the same neurophysiological changes in each population, and does not necessarily imply an inherent similarity in the underlying nature of the disorders. Thus, understanding the underlying causes of WMem deficits across different populations may be a critical component of understanding how to best treat the deficit in that group- there is not likely to be a treatment that is a one-size-fits-all solution. On the other hand, gaining an understanding multiple potential causes for WMem deficits can be an important tool,

because just as there may be many roads to a WMem deficit, there may be many avenues through which improvements can be made. It is possible that if the circuitry is dysfunctional in one modality, it may be difficult to improve the existing pathology, however, our knowledge of the complete system may allow treatments that rely on different, and still intact, mechanisms to boost performance.

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Abbreviations

WMem	working memory
DRT	delayed response task
DAS	delayed anti-saccade task
WCST	Wisconsin card sort task
DLPFC	dorsolateral prefrontal cortex
BA	Brodmann’s area
COMT	catechol-O-methyl transferase
DAT	dopamine transporter
PKU	phenylketonuria
PAH	phenylalanine hydroxylase
22qDS	22q11.2 deletion syndrome or DiGeorge or velocardiofacial syndrome
GABA	*gamma*-aminobutyric acid
DTNBP1	dystrobrevin binding protein-1 or dysbindin
NMDA	N-methyl-D-aspartic acid
SNAP25	synaptosomal-associated protein 25
EPSC	excitatory postsynaptic current
FMRP	fragile X mental retardation protein
mGluR5	metabotropic glutamate receptor 5
LTD	long term depression
NRG1	neuregulin
GMD	gray matter density
MZ	monozygotic
DZ	dizygotic
PET	positron emission tomography
DTI	diffusion tensor imaging

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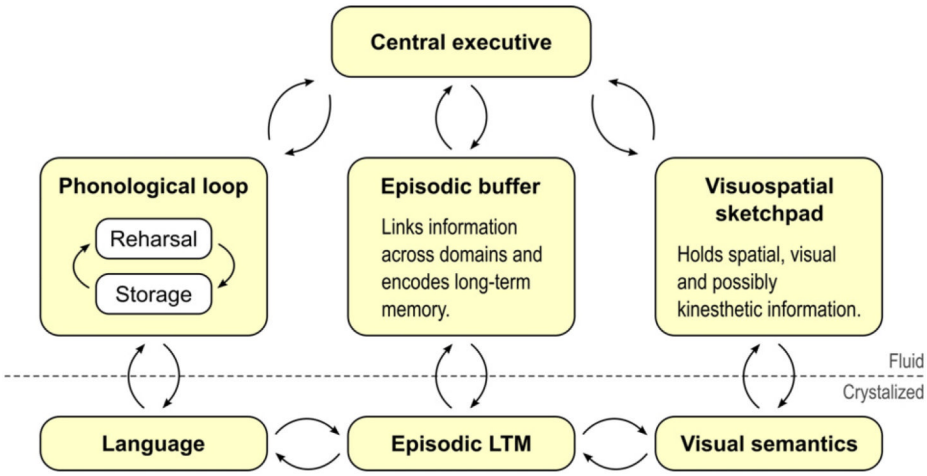

Fig. 1.

Baddeley's model for working memory assumes an attentional controller, the central executive, aided by subsidiary systems capable of holding visuospatial and phonological information, as well as an episodic buffer that provides temporary interface between the controller and long-term memory. Each of the three subsidiary systems, as well as the central executive, are assumed to be "fluid" capacities, that are themselves unaffected by learning. These interact with "crystallized" cognitive systems that accumulate long term knowledge, as language, semantics and long term memory [5,221].

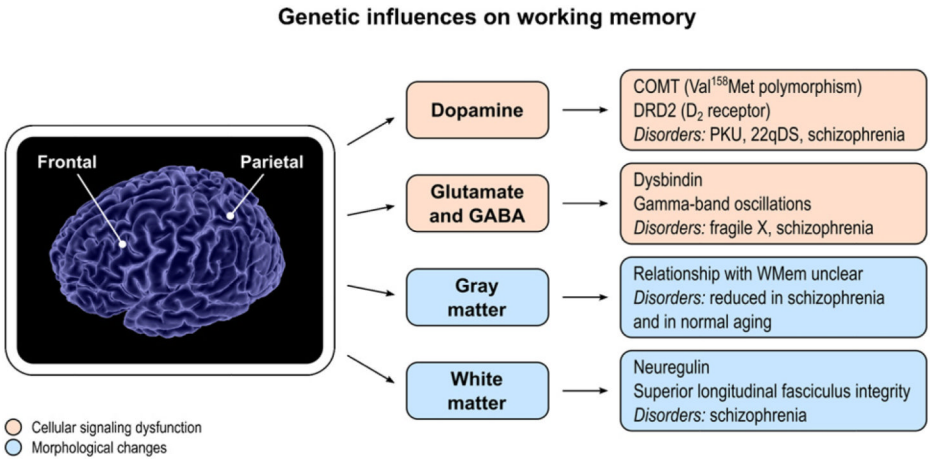

Fig. 2.

Working memory depends on and is influenced by dopaminergic, glutamatergic and GABAergic signaling pathways, particularly in fronto-parietal regions. Integrity of brain structure, notably white matter fibers connecting these two areas seem to have a pivotal role for WMem function. Disruptions of any of these systems lead to WMem impairment, as observed in different disorders.

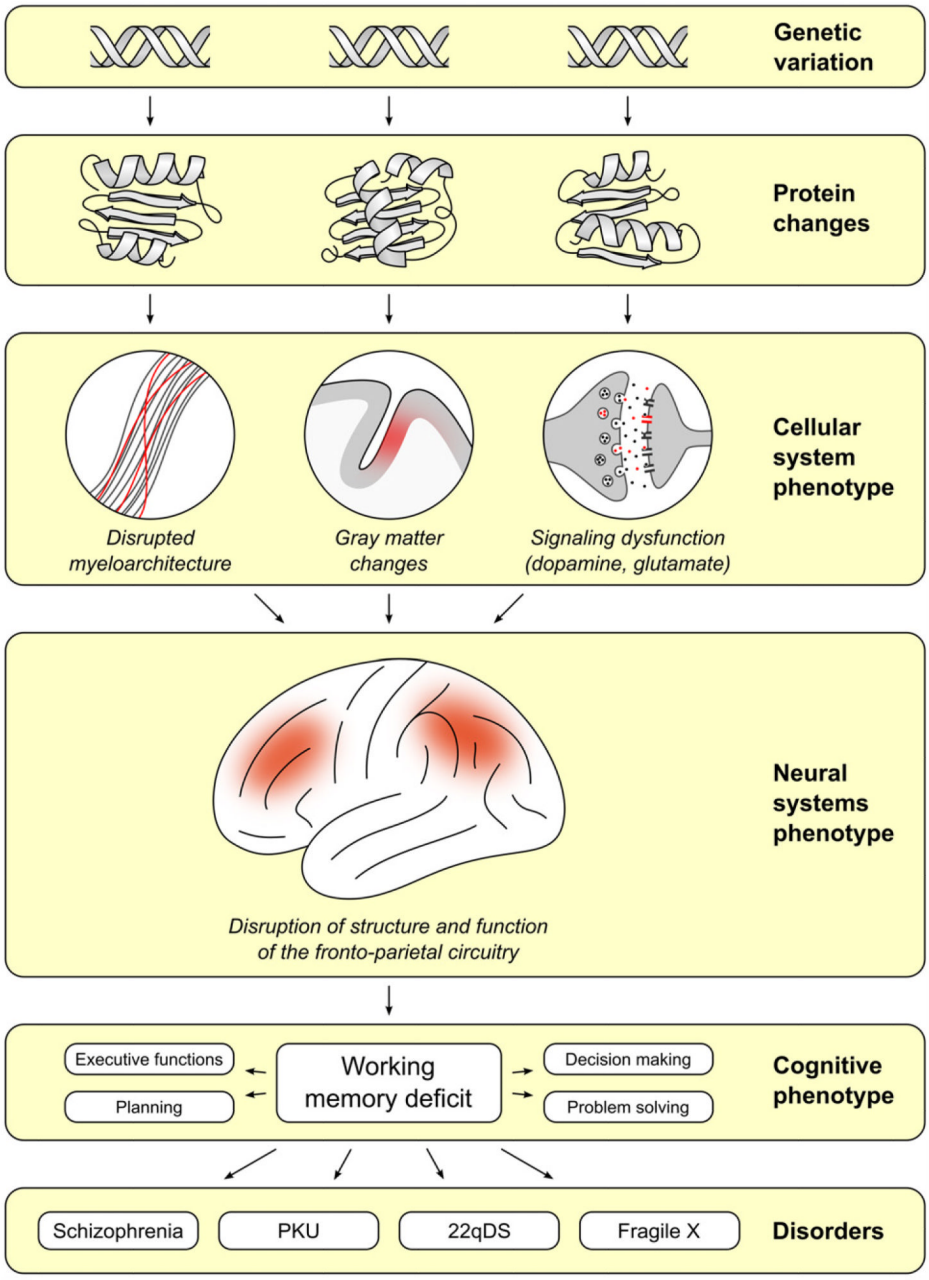

Fig. 3.

Working memory deficits are present in a variety of disorders with either Mendelian or complex patterns of inheritance, and it may serve as an endophenotype for these disorders, as the expression of multiple underlying genetic, functional and structural abnormalities.

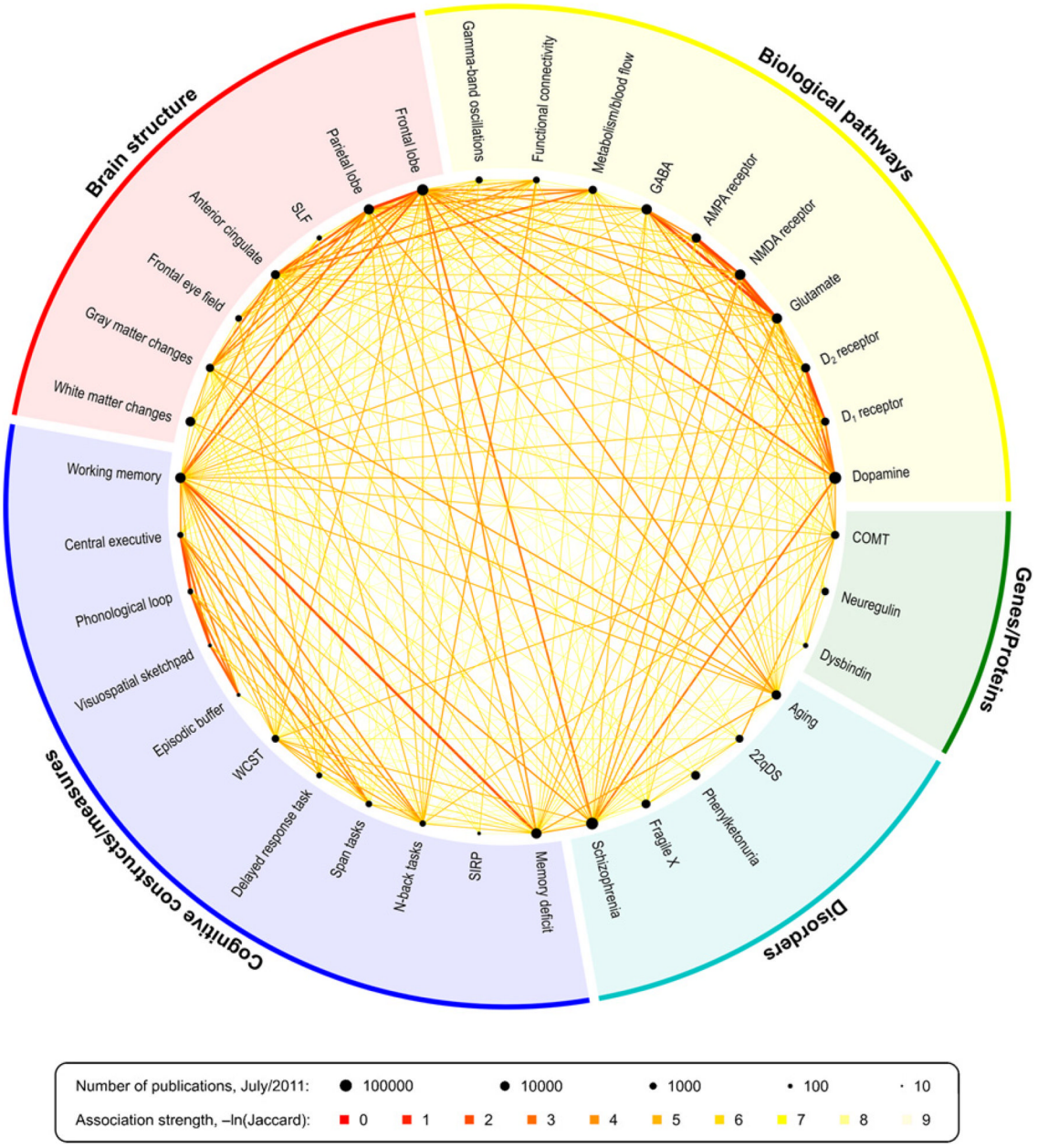

Fig. 4.

Occurrence and co-occurrence of keywords in published literature can highlight interesting associations between different research areas, reveal emergent patterns of research and evidence strong and weak associations. In this figure, each point around the circle represents, in logarithmic scale, the relative number of publications indexed by PubMed in July/2011 containing a given keyword in relation to the others. The links represent the association strength of the association, scaled by the natural logarithm of the Jaccard coefficient. Smaller numbers represent stronger associations. See Parker et al. [222] and http://www.pubatlas.org for more on literature mining and visualization tools. COMT = catechol-O-methyltransferase; AMPA = 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl)propanoic acid; GABA = gamma-aminobutyric acid; SLF = superior longitudinal

fasciculus; WCST = Wisconsin card sorting test; SIRP = Sternberg item recognition paradigm; 22qDS = 22q11.2 deletion syndrome.