

Stress, psychosocial mediators and cognitive mediators in parents of child cancer patients and cancer survivors: Attention and working memory pathway perspectives

Abstract

Objective: This review examines stress and its consequences on attention and working memory, stress symptoms in parents of child cancer patients and survivors and long term consequences of stress on cognitive processing in parents of child cancer survivors. **Method:** Eligible studies were experimental, meta-analyses and qualitative (2000-2013) from Pubmed, Medline, the Cochrane Library, PsycArticles and Google Scholar. **Results:** We identified 92 eligible papers. They showed that elevated stress can impede performances on tasks requiring attention and memory patterns. In paediatric oncology, parental stress increased shortly after diagnosis involving depression and anxiety. Consequences of stress on cognitive performances were observed mainly among depressed individuals. As regards parents of child cancer survivors, female gender, low SES, innate traits of anxiety/anger predicted the development of PTSS. **Conclusion:** Evidence of stress on attention and working memory processes in parents of child cancer survivors is insufficient developed.

Keywords: stress; parents; cancer survivor; working memory; children; PTSS-PTSD

Abbreviations: SES-Socioeconomic Status; PTSS-Posttraumatic Stress Symptoms; PTSD-Posttraumatic Stress Disorder; ALL-Acute Lymphoblastic Leukaemia

Aims of the study

The aims of the present review were to evaluate the methodological strengths and weaknesses of research on the emotional manifestations of stress in parents of children on a paediatric haematology-oncology ward. The prevalence and nature of parental stress according to disease phase will be described. The studies carried out during diagnosis and active cytotoxic treatments (=“on”) will be considered separately from the studies conducted on the parents of child cancer survivors (5 years minimum later) (=“off”). This dichotomy provides a comprehensive state of the art of the literature ranging from the transition from parental experience during active treatment to parental experience during complete remission. The originality of the present review lies in considering the effects of stress on the cognitive processes and specifically those of attention

and working memory pathways in parents of child cancer survivors. In spite of abundant paediatric haematology oncology literature, few authors have attempted to understand the cognitive processes of parents of child cancer survivors, yet the consequences of stress on human cognition are reported in other disciplines. The organization of the review was conceived in accordance within the framework of psychosocial research in paediatric haematology-oncology. First, introductory background material is provided for a comprehensive understanding of paediatric cancer and cognition/stress. Second, the algorithmic methodology is described and aims to target the methodological strengths and weaknesses of studies on the emotional manifestations of stress in parents of child cancer patients and survivors. Third, factors related to being “on treatment and off treatment” are provided in the results section. This allows a comprehensive state of the art of the literature ranging from the transition from active treatment (“on”) to survivorship experience. Fourth, the long term consequences of stress on cognitive processes in parents of child cancer survivors are examined in the last section of the review. This could facilitate the development of future studies centred on cognitive processes in parents of child cancer survivors and open the paediatric haematology oncology field to an integrative cognitive-behavioural and family dynamic dimension. Recommendations will be made for future research.

Paediatric haematology-oncology

During the last decades the prognosis of childhood cancer has dramatically improved. Significant and impressive survival rates were found for some of the more common cancers (e.g., acute lymphocytic leukemia [ALL]). The 5-year survival rate for ALL is now about 86.8% compared to 50% 30 years ago. Cancer remains a rare disease during childhood. Compared to the total cancer burden in our country and Western countries, childhood cancer accounts for less than 1%. Every year, about 320 children (< 15 years) and 180 adolescents (15-19 years) are diagnosed with cancer in Belgium (55% boys and 45% girls). Approximately 70 patients younger than 20 years die from cancer per year. Mortality rates have dramatically declined (nowadays mortality rates are about 13.2% vs. > 80 % during the sixties) for most childhood cancers (Belgian cancer registry (BCR), 2010). A wider reality needs, however, to be considered, with about 200,000

children and adolescents diagnosed with cancer every year worldwide. The triggering factors are unknown and it is recognized that causes are multiple (i.e., epidemiological, genetic, chemical or viral agents and environmental causes) (Tasker, McClure, & Acerini, 2013). Four prime treatments (i.e., chemotherapy or cytotoxic treatments, radiation therapy, surgery and bone marrow transplantation) are available for paediatric cancers, all of which are aimed at eradication and overthrow. Leukaemias, brain tumours, lymphomas (i.e., Hodgkin lymphoma (IIa), non-Hodgkin lymphoma (NHL; IIb) and Burkitt lymphoma (BL; IIIb) and carcinomas) are the most frequent malignancies in children and adolescents. Their incidence varies with age and gender (*male/female ratio* = 1.35) (BCR, 2010).

Cognition and stress

Human cognition has evolved to assimilate, process and transact varying information in order to direct human actions/behaviours (i.e., output responses). Cognitive processes include different mental contents such as encodings of external stimuli or of images, knowledge and other mental materials from short-term and long-term memory (including storage and retrieval) (Pinker, 2013). Cognitive behaviour has the following characteristics: it is goal-oriented (e.g., we do not stumble through life, acting in ways that are unrelated to our intentions), it takes place in a rich, complex and detailed environment, it requires considerable knowledge, the use of symbols, representations and abstractions, it is flexible and a function of the environment. Cognitive behaviour can be modelled as “cognitive architecture”, which filters information or contents in a dynamic manner (flexible) and through an interactional way between subsystems (i.e., *cognitive behaviour* = *cognitive architecture* + *mental content/input*) (Kanai & Rees, 2011). Numerous interactions between these subsystems exist (i.e., attention and memory) (e.g., Wagner, Shannon, Kahn, & Buckner, 2005). The process of attention involves selecting some information for further processing and inhibiting other information. This selection processing can be driven endogenously by individual’s goals or exogenously by an environmental salient or novel stimulus that activates attentional processing (Bachmann, 2011). Attentional processing is modelled as follows: alertness/arousal, focused attention, selective attention (encoding process), divided attention and

sustained attention (vigilance) (Gunstad, Cohen, Paul, & Gordon, 2006) and might be influenced by certain factors either external or internal. Memory is a complex process of encoding, storing and retrieving information and is related to specific subcortical areas (i.e., the paleomammalian brain and the anterior cingulate gyri or supplementary motor cortex area) (e.g., LeDoux, 2002). Memory is divided into three subsystems: the sensory memory, the long-term memory and the short-term memory. The sensory memory is the temporary storage of sensory information for reference, lasting in terms of seconds. The stimuli detected by sense organs can be either ignored (the stimuli disappear instantaneously) or perceived, in which case, they are temporally encoded in the sensory memory. Long-term memory involves the storage and the recall of information over a long period of time and is divided into declarative (explicit or memory of facts and divided into episodic memory and semantic memory) and nondeclarative (implicit or memory based on the recollection of how to conduct certain actions) memory systems. The working memory is a system for temporally storing and managing the information required to carry out complex cognitive tasks such as learning skills, comprehension and reasoning. Working memory is involved in the selection, initiation and termination of information-processing functions like encoding and retrieving data and have a limited capacity (Baddeley, Eysenck, & Anderson, 2009). Contemporary authors describe a unitary system comprising multiple subcomponents. This involves an attentional controller, the central executive, aided by two subsidiary slaves systems, the visuo-spatial sketchpad, which holds and manipulates visual and spatial information, and the phonological loop which performs with verbal-based information. Lastly, the episodic buffer is the newest subcomponent of the unitary working memory model, having been affixed relatively recently. The episodic buffer is a multi-modal component (it uses different types of inputs), which performs closely with the long-term memory (Baddeley, Eysenck, & Anderson, 2009). To date, there has been numerous studies looking at the specific effects of stress on cognitive performances. Theoretical approaches explaining stress have been categorized into three core types. The first theoretical orientation (i.e., responses-based) was conceptualized by Hans Selye (1956) and viewed stress as a defensive response to noxious stimuli (i.e., stressors), progressed in three specific stages

(alarm, resistance and exhaustion). Seyle described that cognitive factors such as the perception displayed central role in contributing to the moderation of the stress response (Seyle, 1983). The second theoretical orientation (i.e., stimulus-based) was initially developed by Holmes and Rahe (1967). The stimulus-based model defined stress as cumulative life events that require adaptation efforts. The stimulus-based model was criticized for its lack of accuracy and because it ignored individual differences, cognitive dimension and neglected entirely the role of individual's emotions. The third theoretical approach (i.e., transactional-based) was established by Lazarus and Folkman (1984) and viewed stress as the result of environmental demands of which exceed individual's resources. The model described stress as a "rubric" for a complex series of subjective phenomena including cognitive appraisals, stress emotions, coping responses and reappraisals. The following section is a overview of how stress affects the primary cognitive processes of attention and working memory. Generally under stress the attention appears to channel with an extremely narrow perspective where the individual focuses his attention on main tasks, reduces cue utilization and diminishes his perception on peripheral components. What determines the task's importance depends on perceived stimuli and their salient nature. This "tunnel hypothesis" was echoed early in numerous studies in the field of cognition (Murata, 2004). Current studies focus on the effect of stress on selective attention. Some authors argue for a negative effect of stress on selective attention with a high reduction of the individual's resources (LeBlanc, Woodrow, Sidhu, & Dubrowski, 2008). Conversely, the beneficial effect of stress on selective attention to filter out irrelevant from relevant information have been underlined (Braunstein-Bercovitz, 2003). The memory capacities may also be affected by stress. Studies described that stress mainly impairs working memory while long-term memory is less impaired under stress (e.g., Lewis, Nikolova, Chang, & Weekes, 2008). It seems to be the process of encoding and maintenance which are the most affected by stressors giving rise to a decrease in working memory resources (Robinson, Sünram-Lea, Leach, & Owen-Lynch, 2008). Indeed, results showed anxiety to be an element which takes up too much space in a limited capacity system which then causes interference on attentional resources for tasks, taking the shape of intrusive thoughts and worries (Dutke & Stober, 2001).

Studies using the thought suppression paradigm (i.e., Wegner, Schneider, Carter, & White, 1987) revealed that anxious individuals have more cognitive deficits in working memory and that they were unable to suppress negative intrusive thoughts. Anxious participants had a significant tendency to present cognitive inhibition deficit and a greater focus on negative than positive items (Brewin & Smart, 2005). Apart from a simple cause and effect structure, interactional models of stress emphasize the mediating role of cognitive dimensions on the relationship between the aversive stimulus and the output responses of the individual. Stress is the result of a dynamic relationship between the individual and environmental requirements. The individual and his social resources manage to cope with these demands and also through his cognitive perception and his individual evaluation of this relationship (Lazarus, 1999; Lazarus & Folkman, 1984).

Method

Search strategy for identification of studies and inclusion/exclusion criteria

Sources in the current review have been drawn from several databases: *PubMed*, *Medline*, *the Cochrane Library*, *PsycArticles* and *Google Scholar*. The following inclusion criteria were established: (1) *year of publication*: studies published between January 1, 2000 and January 1, 2013; (2) *language*: only English publications; (3) *method*: quantitative and qualitative experimental studies; meta-analysis; review; (4) *target population*: mother, father, parents; (5) *therapeutic time*: on active treatment (on), survivors (off) or mixed (on/off). The following exclusion criteria were established: (a) *type of source*: book chapters, guidelines, commentaries and dissertations; (b) *target population*: only paediatric cancer patients/survivors, siblings, grandparents or cultural comparisons; (c) *medical applications*: clinical trials and medical or genetic practices; (d) *clinical time*: anticipatory bereavement, palliative care and bereavement. Please note that studies about recurrent disease and loss of the child were not taken into account because most of the literature consider these issues and would require an additional review of literature. So, excluded studies did not focus on the emotional manifestations of stress in parents of child cancer patients and survivors.

Algorithmic methodology

Figure 1 shows the flow diagram of trial identification and selection. An initial algorithm (*Algorithm A = childhood cancer + parental stress*) (1) was encoded through databases. One hundred and ninety-eight results listed by date (2000-2013) were obtained. Fifty-nine studies were retrieved of which 30 described the “PTSS and the PTSD variable”; 3 investigated the “depression and anxiety variable”; 20 examined the “family functioning variable”; 5 treated the “appraisal coping variable” and one investigated the “social support variable”. Studies not deemed eligible had no decisive criteria. About 2.87% of the studies were clinical trials, 6.47% of these included genetic and medical variables, 10.80% incorporated cultural comparisons, 5.76% only concerned siblings’ experience, 10.07% included solely the sick or surviving child without parental viewpoint, 0.72% were entirely off topic and 29.50% were already found through databases (i.e., redundant data). Remaining percentages (33.81%) were scattered throughout heterogeneous studies with a host of variables such as predominantly psychotherapeutic interventions but, also the development of psychometric tools. The following process was to pigeonhole the 59 studies within the research cluster. These were identified as following: (1) PTSS/ PTSD, (2) anxiety + depression, (3) family functioning, (4) social support and coping (5).

Refinement of data extraction

Further algorithms were encoded. *Algorithm B' = parent of child cancer + PTSS*, which allowed the addition of 14 studies out of 28 available regarding the PTSS / PTSD variable (“on”) (2). *Algorithm B'' = parent of child cancer survivor + PTSS*, which enabled the inclusion of 6 new relevant results out of 12 available regarding the PTSS/PTSD variable (“off”) (3). A fourth combined algorithm (*Algorithm C' = childhood cancer + parental anxiety* and *Algorithm C'' = childhood cancer + parental depression*) (4) enabled the addition of 11 results. A last combined algorithm (*D' = childhood cancer + family functioning* and *D'' = childhood cancer + social support*) was encoded providing two new results. A further algorithm was created through databases (*E = childhood cancer + family coping strategies*) for which no relevant result was available. A final algorithm (*F = Parental cognition + child cancer survivor*) was encoded

providing no relevant result out of the 31 already available results. The majority of studies were already extracted from the initial algorithm (Algorithm A = 64.13%). It is noteworthy that analogies were also considered such as cancer (*neoplasm, tumor, malignant tumor, neoplastic, oncology, cancer*); parents (*caregivers, relative, family, nuclear family*); PTSS/PTSD (*stress disorder, trauma, anxiety, uncertainty*); depression (*mood syndrome, depressed mood, depressed individuals*), anxiety (*anxious, worries, sorrow, distress*) and cognition (*cognitive processing, cognitive performances*). Several spreadsheets were created in order to organize the relevant data. Four tables are included in the appendices section. We do not include tables summarizing family functioning; social support and appraisal coping cluster because these topics have already been studied within the context of paediatric haematology oncology (supplementary Figure 1).

Insert about here Figure 1

Results

A. ON TREATMENT

A.1. Core clinical issues in parents of child cancer patients

Studies evidenced a higher predisposition to anxiety, depression and PTSS in mothers of child cancer patients than in fathers (e.g., Best, Streisand, Catania, & Kazak, 2001; Yeh, 2002). Only one study showed high levels of anxiety and depressive symptoms in fathers (Bonner, Hardy, Willard, & Hutchinson, 2007). Other studies did not find gender differences (e.g., Phipps, Long, Hudson, & Rai, 2005a; Santacroce, 2002). As regards the PTSS and PTSD issue, mothers reported generally more symptoms than fathers (e.g., Rodriguez et al., 2012; Sahler et al., 2002, 2005). Research found equal levels in the emergence of PTSS or PTSD (e.g., Lindahl-Norberg & Boman, 2013). Some gender differences may be explained by the timing of the study. Over the long term, only the fathers' symptoms decreased (Magal-Vardi et al., 2004). However, observed results in these gender differences remain unclear and virtually unexplained.

Anxiety

Fourteen studies have investigated the construct of anxiety in the area of paediatric oncology since the early 2000s until today; of which 6 studies employed a cross-sectional design, two studies were longitudinal and 6 used mixed studies (on/off). Cross-sectional designs show that anxiety occurs frequently in early diagnosis and decreases over time. Anxiety levels are higher for parents of children during treatment than parents of children in remission or parents whose child has a relapse (Santacroce, 2002). Longitudinal studies revealed that levels of anxiety decrease over time but still persist over five years post-diagnosis. This durability of high anxiety levels suggests that some parents became more vulnerable during active treatment and that high anxiety is maintained on the long term for parents. Some studies also highlighted significant relationships between excessive levels of anxiety and a greater disposition to develop PTSS (Best, Streisand, Catania, & Kazak, 2001) (supplementary Table I).

Insert about here Table I

Depression

Following a paediatric cancer diagnosis, parents may react with depressive symptoms. These are varied and may appear as chronic sadness, anxiety, pessimism, guilt feelings, concentration difficulties and sleep disorders (Barrera et al., 2004). Compared to parents of healthy children, parents of paediatric cancer patients have significant levels of depressive symptoms (Lindahl-Norberg, Lindblad, & Boman, 2005b; Yeh, 2002). Longitudinal studies showed depressive symptoms persisting over time. Recurrence of depressive symptoms is more significant if parents already have a priori anger/anxiety traits or initially react with moderate to severe levels of depressive symptoms at diagnosis time (Boman, Lindahl-Norberg, & Björk, 2003).

PTSS-PTSD

Twenty-six studies have investigated the PTSS/PTSD issue since the early 2000s. Eleven studies employed a cross-sectional design, 9 studies a longitudinal design, 3 used mixed methods

(on/off), two were randomized clinical trials and one study was a literature review. Most salient sub-clinical symptoms are physiological arousals, intrusive thoughts, decrease in problem solving skills, feelings of loss of control, and avoidance of treatment related events (Lindahl-Norberg, Pöder, Ljungman, & von Essen, 2011; Sahler et al., 2002, 2005). Parents of children recently diagnosed or currently in cytotoxic treatment present higher levels of PTSS or PTSD compared to parents of healthy children (Jurbergs, Long, Ticona, & Phipps, 2009) or parents of child cancer survivors (Phipps, Long, Hudson, & Rai, 2005a). Some authors showed a relationship between the occurrence of moderate or high parental PTSS with anxiety and depression (Dunn et al., 2012) (supplementary Table II).

Insert about here Table II

A.2. The role of psychosocial processes as mediators for parents of child cancer patients

Some studies have observed a mediating effect of psychosocial variables such as social support and family support in the link between clinical symptomatology and general family functioning. In fact, when parents have a reduced social network and poor family support, their subsequent psychosocial adjustments seem to be undermined by a higher trend towards depression and PTSS/PTSD (Tremolada, Bonichini, Schiavo, & Pillon, 2012). Conversely, extended social support (Lindahl-Norberg, Lindblad, & Boman, 2005b) and high levels of family relationships (Kazak et al., 2006) were described as core mediators allowing parental adaptation and decrease of the trend towards depression, anxiety and PTSS both in mothers and in fathers. Certain socio-demographic predictors were also identified: female gender and innate traits of anger or anxiety seemed to result in more depressive and anxious symptoms (Hoekstra-Weebers, Jaspers, Kamps, & Klip, 2001). Moreover, SES (Lindahl-Norberg, Pöder, Ljungman, & von Essen, 2012) and cumulative stressful events (Yonemoto, Kamibepu, Ishii, Iwata, & Tatzaki, 2012) were seen as robust predictors and could lead to distress and depressive symptoms. Finally, the severity of the diagnosis and its treatment (Harper et al., 2013; Rodriguez et al., 2012) related to a restless child

(i.e., a child with behaviour maladjustments) was considered a predictor of parental depressive symptoms and distress (Barrera et al., 2004).

A.3. The role of coping processes as mediators for parents of child cancer patients

A last mediator has been put forward and concerns parental coping. The term coping is used interchangeably to mean either the ways people try to handle stress (i.e., specific strategies) or how they evolve (i.e., adjustment). We will only consider studies including the first perspective. Certain studies focused on “situation specific coping” in relation to stressors associated with the child’s illness (see e.g., Sloper, 2000). Other researchers used level of distress as a criterion for coping efficacy. Researchers have examined anxiety and depression such as outcome criteria issues (Grootenhuis & Last, 1997a, 1997b), psychiatric problems (Hoekstra-Weebers, Jaspers, Kamps, & Klip, 2001) and psychosomatic problems (Sloper, 2000). Coping strategies are categorised in different ways, and viewed on occasion dichotomously (i.e., emotion-focused vs. problem-focused or avoidance vs. approach coping) (Hoekstra-Weebers, Jaspers, Kamps, & Klip, 2001; Sloper, 2000). At present, the diversity of results on parental coping is not able to generalise and produce robust explanations of the coping process. It appears that parental balanced coping strategies (i.e., low levels of perceived stressor and high levels of perceived social support) allow better internal locus of control and lead to conducive behaviours (Lindahl-Norberg, Lindblad, & Boman, 2005a). For instance, parental perception of an acute stressor as controllable allows to initiate active responses such as information-seeking and social support-seeking. Conversely, if the stressor is not controllable, future coping strategies may be not effective. Lastly, certain predictors were considered like SES, cumulative stressful events or the child’s disease and may lead to more parental symptoms (Wijnberg-Williams, Kamps, Klip, & Hoekstra-Weebers, 2006b) (supplementary Figure 2 – Integrated Figure of point A2 et A3).

Insert about here Figure 2

B. OFF TREATMENT

B.1. Core clinical issues in parents of child cancer survivors

Depression/anxiety

The burden of caring for a cancer survivor may be particularly gruelling for a mother. Analyses reported vulnerabilities among mothers to depression, anxiety and burnout (Robinson, Gerhardt, Vannatta, & Noll, 2007). Considered results may be related to the fact that mothers are more present than fathers during the child's life. Parental distress impacts children's quality of life, both directly and indirectly. Significant links were found between maternal depressive symptoms and children's quality of life during and after treatments. Maternal distress is also associated with a higher level of child emotional distress and higher child somatic distress (Roddenberry & Renk, 2008; Stam, Grootenhuis, Brons, Caron, & Last, 2006). Parental distress also has serious effects on health outcome for parents. Indeed, acute and chronic stress may lead to diminish immune functioning and increased the risk of infectious disease (Cohen, Doyle, & Skoner, 1999).

Depression and cognitive impairments: a neuroclinical genetic perspective

Cognitive impairment in depression has been widely reported. It is generally described as an extension of cognitive symptoms over time, even during remission. Pathologies and cognitive impairments share a common neuropathological "platform" in subcortical areas involved in emotional and cognitive processing, which may result from certain genetic or environmental factors. The aims of this section were to examine cognitive functioning among a clinically depressed population-based group in order to determine whether cognitive performances vary within the group. This section provides significant empirical links for understanding depression in parents of child cancer survivors. Recently researchers have been interested in the consequences of depression over time and during depression remission (Biringer et al., 2005; Paelecke-Habermann, Pohl, & Leplow, 2005; Weiland-Fiedler et al., 2004). Since the early 2000s to date, 56 studies have examined the relationship between depression and cognitive impairments; of which 7 studies were genetic and 49 were neuroclinical. Studies emphasized permanent cognitive symptoms as one of the core features of depressive disorders with a significant impact on functional outcome for the

individual (Beevers, Clasen, Stice, & Schyner, 2010; Biringer et al., 2005; Charney et al., 2003; Gotlib & Joormann, 2010; Rosenberg, Mielke, Xue, & Carlson, 2010). Core characteristics of cognitive impairment in depression disorder are reported, such as attention and/or vigilance, episodic memory, semantic memory, visual memory, verbal memory, fear extinction, processing speed, procedural memory, social cognition and language (Castaneda et al., 2010; Zobel et al., 2010). Current studies have revealed failures through the working memory and at process level of attention and executive functions (Doumas, Smolders, Brunfaut, Bouckaert, & Krampe, 2012; Elderkin-Thompson, Moody, Knowlton, Helleman, & Kumar, 2011). Other studies found no significant relationship between cognitive impairments, severity of depression and types of comorbidities (Bearden et al., 2006; Majer et al., 2004). Despite this evidence, reasons for poor cognitive performance in depression disorder remain unknown and unclear. In vivo and post-mortem investigations suggest that frontal-striatal-thalamic and limbic-thalamic-frontal networks are implied in the pathogenesis of depression disorder and especially a disruption of limbic dopaminergic signalling system which plays a pivotal role in the regulation of mood and emotion, cognition and behaviour (Millan, 2006; Price & Devrets, 2010). Abnormal grey and white matter in dorsolateral prefrontal cortex, cingulate cortex, orbito-frontal cortex and hippocampus were reported in depression and were correlated with cognitive dysfunctions such as working memory, episodic memory but, also processing speed (Ballmaier et al., 2008; Dubin et al., 2012). During cognitive tasks, depressed individuals presented abnormal activity (either hyper-or hypo-) in specific neural regions. Different hypotheses were reported: (1) depression is strongly linked to rumination processing and negative cognitions (Holmes & Pizzagalli, 2008; Pizzagalli, Peccoralo, Davidson, & Cohen, 2006); (2) the existence of an intrinsic process of depression of which the automatic negative thoughts distort the cognitive performance of the subject (Riso et al., 2003; Siegle, Moore, & Thase, 2004); (3) deficits in working memory could lead depressed individuals to select only negative pieces of information, even those irrelevant (Joormann & Gotlib, 2008); (4) damaged connections between the amygdala and the prefrontal cortex are described as a possible cause of cognitive inefficiency and bias in the evaluation of the intrinsic emotional process (Liao et

al., 2012; Moses-Kolko et al., 2010); (5) depressed individuals tend to display a hypo-activity in prefrontal regions during task performance (Audenaert et al., 2002; Pu et al., 2011). Geneticists found some links between cognitive deficits and genetic abnormalities (e.g., Juhasz et al., 2011; Molendijk et al., 2012) (supplementary Table III).

Insert about here Table III

PTSS-PTSD

Twenty-four studies examined the PTSS/PTSD issue, of which 13 studies employed a cross-sectional design, three employed a longitudinal design, four studies were literature reviews, two studies were conducted with qualitative tools, one study was a case study and one study used mixed method (on/off). Included studies only involved major scales with good psychometric properties. Twenty of the studies were conducted on a large sample (smallest $N= 11$, largest $N= 448$), clinical groups were compared with a control group, psychometric scales were valid and took into account mediation paths. Relevant studies described several elements in the prevalence of PTSS/PTSD among survivors and their family. Symptoms of stress (PTSS) or post-traumatic stress disorder (PTSD) were correlated positively or negatively and depended on the presence of risk factors and protective factors. Risk factors were poverty, socio-economic vulnerabilities (Lindahl-Norberg, Pöder, Ljungman, & von Essen, 2012), significant and permanent family dysfunctions (Alderfer, Navsaria, & Kazak, 2009; Doshi et al., 2011; Duran, 2013) and innate traits of anger and anxiety (Hardy et al., 2008). Some additional factors could become a genuine risk for the development of symptoms of stress such as perceptual dissonance of illness, reduced social support or contextual constraints among parents. Noxious effects of emotion-focused coping were also mentioned (Fuemmeler, Mullins, Van Pelt, Carpentier, & Parkhurst, 2005). Conversely, an optimistic mindset (Michel, Taylor, Absolom, & Eiser, 2010) and excellent communication and cohesion within the nuclear family were seen as protective factors (Brown, Madan-Swain, & Lambert, 2003). In addition, some authors (Alderfer, Cnaan, Annunziato, & Kazak, 2005; Taïeb,

Moro, Baubet, Revah-Lévy, & Flament, 2003) indicated that relatives are not immune from PTSS. All families have variable symptoms and intensity of stress, which depend on the family history (e.g., education, values, beliefs, socio-economic status, etc.). As already explained above, mothers tend more easily to develop symptoms of PTSS and PTSD. Some researchers described a biological link between gender and the prevalence of PTSS (Lindahl-Norberg, 2007; Ozono et al., 2007). Lastly, one study (Kazak et al., 2004a) showed cognitive elements in the emergence of PTSS or PTSD. Indeed, the parent could have a heightened trend to present intrusive thoughts, avoidance or physiological arousal (supplementary Table IV).

Insert about here Table IV

B.2. The role of psychosocial processes as mediators for parents of child cancer survivors

The majority of research observed an improvement in psychosocial adjustment within the entire family at the end of the treatment. Nevertheless some studies obtained opposite results showing increased family disorganization (Brown, Madan-Swain, & Lambert, 2003; Streisand, Kazak, & Tercyak, 2003). It was also revealed that marital instability (Yeh, 2002) and poor family functioning with precarious family relationships were important mediators in the raise of anxiety among parents and children and indirectly predicted parental PTSS (Alderfer, Cnaan, Annunziato, & Kazak, 2005). Kazak (2004a) and her associates focused on the lack of family cohesion, family communication and family satisfaction in the development of anxiety disorders and future parental PTSS. Moreover, Van Dongen-Melman (1998) and her collaborators emphasized the consequences of an internal or external control attitude on the family functioning. It appears that parents with extreme internal or external control could have more difficulties in psychosocial adjustment. This dichotomous attitude of control could cause the rise of negative emotions (e.g., anxiety, guilt or depression). However, parents who have balanced control tend to adjust positively to life events and would not often experience feelings of guilt or anxiety. Social support is described as having a mediating effect on the relation between gender and depressive symptoms, PTSS, and anxiety

(Barakat, Alderfer, & Kazak, 2006; Lindahl-Norberg, Lindblad, & Boman, 2006). The mediating effect is greater if the parent has high levels of perceived social support. In fact, studies show a significant decrease in anxiety (Bruce, Gumley, Isham, Fearon, & Phipps, 2011) and degree of PTSS but also a better adjustment to medical disease (Kazak et al., 2004a, 2004b). Conversely, a reduced social network, a high trend to perceive social constraints but, also a less perceived sense of belonging have been associated with more PTSS in parents of paediatric cancer survivors (Forinder & Lindahl-Norberg, 2010; Hardy et al., 2008). Certain studies examined the family functioning and its social and emotional consequences. Researchers highlighted that certain predictors like gender, socio-economic status, cumulative stress events and precarious incomes may lead to significant social, behavioural and emotional difficulties for the survivor and his entire family (Lindahl-Norberg & Green, 2007; Lindahl-Norberg & Steneby, 2009).

B.3. The role of coping processes as mediators for parents of child cancer survivors

Prospective studies demonstrated that balanced coping (i.e., a low level of perceived stress and a high level of perceived social support) predict positively emotional and social issues for parents. Indeed, there is strong evidence to suggest that coping processes are significantly linked to psychological symptoms with problem-focused forms of coping, such as problem solving tasks, which are negatively correlated with symptoms. Conversely, emotion focused forms of coping are positively correlated with symptoms (e.g., avoidant behaviours, anxiety, somatic problems, PTSS). Specific predictors namely the degree of openness/extraversion of communication about personal feelings among parents, parental consciousness, and the child's quality of life (Patterson, Holm, & Gurney, 2004; Wijnberg-Williams, Kamps, Klip, & Hoekstra-Weebers, 2006b) seem to protect parents against psychological symptoms (supplementary Figure 3-Integrated Figure of point B2 and B3).

Insert about here Figure 3

B.4. Other models for parents of child cancer survivors

Innate traits of anxiety and anger are described as a significant predictor in the development of anxiety, depression and PTSS/PTSD. In fact, these parents tend to present a perceptual dissonance of illness and to evaluate negatively social support and contextual constraints leading them to seek less social and familial support (Hardy et al., 2008). This negative emotion-focused coping mediator is described above (Fuemmeler, Mullins, Van Pelt, Carpentier, & Parkhurst, 2005). Finally, some studies described a relationship between socio-economic status and future psychosocial consequences for the parent and the survivor child. It appears that low income and a precarious situation can lead to negative psychosocial issues such as depression, anxiety, and burnout (Patel, Wong, Cuevas, & Van Horn, 2013).

C. PARENTS OF PAEDIATRIC CANCER SURVIVORS: ATTENTION AND WORKING MEMORY PATHWAY PERSPECTIVES

So far, few authors have dealt with the issue of long term cognitive effects on parents of child cancer survivors. Research carried out by Kazak and her collaborators (2004a) identified the presence of avoidant behaviours and intrusive thoughts among participants. Later studies also observed the same types of outcome such as a trend to avoidant behaviours, various mental intrusions and hyper arousal (Lindahl-Norberg, Pöder, Ljungman, & von Essen, 2011). However, no computational study (i.e., empirical models using computer simulation) has been proposed in the literature based on cognitive task performances for the participant. In parallel, studies in the field of cognition emphasized certain biases and interferences caused by stress on attention processing (Murata, 2004) and working memory pattern (Brewin & Smart, 2005). A general trend of working memory dysfunction (i.e., access and retrieval) and attention impairments were found among depressive populations (Dere, Pause, & Pietrowski, 2010; Zobel et al., 2010). So far, no study has focused on understanding involved cognitive processes and their outcomes for parents of child cancer survivors. To this end, an experimental design where the parent should activate specific processes in working memory by performing specific cognitive tasks may be appropriate. According to our exploratory model, it is necessary to take into account three patterns of predictors,

namely: (a) *the socio-demographic factor* (e.g., gender, stressful life events, health behaviours and SES), (b) *the personality factor* (e.g., innate traits of anxiety and anger and extraversion/openness) and (c) *the social and family factor* (i.e., marital status, perceived social support and family cohesion). Within this moderated mediation model (supplementary Figure 4), the moderator is characterized by the complete remission time factor (i.e., from 5 years minimum to 7 years of survival) which may influence certain mediation processes. Two core mediators are to be considered: *attentional and working memory processing* (i.e., encoding, storage and retrieving). Moderated mediation analyses should examine two clusters of outcomes in parents of child cancer survivors: *clinical outcomes* (i.e., PTSS/PTSD, anxiety/depression and somatic problems) and *cognitive outcomes* (i.e., avoidant behaviour, intrusive thoughts and hyperarousal) and should be compared to a control group. Understanding the activated cognitive processes (i.e., attention and working memory pattern) in the participants may provide clinicians and health care professionals with clues for therapeutic support. Besides, this would allow the identification of specific mediators like psychosocial buffers, coping buffers (i.e., coping strategies) and attentional and working memory patterns (i.e., encoding, storage and retrieving). It could prevent cumulative risk factors for this population and in future mitigate the development of pathological symptoms (i.e., anxiety, depression, PTSS/PTSD and cognitive impairments).

Insert about here Figure 4

Discussion

The current review aimed to investigate three core issues. The first concerns the consequences of stress on attention and working memory patterns. A number of experimental studies demonstrated a negative effect of laboratory stressors on cognitive performances within individuals and especially those concerning the attention process and the working memory pattern. Researchers emphasized significant attentional deficits and core difficulties in the process of access and retrieval of the working memory. The second issue aimed to understand which stress

symptoms have been observed in parents of child cancer patients and parents of child cancer survivors. The paediatric oncology field disclosed overwhelming stress for parents of child cancer patients. The treatment of cancer is a chronic process of traumatic stress, including pain, invasive procedures, heart-breaking family separations, hospitalizations away from the family, and physical complications related to chemotherapy treatment or radiation therapy. During treatment, a host of predictors can lead to a greater risk of depression, anxiety and PTSS, which are: female gender, innate traits of anxiety and anger and a low socio-economic status. In conjunction, cognitive studies carried out on depression observed cognitive biases concerning semantic tasks, reasoning, attention and cognitive planning. Besides, neurocognitive studies in the field of depression advanced neurobiological impairments of stress on the brain, where severe neuronal dysfunctions are frequently found in the limbic system and frontostriatal areas leading to cognitive failures during task performances. The paediatric haematology-oncology literature describes two main mediators, the psychosocial factor (i.e., social support and family functioning) and the coping appraisal factor (i.e., coping strategies and adjustment). Researchers described the importance of preserving adequate psychosocial adjustment (family cohesion, family communication and optimal social support) and carried out balanced cognitive appraisals of the situation (seeking social support, optimistic mindset) to counteract some psychological issues such as depression, anxiety and PTSS. Although psychological stress, anxiety, depression and PTSS are most prevalent shortly after diagnosis and diminish over time, persistent PTSS syndrome has been described in a substantial proportion of parents several years after the cessation of treatment. The painful and traumatic experience of cancer can leave serious psychological scars such as post-stress symptoms (PTSS) or post-traumatic stress disorder (PTSD) for the patient and his family. The experience of childhood cancer causes profound and intimate changes in family life, causing uncertainty and trauma. The literature on PTSS/PTSD specifically dealing with parents of child cancer survivors has boomed in recent years and reports that parents have to face residual effects of the disease and its treatments. Indeed, parents continue to struggle with adapting to “new normal life” and remain in fear about the future and well being of their child. Most current research states that some level of

parental distress is on-going, even 5 years after treatment completion. PTSS is frequently observed in families of childhood cancer survivors. Parents reported more stress symptomatology than former hospitalized patients including intrusion thoughts, avoidant conducts and hyperarousal. These symptoms persist long after treatment completion for parents. Recent studies compared parents of survivors of paediatric cancer who continued to accompany their child to appointments at the hospital. The parents reported identical levels of anxiety and distress to parents of children on active treatment. Results suggested that parents may remain psychologically vulnerable many years after the end of treatment, this being particularly gruelling for the mother. Several predictors have been identified through studies, namely: female gender, low socio-economic status and innate traits of anxiety and anger may lead to emergence of PTSS/PTSD. Two mediators have been emphasized and concerned *the psychosocial factor* (i.e., social support and family functioning) and *the coping factor* (i.e., cognitive evaluation and coping strategies), which seem to protect the parents from developing PTSS syndrome if they are adequate. Very recently, a few studies highlighted the emergence of moderate or severe PTSS in at least one family member of a cancer patient survivor. The third issue aimed to investigate the long term consequences on the quality of the cognitive operations of parents of child cancer survivors. Regrettably, few studies focused on understanding the activated cognitive operations (i.e., attention and working memory) and their issues, for parents of cancer survivor patients. This area is still not developed enough and would require strictly cognitive experimental designs with specific tasks performance for parents. Above all studies in the field of depression have pointed to a robust link between stress and its effects on memory and attentional performance outcomes.

Clinical implication of the study

Effective interventions will need to balance theoretically grounded models, careful clinical observations and empirical evidences. There are many opportunities for developing interventions across the treatment spectrum for parents of child cancer patients and survivors. The most promising interventions in pediatric oncology appear to be those that are carefully

tailored to specific outcomes rather than those that rely on global outcomes. For example, the “problem-solving therapy” has been shown to be more effective in reducing negative psychological outcomes (e.g., depression, anxiety and PTSS) and in increasing problem-solving skills for mothers of child cancer patients (see Sahler et al., 2002). The problem-solving therapy is designed to empower parents to manage adverse situations by using adequate coping strategies.

Another reasonable approach that may promote the identification of family risk factors concerns the Olson’s Circumplex Model of Family Functioning (see Olson, 2000). In short, in response to illness a well functioning balanced family with good communication, flexibility and cohesion tend to be more functional across the life cycle. Conversely, in response to illness, an unbalanced family structured by poor communication, rigidity and chaotic cohesion tend to be problematic for individuals and relationship development in the long run.

A last remark concerns more particularly the methodology of all eligible studies. In general, experimental groups are extremely heterogeneous in terms of treatment time and type of cancer, which do not allow generalization of the results. Cross-sectional studies were predominantly found in this area. It would be appropriate to follow parents prospectively through the different phases of illness, treatment and long term survival. Assessment at for instance six and twelve months post-diagnosis would give insight into parental stress symptoms over time and according the phases of illness. A wide variety of assessment measures to investigate parental stress manifestations is seen across studies rendering the empirical generalization of the field more complex. As regards coping studies, parents deal with an abnormal situation and therefore existing instruments may fail to assess their specific needs and difficulties which can cause stigma on parental adaptation. It is necessary to be more accurate in the terminology of stress and to make a specific distinction between stress as a primary reaction and psychological stress as an issue. In addition the inclusion of either mother alone or parents as a couple cause bias and generalization difficulties. Lastly, it would be advantageous for investigators to create a brief screening instrument allowing the

identification of specific risk factors and family risk factors; thus guarding against escalating emotional manifestations of stress.

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Table I

Summary of studies on parental anxiety of child cancer patients, in chronological order

Reference design	Design	Sample	Instruments	Main outcomes
Best, Streisand, Catania, & Kazak, 2001	L	66 M 47 F	T1: PPQ T2: STAI-State / PAAS IES-R/ PTGI /SNRDAT	Anxiety during treatment was a predictor of PTSS for M, not for F. Anxiety, self-efficacy, posttraumatic growth and time since treatment were associated with avoidance.
Mu et al., 2001	MC	100 M	STAI-State / PPUS / BAS SMS	Sense of mastery was a mediator for uncertainty and anxiety. Uncertainty was a good predictor for boundary ambiguity.
Vance, Morse, Jenney, & Eiser, 2001	CR	32 C 36P	PCQL-32 The Disquol GHQ-28	C who self-reported poorer QOL had M who were more depressed. P who reported poorer QOL for their child reported more illness stressors and perceived their child as being more vulnerable.
Mu, Ma, Hwang, & Chao, 2002	CR	80 F	STAI-State /PPUS /PMS	Uncertainty and level of education were good predictors of anxiety levels.
Santacroce, 2002	L	12 M 3F	STAI-State /PTSD-RI/ PPUS	Anxiety level was comparable to hospitalized individuals with anxiety. Level of PTSS was higher than parents of survivors. There was a significant relation between anxiety and PTSS.
Yeh, 2002	CR	164 couples	PSI -SF/ MSS /SCL35-R	M reported higher distress levels than F. P of children newly diagnosed with cancer showed higher levels of depression, anxiety, stress and marital dissatisfaction.
Boman, Lindahl-Norberg, & Björk, 2003	CR	146 M 118 F	PPD-C	Distress levels (loss of control, anxiety, depression, sleep disturbance, psychological and physical distress) were lower with more time elapsed since diagnosis.
Läteenmäki, Sjöblom, & Salmi, 2004	MC	21 P	STAI-State Non-standardized questionnaire	Significant loss of income and strain were intolerable in diagnosis time.
Kazak et al., 2005b	MC	38 caregivers	T1: ASDS T2: STAI-State / IES-R/ SCCIP-ND	Reduced anxiety and PTSS after completion of intervention (SCCIP-ND) was reported.
Phipps, Long, Hudson, & Rai, 2005a	CR	162 P and patients	IES-R / PTSD-RI	Parents of children recently diagnosed reported higher PTSS levels than parents of survivors.

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Lindahl-Norberg, Lindblad, & Boman, 2005b	MC	175 P (on) 238 P (off)	STAI-State / UCL / Social Support Scale	A significant relation between support seeking and perceived support was found. Negative relation between anxiety and social support seeking was observed for M. The pattern of stress symptoms may vary according to educational, ethnicity and gender factor.
Phipps, Larson, Long, & Rai, 2006	MC	99 M 18 F 4 GP 162 CCP	WAI	Low anxious and repressive parents reported lower PTSS levels than high anxious parents.
Gerhardt et al., 2007b	ML	48M 33F 49MHC 29FHC	Measures of adjustment post-diagnosis	M of a child cancer patient reported more anxiety, less family conflict and more social support than controls. It was noted that parents seem to present significant resiliency during active treatment.
Hovén, Anclair, Samuelsson, Kogner, & Boman, 2008	CR	144P (parental distress category) 177P (parental distress after ALL)	A multidimensional questionnaire assessing symptoms of distress was used.	P in the complicated cancer category showed fear, anxiety, depression, loss of control, late effects-related uncertainty and poorer self-esteem compared with parents of children with ALL. Parental distress was associated with the child having been treated with cranial irradiation.

Note. **ALL**= Acute Lymphoblastic Leukaemia; **ASDS**= Acute Stress Disorder Scale ; **BAS**= Boundary Ambiguity Scale ; **C**= Child; **CR**= Cross-sectional design; **CCP**= Child Cancer Patient; **F**= Father; **FHC**= Father of Healthy Child; **GF**= Grandfather; **GHQ-28**= The General Health Questionnaire **GM**= Grandmother; **GP**= Grandparents; **IES-R**= Impact of Event Scale Revised; **L**= Longitudinal design; **M**= Mother; **MC**= Mixed treatment (on/off)/Cross-sectional design; **MHC**= Mother of Healthy Child; **ML**= Mixed treatment (on/off)/Longitudinal design; **MSS**= Marital Satisfaction Scale ; **P**= Parents; **PAAS**= Pediatric Anxiety and Avoidance Scale; **PCQL-32**= The Pediatric Cancer Quality of Life-32; **PMS**= Pearlin Mastery Scale ; **PPD-C**= Parental Psychological Distress in Childhood Cancer ; **PPQ**= Perception of Procedures Questionnaire ; **PPUS**= Parent's Perception of Uncertainty in Illness Scale ; **PSI-SF**= Parenting Stress Index Short Form ; **PTGI**= Post Traumatic Growth Inventory ; **PTSD-RI**= Post-Traumatic Stress Disorder Reaction Index; **SCCIP-ND**= The Surviving Cancer Competently Intervention Program-Newly Diagnosed ; **SCL35-R**= Symptoms Checklist-35-Revised ; **SMS**= Sense of Mastery Scale ; **SNRDAT**= Social Network Reciprocity and Dimensionality Assessment Tool ; **STAI- state**= State Trait Anxiety Inventory; **The Disquot**; **UCL**= Utrecht Coping List scale ; **WAI**= Weinberger Adjustment Inventory.

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Table II

Summary of studies on parental PTSS/PTSD of child cancer patients, in chronological order

Reference design	Design	Variables of interest	Sample	Instruments	Main outcomes
Best, Streisand, Catania, & Kazak, 2001	L	PTSS	66 M 47 F	T1: PPQ T2: STAI-State / PAAS IES-R/PTGI /SNRDAT	Anxiety during treatment was a predictor of PTSS for M and not F. Anxiety, self-efficacy, posttraumatic growth and time since treatment were associated with avoidance.
Sahler et al., 2002	CR	PTSS	92 M	POMS / SPSI-C	M in PTSS-intervention condition showed enhanced problem-solving skills and decreased negative affectivity compared to controls. PTSS had the greatest impact on improving constructive problem solving.
Santacroce, 2002	MC	PTSS	12 M 3 F	STAI-State / PTSD-RI / PPUS	There was a significant relation between anxiety and PTSS.
Magali-Vardi et al., 2004	L	PTSS	20 M 16 F 20 CC	DTS	20 % of parents showed signs of PTSS within the first two weeks after diagnosis.
Kazak, Boeving, Alderfer, Hwang, & Reilly, 2005a	CR	PTSS +PTSD	119 M 52 F	PTSD-RI / IES-R	Mean scores indicated moderate PTSS among families. There were minimal associations between PTSS and time since diagnosis.
Kazak et al., 2005b	RCT	PTSS	38 caregivers	T1: ASDS T2: STAI-State / IES-R/ SCCIP-ND	Reduced anxiety and PTSS after completion of intervention (SCCIP-ND) was reported.
Phipps, Long, Hudson, & Rai, 2005a	CR	PTSS	162 P and patients	IES-R / PTSD-RI	Parents of children recently diagnosed reported higher PTSS levels than parents of survivors.
Sahler et al., 2005	RCT	PTSS	430 M	POMS / BDI-II / IES-R NEO-FFI / SPSI-R	M with PTSS showed enhanced problem solving skills and decreased negative effect compared to controls. Young and single mothers are most prone to PTSS.
Phipps, Larson, Long, & Rai, 2006	MC	PTSS	99 M 18 F 4 GP 162 CC	IES-R / WAI	Low anxious and repressive parents reported lower PTSS levels than high anxious parents. Parents identified as low anxious self-reported lower levels of PTSS than high anxious parents.
Dolgin et al., 2007	CR	PTSS	212 M and CC	PTSS checklist	M demonstrated a pattern of mildly elevated negative affectivity

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				Depressive scale	and posttraumatic symptomatology initially, with steady improvements evident at 3- and 6-month follow-up.
Lindahl-Norberg & Boman, 2008	CR	PTSS	266 M 208 F	IES-R PTSS Anxiety and depression	Elevated stress was associated with the time from diagnosis. Up to 12% of parents for whom >5 years had passed since diagnosis time presented more intrusive thoughts, avoidance and arousal symptomatology.
Pöder, Ljungman, & von Essen, 2008	L	PTSD	214 P (107 M and 107 F)	PCL-C PTSD Index ASDS	According to the PCL-C symptom criteria method, 33% M presented higher levels of ASDS than F at T1, whereas 28% showed higher levels of PTSD at T2 and 22% at T3.
Rabineau, Mabe, & Vega, 2008	R	PTSS	X	X	Factors associated with increased risk of PTSS include poor social support, adverse experience with medical procedures, negative parental beliefs about the child's illness and/or associated treatment, and innate anxiety traits.
Jurbergs, Long, Ticona, & Phipps, 2009	CR	PTSS + PTSD	Parents of 199 CC + 108 PHC	Self-report measure of PTSS.	Within the cancer group, parental reports of PTSS differed according to treatment status and time since diagnosis.
Lindahl-Norberg, Pöder, Ljungman, & von Essen, 2011	L	PTSS +PTSD	111 M 109 F	PTSD-CCV-1	Avoidance during (T1-T3) and immediately after (T4) the child's treatment predicted PTSS among parents one year after (T6) completion of the child's treatment.
Cernvall, Alaie, & von Essen, 2012	L	PTSS+PTSD	249 CC 234 MCC 203 FCC	PTSD- CCV-2	Four main factors have been underlined: re-experiencing, avoidance, dysphoria, and hyper arousal.
Dunn et al., 2012	CR	PTSS	191 MCC 95 FCC	IES-R BDI-2	Substantial subgroups of MCC (41%) and FCC (30%) were characterized by symptoms of depression and anxiety. MCC and FCC reported comparable mean levels of PTSS that were strongly positively correlated with symptoms of anxiety and depression.
Landolt, Ystrom, Sennhauser, Gnehm, & Vollrath, 2012	CR	PTSS +PTSD	287 CC 239 MCC 221 FCC	Self-report questionnaire PTSS checklist.	At the first assessment 11.1% and at the second assessment 10.2% of CC had moderate to severe PTSS. At 5-6 weeks 29.3% of MCC and 18.6% of FCC met criteria for PTSD. M were more vulnerable than F.
Lindahl-Norberg, Pöder, Ljungman, & von Essen, 2012	L	PTSS	224 PCC	Self-report questionnaire and medical records	Parent's perception of child psychological distress and total symptom burden predicted higher levels of PTSS. Immigrants and unemployed parents reported higher levels of PTSS.
Rodriguez et al., 2012	CR	PTSS	106 CC 191 MCC 95 FCC	Perceived stress questionnaire and stressors questionnaire.	MCC reported higher levels of stressors than FCC. Parents rated physical effects as more stressful while children rated role-functioning stressors as more stressful.
Tremolada, Bonichini, Schiavo, & Pillon, 2012	L	PTSS	94 MCC	PCL-C, BSI-18, Problem Scale,	Couple connectedness, family routine reorganisation, parental communication about the child's illness and trust in the medical

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				Couple and familial questionnaires	care significantly increased just after diagnosis.
Yonemoto, Kamibeppu, Ishii, Iwata, & Tatezaki, 2012	MC	PTSS+PTG	28 MCC 30 FCC	IES-R PTGI	A positive correlation was noted between IES-R and PTGI scores in parents.
Boman, Kjällander, Eksborg, & Becker, 2013	CR	PTSS	97 M 72 F 103 CC	IES-R Intrusion, avoidance and hyperarousal questionnaires	Mothers demonstrated more severe PTSS across all symptom dimensions. Traumatic life events were associated with significantly increased hyperarousal symptoms.
Clawson, Jurbergs, Lindwall, & Phipps, 2013	CR	PTSS	199 CC 108 HC + Parents	Self-reported measures.	Increased parental PTSS was associated with better concordance in the cancer group but not in the control group (PHC) .
Harper et al., 2013	L	PTSS	75 CC + Parents	Self-reported measures on PTSS.	Self-efficacy for keeping the child calm during treatments was significantly correlated with distress in parents at the time of procedures, and self-efficacy for keeping the child calm before procedures was significantly correlated with PTSS.
Lindahl-Norberg & Boman, 2013	L	PTSS	36 MCC 26 FCC	PPD Cancer questionnaire PTSD-RI IES-R	The majority of parents, 55% (n = 34), reported loss of control over more than half the competences investigated. Only 5% (n = 3) reported no loss of control. At T2, some degree of PTSS was reported by 89% (n = 55). These outcomes were similar for M and F.

Note. **ASDS**= Acute Stress Disorder Scale; **BDI-2**= Beck Depression Inventory-2; **BSI-18**= Brief Symptom Inventory; **CC**= Child Cancer; **CR**= Cross-sectional design; **DTS**= Davidson Trauma Scale; **F**= Father; **FCC**= Father of Child Cancer; **GM**= Grandmother; **GF**= Grandfather; **GP**= Grandparents; **HC**= Healthy Child; **IES-R**= Impact of Event Scale Revised; **L**= Longitudinal design; **MC**= Mixed treatment (on/off)/Cross-sectional design; **MCC**= Mother of Child Cancer; **ML**= Mixed treatment (on/off)/Longitudinal design; **M**= Mother; **NEO-FFI**= NEO-Five Factor Inventory; **P**= Parents; **PAAS**= Pediatric Anxiety and Avoidance Scale; **PCC**= Parents of Child Cancer; **PCL-C**= Posttraumatic Stress Disorder Checklist; **PHC**= Parents of Healthy Child; **POMS**= Profile Of Mood Scale; **PPD**= The Parental Psychosocial Distress; **PPQ**= Perception of Procedures Questionnaire; **PPUS**= Parent's Perception of Uncertainty in Illness Scale ; **PTGI**= Post Traumatic Growth Inventory ; **PTSD-CCV-1**= PTSD-Checklist Civilian Version 1; **PTSD-CCV-2**= PTSD-Checklist Civilian Version 2; **PTSD-RI**= Post-Traumatic Stress Disorder Reaction Index; **R**= Review of the Literature; **RCT**= Randomized Controlled Trial; **SCCIP-ND**= The Surviving Cancer Competently Intervention Program-Newly Diagnosed ; **SNRDAT**= Social Network Reciprocity and Dimensionality Assessment Tool; **SPSI-C**= Social Problem-Solving Inventory-Cancer; **SPSI-R**= Social Problem-Solving Inventory-R; **STAI-state**= State Trait Anxiety Inventory; **WAI**= Weinberger Adjustment Inventory.

Table III

Summary of studies on depression by research hypothesis

Research Hypothesis	Reference design	Main outcomes
<u><i>Clinical hypothesis</i></u>	<ol style="list-style-type: none"> 1. Spielberger, Ritterband, Reheuser, & Brunner, 2003 2. Biringe et al., 2005 Paelecke-Habermann, Pohl, & Leplow, 2005 Reppermund, Ising, Lucae, & Zihl, 2009 Weiland-Fiedler et al., 2004 	<ol style="list-style-type: none"> 1. Various depressive symptoms over time (e.g., anhedonia, weight loss, insomnia or hypersomnia, psychomotor agitation or slowness, fatigue, etc.). 2. Depressive symptoms persist over time and certain cognitive dysfunction remains unresolved even after remission of depressive symptoms.
<u><i>Cognitive dysfunctioning hypothesis</i></u>	<ol style="list-style-type: none"> 1. Beevers, Clasen, Stice, & Schyner, et 2010 Biringe et al., 2005 Charney et al., 2003 Gotlib & Joormann, 2010 Marazziti, Consoli, Pichetti, Carlini, & Faravelli, 2010 Rosenberg, Mielke, Xue, & Carlson, 2010 2. Castaneda et al., 2010 Dere, Pause, & Pietrowski, 2010 Gorwood, Corruble, Falissard, & Goodwin, 2008 Harmer et al., 2009 Jones, Siegle, Muelly, Haggerty, & Ghinassi, 2010 Marazziti, Consoli, Pichetti, Carlini, & Faravelli, 2010 Zobel et al., 2010 3. Christopher & MacDonald, 2005 Domas, Smolders, Brunfaut, Bouckaert, & Krampe, 2012 Elderkin-Thompson, Moody, Knowlton, Helleman, & Kumar, 2011 Nakano et al., 2008 4. Bearden et al., 2006 Castaneda et al., 2010 Majer et al., 2004 Reppermund, Ising, Lucae, & Zihl, 2009 Wang et al., 2006 5. Riso et al., 2003 Siegle, Moore, & Thase, 2004 6. Joormann & Gotlib, 2008 	<ol style="list-style-type: none"> 1. Cognitive symptoms/deficit are core manifestations of the depressed individual and may be permanent. 2. Main cognitive impairments in depression disorder are attention and/or vigilance, episodic memory, semantic memory, visual memory, verbal memory, fear extinction, processing speed, procedural memory, social cognition and language. 3. Failures in the working memory but also in attention and executive processing among depressed individuals. 4. No relationships between cognitive impairments, severity of depression, and types of comorbidity. 5. Automatic negative thoughts render ineffective the cognitive performances of the depressed subject. 6. Selecting of negative information by the depressed individual.

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<i>Neurological lesions hypothesis</i>	1. Hauber & Sommer, 2009 Millan, 2006	1. Disruption of limbic dopaminergic signalling system.
	2. Mayberg, 2003 Price & Devrets, 2010	2. Dysfunction in subcortical areas playing a pivotal role in the regulation of mood and emotion, cognition and behaviour.
	3. Ballmaier et al., 2008 Dubin et al., 2012 Heiden et al., 2005 Hickie et al., 2005 Huang, Fan, Williamson, & Rao, 2011 Kempton et al., 2011 Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009 Li et al., 2007 Ries, Wichmann, Bendlin, & Johnson, 2009	3. Abnormal grey and white matter in dorsolateral prefrontal cortex, cingulate cortex, orbito-frontal cortex and hippocampus in depressed individuals. White matter damage in frontal and parietal brain areas were correlated with current severity of depression and cognitive deficits.
	4. Holmes & Pizzagalli, 2008 Pizzagalli, Peccoralo, Davidson, & Cohen, 2006	4. Occurrence of rumination process and negative cognitions in depression. Hyperactivity in the hippocampus, which is associated with failures in dorsolateral and prefrontal cortex.
	5. Liao et al., 2012 Moses-Kolko et al., 2010 Siegle, Thompson, Carter, Steinhauer, & Thase, 2007	5. Damaged connections between the amygdala and the prefrontal cortex have been observed and cause cognitive inefficiencies and bias in the evaluation of the intrinsic emotional process.
	6. Audenaert et al., 2002 Fitzgerald et al., 2008 Okada, Okamoto, Morinobu, Yamawaki, & Yokota, 2003 Pu et al., 2011 Schöning et al., 2009 Siegle, Thompson, Carter, Steinhauer, & Thase, 2007	6. Neuronal hypo-activity in prefrontal regions during task performance was observed in depressed individuals.
<i>Genetic polymorphisms hypothesis</i>	1. Cunha, Brambilla, & Thomas, 2010	1. BDNF polymorphisms.
	2. Gatt et al., 2009 Molendijk et al., 2012	2. BDNF polymorphisms/ Val66Met polymorphisms.
	3. Inkster et al., 2009	3. GKS3 polymorphisms.
	4. Juhasz et al., 2011	4. CREBI polymorphisms/BDNF polymorphisms/NTRK2 polymorphisms.
	5. Yang et al., 2010	5. BDNF polymorphisms/GKS3 polymorphisms.
	6. Meyer-Lindenberg et al., 2007	6. DARPP-32 polymorphisms.

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Table IV

Summary of studies on parental PTSS/PTSD of child cancer survivors, in chronological order

Reference design	Design	Variables of interest	Sample	Instruments	Main outcomes
Brown, Madan-Swain, & Lambert, 2003	CR	PTSD	52 ACS 52 MAS 42 HA 42 MHA	Self-report of PTSS	MAS presented more PTSD symptoms than MHA and reported greater recent and past stressful life events.
Taïeb, Moro, Baubet, Revah-Lévy, & Flament, 2003	R	PTSS + PTSD	20 studies	X	Prevalence of PTSS/or PTSD is between 2 and 20 % in survivors and between 10 and 30 % in their parents.
Kazak et al., 2004b	CR	PTSS	150 ACS and parents	SCCIP	Significant reductions in intrusive thoughts among FAS and among ACS were found in the treatment group.
Kazak et al., 2004a	CR	PTSS + PTSD	150 ACS 146 MAS 103 FAS	IES-R /PTSD-RI /Structured Clinical Interview	PTSS is common in families of CS. Parents reported more symptomatology than former hospitalized patients. MAS and FAS had relatively equal rates of PTSS & PTSD.
Alderfer, Cnaan, Annunziato, & Kazak, 2005	CR	PTSS + PTSD	98 PAS	PTSD-RI	Five main clusters for the PTSD-RI: Minimal PTS, Mothers Elevated, Disengaged, Fathers Elevated, and Elevated PTSS.
Fuemmeler, Mullins, Van Pelt, Carpentier, & Parkhurst, 2005	CR	PTSS	47 PCS(1) 31 PCWD	Self-report measures of posttraumatic stress, general psychological distress, coping strategies, social network size, and perceived illness and uncertainty	PCS(1) reported higher levels of PTSS and general distress than parents of children with DM1. Lower levels of emotion-focused coping and greater perceived uncertainty were associated with high levels of PTSS.
Lindahl-Norberg, Lindblad, & Boman, 2005b	MC	PTSS	175 PCC 238 PCS(1)	Psychological distress, arousal, intrusion, SES.	MCC reported higher levels of stress than FCC. Intrusion and arousal were more frequent in parents during ongoing treatment. The pattern of stress symptoms may vary according to gender, educational level and ethnicity.
Barakat, Alderfer, & Kazak, 2006	L	PTSS +PTG	150 ACS 146 MAS 107 FAS	PCS(3) ITSIS	A majority of ACS and PAS reported PTG. Greater perceived treatment severity and life threat were associated with PTG.
Bruce, 2006	R	PTSS + PTSD	24 studies	X	Prevalence of PTSD and PTSS varied widely within the sample.
Gerhardt et al., 2007a	L	PTSS + PTSD	56 CS, PCS(1)	Questionnaires and a semi-structured psychiatric interview.	Late effects were associated with greater number of past PTSS events. Of the 16 cancer survivors who reported

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			and peers		traumatic events, five (31%) were cancer-related.
Lindahl-Norberg & Green, 2007	SC	PTSS	Two family cases	Interviews	Parents are vulnerable and suffer from fatigue, psychological exhaustion and need psychosocial support.
Ozono et al., 2007	CR	PTSS	88 ACS 87 MAS 72 FAS	FRI	Severe PTSS is reported by 10.9% (n=9) of ACS, 20.7% (n=18) of MAS, and 22.2% (n=16) of FAS.
Hardy et al., 2008	CR	PTSS	27 PAS 28 PCC	BSI, IFS, IES-R, PECIS	PAS demonstrated few significant differences in psychological functioning, posttraumatic stress symptoms, and adjustment to the disease experience.
Vrijmoet-Wiersma et al., 2008	R	PTSS	67 studies	X	Most emotional stress reactions were seen in mothers around the time of diagnosis. A subset of parents reported continuing stress even up to 5 years or more post diagnosis.
Alderfer, Navsaria, & Kazak, 2009	CR	PTSD	144 ACS and their parents	FAD + structured diagnostic interview	Families in which ACS had PTSD (8% of the sample) had poorer functioning in the areas of problem solving, affective responsiveness, and affective involvement.
Lindahl-Norberg & Steneby, 2009	QI	PTSS	PCS(1) (CS = 7)	Semi-structured individual interviews.	The main themes are: (1) survivor needed to engage in everyday life activities; (2) every day family life was restricted; (3) parenting role had become more demanding; (4) parents' outlook on life changed (5) and parental worries regarding their survivor child about future well-being were increased.
Forinder & Lindahl-Norberg, 2010	QI	PTSS	11 PCS(1)	Structured interviews were conducted. The Inductive Thematic method was used to analyse the data.	Perceived threat, uncertainty and loss were described as sadness, loneliness and changes in parents' identity and meaning.
Michel, Taylor, Absolom, & Eiser, 2010	L	PTSS	48 CS and their parents	BFSC, QOL, PTSD-RI, illness perception and optimism. PTGI, QOL, PTSD-RI and illness perception.	Diagnosis of leukaemia, greater optimism and illness perception were associated with higher scores on the BFSC. Parents' perceptions of the illness were associated with PTG.
Bruce, Gumley, Isham, Fearon, & Phipps, 2011	CR	PTSD	52 CS 52 PCS(1)	Quality of parent-child interactions, coping styles and PTSS.	35% of CS and 29% of PCS(1) reported severe levels of PTSS.
Doshi et al., 2011	CR	PTSS	86 MAS	PHCBI PCS(2) PCL-C PTGI	Study 1 observed four positive factors for PHCBI: (a) social competence, (b) health perceptions, (c) satisfaction with healthcare, and (d) health apprehension. Study 2 observed three domains of PTGI: (a) interpersonal relationships, (b) life satisfaction, and (c) life outlook.

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					Study 3: qualitative data revealed different maternal reasons to accompany their child to medical appointments.
Lindhal-Norberg, Pöder, Ljungman, & von Essen, 2012	CR	PTSS	224 PCC 224 PCS(1) (Same sample).	Self-report questionnaires and medical records.	Immigrants and unemployed PCS(1) reported significant levels of PTSS. Parents' perception of child psychological distress predicted higher levels of PTSS.
Patel, Wong, Cuevas, & Van Horn, 2013	CR	PTSS	44 CS and parents	PTSS scale Perceived stress Executive functioning (child)	Child executive functioning predicted parental stress levels even after controlling for socio-demographic and clinical factors.
Pollock, Litzelman, Wisk, & Witt, 2013	CR	PTSS	73 case dyads (CC and PCC) 133 control case dyads	Psychological distress and social distress.	PCC presented higher levels of physiological symptoms of stress than PHC. Poor sleep quality and greater social stress were significant correlates of increased levels of stress in parents of children with cancer.
Duran, 2013	R	PTSS	35 studies	X	Five themes were identified: (1) meaning-making, (2) appreciation of life, (3) self-awareness, (4) closeness and family togetherness, and (5) a desire for revenge on society.

Note. **AC**= Adolescent Cancer; **ACS**= Adolescent Cancer Survivor; **BFSC** = Benefit Finding Scale for Children; **BSI** = Brief Symptom Inventory; **CC**= Child Cancer; **CR**= Cross-sectional design; **CS**= Child Survivor; **FAC**= Father of Adolescent Cancer; **FAD**= Family Assessment Device; **FAS** = Father of Adolescent Survivor; **FCC** = Father of Child Cancer; **FHA** = Father of Healthy Adolescent; **FRI**= Family Routines Inventory; **HA**= Healthy Adolescent; **IES-R**= Impact of Event Scale Revised; **IFS** = Impact on Family Scale; **ITSIS**= The Impact of Traumatic Stressors Interview Schedule; **L**= Longitudinal design; **M** = Mixed treatment (on/off); **MAC**= Mother of Adolescent Cancer, **MAS** = Mother of Adolescent Survivor; **MHA** Mother of Healthy Adolescent; **MC** = Mixed treatment (on/off)/Cross-sectional design; **MCC** = Mother of Child Cancer; **ML** = Mixed treatment (on/off) /Longitudinal design; **PAC** = Parent of Adolescent Cancer; **PAS** = Parents of Adolescent Survivor; **PCC**= Parents of Child Cancer; **PCL-C**= Post-traumatic Symptom Disorder Checklist-Civilian Version; **PCS(1)**= Parents of Child Survivor; **PCS(2)**= Parental Coping Scale; **PCS(3)**= The Perceptions of Changes in Self scale; **PCWD**= Parents of Child With Diabetes; **PECIS**= Parent Experience of Child Illness Scale; **PHA** = Parents of Healthy Adolescent; **PHCBI** = The Parental Health Competence Beliefs Inventory ; **PTG** = Post Traumatic Growth; **PTGI** = Post Traumatic Growth Inventory; **PTSSD-RI**, Posttraumatic Stress Disorder Reaction Index; **QOL** = Quality of Life; **QI** = Qualitative study; **R**= Review of the Literature; **SC** = Study Case; **SCCIP** = The surviving Cancer Competently Intervention Program; **SES**= Socioeconomic Status.

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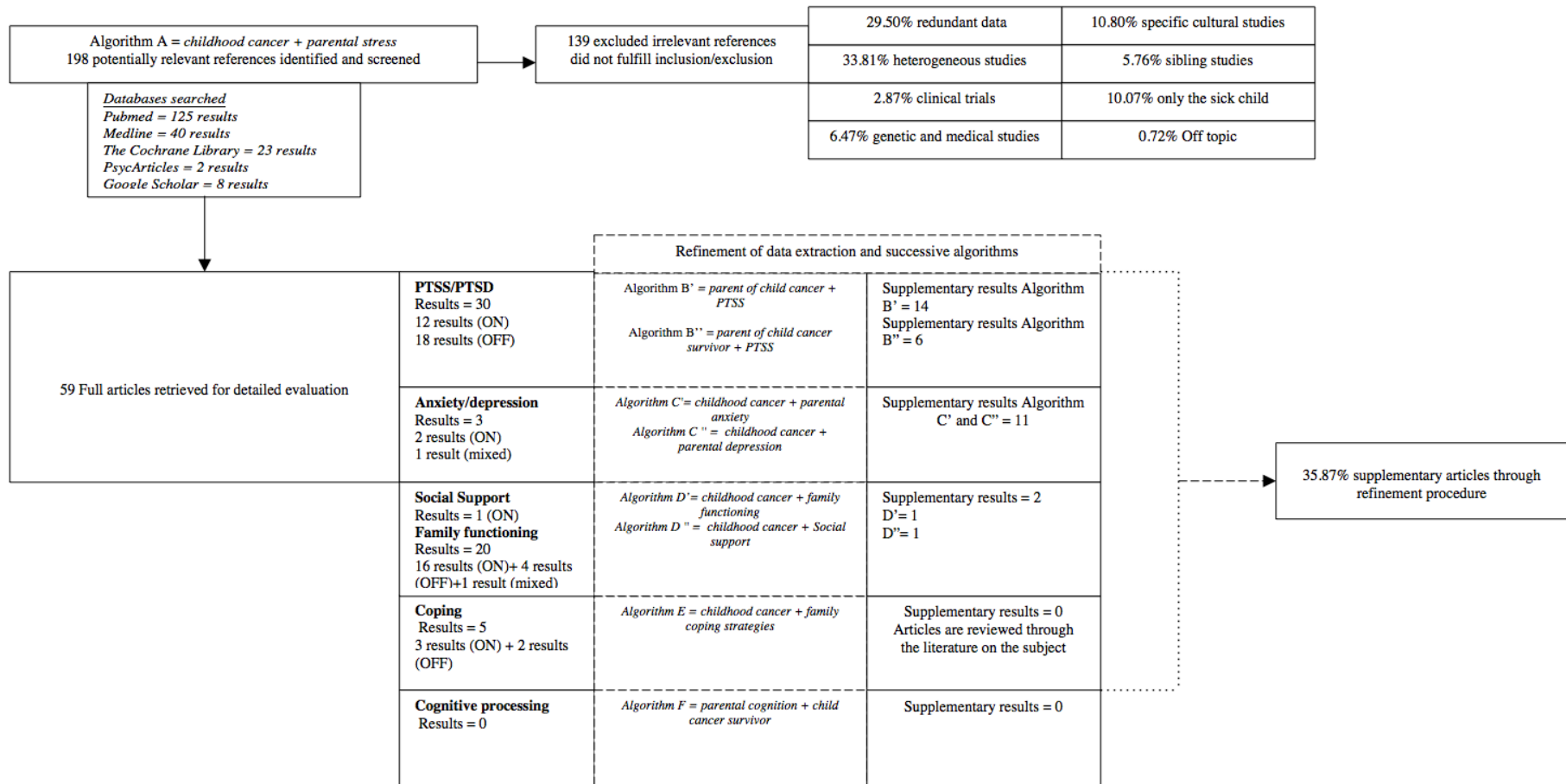


Figure 1. Algorithmic diagram of study identification and selection

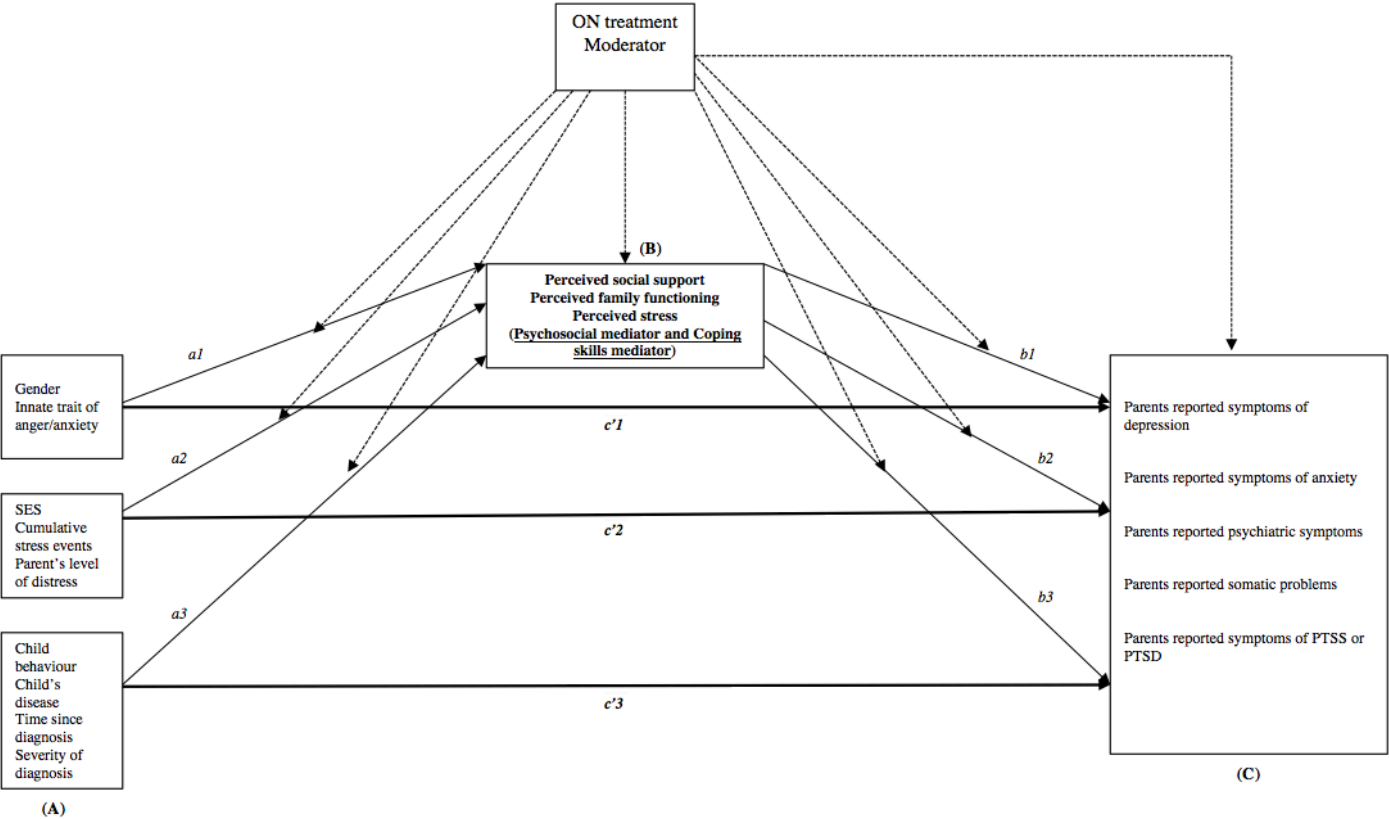


Figure 2. The role of psychosocial mediator and the role of coping mediator (B) (perceived social support, perceived family functioning and perceived stress) for parents of child cancer patients: moderated mediation between specific predictors (A) and issues (C)

Note. Introduction of the psychosocial variable and the parental coping variable (B) as a mediator during active treatment (moderator) influences the relationship between A and C.

----- = Moderator effect on the mediation relationship (B) between A and C

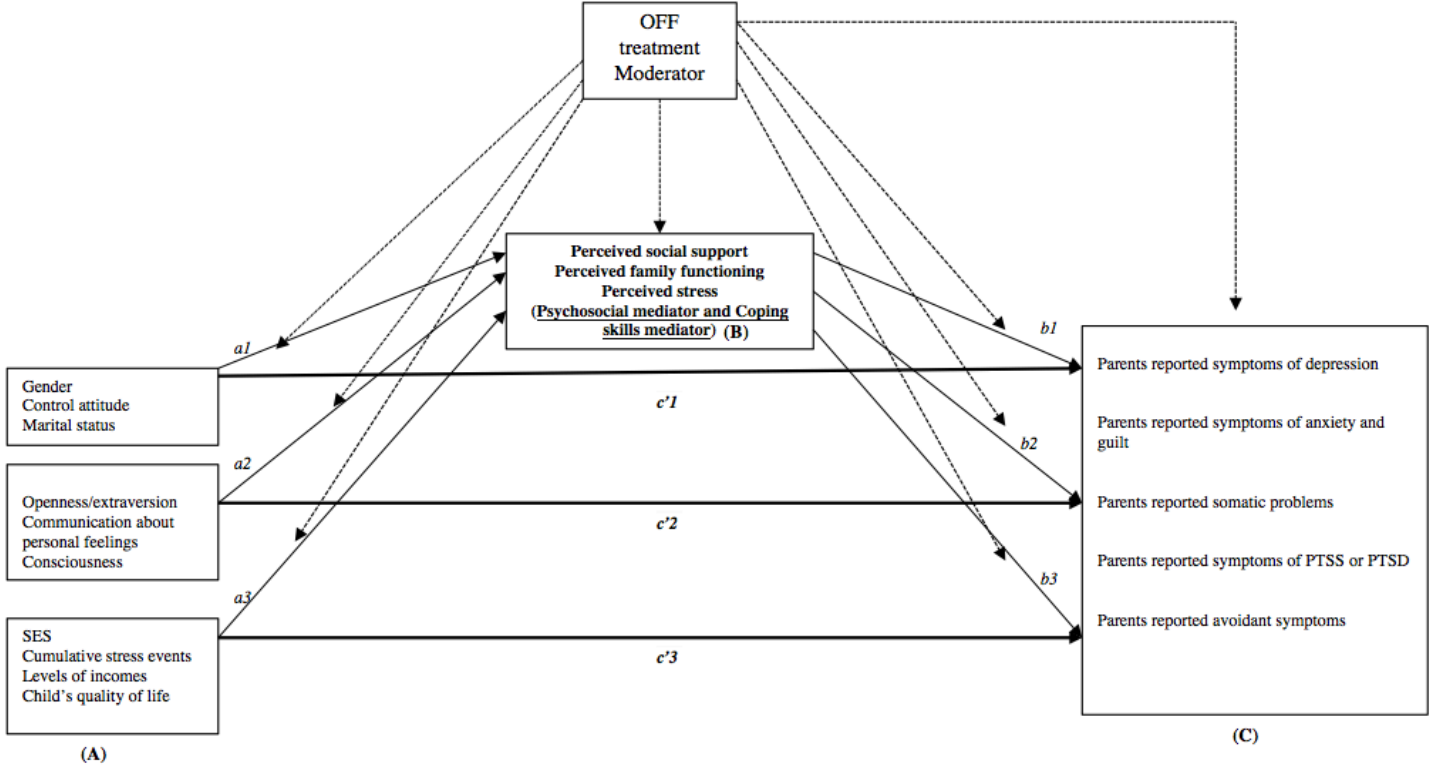


Figure 3. The role of psychosocial mediator and the role of coping mediator (B) (perceived social support, perceived family functioning and perceived stress) for parents of child cancer survivors: moderated mediation between specific predictors (A) and issues (C)

Note. Introduction of the psychosocial variable and the parental coping variable (B) as a mediator for survivor situation (moderator) influences the relationship between A and C.

----- = Moderator effect on the mediation relationship (B) between A and C

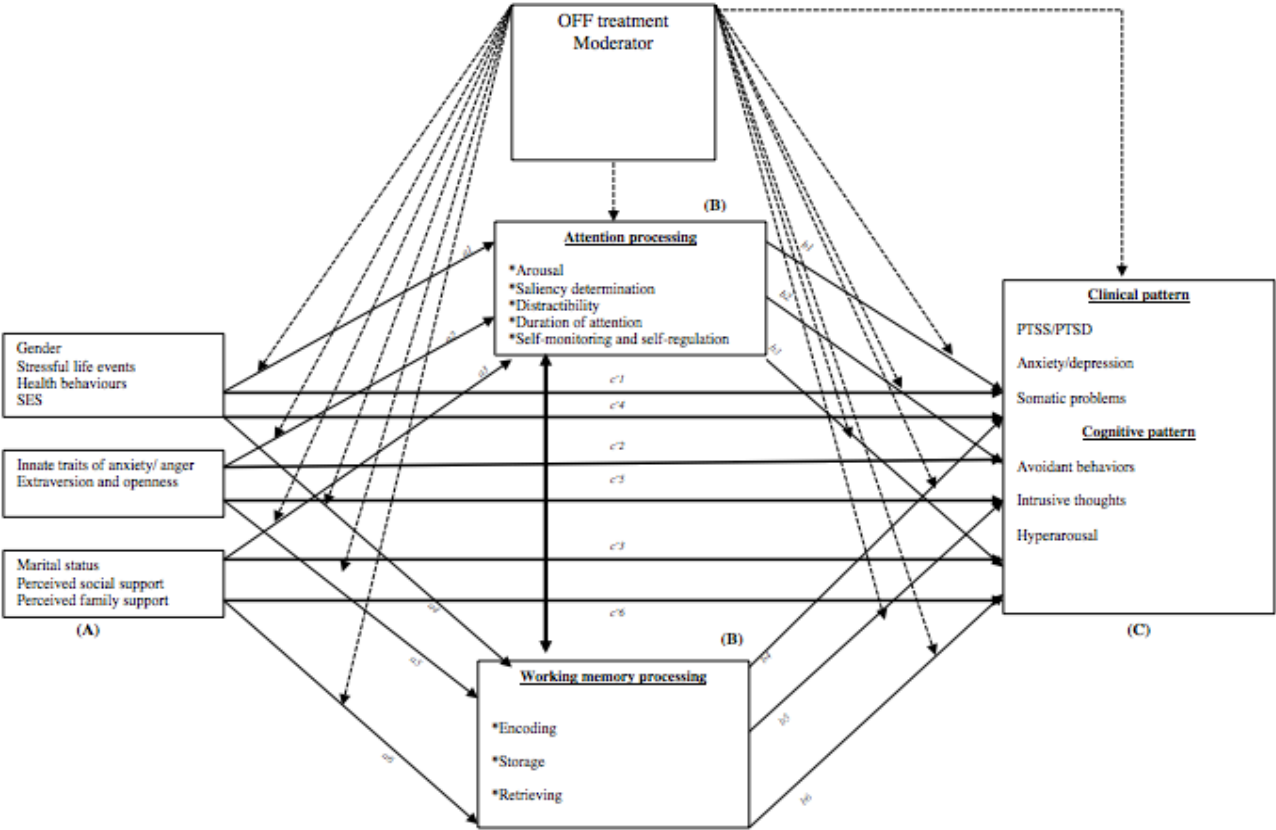


Figure 4. Exploratory representation of research issue: the role of cognitive mediators (B) (i.e. the attention process and the working memory pattern) for parents of child cancer survivors; moderated mediation between specific predictors (A) and issues (C)

Note. Introduction of the cognitive pathways variable (B) as a mediator for survivor situation influences the relationship between A and C.

----- = Moderator effect on the mediation relationship (B) between A and C

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