

# **Autobiographical memory, self, and stress-related psychiatric disorders: Which implications in cancer patients?**

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## **Abstract**

Autobiographical memory refers to information and memories of personal life events, accumulated since childhood, which enable the construction of a feeling of identity and continuity. Autobiographical memory retrieval is a dynamic and reconstructive process, as mental representations change with the passage of time. This flexible aspect of memory is linked to one's changing self and aspirations over time, that evolve according to our personal status and environment. Hence, any breakdown in the continuity of life involves a distortion of memory. Such distortions can be observed in stress-related psychiatric disorders, such as major depression or post-traumatic stress disorder, where autobiographical memory retrieval is characterized by overgenerality (i.e., the tendency to recall generic memories rather than specific events in response to cue words). Such memory disorders can be observed at different degrees in cancer patients. We will report studies focusing on the above-mentioned psychiatric disorders and cancer, and will attempt to establish a relation with autobiographical memory disturbances. The better understanding of such memory deficits could permit new pathophysiological hypotheses to emerge. Recommendations for future research that will enhance understanding of the factors that contribute to autobiographical memory in cancer are suggested.

**Keywords:** Autobiographical memory; Self; Cancer; Depression; Post-traumatic stress disorder

## **Introduction**

A growing body of research focuses on cognitive impairment in cancer patients, mainly in breast cancer. Studies on this topic correspond to a clinical reality, as complaints from patients are particularly numerous in case of chemotherapy: they can report memory, attention and concentration problems. Even if these deficits are mostly quite subtle, they affect patients' quality of life and, as they can persist long after the treatment is finished, they may reduce patients' ability to gradually return to activities of normal everyday life (Tannock et al. 2004; Vardy et al. 2008).

Many studies show cognitive deficits during and after completing adjuvant chemotherapy, often referred to as “chemobrain”, but many of the recent prospective studies – with an assessment before the receipt of chemotherapy – report performances below normal scores even though adjuvant therapy has not yet begun (e.g. Ahles et al. 2008; Cimprich et al. 2010; Quesnel et al. 2009; Schilder et al. 2010; Wefel et al. 2010). Such results clearly bring to light the multifactorial origin of cognitive impairments in cancer. In addition to physiological toxic effects of chemotherapy, combinations of biological and medical factors, such as side-effects of surgical experience and anesthesia, fatigue, and other factors like hormonal changes and hormone-therapy, could also play a role (Joly et al. 2011). Otherwise, a poor body image resulting from cancer treatments is shown to be associated with psychological distress (Przezdziecki et al. 2012) and could lead to dissatisfaction with one's self (Stokes and Frederick-Recascino, 2003). Due to the diagnosis of a life-threatening illness, cancer and its treatments may also involve many stressful events and psychiatric symptoms, such as those reported in post-traumatic stress disorder (PTSD) or in depression.

Such psychiatric symptoms, and psychological distress in general, are known to have adverse effects on cognition. One aspect of cognition that is particularly susceptible to stress-related symptoms is autobiographical memory (e.g. St Jacques et al. 2013). Autobiographical

memory refers to information and personally relevant events extended over time and is important for grounding and modifying the personal identity (self): it enables one to construct a sense of identity and continuity (Conway and Pleydell-Pearce 2000).

The aim of this review is to understand how and why autobiographical memory is particularly susceptible to dysfunction in cancer patients and to make readers aware of the influence of psychological factors on memory dysfunctions in cancer. We will, first, examine autobiographical memory and its relationships with the self and, second, its dysfunction in stress-related psychiatric symptoms, such as PTSD and major depression disorder. We will, then, focus on cognitive dysfunction and specifically on autobiographical memory in cancer patients on the basis of these previous psychiatric disorders.

### **Autobiographical memory and the self: Reciprocal interactions**

Autobiographical memory dysfunction – specifically overgenerality –has been reported in cancer, a life threatening illness in which psychological turmoil may occur. In this way, autobiographical memory models that integrate the influence of self on memory retrieval are of particular interest to better define autobiographical memory deficits in cancer.

There is a bidirectional relationship between autobiographical memory and self: autobiographical memory plays a fundamental role in the formation of self identity and, reciprocally, recollection of the past is influenced by one's self-views, current beliefs and goals (Conway and Pleydell-Pearce 2000; Klein and Lax 2010).

Current cognitive conceptions suggest that autobiographical memory is formed of semantic and episodic components (Conway 2001; Kopelman et al. 1989; Tulving et al. 1988). Episodic autobiographical memory (EAM) refers to personally experienced events situated in a specific time and place and supports our capacity to re-experience past events, i.e. to mentally travel in time (e.g., *I precisely remember the day I broke my arm*). Conversely,

semantic autobiographical memory (SAM) stores general knowledge from our past in the absence of recollection of personal experiences from which they were extracted (e.g., *I know the name of my schoolmates*).

The Self-Memory System (SMS, Conway and Pleydell-Pearce 2000) emphasizes the interrelationship of self and memory (Fig. 1) and proposes a continuous hierarchy between three levels of autobiographical representations: (1) from lifetime periods (extended over long periods of time; e.g., *“my years in college”*), (2) to generic events (events that are repeated or extended in time; e.g., *“my neuropsychology classes in the Copernic lecture hall”*) and (3) event-specific knowledge which contains information about sensory and perceptual details of unique events with images and feelings (specific episodic memories; e.g., *“the day I fell in front of all my colleagues”*). Specific episodic memories can be retrieved via two processes: direct retrieval and generative retrieval.

Direct retrieval is enabled when event-specific knowledge is activated by cues in the environment, rather than retrieved intentionally by the individual. Direct retrieval results in spontaneous memories, usually vivid, and occurs more rarely than generative retrieval in healthy subjects. This retrieval mode, in the form of intrusive memories, is a core symptom of PTSD, but may appear in other stress related disorders such as depression, or even after an isolated stress that not fulfill the A1 and A2 criteria of the PTSD particularly in a vulnerable personality (Rubin et al. 2008). The Impact of Event Scale (IES, Horowitz et al. 1979) is a self-reported questionnaire often used to assess symptomatic responses to specific traumatic experiences, namely intrusive memories and their avoidance.

Generative retrieval provides access to event-specific knowledge via the personal semantic knowledge base (lifetime periods and generic events). Generative retrieval relies on both executive functioning and current self-view, termed the working self which acts as a moderator between the demands of correspondence (memory should correspond to experience

and reality) and coherence (memory should be consistent with one's current goals, self-images and beliefs) in the formation of memories (Conway et al. 2004). This controlled access of EAM has been assessed in cancer patients by semi-structured interviews such as the Autobiographical Memory Task (AMT, Williams and Broadbent 1986) in which cue words (e.g., *party*, *pain*) are presented successively and subjects are instructed to retrieve a specific memory in time and place, and to briefly describe it. More recently, Piolino et al. (2003) proposed the TEMPau task (for *Test Episodique de la Mémoire du Passé autobiographique*) to explore in detail specific events. Like the AMT, subjects have to retrieve specific events from different life periods located in time and space, which occurred once and lasted less than a day. While the AMT uses a time limit, the TEMPau does not. Moreover, the subjective state of consciousness (autonoetic or noetic) associated with memories is assessed using the Remember/Know procedure (Gardiner 1988; Tulving 1985) which makes it possible to differentiate between episodic and semantic memory retrieval. This task has been successful in measuring autobiographical memory in depressed patients and in cancer patients (Lemogne et al. 2006; Bergouignan et al. 2011; for review, see Piolino et al. 2009).

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**Fig. 1** Retrieval modes in the Self-Memory System (adapted from Conway and Pleydell-Pearce 2000)

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The neural basis of autobiographical memory, as revealed by neuroimaging techniques, has shown a core network of brain regions recruited during EAM retrieval, comprising both anterior and posterior regions, including medial and ventrolateral prefrontal cortices, medial and lateral temporal cortices, medial parietal (posterior cingulate and retrosplenial cortices), posterior parietal (precuneus and temporo-parietal junction) and the cerebellum (for reviews, Cabeza and St Jacques 2007; Maguire 2001; Moscovitch et al. 2005; Svoboda et al. 2006;

Viard et al. 2012). While the relationship between autobiographical memory and the self is theoretically documented (Klein 2010), their interconnections at the neural level are less described. A recent meta-analysis investigated the neural substrates of the SMS by comparing three levels of self-representation at different levels of abstraction: EAM, SAM and conceptual self or CS (i.e., abstract trait knowledge about oneself which define our personality and identity: attitudes, values and beliefs, e.g. *I am an honest person*). The rostral part of the medial prefrontal cortex was commonly recruited by all three levels of self-representations, confirming the pivotal role of this region in self-representation. Specifically, EAM activated posterior areas (precuneus, posterior cingulate cortex) involved in vividness and visuo-spatial processes and limbic structures, including the hippocampus which acts as a pointer to sensory and perceptual details (Martinelli et al. 2012). The anterior cingulate cortex (ACC) also has a role in self-referential processes which occur in autobiographical memory retrieval (Northoff and Bempohl 2004), and in the emotional aspects of autobiographical memory. The affective (ventral) subdivision of the ACC is connected to the amygdala, anterior insula, hippocampus and orbitofrontal cortex and is primarily involved in assessing the salience of emotional information and regulation of emotional responses (Bush et al. 2000).

### **Autobiographical memory in stress-related disorders**

If mild stress may enhance memory, including autobiographical memory, severe stress, however, impairs autobiographical memory, particularly when leading to characterized psychiatric disorders, such as depression, acute stress and PTSD. Numerous studies have focused on autobiographical memory functioning of non-traumatic events in these stress-related disorders and they generally show impaired retrieval of EAM. When asked to retrieve a specific episodic life event, like in autobiographical memory tasks (e.g. AMT, TEMPau),

depressed or traumatized patients with PTSD or acute stress disorder (ASD) instead tend to recall broader, repeated and generic events, i.e. overgeneral memories (see Moore and Zoellner 2007; Sumner et al. 2010; Williams et al. 2007 for reviews). For example, in the AMT, the cue *cinema* might evoke the generic response “*I usually go alone to the cinema*” instead of a specific memory such as “*I watched a bad movie at the cinema last Friday*”. Overgenerality is described as a protective mechanism helping to ease the emotional pain associated with trauma. Williams (1996) proposed that trauma exposure is key to the development of overgeneral memories and considered overgenerality mainly as a functional response to traumatic childhood events to regulate intense negative affects. Over time, this tendency generalizes to neutral and positive memories leading to pervasive overgeneral retrieval that continues to be used in adulthood. Although this affect regulation hypothesis may still be valuable, some studies suggest that overgeneral memories may appear in numerous other circumstances. That is the case of individuals exposed to trauma only in adulthood (e.g., Harvey et al. 1998; Kangas et al. 2005). Reciprocally the occurrence of overgeneral memory after a trauma is moderated by the severity and the length of the trauma (Hermans et al. 2004) and the way in which people cope with it (Kuyken and Brewin 1995).

Intrusive memories of stressful events and related avoidance are characteristics of PTSD and are also consistently reported in depression (Brewin et al. 2010; Williams and Moulds 2007). Intrusive memories are spontaneous, painful and enduring memories, often related to stressful events. Many studies highlighted the role of avoidance of intrusive memories in overgenerality; Lemogne et al. (2009) suggested that cognitive avoidance of intrusive memories is associated with a decrease of the episodic components (specificity, autonoetic consciousness, and self-perspective) of autobiographical memory retrieval.

Although some research suggested the importance of traumatic stress *per se* on overgeneral autobiographical memory, this association has been challenged (Brewin 2011).



Studies have shown that individuals with PTSD or ASD retrieved more overgeneral memories than trauma-exposed individuals without PTSD or ASD (Harvey et al. 1998; Kangas et al. 2005). In non-clinical individuals without psychiatric diagnoses, studies comparing autobiographical memory of individuals with and without exposure to potentially traumatic events led to conflicting results. Some suggested, as previously, an absence of link between overgenerality and potential traumatic events (Willebrand et al. 2002), whereas others suggested the existence of a relation between both (e.g. Nilsson-Ihrfelt et al. 2004; Raes et al. 2005; Hauer et al. 2008; Brennen et al. 2010). These conflicting results could be partly due to limitations in the methodology, notably depression diagnosis status which was not always reported (Moore and Zoellner 2007).

Based on Conway and Pleydell-Pearce's (2000) model of autobiographical memory presented above, overgenerality occurs when the generative retrieval search process is aborted prematurely, before reaching the level of event-specific knowledge. This phenomenon may rely on the interaction between executive dysfunction (deficits in executive resources limit the ability to conduct a successful retrieval search) and current self, within the working self. Moreover, positive correlations between overgenerality and avoidance of intrusive memories are often reported (see above), and according to the CaR-FA-X model (capture and rumination, functional avoidance, and impaired executive control) proposed by Williams et al. (2007) on mechanisms underlying overgeneral memories, avoidance would contribute to protect the self against specific stressful memories by decreasing the likelihood of any episodic recollection, as a mean of affect regulation. The CaR-FA-X model also postulates that overgeneral memories occur when the generative retrieval search process is aborted as a result of two other mechanisms: capture and rumination (capture at a general autobiographical level which occurs particularly in individuals prone to rumination), and impaired executive

control (e.g. executive processes such as inhibition and working memory capacity) which plays a role in the strategic retrieval of a specific memory (see Sumner 2012).

Stress-related disorders appear to be associated with abnormalities in brain structures. One of the most consistent finding reported in MRI studies is a reduced hippocampal volume in depressed patients and in PTSD, in particular posterior hippocampus (e.g. Maller et al. 2007; Bonne et al. 2008), compared to control participants (see McKinnon et al. 2009; Woon et al. 2010 for meta-analyses). Reduced prefrontal cortical volume, including ACC, were also reported in depression (Yucel et al. 2008) and in PTSD (Bremner et al. 1999). In depression, other abnormalities were also described such as atrophy in dorsal and ventral lateral prefrontal areas, implicated in executive and control operations and in generative retrieval processes (Regenold et al. 2007), and orbitofrontal cortex (e.g., Lacerda et al. 2004), associated to self-referential (Kelley et al. 2002; Stuss and Levine 2002) and emotional processing (Markowitsch et al. 2003; Piefke et al. 2003). These prefrontal regions are all involved in autobiographical memory retrieval.

Functional neuroimaging studies, through mainly fMRI but also PET and SPECT, have revealed widespread abnormalities in the brain during depression and PTSD, many highlighting dysfunctions in the prefrontal cortex, hippocampus, and amygdala (for more details, see Bremner, 2007; Drevets et al. 2008; Etkin and Wager 2010; Hamilton et al. 2012; Koenigs and Grafman 2009; Korgaonkar et al. 2012; Milne et al. 2012; Patel et al. 2012; Shin and Liberzon 2010; Sripada et al. 2012).

Neuroimaging studies on autobiographical memory and depression or PTSD are scarce. Young et al. (2012) examined depressed patients using an autobiographical test and reported hypoactivations in the hippocampus, ACC, insula and parahippocampal gyrus during autobiographical memory recall in depressed patients – with overgeneral memories –

compared to controls, confirming previous findings presented above. Whalley et al. (2012), in an identification of personal emotional memories task, showed reduced activity in the depressed group in three regions of the prefrontal cortex: bilateral inferior frontal gyrus and the right middle frontal gyrus. They suggested that impairments in autobiographical memory recall results from a failure to suppress emotional interference or emotional information and monitoring processes in episodic retrieval, subserved by these prefrontal regions.

In a study focused on traumatic memories, St Jacques et al. (2011) explored positive and negative autobiographical memories in PTSD versus healthy controls using a generic cue method with highly arousing words combined with fMRI. PTSD patients recruited the amygdala and hippocampus more than controls during the construction of negatively valenced events than controls. However, memories of events of low emotional valence were not studied.

### **Psychopathological and neuropsychological aspects of cancer**

In cancer patients, announcement of the diagnosis, severity of the treatment associated with pain, modified body image and uncertainty about the future can provide sustainable and severe stress that leads in some cases to characterized stress-related disorders. Indeed, PTSD or depression are frequently reported in cancer. The fourth edition of the DSM (American Psychiatric Association 2000) recognized that PTSD may be precipitated by life-threatening illness, such as being diagnosed with cancer. The rates of current or lifetime cancer-related PTSD range from 3 to 22 % (Kangas et al. 2002). This large variability is probably multifactorial, such as the small sample sizes, differences between studies in the timing of assessment after treatment, the use of dissimilar assessment instruments or the non consideration of confounding factors (see O'Connor et al. 2011). Nevertheless, the majority of cancer patients would not meet full criteria for PTSD: many survivors report one or more

symptoms of the disorder, like intrusions and hyperarousal symptoms (intrusive thoughts, emotional numbness and avoidance of reminders of the event, hypervigilance and physiological arousal), but low levels of the avoidance criterion are reported (Elklit and Blum 2011). Concerning depression, the rates range from 20 to 27 %. This relatively high prevalence could signify the expression of psychological effects of the disease, but also of cytokine deregulation (see Reich 2008, for a review). A relationship between depression and PTSD is quite frequently observed in cancer. Intrusive memories of stressful life events, about illness and death, are a common symptom for cancer patients with depression or PTSD (Brewin et al. 1998).

It is worth noting that cancer-related PTSD or depression present distinctive features compared to common PTSD and depression. Major depressive episodes after cancer diagnosis are generally assumed to be reactive and of short duration (Chochinov 2001). The non-specificity of physical symptoms suggests that making a diagnosis of depression in these patients might be difficult. Compared to other traumas, like accidents or natural disasters, cancer is a unique stressor because the threat is chronic, due to the protracted nature of the disease, to the multiple traumatic experiences, or to the future-oriented anxiety concerning cancer recurrence and death. Moreover, the threat is internal with bodily signs serving as persistent reminders of the trauma. As a result, the patients are never free from the source of their traumatic fears (French-Rosas et al. 2011). Cancer represents a distinctive stressor within the PTSD/ASD framework because it may be associated with other factors, including neurotoxic treatments or biological changes.

We previously reported that, in the absence of cancer, depressed and PTSD patients have a hippocampal atrophy (e.g. Sheline et al. 1996; Wignall et al. 2004). Yet, possibly due to the distinctive features of cancer-related PTSD or depression, results are not that straightforward in cancer. Indeed, some studies in cancer patients report no significant

difference in hippocampal volume between breast cancer survivors with depression compared to patients without depression, whether it is minor or major depression (Inagaki et al. 2004; Yoshikawa et al. 2006). Similarly, studies do not show significant differences in hippocampal volume between breast cancer survivors, with or without PTSD, one year after the first experience of their traumas (Nakano et al. 2002). Instead, they show that intrusive symptoms, rather than PTSD, are associated with smaller hippocampal volume. Nevertheless, in some of these studies, patients were not compared with healthy subjects. It is thus possible that both groups of patients present the same hippocampal atrophy. Furthermore, atrophy of the orbito-frontal cortex – a region known to be involved in emotional retrieval – has been observed in cancer-related PTSD when compared to cancer patients without PTSD or to healthy controls (Hakamata et al. 2007).

Until now, neuropsychological cancer studies focused on the effects of adjuvant treatments, mainly chemotherapy, on cognitive functions often in breast cancer patients without characterized psychiatric stress disorder. Indeed, women diagnosed and treated for breast cancer often report problems with memory, concentration, and other cognitive abilities (e.g. Wefel and Schagen 2012). The effect of chemotherapy on brain structures, notably on the hippocampus, has been largely demonstrated in animal studies (e.g., Mustafa et al. 2008): chemotherapy drugs disrupt cell proliferation and the commonly used chemotherapy agent 5-fluorouracil (5-FU) works by blocking the synthesis of thymidine required in DNA replication (Longley et al. 2003) and crosses the blood–brain barrier by simple diffusion (Bourke et al. 1973; Kerr et al. 1984). In human studies, although such adverse affects were not consistently observed on the brain (e.g., Yoshikawa et al. 2005), recent structural neuroimaging studies demonstrate the impact of chemotherapy on temporal and frontal regions and on white matter. The persistence of the effect long after the end of treatment is however not well established. In a MRI study using voxel-based morphometry (VBM) to assess gray matter changes after

breast cancer treatment, Inagaki et al. (2007) reported reductions of prefrontal and parahippocampal volumes one year after adjuvant chemotherapy, but they were no longer apparent four years after completion of the treatment. Other longitudinal studies found decreased grey matter density in frontal and medial temporal regions one month after chemotherapy, followed by partial recovery in certain regions one year after treatment (McDonald et al. 2010, 2012). In a prospective diffusion tensor imaging (DTI) study, Deprez et al. (2012) found changes in white matter tissue integrity after chemotherapy, and these changes correlated with decreased performance in attention and verbal memory tests.

Functional neuroimaging also provides interesting results even if the initial studies focused mainly on the effects of chemotherapy on brain functioning during short-term memory and working memory tasks. In a positron emission tomography (PET) study, Silverman et al. (2007) showed increased cerebral blood flow in the inferior frontal gyrus during a short-term memory task in breast cancer patients 5 to 10 years after chemotherapy. Ferguson et al. (2007) showed frontal and parietal activations during a successful working memory task two years after chemotherapy. These results seem to support the hypothesis of regional brain activation as a possible compensatory process. Long-term effects of high-dose chemotherapy were investigated by de Ruiter et al. (2011). Hyporesponsiveness of the dorsolateral prefrontal and posterior parietal regions during a planning task and of the parahippocampal gyrus during an episodic memory task were revealed 10 years after chemotherapy; neuropsychological performances were impaired compared to cancer survivors who had not received chemotherapy.

While the effects of chemotherapy on brain and cognitive functions are currently greatly studied, a growing body of research on the effect of hormone-therapy and hormonal changes is emerging. In breast cancer, McDonald et al. (2012) reported that some patients experienced menopause, presumably due to chemotherapy, and changes in hormonal status have been

shown to affect brain activation (e.g., Gleason et al. 2006). Concerning hormone-therapy in breast cancer, two types of endocrine therapies include selective estrogen receptor modulators (SERMs; e.g., tamoxifen and raloxifene) and, more recently, aromatase inhibitors (AIs; e.g. anastrozole, letrozole, and exemestane). These hormone-therapies are often proposed in addition to chemotherapy, so that their respective influence on cognitive functions is not always clear. However, Schilder et al. (2010, 2012) evaluated the influence of the SERM tamoxifen and the AI exemestane – without chemotherapy – on cognitive functioning of postmenopausal breast cancer patients. After 1 to 5 years of adjuvant therapy, tamoxifen use was associated with lower cognitive functioning, whereas exemestane use was not associated with significantly lower functioning. Estradiol has a role in neuroprotection (Brann et al. 2007; Bryant et al, 2006) and a morphometric analysis of hippocampal neurons showed that estradiol can stimulate dendritic branching (Audesirk et al. 2003). Studies suggested that endocrine therapy may limit the neuroprotective effect of estradiol (Lee et al. 2003).

Despite such evidence of the damaging effects of adjuvant treatments on cognitive functions, a high incidence of impaired cognitive performance has also been found in patients prior to adjuvant treatment of any sort (Wefel and Schagen 2012). McDonald et al. (2012) revealed frontal hyperactivation during a successful working memory task before adjuvant treatment in breast patients compared with healthy controls. This suggests that even before adjuvant treatment, patients would be engaged in compensatory hyperactivation of brain circuitry to support working memory functioning in response to as yet unknown effects of the cancer disease process, and that host factors and/or the cancer disease process itself may play a role. Lopez-Zunini et al. (2012) revealed that patients prior to chemotherapy activated the right ACC more than controls during verbal memory retrieval. Interestingly, when mood scores such as fatigue and anxiety were added as covariates, a reverse pattern of activation was observed: the anterior cingulate was found to be less activated than for controls.

### **Autobiographical memory in cancer patients**

Investigation of autobiographic memory in cancer patients is of primary interest as it appears to be influenced by psychological and self effects related to the experience of cancer. To our knowledge, only four published studies focused on autobiographical memory in cancer (Table 1). Brewin et al. (1998) compared depressed and non-depressed cancer patients on their intrusive memories and controlled access to autobiographical memory, through the IES and AMT respectively. The IES scores indicated, mainly in depressed cancer patients, intrusive memories and related avoidance of stressful events from the recent or distant past; they concerned illness, injury and death and were partly cancer-related. Moreover, overgeneral memories were observed in response to cue-words of the AMT mainly in depressed cancer patients, and an association was found between this overgeneral recall and avoidance of intrusive memories. This pattern of results is consistent with that revealed in depressed patients without cancer (see above), and could be explained as a way to regulate affect, such as avoidance would contribute to protect the self against specific stressful memories by decreasing the likelihood of any episodic recollection through a direct or indirect retrieval mode (Williams et al. 2007).

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**Table 1** Autobiographical memory studies in cancer patients  
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Autobiographical memory was also studied in cancer-related PTSD and more specifically in newly diagnosed cancer patients with ASD by Kangas et al. (2005). An autobiographical memory cueing task was used to assess controlled retrieval of specific memories in response to positive and negative cue words under two conditions: an unconstrained condition which required participants to retrieve a specific memory from any



life period, and a constrained condition which required participants to recall a specific memory after they were diagnosed with cancer. As expected by the authors, in the unconstrained condition, patients with cancer-related ASD retrieved fewer specific memories than patients without ASD. This finding would suggest that cancer-related ASD is associated with a general deficit in specific autobiographical memory retrieval, and that theories emphasizing childhood trauma in overgenerality may be too restrictive (e.g., Williams 1996), even if here information about childhood events was not reported. However, in the constrained condition, the retrieval of specific memories was comparable for patients with or without ASD. The authors suggest that, considering the distinctive features of the cancer stressor, this unexpected result may be explained by the ongoing threat to cancer patients, who face uncertain prognoses and aversive side effects. These factors would lead all cancer patients in the acute phase to be focused on their cancer experiences, and accordingly, no significant difference was found between both groups in the constrained condition.

Deficits in EAM retrieval were also reported in cancer patients without any psychiatric disorders compared to healthy controls (Bergouignan et al. 2011; Nilsson-Ihrfelt et al. 2004). In Nilsson-Ihrfelt et al's (2004) study, the AMT was administered by phone to 26 former breast cancer patients. Whether these women had already undergone breast reconstruction surgery or not, they retrieved fewer specific autobiographical memories than controls without any history of cancer. This result suggests that overgeneral memories may persist after the end of adjuvant treatments in former patients without psychiatric symptoms. Moreover, this implies that overgenerality may be linked to potentially traumatic events rather than PTSD or depression. However, as pointed out by Moore and Zoellner (2007), the depression diagnosis status was not evaluated, and the method of assessment by phone is largely questionable. Moreover, the AMT scoring involves that memories without any details or reviviscence are considered as specific memories so long as they concern single events lasting less than a day.

Besides, the AMT does not take into account the level of consciousness associated to the memories, so that strictly episodic memories are not clearly identified.

In an MRI study, Bergouignan et al. (2011) showed, in remitted breast cancer patients that had been treated by tumorectomy, chemotherapy and radiotherapy (patients currently in hormono-therapy were included), a smaller hippocampal volume (difference of 8%) especially posterior (11%), compared to healthy controls without history of cancer. This result is consistent with those reported above where no hippocampal volume differences between cancer patients with or without depression were found (Inagaki et al. 2004; Yoshikawa et al. 2006). This could arise from the absence of comparison with healthy controls, as it is possible that both groups of cancer patients (with and without depression) present hippocampal atrophy. In addition, Bergouignan et al. (2011) used the TEMPau (Piolino et al. 2003) in which two positive and two negative memories were collected from three life periods: prior to the last 5 years (the 'no cancer' period), the last 5 years except for the last 12 months (the 'cancer' period), and the last 12 months (the 'past history of cancer' period). After retrieval, the state of consciousness (autonoetic or noetic) was assessed with the remember/know paradigm to ensure the episodic nature of the event. For each episodic event, four scores were obtained: temporal, spatial, factual and emotional. Across all life periods, the remitted patients had significantly less access to episodic memories than healthy controls, and temporal details were significantly less reported by patients than by controls. The positive bias was maintained, since negative autobiographical events were significantly less episodically remembered than positive ones, like in healthy controls. Bergouignan et al. (2011) suggested a relationship between hippocampal atrophy and deficit in EAM retrieval, which could reflect the effect of exposure to negative events *per se* with heavy or cumulative stress, and not a specific effect of psychopathology. They also proposed the influence of aggressive treatments, insomuch as their cross-sectional study cannot dissociate the influence of stressful events

related to the period of announcement for instance from the effect of the chemotherapy or hormonal treatments.

Overall, EAM deficits were reported in cancer patients even in the absence of characterized stress-related disorders (Nilsson-Ihrfelt et al. 2004; Bergouignan et al. 2011). This could mean that, contrary to numerous reported results (Brewin 2011), trauma event *per se* and/or neurotoxic treatment effects would be sufficient to produce these memory deficits. However, it is worth noting that Nilsson-Ihrfelt et al. (2004) did not assess the depression diagnosis status and Bergouignan et al. (2011) showed that cancer patients had a smaller number of specific episodic memories than controls (no difference for overgeneral memories). Besides, in this last study, the positive bias was maintained in remitted patients. The lack of positive bias may therefore be more specific to stress-related disorders and reflect the mood-congruent memory effect. This suggests that, even if memory changes or deficits occur in such life-threatening illnesses, their characteristics are at least partly different from those occurring in stress-related disorders. Yet, these results from cancer patients with or without psychiatric disorders are difficult to compare since the latter (Bergouignan et al. 2011; Nilsson-Ihrfelt et al. 2004) were collected not during the acute phase of cancer, but in remitted breast cancer patients. Numerous answers remain to be addressed, such as the effect of stress related cancer independently of characterized psychiatric disorder on EAM retrieval. One of the ways to respond may be to assess autobiographical memory with a discriminating task, like the TEMPau, before any adjuvant therapy at least to dissociate the effects of adjuvant treatment from that of stressful events.

Moreover, another factor that has scarcely been explored concerns specific personality characteristics. EAM retrieval being strongly dependent on one's self, personality characteristics probably influence cognitive adaptation processes and autobiographic retrieval

modes. Alexithymia, characterized by a reduced ability to identify and describe one's own feelings, has been reported in cancer patients (De Vries et al. 2012; Manna et al. 2007). Hence, when assessing autobiographical memories, often emotionally charged, patients should be free to retrieve events irrespective of their emotional valence, and specific details (in particular emotional) given spontaneously should be preferred.

Concerning the neural basis of autobiographical memory in cancer patients, the only published neuroimaging study suggests the specific involvement of the posterior hippocampus (Bergouignan et al. 2011). The posterior hippocampus is involved in the retrieval of spatiotemporal memories (Bonne et al. 2008; Hoscheidt et al. 2010). The hippocampus, which acts as a pointer to sensory and perceptual details, is often shown to be activated in fMRI studies during EAM retrieval in healthy subjects and seems to be directly linked to reliving episodic experience (Martinelli et al. 2012). Considering that the patients examined by Bergouignan et al. (2011) are remitted breast patients that had received adjuvant therapy (chemotherapy, radiotherapy and/or current hormono-therapy), it is difficult to establish the respective effects of neurotoxic treatments and of cumulative stress events.

Other neuroimaging studies conducted in cancer patients before adjuvant treatment, have revealed atrophy and dysfunction in prefrontal regions. Lopez-Zunini et al. (2012) showed ACC hyperactivation during a memory task. Yet, when anxiety and fatigue factors were removed, this region was found to be less activated than controls. ACC dysfunction or atrophy have been frequently shown in PTSD and depressed patients. The ventral medial prefrontal cortex may be specifically related to the affective processing of self-relevant information (van der Meer et al. 2010), and Schmitz and Johnson (2007) showed that this region is consistently activated during affective appraisal that conveys implications for one's own survival, well-being, and potential goals. The authors proposed a model of two top-down

systems involved in the processing of self-relevant stimuli: the ventral medial prefrontal cortex – ventral ACC and the dorsal medial prefrontal cortex involved respectively in the emotional and cognitive counterparts of self-referential processes. One may suggest that in cancer patients, independently of adjuvant treatment effects and of characterized psychiatric disease, autobiographical memory functioning may be particularly influenced at the self-representation level and the medial prefrontal region would therefore be particularly involved in the autobiographical memory changes of cancer patients.

We are aware that a variety of factors may impact on the cognitive functions in cancer patients, but we chose to focus on the links between self and memory in a comprehensive way. This review suggests that neural changes related to cancer treatments and/or stressful events may affect autobiographical memory retrieval, and that considering such stressful events, different personality traits between cancer patients could lead to different patterns of autobiographical memory. Overall, this review points to an emerging topic which warrants further research to pinpoint memory dysfunction and psychological processes in cancer.

### **Acknowledgements**

The authors wish to thank the “Canceropôle Nord-Ouest”, the French “Ligue contre le cancer”, and the association “Le cancer du sein, parlons-en!” (Pink Ribbon), for their support in this new field of research on oncology we are developing.

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