Review Article

Searching for the Anatomy of Dissociative Amnesia

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Abstract. Brain damage was traditionally seen as the product of a neurological disease or injury. Nevertheless, modern brain imaging techniques have provided increasing evidence for alterations in brain tissue and metabolism for a number of psychiatric disorders. Though for a while "dissociated" (Spiegel, 2006) from the clinical and scientific arena, dissociative disorders have in the last several years received a renewed interest among several groups of researchers, who embarked on the work of disentangling their neural correlates. We review data from our own research as well as others, which point to distinct changes in brain regions underlying dissociative amnes(t)ic disorders. These changes may consist of overall reductions in brain metabolism or more selective alterations primarily in the right temporo-frontal cortices. Recent evidence with refined magnetic resonance imaging techniques furthermore reveals selective fiber degenerations in these regions. While these changes may persist and probably even intensify in some patients, they may be reversible in others – especially if treatment is carried out successfully within short time after onset. Implications of these findings for the pathogenetic conceptualization of dissociative amnes(t)ic disorders are outlined.

Keywords: psychogenic amnesia, temporo-frontal cortex, positron-emission tomography, white matter

The quest for the brain correlates of human intellectual functions, behavior, and emotions has taken a new dimension since increasingly sophisticated neuroimaging techniques have been incorporated into the cognitive neuroscience armamentarium. The employment of these techniques has provided evidence that the environment may have a lasting effect on organization and function of nervous system and that structural brain changes or brain metabolic alterations underlie a variety of mental disorders such as schizophrenia, major depression, obsessive-compulsive disorder (Bao, Meynen, & Swaab, 2008; Gur et al., 2000; Lange & Irle, 2004; Nakamura et al., 2007; Szeszko et al., 1999; van Erp et al., 2004), post-traumatic stress disorder (PTSD) (Nardo et al., 2010; Woodward et al., 2006), dissociative identity disorders (Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006), and even severe deviances in social behavior, such as violent behavior (Boccardi et al., 2010; Glenn & Raine, 2008).

These findings have led to the questioning of old strict distinctions between organic and psychogenic. In the field of memory disorders, an initial challenge to the dichotomy between organic and psychogenic amnesia came from observing that the two conditions may at times overlap. Furthermore it was noted that deliberately feigned amnesia (for primary or secondary gains) could also accompany both of the previously described forms of amnesia. "An epileptic, who also has hysteria and is a malingerer, may have periods of amnesia which exhibit features of all three types ("pathological [organic]," "psychological," and "feigned"; Lennox, 1943, p. 741)." Cases of psychogenic amnesia occurring on a forensic background were reported by several authors. Heine (1911) in his publication on the forensic significance of amnesia listed more than a dozen conditions for amnesia, most of which had a nonorganic origin. Ganser syndrome (see below) – a condition that is, presently less frequently diagnosed (e.g., Cocores, Santa, & Patel, 1984; Staniloiu et al., 2009) – had initially been linked to a forensic context (cf. Hey, 1904; Jung, 1902; Meyer, 1904; Pick, 1905; Stertz, 1910) and is still occasionally so nowadays. At the turn to the 20th century fugue states were also frequently considered to have "forensic relevance" (Zingerle, 1912).

Despite the possibility of these simultaneous occurrences, most researchers and clinicians (including ourselves) would, however, agree with keeping and discussing malingering as much as possible separately, outside of the psychogenic-organic "conundrum" (Lucchelli & Spinnler, 2002).

The most recent debate over the validity of a sharp organic-psychogenic distinction in amnesia has been fueled by findings from brain functional imaging. These yielded evidence for a long searched biological link between the two forms of amnesia, by demonstrating brain functional and metabolic alterations in psychogenic amnesia, which involve anatomical structures that are agreed upon to exert a crucial role in memory processing. Furthermore, these findings have provided proof that successful therapy could reinstate a normal brain metabolism and an almost normal level of cognitive abilities after a previously measured and documented reduction in brain metabolism and cognitive capacities (Markowitsch, Kessler, Weber-Luxenburger, Van der Ven, & Heiss, 2000).

The neural correlates of "psychogenic" amnesia – as evidenced by functional brain imaging – and the putative neurobiological mechanisms underlying them – constitute the main topics that will be outlined in this contribution.

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We named the current paper "Searching for the anatomical basis of psychogenic amnesia" after two previous writings – a paper entitled "Searching for the anatomical basis of retrograde amnesia" (Markowitsch, Calabrese, Haupts, et al., 1993) and a book subchapter with the title "The Search for the Anatomical Bases of Chronic Alcoholism and Korsakoff's Syndrome" (Markowitsch, 1992). These writings, which were produced at a time of fascination with psychogenic amnesia, but only little knowledge about its brain underpinnings, are witnesses of the long, but unfinished journey for disentangling the neural correlates of psychogenic memory loss.

Dissociative Amnes(t)ic Conditions

The term amnesia refers to an inability to learn new information or recall previously learned information or past events, in an otherwise alert, non-delirious individual, which is out of proportion in comparison to dysfunctions in other cognitive domains. It could describe a disorder, a syndrome, or a symptom of another disorder. The diagnosis of an amnestic disorder requires (according to the DSM-IV-TR, 2000) that amnesia does not occur exclusively during the course of delirium. In addition such a diagnosis is not made in the presence of neuropsychological and neurological deficits suggestive of dementia.

Given that various memory systems have different degrees of susceptibility to insults and therefore are most of the time unevenly affected by environmental injuries, the use of the term amnesia requires a clear description of the type and severity of the memory problems involved.

Amnesia without direct evidence of brain damage (as detected by conventional structural imaging techniques) has over the years been captured by different terminologies, including hysterical, psychogenic, dissociative, functional, or medically unexplained.

In the present official nomenclatures (DSM-IV-TR and ICD-10) the earlier designations of hysterical amnesia have preponderantly been subsumed to the categories of dissociative disorders (DSM-IV-TR, 2000) and dissociative (conversion) disorders (ICD-10, 1992), but also to several other subcategories such as somatization disorder (DSM-IV-TR), PTSD, and acute stress disorder (DSM-IV-TR).

Echoing Janet's (1907) superior view of hysteria as "*désagrégation mentale*," DSM-IV-TR describes dissociative disorders as disturbances of the integrated organization of memory, perception, consciousness, or identity. Among dissociative disorders in DSM-IV-TR (2000), dissociative amnesia has as the central symptom the inability to recall important personal information, often of stressful or traumatic nature. The symptoms are not better explained by normative forgetfulness or other psychiatric or medical conditions (such as traumatic brain injury). Deliberate feigning which is consciously motivated by external gains (such as malingering) or is prompted by psychological motivations in the absence of identifiable external incentives (such as in factitious disorder) has to be ruled out. The symptoms of dissociative amnesia cause significant impairment of functioning or distress. The degree of experienced distress may, however, depend on many variables, including the cultural views of dissociative experiences, selfhood, and past. While in DSM-IV-TR the preponderant contribution of psychological mechanisms to the emergence of dissociative amnesia is conveyed in a more implicit way, the ICD-10 explicitly spells out as a criterion for the diagnosis of dissociative amnesia (as well as for the other dissociative disorders) the existence of "convincing associations in time between the symptoms of the disorder and stressful events, problems or needs." The presence of amnesia might, however, pose a significant difficulty to the clinicians and researchers who try to identify the precipitating stressful events. Furthermore we encountered cases of dissociative (psychogenic) amnesia that did not occur as a result of an objectively major psychological stressor, but they were recorded after a seemingly objectively minor stress. In most of the latter cases, a careful history taking and collateral information gathering provided evidence for a series of stressful events often occurring since childhood or early adulthood. These observations are consistent with pathogenetic models of kindling sensitization (Post, Weiss, Smith, Rose, & Frye, 1995), or protracted effects of early life stressful events, due to an incubation phenomenon (Lupien, McEwen, Gunnar, & Heim, 2009). Another factor that may hinder the unearthing of convincing associations between stressful events and onset of dissociative amnesia is the presence in some patients with dissociative (psychogenic) amnesic disturbances of an altered capacity for emotional processing (impaired emotional awareness and clarity) in the face of ongoing stress or recurrent stressful events (Staniloiu et al., 2009).

According to most studies (including our own data) dissociative amnesia affects both genders roughly equally. Dissociative amnesia tends to preponderantly occur in younger people, being most frequently diagnosed in the third and fourth decade of life (Coons & Milstein, 1992; Kanzer, 1939). The younger age distribution of dissociative amnesia on one hand mirrors the findings of increased scores on dissociation scales among the younger age group (Ross, Joshie, & Currie, 1990). On the other hand it may partly reflect developmental differences in windows of vulnerability to stress of key brain structures that are involved in memory processes (Lupien et al., 2009).

Dissociative amnesia typically occurs as a single episode, not uncommonly after a mild traumatic brain injury, although – similarly to dissociative fugue – recurrent episodes have been reported (Coons & Milstein, 1992). Some cases of dissociative amnesia follow a chronic course, in spite of treatment. Comorbidities of dissociative amnesia with major depressive disorder, personality disorders, and bulimia nervosa and somatoform disorders have been reported (Maldonado & Spiegel, 2008). Alterations in personality after the onset of dissociative amnesia in the form of changes in eating preferences, smoking habits, or other previously rewarding activities (such as car driving) have also been reported (Fujiwara et al., 2008; Thomas Antérion, Mazzola, Foyatier-Michel, & Laurent, 2008; Tramoni et al., 2009).

Dissociative amnesia could be differentiated according to the degree and time frame of impairment (global vs. selective,

anterograde vs. retrograde) of autobiographical-episodic memory and the coexistence of deficits in autobiographical-semantic memory and general semantic knowledge (cf. Serra, Fadda, Buccione, Caltagirone, & Carlesimo, 2007). The most frequent types of dissociative (psychogenic) amnesias are retrograde. DSM-IV-TR (2000) distinguishes between localized amnesia, selective amnesia, generalized amnesia, continuous amnesia, and systematized amnesia, while in the psychological literature several other forms of amnesia are found as well (e.g., Markowitsch, 2000a).

A particular form of retrograde dissociative (psychogenic) amnesia has been coined the "mnestic block syndrome" (Markowitsch, Kesseler, Russ, et al., 1999). This form is defined by an episodic-autobiographical block, which may encompass the whole past life. Affected patients otherwise have largely preserved semantic memories; they can read, write, calculate, and *know* how to behave in social situations. Furthermore, they can lay down new long-term autobiographic-episodic memories, though the acquisition of these new events may be less emotionally flavored in comparison to normal subjects (Brand & Markowitsch, 2009; Reinhold & Markowitsch, 2009).

Data about the frequency of dissociative amnesia are still limited and at times difficult to interpret, though Johnson et al. (2006) reported a 12 month prevalence of 1.8% of dissociative amnesia in a USA community of 658 adults. Similarly to other dissociative disorders, cases of dissociative amnesia are likely not accurately reported (Foote, Smolin, Kaplan, Legatt, & Lipschitz, 2006). One possible reason for this is related to the challenges clinicians face when searching for convincing evidence of stressful events or trauma. Another reason is the fact that dissociative amnesia can occur as a symptom of other dissociative disorders such as dissociative identity disorder (DSM-IV-TR) or multiple personality disorder (ICD-10), dissociative fugue, Ganser syndrome, and dissociative trance disorder and possession trance, as well as a symptom of certain anxiety disorders, such as acute stress disorder and PTSD or DSM-IV-TR described somatoform disorders (somatization disorder) or personality disorders, such as borderline personality disorder, but under these circumstances it is not recorded as a separate diagnostic entity.

When retrograde dissociative amnesia is accompanied by suddenly leaving the customary environment – home and city – and compromised knowledge about personal identity – the condition is named dissociative fugue (Markowitsch, Fink, Thöne, Kessler, & Heiss, 1997). Fugues have been reported for over a century (e.g., Woltär, 1906), though they were frequently erroneously associated with epilepsy (e.g., Burgl, 1900; Donath, 1899; Raecke, 1908). A century ago, these conditions were named *Wanderlust* in Germany; cf. e.g., Burgl, 1900. Fugue states were described to be preponderant in children and young adults (Bregman, 1899; Dana, 1874; Donath, 1908; Heilbronner, 1903, 1905; Hey, 1904). They were thought to increase in frequency during wartimes and be more frequent among men, although some studies conducted in the nonwar periods found no gender differences. Identified precipitants included rape, sexual assault, combat, marital distress, and financial problems. Presentations similar to fugues have also been described in certain cultures, where they represent idioms of distress (Maldonado & Spiegel, 2008). Most fugues were not found to involve the formation of a new identity and were usually reported to be brief, but some prolonged courses were also described (Hennig-Fast et al., 2008). Franz (1933) gave a detailed description of a subject, named Jack, who ostensibly traveled between Europe, Africa, and the United States and whom he described as being captured and held as a prisoner during World War I in East Africa. Associations between fugues and Ganser syndrome were also found.

Ganser syndrome is a condition that has been submitted to several diagnostic revisions and debates over the years. In comparison to previous DSM editions, where Ganser syndrome was presented as a Factitious Disorder, Ganser syndrome is currently included under the category of Dissociative Disorders Not Otherwise Specified in DSM-IV-TR and it is simply defined by giving approximate answers to questions (*vorbeireden*). Ganser's (1894, 1904) original description of the syndrome was, however, much broader than the current DSM-IV-TR one. It included a hysterical semitrance or twilight state, characterized by a tendency to give approximate answers, impairments of consciousness, amnesia, and hallucinations, being more consistent with the later views of this disorder as a brief reactive psychosis to stress. Though initially linked to forensic background, Ganser syndrome was also reported in non-forensic contexts. The syndrome was found to affect preponderantly young men with a mean age of 35 years, although there were some case reports in women and children as well (Miller, Bramble, & Buxton, 1997; Nardi & Di Scipio, 1977). Both a transient, limited course and a chronic course have been recorded.

In spite of its current categorization under dissociative disorders in DSM-IV-TR Ganser syndrome has continued to be a diagnostic puzzle for clinicians and a challenge for formal diagnostic classifications. Not infrequently its clinical presentation suggests a mixture of underlying psychological mechanisms, such as dissociative mechanisms intimately interwoven with psychologically motivated exaggeration of symptoms. In the face of such cases it is not surprising that several authors (including the present writers) have continued to employ terminologies such as psychogenic amnesia (McKay & Kopelman, 2009), while acknowledging its imperfections. As opposed to the category of dissociative amnesia that only captures a part of the dissociative amnesic disorders and carries a specific theoretical load, psychogenic amnesia is more comprehensive. It also has the advantage that it emphasizes the preponderant contribution of psychological factors to the emergence of the amnesic episode, without defining from the start the nature of the psychological mechanisms involved.

In comparison to psychogenic amnesia, functional amnesia is a broader category, which encompasses not only "clear-cut" psychogenic amnesic disturbances, but also forms of amnesia with no yet (readily) identifiable psychological or medical precipitants.

Dissociative Amnes(t)ic Disorders and Trauma

Dissociative (psychogenic) amnesic disorders have been linked to psychological trauma or stress in a variety of cultures (Bremner, Steinberg, Southwick, Johnson, & Charney, 1993; Draijer & Langeland, 1999; Jones, Fear, & Wessely, 2007; Kaszniak, Nussbaum, Berren, & Santiago, 1988; Kiersch, 1962; Seligman & Kirmayer, 2008; Spiegel & Cardena, 1991; Thom & Fenton, 1920; Xiao et al., 2006). Although connections between trauma (especially early traumatic experiences) and psychiatric symptomatology were suggested by other psychiatrists or scientists in the 19th century (van der Kolk & van der Hart, 1989), including Freud in his first approach to psychopathology (Breuer & Freud, 1895), it is Janet (1898) who claimed dissociation as a mechanism related to traumatic experiences that accounted for the various manifestations of hysteria (including hysterical amnesia). Janet is credited by several authors (Maldonado & Spiegel, 2008) with a superior view of dissociation that anticipated contemporary theories and involved not just separation or compartmentalization but a failure of integration of various functions. He underlined the importance of memory for a healthy personality, especially of those memories that were accompanied by a particular type of awareness (that seems to resemble what we presently name autonoetic self-awareness). "It is not enough to be aware of a memory that occurs automatically in response to particular current events: It is also necessary that the personal perception 'knows' this image and attaches it to other memories" (p. 135, cited by van der Kolk & van der Hart, 1989). Furthermore, Janet suggested that the impact of trauma on a particular individual may be dependent on a variety of factors (such as the person's characteristics, prior experiences, and the severity, duration, and recurrence of the trauma) and might not become evident immediately, but after a certain latency period (van der Kolk & van der Hart, 1989). Many of Janet's ideas have later received corroboration from both clinical observations (including our own data on dissociative amnesia) and neurobiological investigations and have subsequently been incorporated in current pathogenetic models of dissociative disorders. We describe below our proposed model to account for the findings in patients with dissociative amnesia, which is shown in Figure 1.

As depicted in this model, traumatic situations (especially the ones with an early onset) may change the brain's activation of certain neurotransmitters and may lead to an altered processing of incoming information. The nature and magnitude of these changes depend on the (sometimes synergistic) interaction of these early traumatic experiences with genetic dispositions (with protective or deleterious effect) (Becker-Blease et al., 2004) and other environmental factors (with buffering or exacerbating effects) and the time frame (the developmental window) when this interaction takes place (Lupien, McEwen, Gunnar, & Heim, 2009; McCarthy et al., 2009). If the person subsequently fails to acquire appropriate coping strategies, the appearance of further stress events may result in a dissociation between the processing of emotional and cognitive portions of new information with the result of a full-blown stress reaction (Reinhold & Markowitsch, 2007, 2009). That is, the usual synchronization between emotion-processing regions of the brain (limbic system, in particular the amygdala and the septal region/basal forebrain) (MacLean, 1970) and fact-processing regions is no longer possible with the consequence that one or the other region takes dominance. This then leads to the block of autobiographical information processing, either in general or specific with respect to time-epochs or material. Our model is consistent with accumulating evidence that shows that early life experiences can lead to changes in stress responses, neurotransmitters, synaptic plasticity, brain connectivity, and brain structures, including microstructural changes in the uncinate fascicle (Bluhm et al., 2009; Govindan, Behen, Helder, Makki, & Chugani, 2010; Lupien et al., 2009; Mehta et al., 2009). The latter is highly relevant for the processes of episodic-autobiographical memory (EAM) retrieval (see below). Its changes in children exposed to early trauma are of particular interest, especially when corroborated with findings from other studies that point to reduced autobiographical memory specificity (overgeneral memory effect) in children with a history of abuse or neglect (Valentino, Toth, & Cicchetti, 2009). An optimum balance of glucocorticoids (stress hormones) is essential for the neuronal survival and learning and memory processes (Du et al., 2009). Enduring alterations in stress hormone responses in response to early life experiences might occur via epigenetic mechanisms, which act during windows of heightened vulnerability (McGowan et al., 2009). The effects of stress on mental health might be observed clinically after a lag period. This may be accounted for by the fact that the early stress effects on synaptic organization only emerge after the completion of synaptic organization (Lupien et al., 2009).

Alternatively, this phenomenon might be explained by a mechanism of kindling sensitization (Post et al., 1995). Stressful events could lead to the release of a variety of hormones and initiate a neurotoxicity cascade (Joels & Baram, 2009; O'Brien, 1997; Ulrich-Lai & Herman, 2009). As Figure 1 implies, it is assumed that the release of stress hormones – in particular glucocorticoids – is principally responsible for the block in the function of brain structures essential for the encoding or retrieval of information. In fact, it is known that several key brain structures involved in memory processing show especially during their periods of development or regression (Lupien et al., 2009) an increased susceptibility to the hormonal effects of stress and aside from limbic brain regions, temporo-frontal regions are engaged in triggering the retrieval of already stored information. With respect to the retrieval of memory, it was proposed that a regional combination of inferolateral prefrontal and anterior temporal regions is essential (Fink et al., 1996; Kroll, Markowitsch, Knight, & von Cramon, 1997; Markowitsch, Calabrese, Liess, et al., 1993). LaBar and Cabeza wrote in 2006 that "studies of retrograde amnesia support Markowitsch's proposal that retrieval of remote personal memories involves interactions between the inferior PFC [prefrontal cortex] and its connections with the anteriormedial temporal lobe that course through the

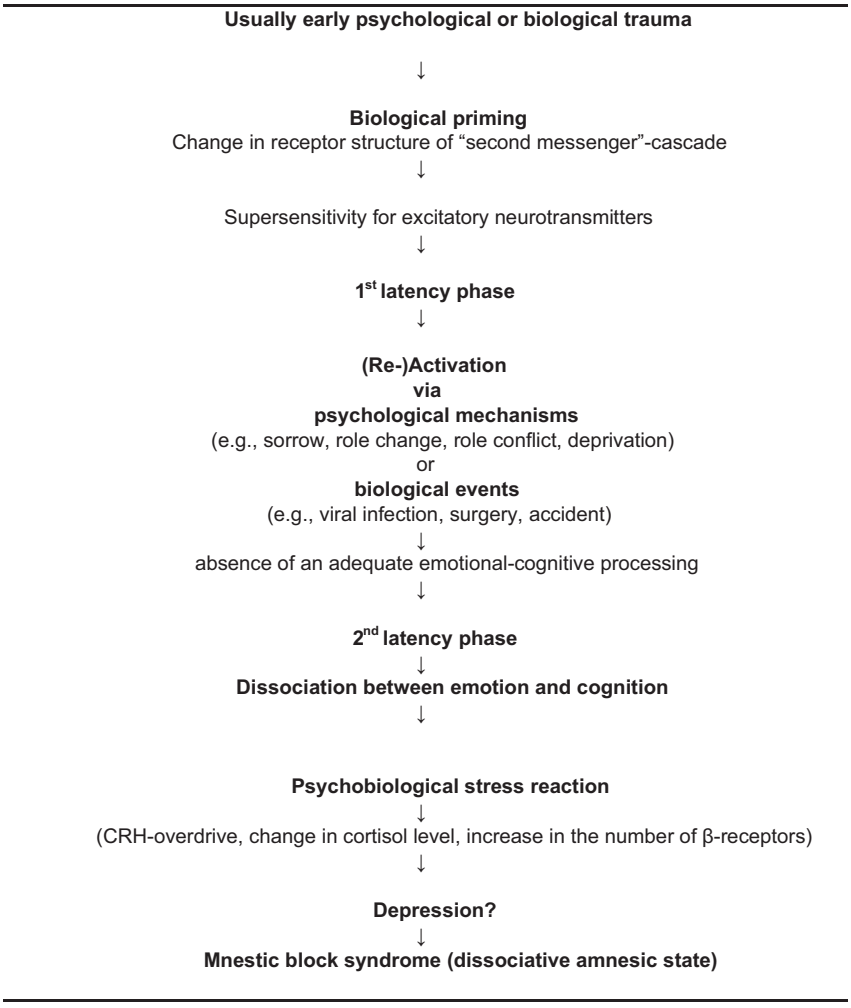

Figure 1. Proposed model of possible changes in brain-behavior interrelations induced by stress conditions (after Aldenhoff, 1997; Markowitsch, 2000b).

uncinate fasciculus." In fact it was established by histological methods that the uncinate fascicle (Figure 2) has 33% more fibers in the right than in the left hemisphere (Highley, Walker, Esiri, Crow, & Harrison, 2002) and that it is the only fiber bundle that may continue to develop beyond the age of 30 years (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). As we and others found, the regional combination of inferolateral prefrontal and polar temporal areas is essential for retrieving two forms of memory, which will be explained in the next section – episodic-autobiographical and semantic memory. EAM is in our experience related to the right hemisphere (i.e., the emotion-processing hemisphere) and semantic memory to the left hemisphere (where also the Broca and Wernicke language areas are situated).

The Nature of Memory Loss in Dissociative Amnes(t)ic Disorders

Our experience with dissociative amnesias confirms other authors' findings, which is that in most cases only one memory system is affected, namely the EAM, while information processing via the other memory systems either is preserved or is easily regained after a significant stressful event. In particular, those memory systems, acting on a subconscious level, like procedural memory and the priming memory system, are intact and even the so-called noetic (conscious reflection requiring) memory systems could remain intact – that is, perceptual and semantic memory.

On the other side, with respect to memory loss there are apparently two forms of dissociative (psychogenic) amnesia, the common form in which retrograde EAM is impaired and an anterograde form where anterograde EAM is impaired. Although anterograde memory deficits could occasionally accompany retrograde dissociative (psychogenic) amnesia, cases of dissociative (psychogenic) anterograde amnesia with preserved retrograde EAM are a much rarer occurrence. Up to now we have studied about three dozen patients with the common, retrograde form, but only three patients with the anterograde form (cf. Markowitsch, Kessler, Kalbe, & Herholz, 1999). Also from other groups reports on patients with psychogenic anterograde amnesia are very rare (Kumar, Rao, Sunny,

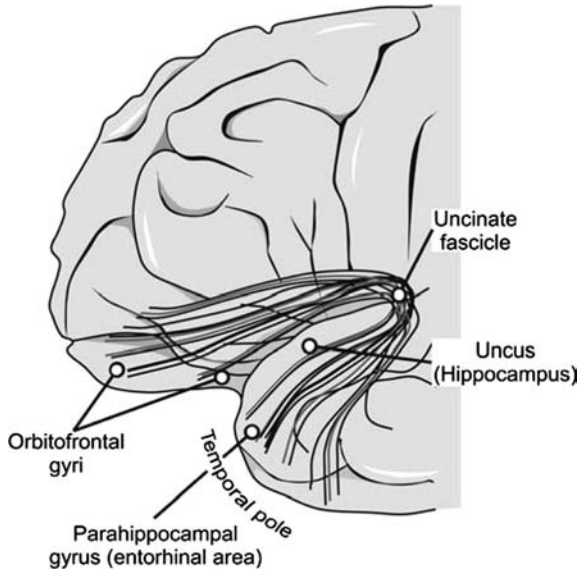

Figure 2. The location of the ventral branch of the uncinate fascicle, interconnecting the inferior lateral prefrontal cortex and the temporopolar cortex. It is assumed that these regions are essential for triggering the retrieval of semantic (left hemisphere) and episodic-autobiographical information (right hemisphere) (cf. Markowitsch & Welzer, 2009).

& Gangadhar, 2007). The differences in the susceptibility to insults among memory systems are mirrored by Tulving's (2002, 2005) classification of memory systems, which corresponds to an ontogenetic and phylogenetic hierarchy. The EAM, which is situated at the top of this hierarchy, entails an ability for flexible mental time traveling in the past and future and a superior capacity for reflection upon oneself in relation to the others (his or her social and biological environment). Furthermore, EAM possesses an intimate link to emotions. The recall of EAMs is usually accompanied by appraisals of their emotional meaning for the individual – whether an event was a happy or a sad one, for example. As emotions might play a motivational role, the ability to access emotionally laden episodic memories of personal experience is important for the maintenance of an enduring sense of personal identity in the face of a changing environment.

The flexible handling of EAMs becomes apparently no longer possible in dissociative amnesic conditions. In the following we briefly review cases with dissociative amnesic conditions in which one or several forms of brain imaging were performed before we provide more general conclusions on possible neuroanatomical correlates of amnesia in dissociative amnesic patients. As neuroimaging methods we typically either measured the glucose metabolism with positron-emission tomography (PET) or applied a paradigm with several conditions under water PET. In addition static magnetic resonance imaging (MRI) was used in all patients. In one patient single photon emission computed tomography (SPECT) was applied in addition to PET and MRI. Furthermore functional magnetic resonance imaging (fMRI) paradigms were employed in the last few years.

Patient NN

NN's case was described in Markowitsch, Fink, et al. (1997). He was a 37-year-old man with low self-esteem. He was the single child of alcohol-dependent parents and had been maltreated by them since birth. He was dressed as a girl until starting elementary school because his mother wanted to have a daughter instead of a son. Later his mother frequently criticized him as being weak and as behaving in a girlish manner. She predicted that he never would become successful in life and instead would ruin their business. Indeed, N.N. grew up with very low self-esteem and was easily frustrated. In his early 20s, he married a woman who apparently was similar in behavior to his mother and possessed the self-confidence he was missing. He took her family name also for himself and she directed his way of life. Reportedly, she one day decided that they will leave with their car for a vacation the following week. Though he knew that they would not have enough financial resources for that, he did not want to object.

Three days prior to the intended start of the holidays NN was supposed to get rolls from the bakery for breakfast. He took his bicycle, but instead of returning home he continued biking for the next days from North to South Germany until reaching the center of a large city. At the central station of this city he was asked about his well-being by a person from the Salvation Army who then suggested to him to enter the city's psychiatric university hospital, what he actually did. All the days he did not remember who he was nor why he was biking – he simply had the drive to do so. As described above, this combination of losing the autobiographical memories and leaving the usual place of living is named *dissociative fugue* in psychiatry.

In the clinic, NN felt quite happy, made friends, and appeared not to care about his condition of having no access to his past – a presentation which has been noted in other patients with dissociative amnesia and has been termed *belle indifférence* by Janet (1907). After a police search, initiated by his wife, NN was found and visited by her after about 10 days. Contrary to the old teaching lore that stated that a confrontation with reality leads to immediate reinstatement of memories, this did not happen to him. He did not recognize his wife and instead believed that the doctors wanted to couple him with a woman, unknown to him. He nevertheless returned with his wife to their home – complaining however at arrival about how one could live with the existing furniture and tapestry. He also failed to recognize his children. Interestingly, he changed his habits (e.g., while having been an avid car driver prior to the onset of his amnesia, he now barely dared to enter a car), and his job, and even ceased having allergy and asthma attacks. He relearned his past and then could

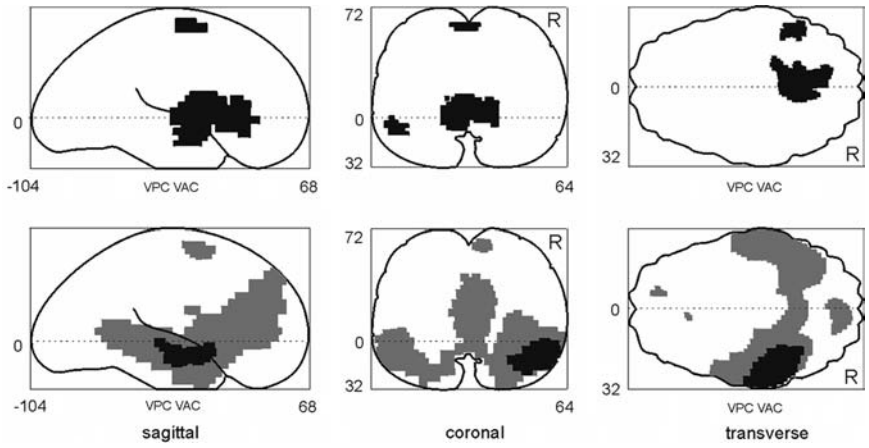

Figure 3. "Glass brain" activations during retrieval of autobiographic events. The top row shows the activations in patient N.N., the bottom row those of comparison subjects.

retrieve portions of it in a neutral, affectless manner. Other cognitive functions were largely spared or regained within weeks.

We tested him neuropsychologically and performed a water-PET where we used the design of Fink et al. (1996) and confronted him with events from his personal past. However, as it can be seen from the outcome illustrated in Figure 3, he was apparently unable to relate events he had experienced in the past to himself: While the normal subjects activated in the water-PET study predominantly the fronto-temporal region of the right hemisphere, he activated largely the left hemisphere which is considered to be relevant for the retrieval of neutral, impersonal facts (De Renzi, Liotti, & Nichelli, 1987; Grossi, Trojano, Grasso, & Orsini, 1988; Markowitsch, Calabrese, Neufeld, Gehlen, & Durwen, 1999).

Patient AD

Another patient appeared to have had a dissociative fugue condition with a forensic background (Markowitsch, Calabrese, et al., 1997). He had burned a house and left with a high amount of money across the border to a foreign country. When he was brought back to his home country, he did not know anything about his personal past. In a neurological university clinic, he was investigated neuropsychologically, with SPECT, glucose-PET, and MRI. A significant finding was a reduction in his right fronto-temporal cortex, that is, in exactly that area that was active in functional brain imaging when normal subjects were asked to recall their personal events from the past (Figure 4). Aside from persistent retrograde amnesia in the autobiographic domain, his memories and other cognitive functions were largely intact. Lumbar puncture did not yield any evidence of infection.

Patient AMN

While both patients described above showed evidence of a change in the right temporo-frontal cortex, patient AMN was somewhat different. This 23-year-old young man one afternoon witnessed the outbreak of an open fire in the cellar of his house. He immediately left the house, shouting "fire, fire" and was apparently shaken up by what he saw. His friend, who had also been present in the house at that time, called the fire-workers who immediately extinguished the fire. AMN then went to bed that night, but when awakening the next morning, he had lost access to the last six years of his life and was also anterogradely amnesic. His semantic memory was quickly regained. Any medical or neurological causation (e.g., hypoxia) was ruled out by a thorough medical workup. We examined this patient neuropsychologically and with glucose-PET a few weeks after the accident (Markowitsch, Kessler, Van der Ven, Weber-Luxenburger, & Heiss, 1998).

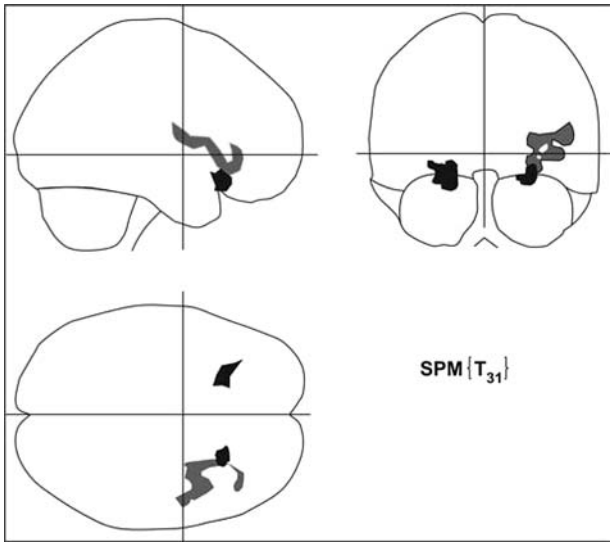

Figure 4. Schematic reconstructions of two horizontal brain sections of two patients. The left brain section represents the brain metabolism (perfusion) of a patient with herpes encephalitis and consequently neurological brain damage (darker shaded areas). The right one represents the brain perfusion of a patient with dissociative amnesia (after PLATE 2 of Markowitsch, Kessler, Kalbe, et al., 1999).

In the course of psychotherapeutic explorations, AMN revealed that when he was 4 years old he witnessed with his mother the death of a man in a burning car. He recalled that that man shouted, cried, and hammered against the windows, but was unable to escape the fire. Since that time, open fire situations were perceived as life-threatening by the patient. We propose that the witnessing of the first fire situation represented the initial traumatic event that likely initiated already subtle biological changes as described in Figure 1, and that the later witnessing of the fire outbreak in his own house resulted in a magnified biological response in the form of a cascade-like release of stress hormones (glucocorticoids; cf. O'Brien, 1997), which led to the mnestic block. The time span covered by memory loss for personal events (the last 6 years) could be related to the negative emotional loading of the life events that happened during that time frame (such as significant conflicts with parents, leaving both home and school) (De Kloet, Joels, & Holsboer, 2005; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). A number of findings, in fact, support the idea that especially traumatic conditions in young age may lead to a later vulnerability to stress-related events (Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005; Weinstock, 2008).

PET revealed an overall reduction in AMN's brain's glucose metabolism. In addition, there was a more severe reduction in his anterior and medial temporal lobes and the diencephalon (cf. Bluhm et al., 2009; Gianaros et al., 2007; Szeszko et al., 2006). Treating the patient psychopharmaceutically and with psychotherapy resulted in a reinstatement of most of his old memories and a reinstatement of his ability to encode new episodic events long term (Markowitsch et al., 2000). This patient therefore resembles one of the few cases with severe autobiographical retrograde amnesia who regained his memories within roughly a year (see also Thomas Antérion et al., 2008).

Patient KP

Patient KP was already over 50 years old when he was found sitting helplessly on a bench in a park of a big city. As he had no papers for identification and did not know who he was, he was brought into a psychiatric hospital. After a press conference, the media revealed his identity. He nevertheless did not recognize his long-term partner, nor did he regain any other personal memory. Only after psychotherapy and an intensive visiting and confrontation with places and persons from his childhood and youth, patient KP regained access to single events while he still does not remember much of his later decades of life. Brain imaging again revealed temporo-frontal glucose reductions (Reinhold, Kühnel, Brand, & Markowitsch, 2006).

Patient CD

Another patient with typical dissociative amnesia was a 33-year-old skilled worker who had been found unconscious in his bathroom by his wife. He had lost access to the last 14 years of life and glucose-PET revealed a significant reduction in glucose metabolism in his fronto-temporal brain areas.

Patient DO

Patient DO had been severely maltreated by her father as a child with the consequence that she still – at age 55 – was undergoing psychotherapy, because she had no access to her personal memories from the epoch between age 10 and 16 years (Markowitsch, Thiel, Kessler, von Stockhausen, & Heiss, 1997). Her therapist suggested to her to draw paintings representing events from her past and DO replied that she could do so when she was in a particular affective state. These pictures could be divided into those representing concrete scenes – usually showing a small, sad, or suffering looking child with or without an adult male person – and those with abstract content. The colors were largely dark, purple or black, or white. DO perceived these abstract paintings as emotionally more negatively arousing than the ones showing concrete scenes. Scanning her brain with water-PET while she viewed her paintings resulted in right temporopolar activations, pointing to a deficiency in integrating emotional and factual components of memory (Reinhold & Markowitsch, 2007, 2009).

Patient KL

A woman of 35 years of age came to our attention because of a peculiar loss of memory affecting the last 14 years of her life. When she awoke from surgery, KL gave as the present date a date that was 14 years back in time compared to the real one. She exactly remembered events and facts until then, but not thereafter. This implied that she still considered the German Democratic Republic to exist as well as Deutschmarks as currency. She was astonished by the existence of small cars (Smarts) on the streets or by what was available in supermarkets. Scanning her brain with water-PET (as she had a heart pacemaker we could not do fMRI) and a paradigm where the brain activity during presentation of events from her last 14 years of life versus the life thereafter was compared revealed activations in the right temporo-frontal zone for recently acquired and properly retrieved events, but not for those of the inaccessible past.

Patient MN

A special variant of dissociative disorder is the Ganser syndrome (Cocores et al., 1984; Ganser, 1898, 1904; Staniloiu et al., 2009), which is sometimes associated with a forensic background. A family father in his middle thirties was suddenly accused of having sexually abused two women years ago. The patient immediately became unable to work and developed very severe changes in cognition and affect. He apparently could no longer perform simple tasks and spent the whole day sitting or lying around without doing

anything. He became totally dependent on his wife. He developed significant difficulties urinating and subsequently his wife had to catheterize him. Glucose-PET revealed significant overall changes in his brain metabolism.

Cases of Dissociative (Psychogenic) Amnesia or Possible Dissociative (Psychogenic) Amnesia Investigated with Brain Imaging Reported by Other Authors

In recent years several other groups have performed static and functional brain imaging in patients with dissociative (psychogenic) amnesia or functional amnesia. Most studies employed fMRI within a task paradigm; these studies have therefore limited relevance with respect to the question of possible neuroanatomical changes as a consequence of the dissociative state and will consequently not be reviewed here, although they specifically point to similar brain mechanisms in "organic" and psychogenic (or functional or dissociative) forms of amnesia (e.g., Botzung, Denkova, & Manning, 2007; Brandt & Van Gorp, 2006; Glisky et al., 2004; Ouellet, Rouleau, Labrecque, Bernier, & Scherzer, 2008; cf. Markowitsch, 1996).

There is, however, one pertinent new case report in which a 34-year-old patient with functional amnesia is described (Tramoni et al., 2009). He was investigated neuropsychologically and with various brain imaging methods. He fell from a ladder and became unconscious. Thereafter he presented with extensive retrograde amnesia in the autobiographical domain, while other cognitive skills were preserved. Investigating his brain with MRI methods sensitive to microstructural and metabolic brain damage (density and magnetization transfer ratio; MR spectroscopic imaging) revealed damage in the right prefrontal white matter involving parts of the superior longitudinal fasciculus, the fronto-occipital fasciculus, and the genu of the corpus callosum. These results reflect subtle focal tissue damage with concomitant neural dysfunction or demyelination. They are consistent with ideas on brain regions relevant for processing of old autobiographical memories (Markowitsch, 1995) and point to a kind of disconnection syndrome, similar to what we had described before (Brand & Markowitsch, 2009; Markowitsch, 2002; Markowitsch, Kessler, Russ, et al., 1999).

Relations Between Dissociative Amnesias and Neuroanatomical Changes

The findings from various brain imaging methods converge in demonstrating that environmental influences such as psychological trauma or stressful experiences could induce alterations on the brain level (Markowitsch, 1999a, 1999b).

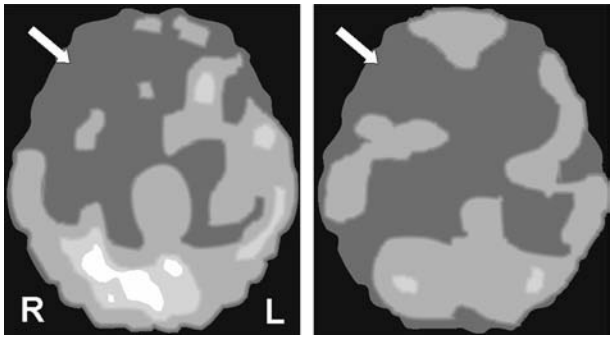

Figure 5. Schematic sagittal (top left), horizontal (bottom left), and frontal sections through the human brain. Areas of relative decrease in regional cerebral glucose metabolism in 14 patients with dissociative amnesia relative to 19 control subjects are shown as "glass brains" (after Figure 1 of Brand et al., 2009).

These changes may be long-lasting, if treatment remains unsuccessful or they have already followed a prolonged course prior to being diagnosed and treated. They can broadly be classified as changes in brain metabolism and changes in brain tissue volume and in brain structure itself.

Changes in brain metabolism are observed most universally and persist weeks to months after the occurrence of the psychotraumatic situation leading to the dissociative condition (Reinhold et al., 2006). Aside from affecting the cerebrum as a whole these seem to be targetable especially in the right-hemispheric temporo-frontal region (Brand et al., 2009; Piolino et al., 2005; Tramoni et al., 2009), though some SPECT data in patients with unclear etiology or diagnosis (traumatic brain injury, post-traumatic retrograde amnesia) also point to changes in other cortical regions (Cantagollo, Grassi, & Della Sala, 1999; Stracciari, Ghidoni, Guarino, Poletti, & Pazzaglia, 1994). Our search for the neural signature of psychological stress in dissociative (psychogenic) amnesia in a relatively large sample of 14 patients with dissociative (psychogenic) amnesia characterized by severe retrograde EAM deficits and no overt structural abnormalities as detected by conventional imaging methods found evidence of functional changes (hypometabolism) during resting state in the right temporo-frontal region with a significant decrease in the inferolateral prefrontal cortex (Figure 5) (Brand et al., 2009). These changes are in striking agreement with the findings of Tramoni et al. (2009), based on a different methodology (see above).

We therefore can conclude that there is accumulating evidence from several sources for the existence of significant brain alterations in patients with dissociative (psychogenic) amnes(t)ic disorders. These changes reflect most likely more subtle fiber damage and/or reductions in functionality in the regions of the right anterior hemisphere, in particular in right fronto-temporal areas and their interconnecting fiber tracts. As it was stated previously, these findings point to similar neurobiological mechanisms underlying the "organic" and "psychogenic" memory loss conditions. They suggest that it might indeed be the case that these conditions represent

two sides of the same coin (Markowitsch, 1996) and the gap that we still perceive between the two is mainly a consequence of technological limitations.

We end by citing Pietro Pietrini, who stated in 2003 in the *American Journal of Psychiatry* (p. 1908): "It was not long ago that psychiatric disorders were grossly classified as 'organic' and 'functional' according to whether there was a known brain structural alteration (e.g., dementia) or not (e.g., depression or schizophrenia). This merely reflected our inability to go beyond what could be visible to the naked eye in the brain. Functional brain studies . . . have given us a powerful microscope to dissect the intimate molecular aspects of brain function."

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