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Neuroimaging and Dissociative Disorders

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1. Introduction

Although they were 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 identifying and describing their underlying neural correlates. Dissociative disorders are characterized by transient or chronic failures or disruptions of integration of otherwise integrated functions of consciousness, memory, perception, identity or emotion. The DSM-IV-TR (2000) includes nowadays under the heading of dissociative disorders several diagnostic entities, such as dissociative amnesia and fugue, depersonalization disorder, dissociative identity disorder and dissociative disorder not otherwise specified (such as Ganser syndrome). In contrast to DSM-IV-TR, ICD-10 (1992) also comprises under the category of dissociative (conversion) disorder the entity of conversion disorder (with its various forms), which is in DSM-IV-TR (2000) captured under the heading of somatoform disorders (and probably will remain under the same heading in the upcoming DSM-V).

Dissociative disorders had been previously subsumed under the diagnostic construct of hysteria, which had described the occurrence of various constellations of unexplained medical symptoms, without evidence of tissue pathology that can adequately or solely account for the symptom(s). Although not the first one who used the term dissociation or who suggested a connection between (early) traumatic experiences and psychiatric symptomatology (van der Kolk & van der Hart, 1989; Breuer & Freud, 1895), it is Janet (1898, 1907) who claimed dissociation as a mechanism related to traumatic experiences that accounted for the various manifestations of hysteria.

By definition, dissociative disorders are viewed in international nosological classifications as underlain by the mechanism of dissociation; there is still debate if the mechanism of dissociation that is involved in dissociative disorders is distinct from the so-called non-pathological or normative dissociation (that includes absorption or reverie) or a continuum exists between the two (Seligman & Kirmayer, 2008). Janet had reportedly viewed on one hand, dissociation as being intrinsically pathological and causally bound to unresolved traumatic memories (Bell, Oakley, Halligan, & Deeley, 2011). On the other hand, Janet had suggested that the impact of trauma on a particular individual may depend 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). Janet is credited by several authors (Maldonado & Spiegel, 2008) with a superior view of dissociation that anticipated contemporaneous theories. Freud, a pupil of Charcot, proposed in collaboration with Breuer (Breuer & Freud, 1895) that the dissociative process was the result of the repression of traumatic material into unconscious (Bell et al., 2011). This process of repression was intimately connected to the one of conversion, during which the affective discomfort accompanying the repressed memories of trauma led to a conversion of the psychological emotional distress into physical symptoms (conversion hysteria). Repression, conversion and dissociation occurred without awareness or intentionality (Markowitsch, 2002), which distinguishes them from memory suppression or motivated forgetting (Anderson & Green, 2001). Later elaborations on the mechanisms of repression versus dissociation posited that they corresponded to various views of the self-one that is vertically organized (such as in the case of repression) versus one that is horizontally aligned, with areas of incompatibility separated by dissociation (Mitchell & Black, 1995). Many of Janet's ideas presented above received corroboration later from both clinical observations and neurobiological investigations and have subsequently been incorporated in contemporaneous pathogenetic models of dissociative disorders. Though some authors still dispute their legitimacy (Pope, Poliakof, Parker, Boynes, & Hudson, 2007), dissociative disorders have indeed been linked to psychological trauma or stress in a variety of cultures (Maldonado & Spiegel, 2008).

In the present chapter, after a brief description of the dissociative (conversion) disorders, we review neuroimaging data pertaining to dissociative (conversion) disorders, which were obtained with functional imaging methods performed during rest or various tasks, such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), as well as structural imaging techniques, including newer structural imaging methods such as diffusion tensor imaging (DTI) or magnetization transfer ratio measurements. In particular, we focus on reviewing neuroimaging data from studies of patients with dissociative amnesia and fugue, dissociative identity disorder (multiple personality disorder) and Ganser syndrome (Dissociative Disorders Not Otherwise Specified [NOS]). We also review functional brain imaging studies of patients with various forms of conversion disorder (e.g. psychogenic motor or sensory changes, psychogenic blindness, pseudoseizures) as well as depersonalization disorder. As hypnotizability traits have been postulated to be associated with a higher tendency for developing dissociative symptoms, we briefly refer to functional imaging studies of hypnosis. In addition we make reference to neuroimaging investigations pertaining to dissociative symptoms of psychiatric conditions that are not categorized under the heading of dissociative (conversion) disorders, but may have dissociative symptoms as part of their clinical presentations (such as post-traumatic stress disorder or borderline personality disorder). Given that the concept of mindfulness is often viewed as being situated at the opposite pole of that of dissociation, we discuss the neuro-imaging findings of the so-called dispositional mindfulness as well as of the mindfulness-based cognitive therapy in patients with conditions that may be associated with dissociative symptoms (such as borderline personality disorder).

2. Dissociative amnesic disorders

Several dissociative disorders have as hallmark amnesia for autobiographical events. Among them, the most frequently mentioned are dissociative amnesia and its variant dissociative fugue. The inability to recall personal events is however also a common occurrence in other dissociative disorders, such as dissociative identity disorder or multiple personality disorder, a characteristic that is going to be underlined in the upcoming edition of the DSM–V. Also Ganser syndrome (see below) was initially described to feature amnesia as part of its constellation of symptoms. Dissociative amnesia has as its central symptom the inability to recall important personal information, usually from an epoch encompassing events 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 that is consciously motivated by external incentives (such as malingering) or is prompted by psychological motivations in the absence of identifiable potential external gains (such as in Factitious Disorder) has to be ruled out. This is not always an easy task. Especially the psychologically motivated exacerbation of symptoms has been found to accompany a variety of disorders, including dissociative disorders, major depressive disorder, traumatic brain injury. The symptoms of dissociative amnesia are assumed to 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 (Seligman & Kirmayer, 2008). 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 (which in psychoanalytic theories is posited to have the role of covering the unfortunate past) might, however, pose a significant challenge to clinicians trying to identify the precipitating stressful events. Furthermore some cases of dissociative (psychogenic) amnesia did not occur as a result of an objective major psychological stressor, but were recorded after a seemingly objective minor stress (Staniloiu et al., 2009). 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, Rosen, & Frye, 1995), or protracted effects of early life stressful events, due to an incubation phenomenon (Lupien, McEwen, Gunnar, & Heim, 2009). Another factor that may prevent the identification of convincing associations between stressful events and onset of dissociative amnesia is the presence in some patients with dissociative amnesia of an impaired capacity for emotional processing in the face of ongoing stress (Staniloiu et al., 2009).

According to most studies dissociative amnesia affects both genders roughly equally. Dissociative amnesia is most frequently diagnosed in the third and fourth decade of life. 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, despite treatment. Comorbidities of dissociative amnesia with major depressive disorder, personality disorders, bulimia nervosa, conversion disorder and somatisation disorder have been reported (Maldonado & Spiegel, 2008). Changes in personality after the onset of dissociative amnesia in the form of changes in eating preferences, smoking or drinking habits or other engagement in various activities have also been reported (Fujiwara et al., 2008; Tramoni et al., 2009; Thomas Antérion, Mazzola, Foyatier-Michel, & Laurent, 2008).

Dissociative amnesia could be differentiated according to the degree and timeframe of impairment (global versus selective, anterograde versus retrograde) of autobiographical-episodic memory and the co-existence of deficits in autobiographical-semantic memory and general semantic knowledge. The most frequent types of dissociative amnesias are retrograde, a fact that is in fact captured by the diagnostic criteria of DSM-IV-TR (2000). The latter distinguishes between localized amnesia, selective amnesia, generalized amnesia, continuous amnesia and systematized amnesia.

Retrograde dissociative amnesia may sometimes present as 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. Additionally, they can encode new autobiographic-episodic memories long term, though the acquisition of these new events may be less emotionally-tagged in comparison to normal probands, often lacking that feeling of warmth and first person autonoetic connection (Reinhold & Markowitsch, 2009 ; Levine, Svoboda, Turner, Mandic, & Mackey, 2009). Although anterograde memory deficits could occasionally accompany retrograde dissociative (psychogenic) amnesia, cases of dissociative (psychogenic) anterograde amnesia with preserved retrograde memory are a much rarer occurrence (for a review see Staniloiu & Markowitsch, 2010).

When retrograde dissociative amnesia is accompanied by suddenly leaving the customary environment and compromised knowledge about personal identity – the condition is named dissociative fugue. Fugues have been reported for over a century, though they were frequently erroneously associated with epilepsy (e.g., Burgl, 1900; Donath, 1899). 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 (Dana, 1894; Donath, 1908). Identified precipitants included sexual assault, combat, marital and financial problems. Presentations similar to fugues have also been described in certain cultures, where they might represent idioms of distress (Maldonado & Spiegel, 2008). Most fugues were usually reported to be brief, but some prolonged courses were also described (Hennig-Fast et al., 2008). Associations between fugues and Ganser syndrome (see below) were also found.

Dissociative Identity Disorder (DID) or multiple personality disorder is assumed to have its onset in childhood, but it is usually diagnosed in the fourth decade. It affects preponderantly women and typically runs a chronic, waxing and waning course. Comorbidities with other conditions (such as mood disorders and substance abuse) and its plethora of clinical manifestations may hinder timely diagnosing. Apart from marked impairments in the sense of identity and self (in the form of the existence of two or more distinct identities or personality states), inability to recall personal information (amnesia) is a common occurrence in DID. Currently included under the separate entity of dissociative trance disorder, possession trance seems to be an equivalent of dissociative identity disorder. It involves episodes of consciousness alteration and perceived replacement of the usual identity by a new identity, which is attributed to the influence of a supernatural entity (deity, spirit, power) (DSM –IV-TR, 2000).

3. The "dissociation"of memory systems

In order to better understand the clinical manifestations and neuroimaging data of those dissociative disorders, which have as hallmark inability to recall personal past events, we will briefly review the current classifications of the long-term memory systems. Two overlapping classifications currently dominate the memory research literature – the one that was initiated by Larry Squire and the one that was advanced by Endel Tulving. In Squire's classification, a main distinction is made between declarative and non-declarative memory. Under declarative memory, episodic and semantic memories – that is (biographical) events and general facts – are listed. Non-declarative memory contains several other forms of memory, which are considered to be automatically processed.

Tulving's classification is depicted in Figure 1 and, in our opinion, offers clinicians the best framework for describing the pattern of memory impairment in amnesic conditions. Aside from short-term memory (not illustrated in Fig. 1), it contains five long-term memory systems. These memory systems are considered to build up on each other phylo- and ontogenetically. Procedural memory and priming constitute the first developing memory systems, being still devoid of the need for conscious reflection upon the environment ("anoetic"). Procedural memory is largely motor-based, but includes also sensory and cognitive skills ("routines"). Examples are biking, skiing, playing piano, or reading words presented in a mirror-image. Priming refers to a higher likelihood of re-identifying previously perceived stimuli, either identical or similar ones. An example is the repetition of an advertisement which initially may not be in the focus of attention, but may leave a prime in the brain so that its repetition will make it likely to become effective. Perceptual memory enables distinguishing an object or person on the basis of distinct features; it works on a pre-semantic, but conscious ("noetic") level. It is effective for identifying, for example, an apple as an apple, no matter what color it is or if it is half eaten or intact. It also allows distinguishing an apple from a pear or peach. Semantic memory that was also termed 'knowledge system' is context-free and refers to general facts. It is considered to be noetic as well. The episodic-autobiographical memory system is context-specific with respect to time and place. It allows subjective mental time travel and re-experiencing of the event by attaching an emotional flavor to it. Examples are events such as the last vacation or the dinner of the previous night. Tulving (2005) defined episodic –autobiographical memory as being the conjunction of autonoetic consciousness, subjective time, and the experiencing self where autonoetic consciousness represents the capacity "that allows adult humans to mentally represent and to become aware of their protracted existence across subjective time" (Wheeler, Stuss, & Tulving, 1997, p.335).

Each memory system is embedded in specific brain networks. In a simplified way, there are primarily subcortical and cortical motor-related structures for the procedural memory system, neocortical, modality-specific regions for the priming system, the neocortical association cortex for perceptual memory, and cortical and limbic regions for semantic memory. In the case of episodic-autobiographical memory system, several widespread limbic and cortical (including prefrontal) regions are of importance, rendering this memory system more susceptible to environmental insults in comparison to the other systems.

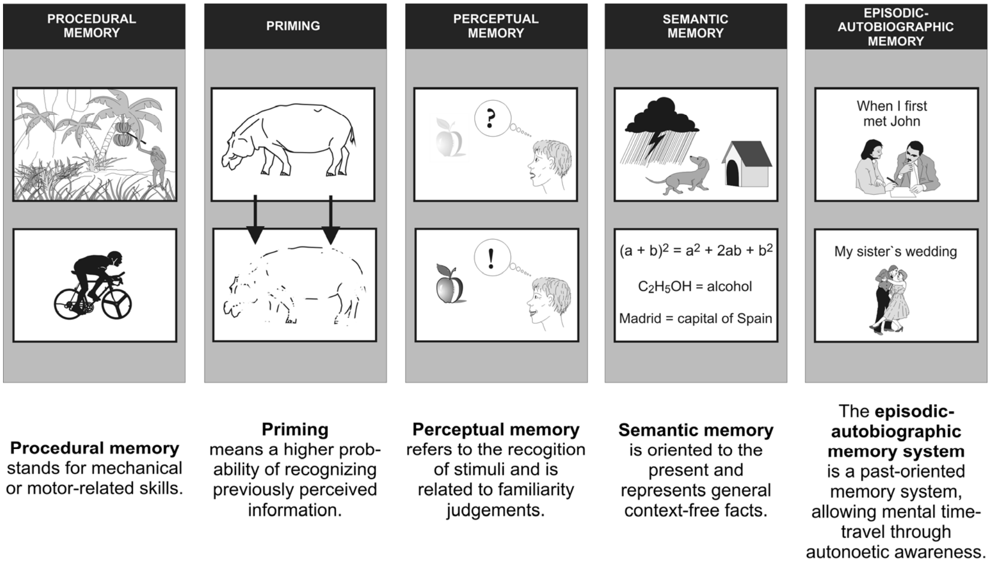

Fig. 1. The five long-term memory systems. Procedural memory is largely motor-based, but includes also sensory and cognitive skills (“routines”). Priming refers to a higher likeliness of re-identifying previously perceived stimuli. Perceptual memory allows distinguishing an object, item, or person on the basis of distinct features. Semantic memory is context-free and refers to general facts. It is termed the knowledge systems as well. The episodic-autobiographical memory system is context-specific with respect to time and place. It allows mental time travel. Examples are events such as the last vacation or the dinner of the previous night. Tulving (2005) defined it as the conjunction of autonoetic consciousness, subjective time, and the experiencing self.

A main feature of episodic-autobiographical memory is its state-dependency. This implies that episodic-autobiographical memories are best retrieved when the conditions during encoding (mood and environment) match those during retrieval. A mismatch between encoding and retrieval conditions may result in a gamut of memory retrieval disturbances, ranging from the tip-of-the-tongue phenomena to complete blockades, such as in dissociative amnesic disorders. The blockade in dissociative amnesia is posited to preponderantly reflect a desynchronization during retrieval between emotional and fact-based information processing (Markowitsch, 2002). This blockade is opined to be caused by adverse life conditions in the form of massive acute stress or chronic stress, which elicits the release of several stress hormones (O`Brien, 1997; Joels & Baram, 2009), which then bind to the amygdala and the hippocampus – areas with a high density of glucocorticod receptors (Rodriguez, LeDoux, et al., 2009). This process then may initiate changes of the morphology or functional connectivity of the above mentioned structures, which in turn may lead to severe and persisting impairments of recollecting the episodic-autobiographical material.

4. The neuroimaging of dissociative amnesia and fugue

Dissociative amnesia and fugue conditions typically occur in the absence of significant brain damage as detected by conventional structural brain imaging techniques. When some brain damage exists, the extent of amnesia cannot be accounted for by the locus and degree of brain damage and amnesia is often labeled as "disproportionate amnesia" (Piolino et al., 2005). In the last years, functional brain imaging was used with increasing frequency in patients with various forms of dissociative amnesic disorders (Figure 2). Most frequently, and particularly in the first publications, positron-emission-tomography (PET) was applied (Markowitsch, 1999; Markowitsch, Calabrese et al., 1997a; Markowitsch, Fink, Thöne, Kessler, & Heiss, 1997b; Markowitsch, Thiel, Kessler, von Stockhausen, & Heiss, 1997c; Markowitsch, Kessler, Van der Ven, Weber-Luxenburger, & Heiss, 1998; Markowitsch, Kessler et al., 2000). The studies using glucose PET attempted to find changes in cerebral metabolism associated with dissociative memory impairments, in particular persistent retrograde dissociative amnesia affecting episodic-autobiographical domain in single cases with dissociative amnesia. Markowitsch, Kessler et al. (1998, 2000), for example, found significant reductions in glucose metabolism in the brain of a patient (case A.M.N.) with dissociative (psychogenic) amnesia; these reductions were observed all over the cerebrum, but in particular in memory-processing regions of the medial temporal lobe and the diencephalon. In these regions the reductions amounted to 2/3 of the normal level in both hemispheres. A.M.N. was a 23 year- old employee of an insurance company with 11 years of education. After discovering one evening the outbreak of a fire in the cellar of his house, he immediately left the house shouting "Fire, fire" while his friend – who was in the house at the time as well – called the fire workers who immediately extinguished the fire. In the night of the event A.M.N. and his friend retired to bed as usually, but the next morning, upon waking up, A.M.N. thought that he was 17 years old only, did not remember any personal events beyond this age and also became unable to acquire new events long-term. Three weeks later he was admitted to an university clinic, where he underwent medical and laboratory work up (that included structural brain MRI, EEG, carotid arteries ultrasound, chest X-ray and ECG), which was unremarkable. After three weeks of psychotherapeutic interventions in the hospital the patient recollected one of his childhood memories. He remembered that at age 4 years he saw a car crash with another car in flames. He was then witness to the driver's death in flames. This memory was confirmed by the patient's mother, who witnessed that event as well. Since then the open fire was reportedly perceived as life threatening by him. The authors hypothesized that the witnessing of the traumatic incident at age 4 already initiated subtle biological changes and that the latter witnessing of the fire outbreak in the house triggered a magnified biological response in the form of a neurotoxic cascade-like release of stress hormones, such as glucocorticoids (O'Brien, 1997), which led to the mnestic blockade that covered his last 6 years of life. The fact that the blockade of his conscious memories for personal events spanned the last 6 years of his life may have been accounted for by several experiences he had during that time, which had an intense and negative emotional connotation: he disclosed to his parents and his entourage his sexual preferences, he experienced conflicts with parents and ended up leaving both school and his parents' house. In a subsequent paper from 2000 the authors could demonstrate that, after combined psycho-pharmaceutical (antidepressant medication treatment) and psychotherapeutic interventions, memory recovered and the brain's glucose level returned to normal values in all areas. Probably this was the first paper that provided objective evidence via brain imaging for functional brain changes paralleling successful combined psychiatric treatment.

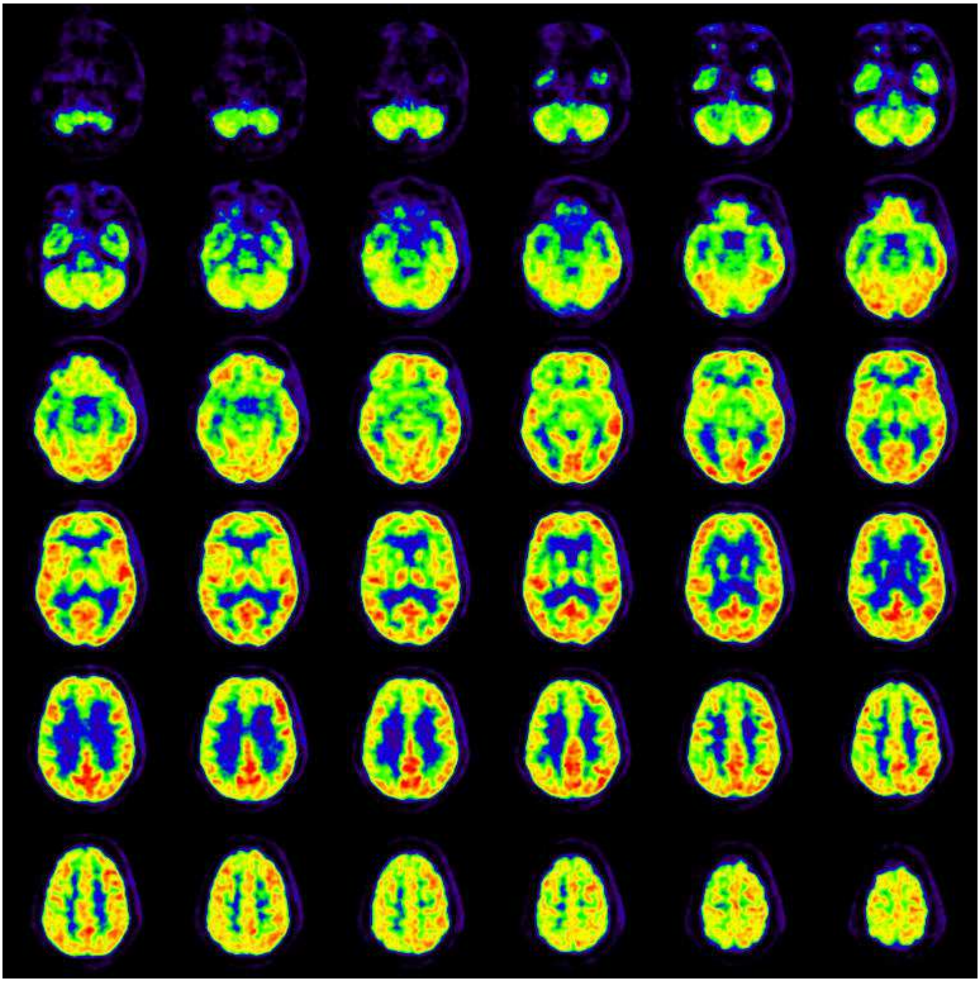

Fig. 2. Example of reduced regional cerebral glucose metabolism in the anterior temporo-frontal cortices in a patient with dissociative amnesia.

In likely the first paper on functional brain imaging in a variant of dissociative amnesia (dissociative fugue condition), Markowitsch, Fink et al. (1997b) used water-PET in order to find out whether the retrogradely amnesic patient showed any differences in functional activations in comparison to controls (Fink et al., 1996) when confronted with episodes from his personal past. Indeed, the patient's brain showed markedly different activations in comparison to that of the normals: While the normal probands had predominantly right temporo-frontal activation (Fink et al., 1996), the patient had a left-hemispheric activation of these regions. In light of other data on brain activations during memory retrieval (e.g., Reinhold, Kühnel, Brand, & Markowitsch, 2006; LaBar & Cabeza, 2006), this finding was interpreted as suggesting that the patient perceived his own episodic-autobiographical episodes as if they were belonging to a third, neutral person.

In a paper in which glucose-PET data from 14 patients with dissociative amnesia and severe episodic-autobiographical memory deficits were analyzed in combination, it was found that again the right temporo-frontal region was hypometabolic in a significant number of patients, with a significant reduction in the right inferolateral prefrontal cortex (Brand et al., 2009). This finding has possible therapeutic implications. It suggests that if the brain regions of the right temporofrontal cortex, which are interconnected by the uncinate fascicle, were brought to normal metabolic activity via environmental manipulations, the patients' ability to recollect personal events from the past might be reinstated. A kind of confirmation and extension of these results came in same year from the work of Tramoni et al. (2009), who in a patient with dissociative ("functional") amnesia performed magnetization transfer ratio measurement and MR spectroscopic imaging - methods sensitive to microstructural and metabolic brain changes. They found evidence of significant metabolic changes and subtle structural alterations of the white matter in the right prefrontal region.

In other reports on patients with dissociative amnesia glucose-PET, single photon emission computed tomography (SPECT) or fMRI, or combinations of several of these methods were used (Sellal, Manning, Seegmuller, Scheiber, & Schoenfelder, 2002, Glisky et al., 2004; Botzung, Denkova, & Manning, 2007; Hennig-Fast et al., 2008; Serra, Fadda, Buccione, Caltagirone, & Carlesimo, 2007; Stracciari, Fonti, & Guarino, 2008; Yang et al., 2005; Piolino et al., 2005; Yasuno et al., 2000; Thomas- Antérion, Guedj, Decousous, & Laurent, 2010 ; Arzy, Collette, Wissmeyer, Lazeyras, Kaplan, & Blanke, in press; Kikuchi et al., 2010). In most cases brain metabolic and functional changes were found, which involved areas that are agreed upon to play crucial roles in mnemonic processing. The differences in the localization and nature of the changes, which were at times reported, might be accounted for by several factors, such as the individual characteristics of the patients, the lack of control for variables, such as sex, differences in methodology (types of imaging methods used, the performance of functional imaging during rest versus administration of various tasks, differences in the task paradigms employed etc). In the case report of Thomas- Antérion , Guedj, Decousous and Laurent (2010), FDG-PET in resting state was performed in a right handed 30-40 year old male of probably Chinese origin who spoke French and had retrograde dissociative amnesia with personal identity loss approximately 15 months after he had been found in a French city. The PET scan demonstrated major hypometabolism, especially in left medial temporal lobe and insular/opercular area. The hypometabolism affected areas in termporal polar cortex, the amygdala, the hippocampus, the parahippocampus and the fusiform gyrus. The structural MRI was found to be within normal limits. Three years later, the patient still showed retrograde amnesia and loss of personal identity. In the paper of Glisky, Ryan, Reminger, Hardt, Hayes, and Hupbach (2004) a patient with a psychogenic fugue condition is presented, who lost conscious access to his autobiography together with native German language, while his implicit memory and knowledge of German grammar structure remained intact. Neuroimaging data revealed a reduced prefrontal metabolism, which was in conformity with his poor performance on tests of executive functions.

5. The neuroimaging of dissociative identity disorder

Research on structural brain changes in patients with dissociative identity disorder produced non-uniform results. One study reported volumetric decreases in amygdala and hippocampus in patients with dissociative identity disorder (Vermetten et al., 2006), while another yielded negative results (Weniger, Lange, Sachsse, & Irle, 2008). The non-homogeneity of these results may partly be understood in the light of new research data, which suggest that the impact of stress on structures involved in mnemonic processing (such as hippocampus and amygdala) has a differentiated response, which is modulated by the existence of certain developmental windows of vulnerability (Lupien et al., 2009). Several researchers investigated patients with dissociative identity disorder via functional imaging. Saxe, Vasile, Hill, Bloomingdale and van der Kolk (1992) found in a study using single emission computerized tomography (SPECT) that changes in personality state in a patient with DID were associated with significant fluctuations in the right temporal lobe blood flow. Sar, Unal, Kiziltan, Kundakci, and Ozturk (2001) and Sar, Unal, and Ozturk (2007) studied brain perfusion in a considerable number of patients (15 in one study, 21 in the other) with DID. Regional cerebral blood flow was found to be decreased in the left and right orbitofrontal cortex of the DID patients and increased in their left (dominant) lateral temporal (Sar et al., 2001) or bilaterally in the occipital cortex (Sar et al., 2007).

Two interesting studies were performed by Simone Reinders from the Netherlands (Reinders et al., 2003, 2006). Together with her colleagues she studied patients with DID. Using fMRI she found different brain activations when the patients where in distinct mental states of self-awareness, each with its own access to autobiographical trauma-related memory. As in many other studies, the medial prefrontal cortex was related to these self-states and the ability of conscious reflection. Verbal working memory was investigated in 16 patients with the diagnoses DID or Dissociative Disorder – not otherwise specified (DD-NOS) (Elzinga et al., 2007). They found that the patients and 16 matched normal subjects activated similar brain regions , which are typically involved in working memory (especially dorsolateral prefrontal and parietal cortex); however, the patients showed a higher activation in these areas and made fewer errors with increasing task load compared to the healthy individuals (though they felt more anxious and less able to concentrate).

6. Ganser syndrome and neuroimaging

A particular form of dissociative disorder is the Ganser syndrome. The syndrome has been submitted to several diagnostic revisions and debates over the years (Cocores, Santa, & Patel, 1984). 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 NOS (Not Otherwise Specified) in DSM-IV-TR (2000) and it is simply defined by giving approximate answers to questions (*vorbeireden*). Ganser's (1898, 1904) original description of the syndrome was, however, much broader than the current DSM-IV-TR one. It featured a hysterical semitrance characterized by a tendency to give approximate answers, amnesia and hallucinations. 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 case-reports in women and children as well (Nardi & Di Scipio, 1977). The onset of Ganser syndrome is usually acute in nature, often with a picture suggestive of a hysterical pseudo-dementia. Its course can be transient or chronic. A higher incidence of Ganser syndrome in patients with immigrant background or ethnic minorities has also been suggested (Staniloiu et al., 2009).

Comorbidity with other psychiatric (such as major depressive disorder, conversion disorder) or neurological conditions (e.g. mild traumatic brain injury) are very common, which may make imaging data more difficult to interpret. Functional imaging data in patients with Ganser syndrome is however very scant. So far, we have been aware of only two studies: one performed by Markowitsch and co-workers (described in Staniloiu & Markowitsch, 2010) and an older report by Snyder and co-workers (1998). Snyder, Monte, Buchsbaum and Krishnab (1998) described the case of a 32 year old man of Spanish origin who since age 9 had been raised bilingually in both Spanish and English and while recovering from an asthma attack presented with conversion symptoms (psychogenic blindness), Ganser-like presentation (approximate answers), memory difficulties, naming and calculation difficulties and a lack of concern about his symptoms - "la belle indifference" (Janet, 1907). Head CT scan without contrast was within normal limits. MRI without contrast revealed a signal abnormality in the right parietal cortex. Cerebral angiogram was within normal limits. Glucose PET revealed severe bilateral hypometabolic regions in the posterior cortex. His visual symptoms disappeared 37 days after the asthma attack, but 83 days after the attack he continued to have naming difficulties.

Markowitsch and co-workers described two male patients in their 30's with this syndrome, one with a clear forensic background (Staniloiu and Markowitsch, 2010) and one without (Staniloiu et al., 2009). In the patient without forensic background, the condition emerged after a mild traumatic brain injury and was accompanied by symptoms of major depressive disorder. Both patients showed in addition to symptoms of *vorbeireden* (giving approximate answers) a global deterioration of their intellectual capacities suggestive of a pseudo-dementic picture as well as conversion symptoms. One for example exhibited psychogenic urinary retention. Their clinical presentation followed a chronic course that extended beyond two years, despite treatment.

Although in both cases of Ganser syndrome the structural brain imaging investigations were not indicative of organic impairment, in the patient where additional functional imaging (glucose PET) was performed, a global significant reduction in the brain metabolism was visualized. The mentioned functional imaging result and the chronic course of the above mentioned two patients are relevant, in the light of findings from previous studies. Some of those studies pointed to a possible organic basis to the psychiatric presentation of the Ganser syndrome that can especially become apparent over time. For example, Ladowsky-Brooks and Fischer (2003) described a patient, who presented with features of Ganser syndrome and severe cognitive deficits in other domains. However, the individual's cognitive decline over a period of a year, in combination with findings from functional imaging, led to a diagnosis of fronto-temporal dementia.

7. Depersonalization disorder and neuroimaging

The manifestations and courses of dissociative disorders vary widely (Priebe & Schmahl, 2009). Depersonalization disorder involves a dissociation of perceptions (e.g. feeling detached from own body or mental activity, like in a dreaming state or like an outsider observer), in the absence of significant impairment of reality testing. It is characterized by an alteration of the subjective experience of self. Its onset dates back to adolescence or adult life. Comorbidity with other mood or anxiety disorders is common and may hinder its timely diagnosis, promoting therefore a chronic course of the illness. While several imaging studies of depersonalization focused on targeting the neural correlates of depersonalization as a symptom of other disorder (Lanius et al., 2005) or a symptom that was induced via various environmental manipulations (Blanke & Metzinger, 2009; Mathew et al., 1999) only a few studies looked at the neural correlates of depersonalization disorders. Simeon et al. (2000) investigated 8 subjects with depersonalization disorder and 24 healthy matched-controls with both structural (MRI) and functional imaging (FDG-PET). During the PET scanning the subjects were given a variant of California Verbal Learning Test modified for use in imaging study. The depersonalization disorder group showed significantly lower metabolic rates in areas belonging to the right superior temporal gyrus and middle temporal gyrus. In addition, they showed higher metabolic rates in parietal lobe in comparison to normal probands. In occipital lobes, left Brodmann area 19 was significantly more active in the depersonalization group. The authors concluded that depersonalization disorder is associated with functional abnormalities in sensory cortex (visual, auditory and somato-sensory) as well as areas that are important for body schema (such as parietal cortex).

8. Conversion disorder and neuroimaging

Other dissociative disorders are those which present with impairments of perceptual or motor functions that cannot be explained by medical or neurological conditions (Stone, Vuilleumier, & Friedman, 2010).They are subsumed under dissociative (conversion) disorders in ICD-10, but belong to the category of somatoform disorders in DSM-IV-TR. Although Sigmund Freud described “Die psychogene Sehstörung in psychoanalytischer Auffassung“ [Psychogenic visual disturbance in psychoanalytic view] already in 1910, data on functional imaging in this condition is scant. Apart from the glucose PET study of the Ganser-like presentation with accompanying psychogenic blindness presented above (Snyder et al., 1998) we found one functional magnetic resonance imaging study on visual symptomatologies in dissociative patients. Werring, Weston, Bullmore, Plant, and Ron (2004) observed reduced activation in visual cortical areas during flicker-light stimulation and decreased anterior cingulate activation. The posterior cingulate cortex on the other hand showed increased activity, as did the insula, the temporopolar areas, striatum, and thalamus. The data were interpreted as demonstrating visual blocking via limbic activation.

For somatosensory and motor disturbances, on the other hand, first studies using SPECT started in 1995 in a patient with hemisensory disturbances and revealed some qualitative changes in fronto-parietal regions (Tiihonen, Kuikka, Viinamäki, Lehtonen, & Partanen, 1995). Three years later, another study (Yazici & Kostakoglu, 1998) investigated five patients with more heterogeneous symptomatologies and more heterogeneous reductions in brain perfusion, in particular in left temporo-parietal regions. In 2006, Ghaffar and his co-workers (Ghaffar, Staines, & Feinstein, 2006) assessed three individuals with unexplained sensory loss using fMRI during unilateral and bilateral vibrotactile stimulation. They found that stimulation of the affected limb did not produce activation of the contralateral primary sensory cortex, while this was elicited with bilateral stimulation. The authors emphasized the role of attention mechanisms in the conversion disorder (Bell et al., 2011).

Movement-related conversion disorders (unilateral limb weaknesses) were studied with functional brain imaging in more detail (Cojan, Waber, Carruzzo, & Vuilleumier, 2009; Stone et al., 2007; Vuilleumier et al., 2001; Spence, Crimlisk, Cope, Ron, & Grasby, 2000) . In the SPECT study published in 2001 by Vuilleumier and co-workers (Vuilleumier et al., 2001), the authors used three different conditions: a baseline resting condition, a passive activation condition, and vibrotactile stimulation of the affected and unaffected limbs (for some patients after the motor symptoms had recovered). Vibrotactile compared to baseline condition activated frontal and parietal regions related to somatosensory and motor functions. A further comparison in the recovered patients revealed in the hemisphere contralateral to the motor deficits basal ganglia and thalamus decreases when the deficit was present.

Burgmer et al. published in 2006 a report on patients who due to psychic changes were unable to lift their hands. The authors used fMRI to study their brain activations, when the patients either tried to lift their hands or observed other persons lifting their hands. Main results were that when normal subjects lifted hands or observed others lifting theirs, the hand region of their motor cortex was activated; in the case of the patients this activation failed to occur. The authors interpreted their findings as suggesting that in normal individuals mirror neurons (or the so-called mirror system) "mimic" the action of the other, while in the brains of patients with movement-related dissociative disorders, no such activity occurs.

An unusual case of conversion disorder is that of a woman with spatial neglect due to conversion disorder (Saj et al., 2009), who presented with left spatial neglect as assessed by line- bisection and bell-cancellation tests. Findings from fMRI pointed to selective activation of the posterior or parietal cortex, primarily in the right side when comparing lines with deviated bisection relative to centered bisection (which was similar to those from normal probands performing comparable tests), together with increased activity in the anterior cingulate cortex. The results were interpreted as supporting the impaired access to conscious control in patients with conversion disorder and extending the findings about the role of anterior cingulate cortex in conversion disorder, which may relate to the anterior cingulate's functions in attention and inhibitory processes.

Psychogenic non-epileptic seizures are also possible manifestations of conversion disorder. The differential diagnosis of these conditions might pose a variety of challenges , given that psychogenic non-epileptic seizures might at times occur after traumatic brain injury, neurosurgery or in patients with an already diagnosed epileptic condition. Several methods have been used to distinguish psychogenic non-epileptic seizures from true epileptic seizures. Among them, the performance of interictal SPECT might be a useful tool (Scevola et al., 2009).

9. Imaging the symptom of dissociation

Various dissociative symptoms can accompany a number of psychiatric diagnostic entities (other than dissociative or conversion disorders) and have been targeted by several functional imaging studies (Kraus et al., 2009; Ludaescher et al., 2010). For example dissociative amnesia can occur as a symptom in certain anxiety disorders, such as acute stress disorder and post-traumatic stress disorder (PTSD) or in the DSM-IV-TR described somatization disorder or in borderline personality disorder (Zanarini, Frankenburg, Jager-Hyman, Reich, & Fitzmaurice, 2008).

PTSD conditions which are accompanied by "positive" dissociative symptoms such as flashbacks and intrusions seem to engage different neural networks than PTSD conditions that are accompanied by "negative" dissociative symptoms such as amnesia (Oakley, 1999). Lanius, Williamson et al. (2005) found that in general a network of prefronto-temporo-parietal areas was engaged in all patients, but that the group with "positive" symptoms had – compared to normal subjects – in addition a greater covariation with the right insula and right visual association cortex (compared to the reference in the left ventrolateral thalamus). Between the two groups, that with "negative" symptoms of dissociation showed – compared to the "positive" (flashbacks) group – a more significant covariation in the left inferior frontal gyrus, while vice versa the "positive" symptoms group had more significant covariations with posterior cingulate/precuneus regions, the right middle temporal and the left inferior frontal gyri. In a recent review arguments were made for a mechanism of undermodulation of emotion via failure of prefrontal inhibition of limbic regions (such as amygdala) underlying the re-experiencing/hyperarousal PTSD subtype and one of overmodulation of the emotional limbic reactions in the ("negative") dissociative PTSD subtype (Lanius et al., 2010).

10. Imaging and hypnosis

Hypnotizability traits have been postulated to be associated with a higher tendency for developing dissociative symptoms (Maldonado & Spiegel, 2008). Recently, we have witnessed an increase in studies investigating the relationship between trait hypnotizability and risk for developing various dissociative (conversion) disorders. As Bell et al. (2011) pointed to in a recent comprehensive review article, the results are mixed. Despite this, several studies tried to model various dissociative (conversion) symptoms via hypnotic suggestions. One functional MRI study employed hypnosis to affect memories for scenes of a movie when a posthypnotic cue was given (Mendelsohn, Chalamish, Solomonovich, & Dudai, 2008). The study compared three groups: one group that scored high on hypnotizability, another group that was characterized by low hypnotizability traits and a group that was asked to simulate high hypnotizability. According to the findings of the study, only the group with high hypnotizability traits manifested impaired recall. The latter was associated with diminished functional brain activity particularly in the left extrastriate occipital lobe and left temporal pole and heightened activity in the left rostro-lateral prefrontal cortex. Following the reversal of 'forget´ suggestion and normalization of memory performance, an increase in brain activity was observed in several regions, including areas in the occipital, parietal and dorso-lateral frontal regions. This result was interpreted (Bell et al., 2011) as being in the line with the advanced model of exaggerated inhibition in psychogenic (dissociative) amnesia (Kopelman, 2000; Anderson & Green, 2001). This model proposes that the inability to retrieve personal events in psychogenic (dissociative) amnesia reflects an increase in the activity of inhibitory regions of the prefrontal cortex coupled with a subsequent decrease in the activity of hippocampus, similar to the one that occurs in suppression or motivated forgetting. The other main model of dissociative amnesia (which we already described above) posits that the recollection deficit in dissociative amnesia reflects a stress hormone-triggered and -mediated memory blockade, underpinned by a desynchronization during retrieval between a frontal lobe system, important for autonoetic consciousness, and a temporo-amygdalar system, important for emotional processing and colorization (Markowitsch, 2002).

11. Mindfulness versus dissociation

The concept of mindfulness is often viewed as being situated at the opposite pole of that of dissociation. In a simplified way, Kabat-Zinn refers to mindfulness as moment-to-moment awareness (Kabat-Zinn, 2005). This awareness arises through intentionally attending to one's moment to moment experience in a non-judgmental and accepting way (Shapiro, Oman, Thoresen, Plante, & Flinders, 2008). Mindfulness is considered an inherent human capacity that can however be enhanced through training and practice through meditation techniques. In the recent past, there has been an increased interest in integrating the ancient Buddhist practice of mindfulness meditation (MM) with current psychological and medical practice as means to treat a variety of psychological and physical disorders (Baer, 2003; Grossman et al., 2004), to reduce stress in healthy individuals and to enhance the well being and overall health. Mindfulness based interventions (MBI), which include, but are not limited to mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) have flourished from the fertile ground of mindfulness meditation (Grossman, Niemann, Schmidt, & Walach, 2004). Both MM and MBIs aim to reduce the onset and maintenance of negative emotions such as anger while enhancing happiness and compassion (Chiesa & Malinowski, 2011; Sharot, Riccardi, Raio, & Phelps, 2007).

Numerous studies evaluated mindfulness' effects on well-being. Imaging techniques were employed to unveil the neuronal circuitry underlying the neurobiological mechanism, as well as the structural changes occurring in the brain during mindfulness meditation or any derivates of this technique, however, their review is beyond our scope. We will instead focus on available evidence from neuroimaging on identifying the neural correlates of dispositional mindfulness and the clinical application of MBCT to conditions that might be accompanied by dissociative symptoms such as BPD (borderline personality disorder) and PTSD (post traumatic stress disorder).

MBCT is a 8-week training program rooting from MM and CBT with direct application as additive therapy to prevent relapses in major depression, anxiety disorders and bipolar disorder. Attempts have been made to use this technique in BPD (Sachse, Keville, & Feigenbaum, in press) with the conclusion that further exploring may be worthwhile due to the observed effects of MBCT on mindfulness, experiential avoidance, state anxiety, and somatoform dissociation. However, to our knowledge there are no functional imaging data available to further support these findings.

With respect to the potential impact of MBCT on mechanisms that might perpetuate/exacerbate recollection impairment in dissociative amnesia, such as cognitive avoidance (Fujiwara et al., 2008), one study is worthwhile to be mentioned (Williams, Teasdale, Segal, & Soulsby, 2000). The authors of this study used MBCT in patients who recovered from major depressive disorder - a condition characterized by episodic-autobiographical memory impairments in the form of overgeneralized memory that may persist beyond the recovery of classical depressive symptoms (Williams & Scott, 1988). They showed that in comparison to controls (recovered depressed patients who received no MBCT), patients with recovered major depression who received MBCT experienced a reduction in their overgeneralized autobiographical memories. (People are considered to have overgeneralized autobiographical memories when in response to a verbal cue they retrieve generic summaries of their personal past rather than specific events.) Again no functional imaging paradigm was employed in this study.

Five main meditation practices are identified (Ospina et al., 2007).

- Mantra meditation (Transcendental meditation, relaxation response, clinically standardized meditation);
- Mindfulness meditation (Vipassana, Zen, MBSR);
- Yoga;
- Tai-chi and
- Qi Gong.

In order to attain the "meditative" state two main approaches are employed: focused attention FA (direct and sustained attention on a selected object, detecting distractions and disengagement of attention from distractions with cognitive reappraisal of the distracter) and objective monitoring OM (non reactive cognitive monitoring and awareness of sensory, perceptual and endogenous (Lutz, Slagter, Dunne, & Davidson, 2008).

Evidence on the EEG profile supports differences in the frequency bands between the two approaches as follows: FA is associated with beta 1 and gamma frequency bands while OM (Vipassana, Zen), with theta frequency bands. There is also evidence for a third type of frequency band, alpha1, associated with an automatic self-transcending encountered during Transcendental Meditation (Travis & Shear, 2010).

An fMRI study contrasted FA and OM meditation forms in expert meditators versus novices (Manna et al., 2010) and concluded that experienced meditators control cognitive engagement in conscious processing of sensory-related, thought and emotion contents by massive self regulation in fronto-parietal and insular areas in the left hemisphere in a meditative state when compared with rest. They also concluded based on their findings that the anterior cingulate and dorso-lateral prefrontal cortex seem to play antagonist roles in the executive control of the attention setting during meditation task. This in their opinion reconciled findings of transient hypofrontality in meditation with evidence of activation of executive brain areas during meditation. They proposed that the practice of mediation leads to a functional reorganization of activity of prefrontal cortex and insula. Insula is a structure that has been hypothesized to sustain the so-called "sentient" (feeling) self (Craig, 2009). It has recently received an increased interest in stress related disturbances of self and consciousness (Lanius et al., 2005, 2010), including the ones accompanying the dissociative memory "loss" (Thomas-Anterion et al., 2010; Brand et al., 2009). Hidden in the Sylvian sulcus in the triangle of frontal, parietal, and temporal cortex, the insula is connected to numerous brain regions, including inferior frontal gyrus, septum and amygdala (Markowitsch, Emmans, Irle, Streicher, & Preilowski, 1985, Augustine. 1996). It sends projections to hippocampus and receives efferents from the entorhinal cortex. The most anterior and ventral portion of the insula that is close to the frontal operculum contains the so-called Von Economo neurons (VEN) (Allman, Watson, Tetreault, & Hakeem, 2005). The VEN neurons, which are also present in the anterior cingular cortex (ACC), might play functions in consciousness and emotional awareness (Allman et al., 2005). Insula has also been assigned functions in verbal memory tasks, inner speech, time perception , self projection (Arzy et al., 2009) , drug smoking cravings , eating regulation, taste, pain and temperature perception. In normal subjects increased activations of the insula have been evidenced in tasks involving self versus other conditions (Schilbach et al., 2006) and the right insula was found to be activated during self face recognition (Devue et al., 2007).

As mentioned above the insula has bilateral connections with the amygdala. The amygdala is a structure involved in integrating emotions with cognition and is connected with the prefrontal cortex via uncinate fascicle and other fiber bundles. Interestingly, the uncinate fascicle has a temporal, frontal and insular part and was ascribed functions in memory and emotional processing (Markowitsch, 1995). The ventromedial portion of uncinate fascicle primarily connects the amygdala and uncus with the gyrus rectus and the subcallosal area (Ebeling & von Cramon, 1992). Associating events mindfully to oneself appears to be one of the major functions of amygdaloid neurons in the human brain (Stein, Ives-Deliperi, & Thomas, 2008). Furthermore, traits like the optimism bias were suggested to be underpinned by the strength of the connectivity between the rostral anterior cingulate cortex and amygdala (Sharot, Riccardi, Raio & Phelps, 2007). An fMRI study that investigated the neural correlates of dispositional mindfulness during affect labelling found strong negative associations between areas of prefrontal cortex and right amygdala in subjects with high mindfulness, but not in participants low in mindfulness (Creswell, Way, Eisenberger & Lieberman, 2007).

The pathophysiological changes associated with different mindfulness-based practices and various meditation practices and the biological mechanisms through which mindfulness – based practices may prevent, alleviate or undo various dissociative symptoms remain a topic for future research. There is however preliminary evidence from various sources that these mechanisms might involve biological changes related to modulation of hormonal stresses responses such via alterations of the function of hypothalamic-pituitary-adrenal (HPA) axis (Vera et al., 2009; Infante et al., 1998).

12. Conclusions

Dissociative disorders have been linked to psychological trauma and stress in a variety of cultures. The advent of functional brain imaging techniques and newer sophisticated structural brain imaging methods has considerably improved and will continue to further our understanding of the neurobiological underpinnings of these conditions. The use of these techniques has shown that environmentally-driven alterations of cognition, perception, behavior and self-related processing are accompanied by metabolic and probably even structural brain changes. These findings have called into questioning the strict traditional dichotomy between neurological-organic and psychiatric-mind based illnesses and prompted several researchers and clinicians from both psychiatry and neurology fields to advocate for moving beyond this dichotomy, by abandoning the organic-functional distinction from formal classification systems or everyday medical jargon. As Pietro Pietrini 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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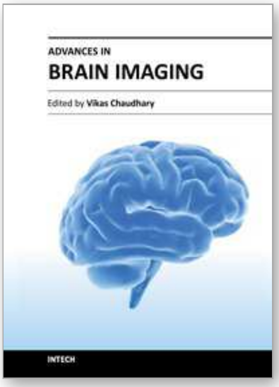

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Remarkable advances in medical diagnostic imaging have been made during the past few decades. The development of new imaging techniques and continuous improvements in the display of digital images have opened new horizons in the study of brain anatomy and pathology. The field of brain imaging has now become a fast-moving, demanding and exciting multidisciplinary activity. I hope that this textbook will be useful to students and clinicians in the field of neuroscience, in understanding the fundamentals of advances in brain imaging.