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# Neurophysiological correlates of dissociative symptoms

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## ABSTRACT

**Objective** Dissociation is a mental process with psychological and somatoform manifestations, which is closely related to hypnotic suggestibility and essentially shows the ability to obtain distance from reality. An increased tendency to dissociate is a frequently reported characteristic of patients with functional neurological symptoms and syndromes (FNSS), which account for a substantial part of all neurological admissions. This review aims to investigate what heart rate variability (HRV), EEG and neuroimaging data (MRI) reveal about the nature of dissociation and related conditions.

**Methods** Studies reporting HRV, EEG and neuroimaging data related to hypnosis, dissociation and FNSS were identified by searching the electronic databases Pubmed and ScienceDirect.

**Results** The majority of the identified studies concerned the physiological characteristics of hypnosis; relatively few investigations on dissociation related FNSS were identified. General findings were increased parasympathetic functioning during hypnosis (as measured by HRV), and lower HRV in patients with FNSS. The large variety of EEG and functional MRI investigations with diverse results challenges definite conclusions, but evidence suggests that subcortical as well as (pre)frontal regions serve emotion regulation in dissociative conditions. Functional connectivity analyses suggest the presence of altered brain networks in patients with FNSS, in which limbic areas have an increased influence on motor preparatory regions.

**Conclusions** HRV, EEG and (functional) MRI are sensitive methods to detect physiological changes related to dissociation and dissociative disorders such as FNSS, and can possibly provide more information about their aetiology. The use of such measures could eventually provide biomarkers for earlier identification of patients at risk and appropriate treatment of dissociative conditions.

## INTRODUCTION

Dissociation is a mental process in which one's consciousness is detached from thoughts, memories, feelings and sense of identity. Dissociation is part of normal functioning, allowing us to be able to complete two tasks at once, but extreme forms of dissociation (eg, shock, fugue) are considered pathological. Dissociation can be regarded as a spectrum, covering distinct but related concepts such as suggestibility and fantasy proneness, but also hypnotic states and dissociative disorders.[1] The dissociation involved in hypnosis is considered mild in nature, temporarily decoupling executive control from other functions such as emotional control, sensory perceptions and motor functions.[2] Pathological dissociation, observed as spontaneous and uncontrollable hypnosis-like episodes, is considered a severe and aberrant form of dissociation, and has been related to emotional stress and traumatic experiences.[3 4] However, the exact emotional function of such dissociative episodes remains unclear.

In neurological practice, dissociation is seen as a common mechanism involved in many functional neurological symptoms and syndromes (FNSS).[5 6] Patients with FNSS are often initially misdiagnosed with a neurological condition, as the psychogenicity of FNSS is not always immediately recognised. The relationship between FNSS and dissociation is presumed because patients with FNSS often show a high level of hypnotisability, and a high prevalence of dissociative symptoms and dissociative disorders.[6] In fact, the symptoms may be considered dissociative episodes with somatoform manifestations.[7] However, the dissociative nature of FNSS remains a matter of debate.[8] As a consequence, the unravelling of the pathological mechanism and the emotional function of the symptoms is an ongoing challenge.

Since the tendency to dissociate is considered an innate characteristic,[9] the question arises as to whether there is a biological basis. Such a biological basis could provide information about the underlying mechanisms and functions of dissociation. Examples of possible biomarkers of dissociation are brain structure (obtained by MRI), brain activation (obtained by EEG and functional MRI) and functional networks (functional connectivity analyses). Additionally, cardiovascular parameters, measured using ECG or photoplethysmography, could provide information about fluctuations in autonomic function before, during and after dissociative episodes, and as such provide information about the role of (emotional) arousal in dissociation processes. The aim of this narrative review, based on a systematic search strategy, is to summarise and discuss the results and future possibilities of these physiological methods in relation to dissociation disorders and the related FNSS.

## METHODS

Relevant studies were identified by searching the electronic databases Cochrane, PubMed and ScienceDirect, performed on 1 August 2012.

Articles included in this review were identified by searching the Medical Subject Heading (MeSH) terms 'hypnosis, dissociation, functional, conversion symptoms' and any combination possible with 'heart rate variability (HRV), EEG, neuroimaging, MRI, voxel based morphometry, functional MRI and diffusion tensor imaging (DTI)'. Titles of articles and abstracts selected from the search were reviewed for relevance, and when regarded as applicable, the full text article was retrieved. Case and small N (<5) reports were not incorporated. Articles obtained via citation tracking were also included.

## RESULTS

### Heart rate variability

The relationship between emotional distress and dissociative episodes has remained unclear. Even in extreme cases such as in FNSS, patients commonly fail to report the exact feelings (eg, stress, anxiety) or the circumstances that provoke symptoms. Often there is even denial of psychogenicity, which is understandable as the symptoms may serve as a means to avoid confrontation with intolerable feelings (with, as a consequence, a dissociative episode). Physiological parameters that change in function on emotional arousal, and that are independent of subjective reports, could elucidate the role of emotional stress in the development of symptoms. Examples are cardiovascular functioning, skin conductance and muscle tension.

In particular, HRV is considered to be a clinically relevant physiological measure for emotional arousal.[10] HRV is the variation in the beat to beat interval between heart beats, also called interbeat interval (IBI). The most widely used HRV analysis methods can be grouped into time domain and frequency domain methods. Time domain methods are based on the analysis of beat to beat intervals, with outcome measures such as RMSSD, the root of the mean squared difference of successive IBIs. Frequency domain methods analyse the frequency domain after Fourier transformation of the time domain, and use the various spectral components of HRV, such as low frequency (LF) and high frequency (HF) components. The most frequently used HRV metrics are IBI, RMSSD, the power and amplitude of LF and HF components, their normalised values (LFnu and HFnu) and the LF/HF ratio.[11] All of these measures vary in relation to changes in autonomic modulations of the heart rhythm. An increased HRV reflects a shift in cardiac balance in favour of the parasympathetic system.[12] This shift reflects the body being in 'rest and digest' mode rather than the state of vigilance associated with the sympathetic nervous system. One important source of individual variability in HRV is negative emotional wellbeing or worry, which suppresses parasympathetic cardiac control, as confirmed by a variety of studies in healthy and depressed subjects.[13–15]

Studies assessing the relationship between HRV and hypnosis, dissociation and FNSS are summarised in online supplementary table S1. The general conclusion is that during hypnosis, HRV increases without a concomitant change in heart rate, suggesting an increase in parasympathetic modulation of cardiac activity.[16–18] The two HRV studies that assessed the tendency to dissociate show that a high tendency to dissociate is significantly related to decreased HRV.[19 20] This finding corresponds with the results of investigations in patient populations with dissociative symptoms: patients with FNSS demonstrate lower HRV compared with healthy controls.[21 22] During rest as well as during recovery from a social stress test, patients with psychogenic non-epileptic seizures (PNES) show significantly lower HRV compared with controls.[21 22] Within subject comparisons demonstrate that in patients with dissociative identity disorder (DID), HRV decreases during confrontation with trauma related memories, with a stronger effect with the participant being in the trauma related identity state.[23]

### EEG

To investigate EEG changes during hypnosis, and to identify electrophysiological markers of dissociation and dissociative disorders, frequency band analysis has been performed. The quantity of EEG based research on physiological indicators of hypnotic responding and hypnotic susceptibility is considerable, and has been summarised repeatedly. For example, in 1977, Dumas reviewed the literature on EEG alpha (8–12 Hz) indices of hypnotic susceptibility and concluded that there is no simple correlation in the overall population.[24] In 1991, Perlini and Spados came to the same conclusion in their literature review.[25] However, in 1997, Ray concluded that the most solid relationship between EEG and hypnotisability exists in the theta frequency range (4–8 Hz).[26] Highly susceptible individuals show relatively more theta activity in the EEG not only at baseline but also during hypnotic induction. This suggests that EEG theta activity is a characteristic of these individuals rather than an experimentally induced effect. Ray also reports anterior–posterior differences in the theta frequency band to be related to hypnotic susceptibility, with relatively more theta activity in the more frontal areas of the cortex. These results indicate altered frontal directed strategic control during exploratory choices in reinforcement learning, because neurophysiological processes linking uncertainty and the exploration/exploitation trade off are reflected in oscillations of the frontal theta rhythm.[27] The most recent literature review on EEG correlates of hypnosis and hypnotic susceptibility was written by De Pascalis in 1999.[28] He concluded, based mainly on findings from his own laboratory, that differences in occurrence of 40 Hz (about 40 Hz band) activity appear to discriminate high and low hypnotisables both in and outside hypnosis, which was seen as evidence of an alteration in attention.

More recent findings, not previously reviewed in the literature, are summarised in online supplementary table S2. Measures of synchronisation or synchronicity in particular, which represent cooperation within and between cortical regions, have been reported. For example, during hypnosis, decreases in gamma band (>30 Hz) coherence have been reported, which reflect a decrease in frontal connectivity.[29] Similarly, frontoparietal synchrony has been reported to decrease during hypnosis,[30 31] and lower synchronisation of frontal lobe channels during hypnosis has been observed in highly hypnotisable subjects compared with people with medium and low hypnotisability.[31 32] In a cohort of psychiatric patients, more random and less correlated fractal dynamics of EEG rhythm have been observed during hypnosis, which also reflect decreased synchronicity.[33] Decreased global functional coherence has been specifically related to the occurrence of imagery and transcendent experiences during hypnosis.[34]

EEG data can also be analysed as sequences of maps of the spatial distributions of the electric potential on the scalp, which are called 'microstates'. The classes of microstates may correspond to basic building blocks of human information processing: microstates of class A are associated with abstract thoughts, class B with visualising thoughts, class C with increased and class D with decreased attention.[35] Decreased occurrence and duration of microstates of classes B and D have been observed during deep hypnosis compared with light hypnosis, while the microstates of classes A and C showed the opposite behaviour. These results led to the conclusion that light and deep hypnosis require different types of electrophysiological information processing: the decreased duration and occurrence of class B and D microstates, also observed in schizophrenia, may reflect minimised control/executive functions during deep hypnosis. The changes in class A and C microstates during light hypnosis resemble electrophysiological changes during meditation, which suggests that these microstate changes may be related to mental relaxation and attentional processes.[36]

Only one study showed correlations between EEG analyses and FNSS. The investigation was conducted in patients with PNES and in healthy controls, and showed decreased prefrontal and parietal synchronicity in the interictal EEG of patients with PNES. Correlation analysis suggests that these synchronicity measures are related to the frequency of the symptoms.[37]

## Neuroimaging

Neuroimaging can be used to investigate cerebral structure and functioning in various ways. The most accepted technique to detect differences in the brain's soft tissue anatomy is MRI. To analyse MR images at a more detailed structural level, for example to investigate cortical thickness and white matter integrity, techniques such as voxel based morphometry and DTI are available. Patterns of brain activation can be visualised using positron emission tomography (PET)/single photon emission computed tomography and functional MRI. Furthermore, characteristics of networks in the brain—that is, brain regions that share structural connections or that functionally interact—can be analysed using DTI tractography and functional MRI connectivity techniques, respectively.

Cortical thickness and anatomical brain abnormalities have been related to hypnotisability and dissociation (see online supplementary table S3a). Corpus callosum size has been positively related to hypnotisability,[38] and the tendency to dissociate has been shown to correlate negatively with frontal white matter integrity, as measured by DTI.[39] More investigations have focused on cerebral anatomy and functional neurological symptoms. Structural brain abnormalities such as postoperative defects, arachnoid cysts and atrophy were more common in patients with PNES than in the general population.[40] In fact, 25% of a sample of patients with PNES (with and without comorbid epilepsy) have been reported to display structural abnormalities on MRI.[41] More recently, cortical thickness analyses revealed abnormal cortical atrophy of the motor and premotor regions in the right hemisphere and in the cerebellum of patients with PNES. Premotor cortex atrophy appeared to be significantly related to depression scores.[42] In another sample of patients with motor conversion disorder, decreased volumes of the caudate nuclei, lentiform nuclei and thalami have been observed.[43]

Functional neuroimaging has been used to examine brain activation during hypnosis (see online supplementary table S3b). The brain regions mostly activated during hypnotic PET imaging are the anterior cingulate cortex (ACC) and the thalamus.[44–46] Functional MRI during hypnosis also identified the ACC as a region with increased activation,[23 47 48] while activation of the somatosensory cortex decreased.[49 50] Conversely, decreased activation of the ACC during hypnosis has also been reported.[51 52]

Two studies overlapped the fields of hypnosis and dissociative symptoms, using hypnosis to investigate differences in brain activation between subjectively experienced paralysis and intentionally simulated paralysis. Relative increases in PET signal in the prefrontal cortex, thalamus and putamen during subjectively experienced paralysis, and relatively increased activation of prefrontal and posterior cortical regions during intentionally simulated paralysis were identified.[53] Functional MRI revealed hypoactivation of the sensorimotor cortex and cerebellum, and increased activation of the ACC, frontal gyrus and insula during movement imitation in hypnotic paralysis.[54]

In a sample of patients with borderline personality disorder, acute dissociation was not related to differences in regional (orbitofrontal) brain activation.[55] However, in patients with primarily dissociative symptoms, significant differences in brain activation have been reported. For example, in patients with DID, within subject analyses of PET imaging during neutral and trauma related identity states demonstrated widespread changes in subcortical regions, including the insula, during the trauma related identity state.[23] Compared with healthy controls, another group of patients with DID demonstrated decreases in orbitofrontal neuronal activation, and increased activation in median and superior frontal regions and occipital regions.[56] Similarly, in patients with dissociative amnesia, PET imaging has demonstrated decreased neuronal activity in the right inferolateral prefrontal cortex.[57]

Functional motor symptoms have been associated with lower activity in the temporoparietal junction,[58] supplementary motor area[59] and supramarginal gyrus,[60] and higher activity in the right amygdala, left anterior insula and bilateral posterior cingulate cortices.[59]

In patients with the dissociative subtype of post-traumatic stress disorder (PTSD), functional MRI activation patterns suggest that prefrontal and limbic structures underlie the dissociative responses.[61 62] Furthermore, comparisons between conscious and non-conscious processing of fear stimuli in patients with dissociative PTSD demonstrate enhanced prefrontal activity to conscious fear and enhanced activity in limbic regions to non-conscious fear processing.[63] These findings support the theory that dissociation is a regulatory strategy invoked to cope with extreme emotional arousal in PTSD.

In contrast, a possibly negative influence of dissociation in trauma survivors has also been reported. A recent study demonstrated a persisting effect of peritraumatic dissociation on brain functioning: 2–4 months after acute trauma, individuals who experienced peritraumatic dissociation showed greater activation of the occipital lobe than trauma survivors without dissociation, and a higher incidence of PTSD.[64]

Functional connectivity analyses have been employed to investigate the functioning of brain networks during hypnosis. Increased functional connectivity of the prefrontal cortex and precuneus with motor and somatosensory areas has been reported.[65–67] Reductions in functional connectivity have been found within the lateral frontoparietal cortex and parahippocampal region.[68]

In patients with borderline personality disorder, acute dissociation has been related to increased functional connectivity in the insula and decreased connectivity in the cuneus.[69]

In addition, functional connectivity analyses have identified alterations in functional brain networks in patients with FNSS. One investigation in patients with functional motor symptoms revealed that these patients had a higher functional connectivity between the amygdala and the supplementary motor area during processing of positive and negative emotional stimuli.[70] Another investigation identified lower functional connectivity between the supplementary motor and dorsolateral prefrontal cortices during internally generated action.[59] In patients with PNES, increased resting state connectivity between the insula and precentral regions has been described.[71]

## CONCLUSIONS

This review identified several possible neurobiological substrates of dissociation, the related concept of hypnosis and some of the FNSS associated with it. Although the available empirical evidence is modest, some tentative conclusions can be drawn.

Starting with HRV, it appears that hypnosis significantly activates parasympathetic functioning, reflecting increased relaxation during hypnotic conditions. In contrast, those with a higher tendency to dissociate and with FNSS demonstrated significantly lower HRV compared with controls. This apparent discrepancy can be explained by the fact that dissociation reactions in FNSS are a sign of negative overall emotional well being, accompanied by decreased HRV. At times this underlying hypervigilance may need temporary relieve, resulting in increased HRV, a phenomenon previously described as bottom up hijacking. In such situations, adaptive top down processing is lost, probably resulting in dissociative episodes.[72] The positive effects of hypnosis on HRV may provide possibilities for therapeutic intervention in dissociative conditions, for example in the form of mindfulness and meditation (auto-hypnosis) techniques, which also promote a more adaptive and objective manner of responding to emotional triggers, as neuroimaging suggests.[73]

Measures of EEG synchronicity have been used to evaluate brain network states believed to represent communication within the brain. EEG during hypnosis has provided evidence of decreased functional connectivity, which has been specifically related to the occurrence of imagery and transcendent experiences. Microstate analyses indicate differences between light and deep hypnosis, which may complicate research even further. The only study conducted in patients with FNSS suggests that decreases in prefrontal and parietal synchronicity, indicative of altered brain connectivity, are related to the frequency of the symptoms.

Structural neuroimaging demonstrates that functional neurological symptoms may be associated with decreased frontal white matter density and atrophy within the basal ganglia and motor cortex. Functional imaging during hypnosis and after autogenic (self-hypnosis) training indicates an increase in activity of the ACC, thalamus and insula, and a decrease in activity of the somatosensory cortex. Hypnotic paralysis activated similar brain areas, while simulated paralysis showed different activation patterns, suggesting different neural mechanisms to be involved in the processes of dissociation and malingering.

Functional imaging in patients with DID suggests that frontal cortex activation is significantly decreased compared with healthy controls, and subcortical regions are involved in trauma processing during the trauma related identity state. Decreased neuronal activity in the prefrontal cortex was also found in patients with dissociative amnesia. These results are comparable with findings in patients with the dissociative subtype of PTSD. Functional MRI analyses suggest that enhanced prefrontal activity is related to conscious fear processing, and enhanced activity in limbic networks is related to nonconscious fear processing. In brief, these findings suggest that subcortical as well as (pre)frontal regions have a function in a dissociative mechanism that serves emotion regulation in these conditions.

The latter assumption corresponds with the model proposed by Thayer *et al*,[74] who describe a possible integration of HRV and neuroimaging findings in emotion regulation. They suggest a positive relationship between activation of prefrontal and limbic areas and HRV, and deactivation of the prefrontal cortex during emotional stress to let automatic and prepotent processes regulate behaviour. Although not discussed by the authors, dissociation may be one of such prepotent behaviours, explaining the associations with decreases in prefrontal activation and HRV.

In patients with functional neurological symptoms, functional imaging has revealed lower activity in the temporoparietal junction, supplementary motor area and supramarginal gyrus, and higher activity in the limbic and cingulate regions. These results indicate a possible lack of proprioceptive feedback or disturbed higher order motor control, which would lead to the perception that the functional motor symptoms are not self-generated.

Functional connectivity analyses have revealed altered functional networks in dissociation and FNSS. The available evidence suggests that acute dissociation influences functional connectivity in the insula and cuneus. Functional neurological symptoms have been associated with an increased functional connectivity between the amygdala and supplementary motor areas, or between the insula and premotor cortex. Decreased functional connectivity between the supplementary motor and dorsolateral prefrontal cortices during voluntary action selection has also been reported. In order to provide a meaningful clarification of the aetiology of functional neurological symptoms, the data must be interpreted relative to a model of the condition. We propose that the increased functional connectivity between limbic and frontal motor areas suggests a 'hyperlink' that may underlie the pathophysiology of functional neurological symptoms.[61] Decreased functional connectivity between the supplementary motor and prefrontal areas may provide evidence for hijacking of voluntary action selection.[59] Dissociation might be one of the mechanisms through which an emotional state can influence motor control, resulting in functional neurological symptoms (figure 1).

### Future directions

The search for possible biological substrates of dissociative conditions has provided somewhat more insight into their nature. Future studies are required to address some unanswered

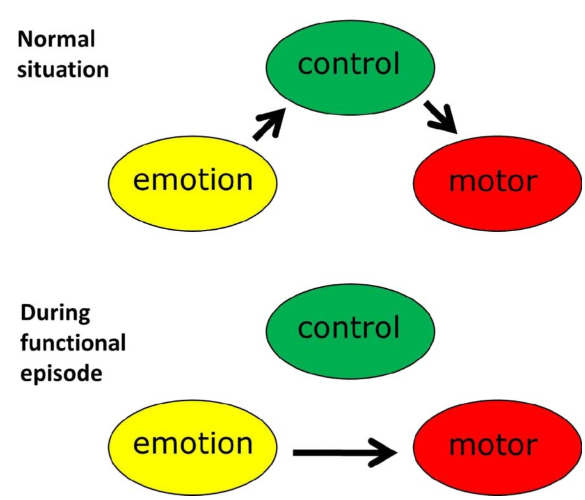


**Figure 1** Schematic overview of a plausible pathological functional neurological mechanism involved in cognitive–emotional executive control. It appears that normally, motor functions can be controlled without strong influence of emotions, whereas in patients with functional neurological symptoms and syndromes, emotions can bypass executive control and cause involuntary movement (adapted from Van der Kruijs *et al* 2012[71]).

questions. Longitudinal (ambulatory) measurements of HRV could assess the relationship between dissociative episodes and arousal, providing more insight into the process of emotional failure underlying the symptoms. For example, dissociative episodes and functional neurological symptoms could serve as an escape mechanism or a relaxation technique after a build up of emotions. With longitudinal measurements, preferably in the patient's own environment, the fluctuations in HRV could be assessed in more detail.

EEG and functional MRI should be used to investigate cerebral networks in larger groups of highly dissociative persons or patients with functional neurological symptoms. More sophisticated methodology could help to interpret the findings. For example, Granger causality tests could provide more clarity about the direction of functional connectivity analysis, for example identify whether the increased connectivity between the amygdala and motor cortex implies increased influence of the amygdala on motor functioning or whether the effect is in the opposite direction.[75] The integrity of the identified networks could also be examined in more detail using graph theoretical analyses.[76] For such analyses, functional connectivity data are converted into schematic graphs, in which measures of path length and clustering can be identified that indicate how well integrated a graph is and how efficient information can be exchanged. These techniques could also be addressed to evaluate patients from diagnosis until after remission. Until such longitudinal study designs are used, the nature of altered networks as a cause or a consequence of the condition cannot be distinguished. Identification of neurophysiological factors contributing to the underlying mechanism of dissociation in functional neurological symptoms might eventually lead to earlier identification and therapeutic intervention in the future.

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