When neurology and psychiatry moved apart from each other around the turn of the 20th century, casualties included the many patients with unexplained neurological disorders. Many labels have been applied to these patients. Some are descriptive (functional disorders, medically unexplained symptoms), while others refer to a presumed aetiology (psychogenic, hysteria, non-organic) or putative mechanism (dissociative or conversion disorder). Whatever is the label, for some physicians these patients are among the most interesting and challenging in the clinic. For others they are frustrating, using much time and resources for an often disappointing outcome.

Whether you are an enthusiast or nihilist, it is clear that neither neurology nor psychiatry alone have succeeded in sufficiently advancing our neurobiological understanding or management of these disorders. The slow progress is in stark contrast to the scale of the problem. Medically unexplained neurological symptoms account for ~30% of referred neurology out-patients (Carson et al., 2000; Stone et al., 2009). Conversion disorder alone, explicitly associated with psychological stressors at the outset, accounts for ~5% of referrals and is a stable, accurate diagnosis (Perkin, 1989; Stone et al., 2005, 2009).

Psychogenic movement disorders are common in neurological practice, including tremor, dystonia, gait change and paralysis. Diagnostic criteria emphasize clinical observations such as inconsistency, distractibility and false neurological signs (Fahn and Williams, 1988). These can be both sensitive and specific, at least in the context of a movement disorder clinic (Shill and Gerber, 2006). Physiological criteria have also been developed, such as coherence of tremor oscillations distinguishing psychogenic from organic syndromes (McAuley and Rothwell, 2004). The emphasis in this 'neurological' approach is on the physical examination, supplemented by physiological tests. The psychological aspects of the disease take second place, e.g. requiring ‘obvious’ but not specified psychiatric or emotional disturbance (Fahn and Williams, 1988; Shill and Gerber, 2006).

In contrast, the ‘psychiatric’ approach emphasizes features of the clinical interview, including psychological factors at outset and inferences of intent. This is not ideal as a diagnostic ‘gold standard’ for developing a biological science of conversion disorder but the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) at least provides strict diagnostic criteria. The diagnosis requires the temporal association of psychological factors with the neurological symptoms (Criterion B: note that in the current revision of DSM, the aetiological relevance of the psychological factors has been downgraded from causal to association only). A further condition (Criterion C) is the lack of wilful simulation of symptoms (otherwise indicative of malingering, factitious disorders or ‘Munchausen syndrome’) but this is difficult to substantiate.

The neurological approach to psychogenic movement disorders and the psychiatric approach to conversion movement disorder are therefore both problematic. Many patients move between neurological and psychiatric services, but a unified formulation may not emerge, contributing to an unsatisfactory outcome. Importantly, we lack mechanisms to explain the neurological manifestation of the conversion disorder, even when likely psychological aetiologic factors are established. An objective, explanatory framework for conversion disorder is clearly required, one that brings together both psychological and physiological phenomena.

Against this troubled background, in the current issue, Voon et al. (p 1526) use functional magnetic resonance imaging to study conversion movement disorders. The combination of psychiatrists and neurologists among the research team is important, and not just for the credibility of this particular study. It also signifies a trend towards a common understanding of conversion disorder, which is important for developing effective neuropsychiatric management strategies.

Voon et al. are not the first to use neuroimaging methods to study conversion disorder or psychogenic movement disorders [see Nowak and Fink (2009) for a review of ‘psychogenic paralysis’]. However, previous studies often used motor tasks that are close to the functional deficit. For example, in studies of conversion/psychogenic paralysis, participants have been asked to try to move the affected limb, imagine moving the paralysed limb or feign immobility of the ‘good’ limb (Marshall et al., 1997; Halligan et al., 2000; Spence et al., 2000; Ward et al., 2003; de Lange et al., 2007). These studies indicate abnormalities outside the core motor network, including the prefrontal cortex and anterior cingulate cortex. The results support the hypothesis of abnormal...
inhibition of motor systems by limbic regions (Marshall et al., 1997; Halligan et al., 2000; Spence et al., 2000; Ward et al., 2003) or impairments of motor conceptualization (Burgmer et al., 2006; de Lange et al., 2007). However, imaging abnormalities identified from tasks that are based directly on the motor deficits can be confounded by differences in motor performance and sensory feedback (the latter studied directly by Vuilleumier et al., 2001). In addition, the interactions between limbic and motor areas are inferred, but have not been shown directly in the previous studies.

A different strategy has been taken by Voon et al. They study patients using a task that they can perform normally, and one that is at first sight unrelated to the motor deficit: a gender discrimination task with face pictures. By manipulating the emotional expression of the faces, irrelevant to the task at hand, they are able to study a robust neurocognitive system for emotion processing and arousal, including the amygdala. This choice of task is very important, given the emotional events that may contribute to the initiation or maintenance of conversion disorder.

A second interesting aspect of this study is the inclusion of a diverse patient population with tremor, gait disorder, dystonia or mixed syndromes. This contrasts with smaller series (median n = 4) of closely matched patients in previous neuroimaging studies (Marshall et al., 1997; Halligan et al., 2000; Spence et al., 2000; Ward et al., 2003; de Lange et al., 2007). Whereas clinical heterogeneity can reduce sensitivity to the neural correlates of individual phenotypes, it also means that results reflect the commonalities, not differences, of conversion movement disorders. It is all the more interesting, therefore, that common abnormalities are seen in the amygdala and its interaction with the supplementary motor area. This provides direct support for a model of conversion disorder based on abnormal limbic–motor interactions.

Is it sufficient to identify neural correlates of chronic conversion movement disorder? Several issues arise here. First, one must acknowledge that, in isolation, physiological correlations do not provide the cause or mechanisms of disease. However, they do support a change in the direction of research, striving for a neurobiological model. This should not discard the importance of psychological or psychodynamic factors, but they must lie within an evidence-based functional and causal (mechanistic) neuroanatomical model. Second, the search for a neural signature of conversion disorder implicitly challenges the historical ‘non-organic’ model. This problem is not unique to conversion disorder, but applies to other major psychiatric syndromes including depression or schizophrenia.

The observed neural correlates of conversion disorder might also be due to late epiphenomena or comorbidities in chronically disabled patients, e.g. depression. In the study by Voon et al., the patients do not meet diagnostic criteria for major affective or psychotic disorders or substance misuse. However, they do have significantly higher rates of depression and anxiety symptoms than controls. In separate studies, depression, remitted depression or elevated depressive symptoms without depression have been shown to influence the activity of the amygdala (Drevets, 2000) and its response to salient stimuli (Taylor Tavares et al., 2008; Beesdo et al., 2009). Voon et al. argue cogently that their findings are independent of depressive or anxiety symptoms. However, they rely partly on a lack of significant correlation between depression scores and amygdala activity (possible risk of type II error) and partly on interpretation of left versus right differences (possible risk of false lateralization arising in thresholded images). Nonetheless, the depression scores in their patients may have been elevated by somatic symptoms, a common feature of conversion disorder, rather than mood disturbance per se.

A third important aspect of the study by Voon et al. is their analysis of the connectivity of the amygdala. It has previously been proposed that conversion disorder arises from abnormal interactions between limbic and motor regions. To test hypotheses of interacting neural systems calls for formal analyses of network connectivity, but this has been lacking in previous studies. Voon et al. use two methods to study connectivity. The first is physiologically interacting neural systems (Friston et al., 1997), revealing that patients viewing salient stimuli have abnormal connectivity between the amygdala and the supplementary motor area. The second method, Granger Causality Modelling (Roebroeck et al., 2009), is used to identify the directionality of this effect: amygdala activity is predictive of future changes in the supplementary motor area, but not vice versa. Future studies will no doubt refine task designs and analysis options to include more realistic biophysical models with anatomically defined networks (Friston, 2009). As a first step, however, the concordance between connectivity methods and their immediate relevance to the predicted limbic–motor interactions is impressive.

There remain many unanswered questions. For example, firstly, why do even common and mild mood disorders or stressors lead to bizarre and disabling conversion disorders/psychogenic movement disorders? Secondary gain, or exposure to neurological illness in personal or professional life, may be relevant (Shill and Gerber, 2006), but they lack objective measures and are prone to recollection bias. Secondly, what determines the nature of the neurological deficit—tremor, paralysis, blindness, sensory loss? Here, at least the approach taken by Voon et al. provides clear testable hypotheses regarding interactions between amygdala and visual or sensory cortex in other syndromes. Thirdly, why do patients experience a sense of loss of control over their movements? This speaks to the broader neuroscience of volition (Haggard, 2008) and disturbed sense of ‘agency’ in neurological disorders (Moore et al., 2009).

Answers to these questions will require further long-term integration of psychiatry and neurology during training, in the clinic and in the laboratory. With its high prevalence and disability, conversion disorder clearly requires higher priority for research, into both basic mechanisms and effective therapies. In the meantime, be inspired by the work of Voon et al., whose results are a significant step towards understanding the neurobiological basis of conversion disorder and developing better therapies.

James B. Rowe

Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
E-mail: james.rowe@mrc-cbu.cam.ac.uk
doi:10.1093/brain/awq096
The main features of Alzheimer’s disease are extracellular accumulation of amyloid β-protein (Aβ) in the form of plaques and in blood vessel walls as cerebral amyloid angiopathy; intraneuronal accumulation of tau protein forming tangles in neuronal cell bodies as well as in neuronal processes situated close to plaques (dystrophic neurites) and elsewhere (neuropil threads); activation of microglia and astrocytes; and neuronal and synaptic loss. However, histological assessment of the disease has several limitations including, almost by definition, observations made at only one time point in the disease, usually the end-stage of a neurodegenerative process that has been developing over many years. This means that using post-mortem neuropathology, we have little or no notion of the dynamics of the pathological processes involved, how they are interrelated in terms of cause and effect, and which feature, if any, best correlates with, or causes, the cognitive dysfunction.

The principal hypothesis for the pathogenesis of Alzheimer’s disease for two decades or more has been built around amyloid, either in the form of extracellular amyloid plaques or in soluble or oligomeric forms, has the key role in initiation of the disease. A powerful way to test the Aβ hypothesis is to modify this aspect of the pathophysiology and observe any effects on other aspects of the pathology and on brain function. In this issue of Brain, Serrano-Pozo and colleagues (page 1312) have studied the effects of Aβ immunization on neuronal and tau pathology in Alzheimer’s disease. Active immunization with one of the Aβ peptides, immunization with the Aβ protein itself, or administration of antibodies against Aβ, reduces the amount of Aβ in the brain, and delays or prevents the development of the disease. However, the results are not consistent across studies, and the effects on other pathological processes are not well understood. It is possible that the effects of Aβ immunization are due to another mechanism, such as the clearance of other pathological proteins or the modulation of inflammatory responses.

References


