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Chapter 6

Neurophysiologic studies of functional neurologic disorders

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Abstract

Functional neurologic disorders are largely genuine and represent conversion disorders, where the dysfunction is unconscious, but there are some that are factitious, where the abnormality is feigned and conscious. Malingering, which can have the same manifestations, is similarly feigned, but not considered a genuine disease. There are no good methods for differentiating these three entities at the present time. Physiologic studies of functional weakness and sensory loss reveal normal functioning of primary motor and sensory cortex, but abnormalities of premotor cortex and association cortices. This suggests a top-down influence creating the dysfunction. Studies of functional tremor and myoclonus show that these disorders utilize normal voluntary motor structures to produce the involuntary movements, again suggesting a higher-level abnormality. Agency is abnormal and studies shows that dysfunction of the temporoparietal junction may be a correlate. The limbic system is overactive and might initiate involuntary movements, but the mechanism for this is not known. The limbic system would then be the source of top-down dysfunction. It can be speculated that the involuntary movements are involuntary due to lack of proper feedforward signaling.

INTRODUCTION

Almost by definition, functional neurologic disorders (FNDs) have no identifiable, responsible pathology. Yet, something is wrong. As we often say to patients (and which may be at least partly true), "the hardware is all right, it's the software that is the problem." The prevailing etiologic theories are psychosocial and still strongly dominated by the Freudian concept of conversion. A psychologic symptom is converted into a somatic symptom as a way of dealing with the distress of the symptom. With the conversion, the distress is ameliorated, and in fact by this logic, if the conversion is successful, the psychologic symptom is gone. Even if this is in some sense what happens, there still needs to be a physiologic mechanism responsible. The software is the way the brain functions, and this is amenable to study. Physiologic studies are necessary to understand what is happening, and they are beginning to illuminate the pathophysiology. These studies also define methods to help with diagnosis of FNDs, and "laboratory-supported" criteria can make a diagnosis more secure (Lang and Voon, 2011; Schwingenschuh et al., 2011b). Functional neuroimaging is a method of neurophysiology, but since this topic will be the focus of the next chapter, this chapter will only touch on functional neuroimaging results briefly.

This chapter will focus on conversion, a type of somatic symptom disorder, which has a fundamental feature of being the product of an unconscious process. Two other entities may have a similar clinical presentation: factitious disorder and malingering. The critical feature of these two entities separating them from conversion is that the symptoms are feigned; they are voluntarily produced. Factitious disorder arises to satisfy a psychologic need for medical care and is a psychiatric disorder also categorized under somatic symptom disorder. Malingering is the feigning of symptoms for nonhealthcare reasons and without any psychiatric disorder. In both

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factitious and malingering disorders, although the symptoms may look the same as with conversion disorders, the patients are lying. Unfortunately, doctors (and everyone else) are not good at determining whether someone is lying (Levine and Bond, 2014).

Secret surveillance has been used to document these disorders, but generally physicians do not hire detectives. The lie detector test depends on autonomic responses, but has many false-positive and negative results (Grubin, 2010). Eye blink frequency declines with deception, but it also has false positives and negatives (Perelman, 2014). Electroencephalogram (EEG) methods, such as event-related potentials (Proverbio et al., 2013; Rosenfeld et al., 2013; Pfister et al., 2014), and functional magnetic resonance imaging (fMRI) methods (Rusconi and Mitchener-Nissen, 2013; Farah et al., 2014) have also been proposed to evaluate truth or lying, but these too are not definitive. As to the physiology, presumably in factitious and malingering disorders the findings would be the same as in normal persons, although there may be excessive autonomic activity. In conversion disorders, the abnormality is unconscious and the physiology should differ in some ways from normal processing. In conversion blindness, the patient does not see; in conversion movement disorders, the movement is involuntary. In this chapter, there are some reports of physiologic changes in conversion. In order to understand FNDs completely, it is really necessary to understand the physiology of consciousness. If it would be possible to read the content of consciousness, we could more easily differentiate conversion from factitious disorder and malingering.

We certainly do not understand consciousness at this time, but some generalities can be stated. The brain is likely doing many things at all times. Information of many types is being passed around brain networks. At any one moment, only one (or very few) of these processes is manifest in consciousness. It is possible that conscious awareness is associated with a greater prominence of activity within the specific network for that process (Baars et al., 2013; Barttfeld et al., 2015). Increased activity and higher probability of getting into consciousness may result from bottom-up or top-down mechanisms (Corradi-Dell'Acqua et al., 2015). Consider why a sensory stimulus might get into consciousness. Bottom-up would be a strong sensory stimulus, such as an acute pain. That will come into consciousness almost no matter what else is happening. Top-down likely implies a cortical process which can regulate which networks have prominence. It is as if there is a conscious decision to pay attention to sensory stimuli of a certain type, and then even a weak stimulus would be appreciated. In relation to the issues discussed here, top-down mechanisms could also prevent a process from coming into consciousness. It is likely, for example, that this is the reason that soldiers in the heat of battle often do not feel their injuries.

FUNCTIONAL WEAKNESS AND PARALYSIS

In the face of functional weakness, routine nerve conduction studies are normal. In the electromyogram (EMG) examination, there is no spontaneous activity and motor units are normal. The interference pattern, however, is reduced. There is no clear difference of a reduced interference pattern from decreased effort and from a central nervous system lesion. In both circumstances there is reduced central nervous system drive.

A method that can separate a central nervous system lesion and reduced effort is transcranial magnetic stimulation (TMS) of the motor cortex. TMS will produce a normal motor evoked potential (MEP) with normal latency in the setting of functional weakness, and routine studies of motor cortex excitability are normal (Liepert et al., 2008). Such studies are abnormal with lesions anywhere along the corticospinal tract from motor cortex to spinal cord (Hallett, 2007). With severe lesions, the MEP will be absent. With compressive lesions, such as cervical spondylosis, or demyelinating disorders, such as multiple sclerosis, the central motor conduction time may be prolonged. Not only can a normal MEP be diagnostic, it can also be therapeutic. Patients have been described who improve after normal motor responses are produced by stimulation (Chastan and Parain, 2010; Pollak et al., 2014).

From the early days of TMS studies, it has been appreciated that motor imagery of moving a body part will increase the MEP amplitude of muscles acting on that part. In patients with functional paresis, opposite to normal, motor imagery suppresses the MEP amplitude (Fig. 6.1) (Liepert et al., 2009, 2011). Normal subjects feigning weakness also show reduced MEP amplitude (Liepert et al., 2014). On the other hand, movement observation, which also increases MEP amplitude in normal subjects, similarly increases the MEP in functional patients (Liepert et al., 2011). Motor imagery of simple movements in normal subjects in fMRI produces activations in most of the same parts of the motor system as does actual movement, except for the motor cortex (Hanakawa et al., 2008). There have not been similar studies with fMRI in patients. However, there have been functional studies in patients attempting to make movements, which have not occurred. In these few studies, dysfunctional activation is seen in the frontal lobes (Nowak and Fink, 2009), and the frontal areas are particularly strongly connected to the "paretic" motor cortex (Cojan et al., 2009).

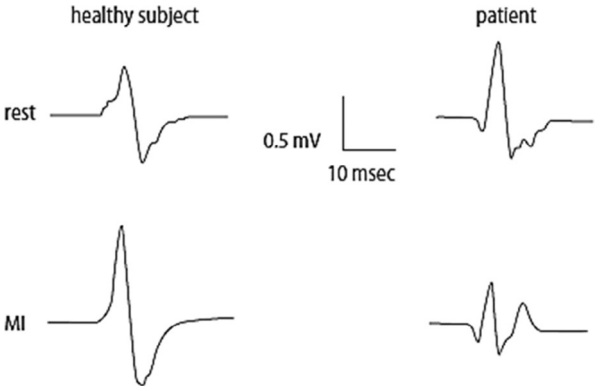

Fig. 6.1. Examples of motor evoked potentials during the resting condition and while performing motor imagery (MI). Electromyogram recording is from the right first dorsal interosseous muscle, and the subjects are asked to imagine a tonic adduction of the right index finger. (Reproduced from Liepert et al., 2009, with permission.)

The physiology of motor preparation in patients with conversion paresis has been studied with the contingent negative variation (CNV), a widespread cortical negativity measured with EEG in between a warning stimulus (S1) and the go stimulus (S2). Patients with unilateral conversion weakness were compared to normal subjects performing normally and normal subjects feigning weakness (Blakemore et al., 2015). A low-amplitude CNV was found only for the symptomatic hand of the conversion patients. In this study only partial information for the required movement was given with S1. In an earlier study by the same group (Blakemore et al., 2013), S1 conveyed full information about the upcoming movement and the emphasis of the study was on the response to S1 and less on the movement preparation. The authors interpreted this study as showing a larger than normal P3 (or P300), and that this positivity drove the EEG down so that the subsequent CNV was low for that reason, but the CNV could be interpreted similarly to their later experiment. In regard to the large P3, one possible interpretation offered by the authors was that it might have been due to increased emotional response to an instructed movement of the affected limb. It is certainly of interest that the findings in these two studies were restricted to the affected limb of conversion patients and were not seen in feigned weakness. The low-amplitude CNV could well be indicative of suppressed motor preparation.

Interpretation

The motor system from motor cortex to muscle is fully normal. With motor imagery of movement, the motor cortex is depressed rather than facilitated. There also appears to be reduced motor preparation. With "voluntary attempts" to move, there is activation of frontal areas that have been associated with "voluntary inhibition" of movement. Voluntary inhibition can be studied in a number of different tasks. One such task is the "stop signal task," where subjects get a second stimulus to inhibit a movement shortly after a first stimulus to make the movement. In one study, the right inferior frontal gyrus was particularly activated in stop trials (Sebastian et al., 2016). In another study, the inferior frontal cortex bilaterally was a critical node for other cortical areas and the subthalamic nucleus (Rae et al., 2015). These results would seem consistent with a top-down inhibition of the motor system causing the weakness or paralysis. As noted by Cojan and colleagues (2009), the areas of frontal cortex activated are related to emotional regulation. An additional conclusion appears to be that abnormalities are brought out with attention to the weak body part.

FUNCTIONAL SENSORY LOSS

Somatic sensation

Somatosensory evoked potentials (SEPs) are good probes for the large-fiber, dorsal-column, primary sensory cortex pathway. The presence of good potentials documents that this pathway is intact and is not compatible with total anesthesia. Such studies with normal potentials have been reported in the literature (Halliday, 1968; Kaplan et al., 1985), and although there are not many contemporary studies, this is the expected result. However, there was a case report of a patient with a functional sensory loss whose SEP was abnormally low in the anesthetic limb, but then became normal when the patient was put under light general anesthesia (Hernandez Peon et al., 1963). The authors postulated that a top-down control of sensory input might be responsible for the findings. In another case report of functional sensory loss, the SEP was absent with weak stimuli but normal with stronger stimuli, and again the authors postulated a top-down explanation (Levy and Behrman, 1970). It is important to be aware that there might well be false positives and false negatives (Howard and Dorfman, 1986). Using magnetoencephalography, it is possible to pick up a signal from the secondary somatosensory cortex, and, in a small case series of 3 patients, they all showed normal responses in both primary and secondary cortices (Hoechstetter et al., 2002).

Later SEP components are not often studied, but indicate further processing of the sensory stimuli. A P300 potential is seen in response to a rare stimulus in a series of stimuli with both common and rare stimuli. In 1 patient, the P300 component produced by stimulating the anesthetic limb was absent, whereas it was present on the normal limb and also present in a normal

subject feigning sensory loss to mimic malingering (Lorenz et al., 1998).

If the symptom is restricted to loss of pain or small-fiber sensation, the ordinary SEP would not be a good test. To evaluate the spinothalamic tract, there are now methods coming into more routine use to look at sensory evoked potentials from heat stimuli. One method for doing this is laser stimulation, and at least in 1 patient with a functional sensory loss, the potential was normal (Lorenz et al., 1998). Another method is the "contact heat-evoked potentials." Test–retest reliability for this technique has been demonstrated (Kramer et al., 2012), but this has not been applied to the study of functional patients as yet.

Neuroimaging of sensory responses in functional sensory loss has only limited results. In one study of 4 patients (who had normal SEPs), there was actually a deactivation of primary and secondary somatosensory cortices, decreased activation of more upstream areas, but increased activation of the anterior cingulate cortex (Mailis-Gagnon et al., 2003). An older study using single-photon emission computed tomography in a single patient with functional sensory loss had similar findings of normal SEP, and decreased parietal perfusion and increased frontal perfusion with median nerve stimulation (Tiihonen et al., 1995). In 7 patients with functional sensorimotor symptoms, bilateral vibration led to asymmetric depressed response only in contralateral thalamus and basal ganglia (Vuilleumier et al., 2001). Three patients with unilateral sensory loss were studied with fMRI and vibrotactile stimulation (Ghaffar et al., 2006). With stimulation of the anesthetic limb, there was no activation of the primary sensory cortex. With bilateral stimulation, however, there was activation of the primary sensory cortex opposite the anesthetic limb, as well as the "normal" activation of the cortex opposite the normal limb. Hence, it appears that the primary sensory cortex can be activated, even if not by stimulation of the anesthetic limb by itself.

Vision

Visual evoked potentials (VEPs) can be done with full-field or hemifield stimulation of each eye and explored objectively for uniocular or hemifield abnormality. The stimulus is typically patterned, such as a checkerboard. The prominent potentials come from the primary visual cortex. If a subject does not look at the stimulus, then there might be a false-positive abnormality. It is also possible to do just a flash evoked response, which does not require attention. Retinal function can be examined with electroretinograms.

In nonorganic visual loss, VEPs can be normal (Kramer et al., 1979; Yoneda et al., 2013). When normal, that almost always indicates functioning of the early parts of the visual pathway, although there are some patients who do have abnormalities but still test normal. Decreased amplitude of the VEP is also reported (Schoenfeld et al., 2011). When abnormal, it is more difficult to interpret due to the possibility of false positives, as noted already. When abnormal in a patient with conversion, it might be possible to change the result to normal using distraction. This was noted in a case report (Manresa et al., 1996).

An interesting case report of a patient with multiple personalities was published in German (Waldvogel et al., 2007) and subsequently in English also (Strasburger and Waldvogel, 2015). In some personalities, the patient could see and VEPs were present, and in other personalities, the patient could not see and VEPs were absent. Whether this was a conversion patient or a factitious patient with "defocusing" is not clear.

Using pattern VEPs with different check size, it is possible to get an objective measure of acuity. Using this method in malingering patients, it was possible to show better acuity than claimed (Gundogan et al., 2007).

The P300 was evaluated in 2 patients with malingering and 1 patient with conversion, and it was present in all 3 (Towle et al., 1985). All 3 patients did have VEPs at least some of the time. While statistics were not possible in these few cases, the authors did comment that the P300 amplitude seemed small in the conversion patient.

Audition

Auditory evoked potentials, as ordinarily done, explore the brainstem pathway for auditory information. There is a potential as well from auditory cortex. Late potentials have been studied in this situation also, and the P300 was reduced unilaterally in a patient with functional hearing loss (Fukuda et al., 1996). Mismatch negativity is an electrographic component similar to the P300, seen with target stimuli in the midst of background stimuli. In a group of 10 patients with somatization disorder, the mismatch negativity was smaller than normal (James et al., 1989).

Interpretation

In all these sensory functional disorders, it is usually possible to demonstrate normal functioning of the early part of the afferent pathway, including the primary sensory cortices. Beyond the primary sensory cortices, the information is less clear since the understanding of later evoked potential waves is not well known and less studied. Perception certainly involves brain structures beyond the primary cortices. However, it does seem that the P300 can be abnormal in conversion and this has interesting implications. On the other hand, the P300

might be normal in malingering, and this may well have diagnostic value for differentiating it from conversion.

Sensory systems have top-down operations as well as bottom-up. Attention can certainly modulate sensation, and top-down mechanisms can shut down sensory activity (Nunez and Malmierca, 2007). The notion of increased inhibition of sensory function in conversion disorders by corticofugal tracts has been proposed (Ludwig, 1972).

FUNCTIONAL MOVEMENT DISORDERS

Functional myoclonus

The methods for analysis of myoclonus (Hallett and Shibasaki, 2008) and for functional myoclonus (Hallett, 2010) in particular have been described in detail, and will only be summarized here. There are three steps in the evaluation of myoclonus: (1) the analysis of the EMG underlying the movement, generally with at least the simultaneous recording of both muscles of an antagonist pair; (2) to record the EEG simultaneously with the EMG to look at their correlation; and (3) to analyze reflex myoclonus, if present, for EMG latencies and EEG evoked responses.

In myoclonus that is a fragment of epilepsy, the EMG burst length is generally 30–50 ms and antagonist muscles are always synchronous. In other forms of myoclonus, the EMG burst length is longer and antagonist muscle relationships are variable. Functional myoclonus falls into this latter category. Hence, epileptic myoclonus can be ruled out with this method, but nonepileptic myoclonus cannot be. Additionally, some forms of nonepileptic myoclonus have characteristic EMG patterns, and this would help identify them as such. For example, in startle, orbicularis oculi is the first and most consistent muscle, sometimes with apparent double burst. This is followed by activity in lower cranial nerve muscles and subsequently by upper cranial nerve muscles and limb muscles (Matsumoto and Hallett, 1994). Functional myoclonus may well show highly variable patterns.

The EEG correlate is obtained by backaveraging the EEG using the onset of EMG (or movement) as the fiducial point. Each type of epileptic myoclonus has a characteristic EEG correlate. The best known is the potential associated with cortical myoclonus, a brief negative–positive potential about 20 ms prior to the EMG. In nonepileptic myoclonus, generally a potential is not identified. In functional myoclonus, very frequently a normal-looking Bereitschaftspotential can be identified (Fig. 6.2) (Terada et al., 1995). This indicates activity in the premotor cortex (Shibasaki and Hallett, 2006). In a study of 29 patients with functional myoclonus, 25 had a Bereitschaftspotential (van der Salm et al., 2012). As an unexpected finding in the latter study, there was often an absent Bereitschaftspotential prior to a voluntary wrist flexion movement. The explanation for this is unclear, and the authors raised issues of attention and motivation.

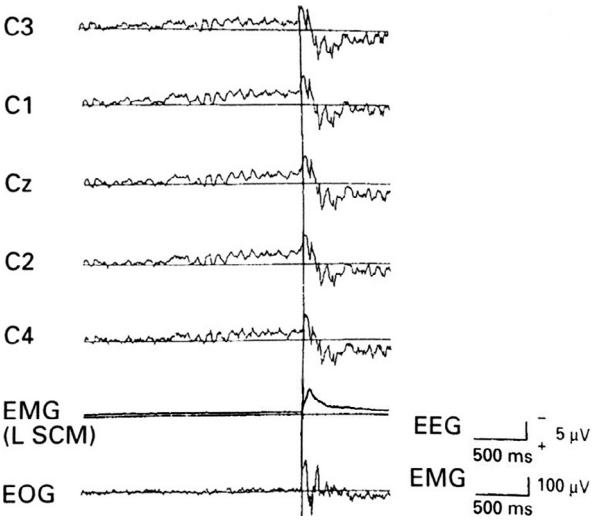

Fig. 6.2. Electroencephalogram (EEG) backaverage from functional myoclonus showing a normal-looking Bereitschaftspotential. L SCM, left sternocleidomastoid; EOG, electrooculogram; EMG, electromyogram. (Reproduced from Terada et al., 1995, with permission.)

The physiologic correlate of reflex myoclonus is called the C-reflex. In organic myoclonus syndromes the C-reflex comes from hyperexcitability of one of several long-latency reflex pathways. All of these pathways produce shorter latencies than the fastest voluntary reaction times, about 40–50 ms. In functional reflex myoclonus, the latencies are variable and similar to, and never faster than, the fastest voluntary reaction time, 100 ms or longer depending on the type of sensory stimulus (Thompson et al., 1992).

Interpretation

Functional myoclonus has the EMG signature of voluntary movement and even the expected EEG correlate of a Bereitschaftspotential. Since functional myoclonus is involuntary, the presence of a Bereitschaftspotential in this situation is evidence that the Bereitschaftspotential is not indicative of voluntariness. What it does appear to indicate is movement preparation in the premotor cortex. Another feature of functional myoclonus similar to normal voluntary movement is reaction time latencies. Hence it appears that normal voluntary mechanisms are utilized to produce functional myoclonus and that these mechanisms are operating normally. It must be that some top-down process co-opts this mechanism to produce movement, but not the sense of willing the movement.

Functional tremor

As with functional myoclonus, the testing for functional tremor is very good, and should be able to support the diagnosis. Tremor can be measured with EMG and/or with accelerometry, or both. Functional tremor may show marked variation in frequency and amplitude (O'Suilleabhain and Matsumoto, 1998). Additionally, functional tremor is typically exactly the same frequency and in phase in different limbs; this virtually never happens in organic tremors. This can be formally assessed with coherence analysis (McAuley and Rothwell, 2004).

The most useful physiologic method is the entrainment test (Hallett, 2010). In this test, the patient is asked to tap voluntarily at various frequencies with a body part unaffected by the tremor. If all body parts show tremor, this still can be done, with voluntary tapping of one body part while monitoring the response of the "involuntary" tremor in another body part. The tremor is entrained if the tremor takes up the frequency of the voluntary tapping. Another clue of psychogenicity is that the patient might have considerable difficulty in doing the voluntary tapping at the requested rate (Zeuner et al., 2003). Most commonly the test is done by measuring tremor of one hand and performing voluntary tapping with the other hand at a series of different frequencies. The different frequencies can be demonstrated for the subject with a metronome. The tremor might stop completely, change its frequency, or will take up the frequency of the voluntary tapping. Coherence analysis can quantify this. While this is a very good test, there are some functional tremors that do not entrain (Raethjen et al., 2004). The ballistic movement test is a variation on entrainment (Kumru et al., 2004). Here, patients are asked to make a quick movement with one limb. In functional tremor, there might be a pause in the tremor during the movement.

In a small group of patients, their functional tremor has been compared to voluntarily mimicked tremor using fMRI (Voon et al., 2010b). The most prominent difference was in the activation of the temporoparietal junction (TPJ) region, including connectivity of this area to parts of the motor system. As the TPJ appears relevant to the sense of self-agency for movement (Nahab et al., 2011), the lack of activation was speculated to be a correlate for the tremor being involuntary. Abnormal activation of the TPJ was also seen in conversion disorder patients when recalling past stressful life events (Aybek et al., 2014).

Interpretation

Similar to functional myoclonus, functional tremor appears to use a normally functioning motor system for the manifestation of the movement disorder. A higher-level brain network controls the motor network to produce tremor without producing the sense of voluntariness or agency. The lack of TPJ activation could be due to a failure of feedforward signaling at the time of movement generation.

Further evidence for a failure of feedforward signaling comes from studies of sensory gating. Sensory gating is the reduction of sensation and SEPs from a limb at the onset of, and during, self-generated movement. Studied in a mix of functional movement disorder patients, sensory gating was decreased in the patients (Pareés et al., 2014; Macerollo et al., 2015b). In one study of force matching, patients did not overestimate the force required as the normal controls did, indicating that they did not have normal gating (Pareés et al., 2014). In an SEP study, the N20 and N30 potentials were not suppressed at all (Macerollo et al., 2015b). Gating must be due to feedforward signaling from the motor command to the sensory system, thus dampening the sensory feedback from the movement. This avoids the brain being "bothered" by expected sensory events. There are two important implications. First, this is evidence for abnormal top-down control of sensation in these patients. Second, a loss of the gating function would mean that the movement related to the sensation would be more likely to be interpreted as externally generated rather than internally generated; this would then lead to a loss of the sense of agency.

However, the ultimate source of the motor command remains unknown. Imaging studies do suggest that the limbic system is overactive in functional movement disorders in general (Voon et al., 2011). As the limbic system provides important drive to movement, this could be the primary source, but this remains speculative.

Functional dystonia

Functional dystonia is often difficult to diagnose even with physiologic testing. For some reason, not yet fully understood, functional dystonia and organic dystonia often show the same findings.

Dystonic movement is usually characterized by co-contraction of antagonist muscles, but this is not always the case (Malfait and Sanger, 2007). In a study of patients with fixed dystonia and acquired (secondary) dystonia, those with fixed dystonia had less co-contraction as a group, but there was significant overlap between the findings in the two groups (Macerollo et al., 2015a). Hence, while lack of (or less) co-contraction might suggest that the disorder is functional, this is not a definitive observation. A pathologic drive at 4–7 Hz to muscles in patients with cervical dystonia and DYT1 dystonia was not seen in normal subjects and patients with fixed dystonia (assumed to be mostly functional) (Grosse et al., 2004). However, such drive

was not seen in patients with writer's cramp (Cordivari et al., 2002). Hence, this observation cannot be used as a definitive test either.

There are a large number of physiologic abnormalities in organic dystonia, most relating to loss of inhibition. These abnormalities can be seen at spinal level, such as reciprocal inhibition, and cortical level, such as short intracortical inhibition assessed with TMS. Most of these abnormalities are shared with functional dystonia (Espay et al., 2006; Avanzino et al., 2008). Temporal discrimination is also similarly abnormal in organic and functional dystonia (Morgante et al., 2011). One inhibitory mechanism not shared is the blink reflex recovery curve (Schwingenschuh et al., 2011a). In organic dystonia affecting cranial muscles, there is a loss of normal inhibition in blink reflex recovery. There is no such loss in functional blepharospasm. Eye blink conditioning is similarly normal in unmedicated patients with fixed dystonia (Janssen et al., 2014).

One important physiologic difference might be a measure of central nervous system plasticity called paired-associative stimulation. This method repetitively pairs a shock to the median nerve with a TMS to the motor cortex. Similar to long-term potentiation, this repetitive pairing leads to an increase in excitability of the motor cortex as assessed by the amplitude of the MEPs in muscles innervated by the median nerve and adjacent muscles. While organic dystonia shows an increased plasticity with this method, functional dystonia does not show this abnormality (Quartarone et al., 2009).

Interpretation

The physiologic overlap of organic and functional dystonia is not understood. One possibility is that the physiologic abnormalities indicate a propensity to dystonia that can be either organic or functional in the correct setting. Another possibility is that they are the result of dystonia rather than the cause. There are some tests that are different, including the blink reflex recovery curve and the paired-associative stimulation. However, how they illuminate the nature of functional dystonia is not clear.

OTHER FUNCTIONAL MOVEMENT DISORDERS

Functional gait disorders are common, but there are no physiologic studies. Most patients complain of poor balance, but it is clear from observing the gait that balance is very good. Quantitative balance testing has been undertaken. In one study, balance was assessed in conversion disorder patients and controls standing quietly, standing with eyes closed, and standing with an attention-demanding cognitive task (Stins et al., 2015). Sway increased more in patients in the eyes-closed condition, but it normalized in the attention task. Presumably, when the patients focused attention away from balance, it became normal. In another study, conversion disorder patients were compared with controls and patients with multiple sclerosis, in eight conditions, standing on solid floor or foam, eyes open or closed, and with and without distraction (Wolfsegger et al., 2013). Distraction here was recognizing numbers drawn on the back. Again, balance improved with distraction only in the conversion disorder patients.

Functional parkinsonism is not common, and again there have not been any physiologic investigations other than examination of tremor, as described above.

Functional seizures (psychogenic nonepileptic seizures: PNES)

Video-EEG is the standard technique for evaluating patients with suspected PNES (Gedzelman and LaRoche, 2014). A normal EEG in the face of an episode is strong evidence for its functional nature. There are some examples of false negatives, particularly frontal-lobe sources, which are sometimes missed with scalp recordings. Nocturnal dystonia was a subclass of paroxysmal dystonia until it was recognized that this was a form of epilepsy. It is also fair to say that an EEG is full of movement and muscle artifacts during any seizure, making the identification of subtle changes difficult to identify. Curiously, interictal epileptiform abnormalities are almost twice as common in PNES patients as in normal subjects, but it is not clear what that means (Reuber et al., 2002).

Resting EEG networks have been investigated in PNES patients. In general, these studies show a variety of weakened connections between parts of the brain (Knyazeva et al., 2011; Barzegaran et al., 2012, 2016). Perhaps most interesting is the finding of decreased prefrontal and parietal synchronization. Speculatively, that could underlie a weakness of possible feedforward connections in the brain.

Interpretation

While useful for diagnosis, a normal EEG does not inform us much about the pathophysiology of nonepileptic attacks. More work might be undertaken to study brain networks in these patients, including during the seizures themselves.

Synthesis

The physiology of conversion is not well understood, and motor and sensory disorders should be particularly helpful in studying this phenomenon since they can be objectively measured. The evidence seems clear that the

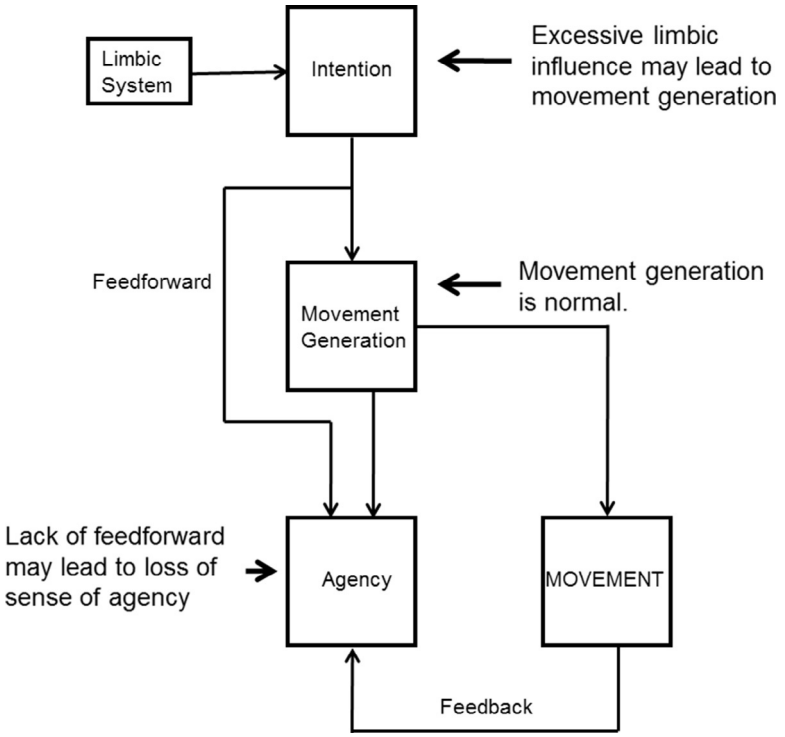

Fig. 6.3. Model of how involuntary movements might be generated and how they might not acquire a sense of agency. The model speculates that excessive limbic activity leads to movement generation, but does not produce a normal feedforward signal. Although movement is generated in a normal fashion and feedback occurs, there is a mismatch between feedforward and feedback and agency is not generated.

elementary motor efferent system beginning in motor cortex and the elementary sensory afferent systems extending to primary sensory cortices are functioning normally. The premotor systems and the sensory association areas are where the dysfunction is. fMRI, which is a major addition to clinical neurophysiology in assessing brain networks beyond primary cortices, is already shedding some light on these higher-level functions.

There is much evidence supporting an abnormality of top-down control with derangement of feedforward signaling. Attention to a disorder seems to aggravate or maintain it, while distraction might improve function. The failure of feedforward communication in the brain appears to give rise to sense of loss of control.

The primary site of the functional abnormalities, if there is one, is not clear. As noted earlier, some studies give evidence of increased influence of the limbic system in driving movement. Patients with functional movement disorders show an increased startle response to positive affective pictures as well as negative ones, indicating abnormal regulation of the startle response (Seignourel et al., 2007). In an fMRI study of faces showing different affects, patients with functional movement disorders showed increased activation of the right amygdala (Voon et al., 2010a). In a choice reaction time task, patients with functional movement disorders showed increased limbic activity and increased connectivity of the limbic system to the motor system (Voon et al., 2011). The limbic system can drive the motor system. Indeed, emotions are one of the major factors influencing movement choice. Limbic structures, such as the amygdala, can be influenced by genetic factors and/or early life stress. At this time, the idea is rather speculative, but it could be that abnormal functioning of the limbic system, both because of intrinsic "vulnerability" as well as traumatic life experiences, upsets brain networks and leads to functional disorders by deranged top-down control (Fig. 6.3). Freud might well have liked that idea.

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References

Avanzino L, Martino D, van de Warrenburg BP et al. (2008). Cortical excitability is abnormal in patients with the "fixed dystonia" syndrome. Mov Disord 23 (5): 646–652.

Aybek S, Nicholson TR, Zelaya F et al. (2014). Neural correlates of recall of life events in conversion disorder. JAMA Psychiatry 71 (1): 52–60.

Baars BJ, Franklin S, Ramsoy TZ (2013). Global workspace dynamics: cortical "binding and propagation" enables conscious contents. Front Psychol 4: 200.

Barttfeld P, Uhrig L, Sitt JD et al. (2015). Signature of consciousness in the dynamics of resting-state brain activity. Proc Natl Acad Sci U S A 112 (3): 887–892.

Barzegaran E, Joudaki A, Jalili M et al. (2012). Properties of functional brain networks correlate with frequency of psychogenic non-epileptic seizures. Front Hum Neurosci 6: 335.

Barzegaran E, Carmeli C, Rossetti AO et al. (2016). Weakened functional connectivity in patients with psychogenic non-epileptic seizures (PNES) converges on basal ganglia. J Neurol Neurosurg Psychiatry. 87 (3): 332–337.

Blakemore RL, Hyland BI, Hammond-Tooke GD et al. (2013). Distinct modulation of event-related potentials during motor preparation in patients with motor conversion disorder. PLoS One 8 (4): e62539.

Blakemore RL, Hyland BI, Hammond-Tooke GD et al. (2015). Deficit in late-stage contingent negative variation provides evidence for disrupted movement preparation in patients with conversion paresis. Biol Psychol 109: 73–85.

Chastan N, Parain D (2010). Psychogenic paralysis and recovery after motor cortex transcranial magnetic stimulation. Mov Disord 25 (10): 1501–1504.

Cojan Y, Waber L, Carruzzo A et al. (2009). Motor inhibition in hysterical conversion paralysis. Neuroimage 47 (3): 1026–1037.

Cordivari C, Lees AJ, Misra VP et al. (2002). EMG-EMG coherence in writer's cramp. Mov Disord 17 (5): 1011–1016.

Corradi-Dell'Acqua C, Fink GR, Weidner R (2015). Selecting category specific visual information: top-down and bottom-up control of object based attention. Conscious Cogn 35: 330–341.

Espay AJ, Morgante F, Purzner J et al. (2006). Cortical and spinal abnormalities in psychogenic dystonia. Ann Neurol 59 (5): 825–834.

Farah MJ, Hutchinson JB, Phelps EA et al. (2014). Functional MRI-based lie detection: scientific and societal challenges. Nat Rev Neurosci 15 (2): 123–131.

Fukuda M, Hata A, Niwa S et al. (1996). Event-related potential correlates of functional hearing loss: reduced P3 amplitude with preserved N1 and N2 components in a unilateral case. Psychiatry Clin Neurosci 50 (2): 85–87.

Gedzelman ER, LaRoche SM (2014). Long-term video EEG monitoring for diagnosis of psychogenic nonepileptic seizures. Neuropsychiatr Dis Treat 10: 1979–1986.

Ghaffar O, Staines WR, Feinstein A (2006). Unexplained neurologic symptoms: an fMRI study of sensory conversion disorder. Neurology 67 (11): 2036–2038.

Grosse P, Edwards M, Tijssen MA et al. (2004). Patterns of EMG-EMG coherence in limb dystonia. Mov Disord 19 (7): 758–769.

Grubin D (2010). The polygraph and forensic psychiatry. J Am Acad Psychiatry Law 38 (4): 446–451.

Gundogan FC, Sobaci G, Bayer A (2007). Pattern visual evoked potentials in the assessment of visual acuity in malingering. Ophthalmology 114 (12): 2332–2337.

Hallett M (2007). Transcranial magnetic stimulation: a primer. Neuron 55 (2): 187–199.

Hallett M (2010). Physiology of psychogenic movement disorders. J Clin Neurosci 17 (8): 959–965.

Hallett M, Shibasaki H (2008). Myoclonus and myoclonic syndromes. In: J Engel Jr, TA Pedley (Eds.), Epilepsy: A Comprehensive Textbook, Lippincott, Williams & Wilkins, Philadelphia, pp. 2765–2770.

Halliday AM (1968). Computing techniques in neurological diagnosis. Br Med Bull 24 (3): 253–259.

Hanakawa T, Dimyan MA, Hallett M (2008). Motor planning, imagery, and execution in the distributed motor network: a time-course study with functional MRI. Cereb Cortex 18 (12): 2775–2788.

Hernandez Peon R, Chavez Ibarra G, Aguilar Figueroa E (1963). Somatic evoked potentials in one case of hysterical anaesthesia. Electroencephalogr Clin Neurophysiol 15: 889–892.

Hoechstetter K, Meinck HM, Henningsen P et al. (2002). Psychogenic sensory loss: magnetic source imaging reveals normal tactile evoked activity of the human primary and secondary somatosensory cortex. Neurosci Lett 323 (2): 137–140.

Howard JE, Dorfman LJ (1986). Evoked potentials in hysteria and malingering. J Clin Neurophysiol 3 (1): 39–49.

James L, Gordon E, Kraiuhin C et al. (1989). Selective attention and auditory event-related potentials in somatization disorder. Compr Psychiatry 30 (1): 84–89.

Janssen S, Veugen LC, Hoffland BS et al. (2014). Normal eyeblink classical conditioning in patients with fixed dystonia. Exp Brain Res 232 (6): 1805–1809.

Kaplan BJ, Friedman WA, Gravenstein D (1985). Somatosensory evoked potentials in hysterical paraplegia. Surg Neurol 23 (5): 502–506.

Knyazeva MG, Jalili M, Frackowiak RS et al. (2011). Psychogenic seizures and frontal disconnection: EEG synchronisation study. J Neurol Neurosurg Psychiatry 82 (5): 505–511.

Kramer KK, La Piana FG, Appleton B (1979). Ocular malingering and hysteria: diagnosis and management. Surv Ophthalmol 24 (2): 89–96.

Kramer JL, Taylor P, Haefeli J et al. (2012). Test-retest reliability of contact heat-evoked potentials from cervical dermatomes. J Clin Neurophysiol 29 (1): 70–75.

Kumru H, Valls-Sole J, Valldeoriola F et al. (2004). Transient arrest of psychogenic tremor induced by contralateral ballistic movements. Neurosci Lett 370 (2–3): 135–139.

Lang AE, Voon V (2011). Psychogenic movement disorders: past developments, current status, and future directions. Mov Disord 26 (6): 1175–1186.

Levine TR, Bond Jr CF (2014). Direct and indirect measures of lie detection tell the same story: a reply to ten Brinke, Stimson, and Carney (2014). Psychol Sci 25 (10): 1960–1961.

Levy R, Behrman J (1970). Cortical evoked responses in hysterical hemianaesthesia. Electroencephalogr Clin Neurophysiol 29 (4): 400–402.

Liepert J, Hassa T, Tuscher O et al. (2008). Electrophysiological correlates of motor conversion disorder. Mov Disord 23 (15): 2171–2176.

Liepert J, Hassa T, Tuscher O et al. (2009). Abnormal motor excitability in patients with psychogenic paresis. A TMS study. J Neurol 256 (1): 121–126.

Liepert J, Hassa T, Tuscher O et al. (2011). Motor excitability during movement imagination and movement observation in psychogenic lower limb paresis. J Psychosom Res 70 (1): 59–65.

Liepert J, Shala J, Greiner J (2014). Electrophysiological correlates of disobedience and feigning-like behaviour in motor imagery. Clin Neurophysiol 125 (4): 763–767.

Lorenz J, Kunze K, Bromm B (1998). Differentiation of conversive sensory loss and malingering by P300 in a modified oddball task. Neuroreport 9 (2): 187–191.

Ludwig AM (1972). Hysteria. A neurobiological theory. Arch Gen Psychiatry 27 (6): 771–777.

Macerollo A, Batla A, Kassavetis P et al. (2015a). Using reaction time and co-contraction to differentiate acquired (secondary) from functional 'fixed' dystonia. J Neurol Neurosurg Psychiatry 86 (8): 933–934.

Macerollo A, Chen JC, Pareés I et al. (2015b). Sensory attenuation assessed by sensory evoked potentials in functional movement disorders. PLoS One 10 (6): e0129507.

Mailis-Gagnon A, Giannoylis I, Downar J et al. (2003). Altered central somatosensory processing in chronic pain patients with "hysterical" anesthesia. Neurology 60 (9): 1501–1507.

Malfait N, Sanger TD (2007). Does dystonia always include co-contraction? A study of unconstrained reaching in children with primary and secondary dystonia. Exp Brain Res 176 (2): 206–216.

Manresa MJ, Bonaventura I, Martinez I et al. (1996). Voluntary changes of visual evoked potentials in cases with hysteria and/or simulation. Rev Neurol 24 (127): 285–286.

Matsumoto J, Hallett M (1994). Startle syndromes. In: CD Marsden, S Fahn (Eds.), Movement Disorders 3, Butterworth-Heinemann, Oxford, pp. 418–433.

McAuley J, Rothwell J (2004). Identification of psychogenic, dystonic, and other organic tremors by a coherence entrainment test. Mov Disord 19 (3): 253–267.

Morgante F, Tinazzi M, Squintani G et al. (2011). Abnormal tactile temporal discrimination in psychogenic dystonia. Neurology 77 (12): 1191–1197.

Nahab FB, Kundu P, Gallea C et al. (2011). The neural processes underlying self-agency. Cereb Cortex 21 (1): 48–55.

Nowak DA, Fink GR (2009). Psychogenic movement disorders: Aetiology, phenomenology, neuroanatomical correlates and therapeutic approaches. Neuroimage 47 (3): 1015–1025.

Nunez A, Malmierca E (2007). Corticofugal modulation of sensory information. Adv Anat Embryol Cell Biol 187. 1 p following table of contents, -74.

O'Suilleabhain PE, Matsumoto JY (1998). Time-frequency analysis of tremors. Brain 121 (Pt 11): 2127–2134.

Pareés I, Brown H, Nuruki A et al. (2014). Loss of sensory attenuation in patients with functional (psychogenic) movement disorders. Brain 137 (Pt 11): 2916–2921.

Perelman BS (2014). Detecting deception via eyeblink frequency modulation. PeerJ 2. e260.

Pfister R, Foerster A, Kunde W (2014). Pants on fire: the electrophysiological signature of telling a lie. Soc Neurosci 9 (6): 562–572.

Pollak TA, Nicholson TR, Edwards MJ et al. (2014). A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms. J Neurol Neurosurg Psychiatry 85 (2): 191–197.

Proverbio AM, Vanutelli ME, Adorni R (2013). Can you catch a liar? How negative emotions affect brain responses when lying or telling the truth. PLoS One 8 (3): e59383.

Quartarone A, Rizzo V, Terranova C et al. (2009). Abnormal sensorimotor plasticity in organic but not in psychogenic dystonia. Brain 132 (Pt 10): 2871–2877.

Rae CL, Hughes LE, Anderson MC et al. (2015). The prefrontal cortex achieves inhibitory control by facilitating subcortical motor pathway connectivity. J Neurosci 35 (2): 786–794.

Raethjen J, Kopper F, Govindan RB et al. (2004). Two different pathogenetic mechanisms in psychogenic tremor. Neurology 63 (5): 812–815.

Reuber M, Fernandez G, Bauer J et al. (2002). Interictal EEG abnormalities in patients with psychogenic nonepileptic seizures. Epilepsia 43 (9): 1013–1020.

Rosenfeld JP, Hu X, Labkovsky E et al. (2013). Review of recent studies and issues regarding the P300-based complex trial protocol for detection of concealed information. Int J Psychophysiol 90 (2): 118–134.

Rusconi E, Mitchener-Nissen T (2013). Prospects of functional magnetic resonance imaging as lie detector. Front Hum Neurosci 7: 594.

Schoenfeld MA, Hassa T, Hopf JM et al. (2011). Neural correlates of hysterical blindness. Cereb Cortex 21 (10): 2394–2398.

Schwingenschuh P, Katschnig P, Edwards MJ et al. (2011a). The blink reflex recovery cycle differs between essential and presumed psychogenic blepharospasm. Neurology 76 (7): 610–614.

Schwingenschuh P, Katschnig P, Seiler S et al. (2011b). Moving toward "laboratory-supported" criteria for psychogenic tremor. Mov Disord 26 (14): 2509–2515.

Sebastian A, Jung P, Neuhoff J et al. (2016). Dissociable attentional and inhibitory networks of dorsal and ventral areas of the right inferior frontal cortex: a combined task-specific and coordinate-based meta-analytic fMRI study. Brain Struct Funct 221 (3): 1635–1651.

Seignourel PJ, Miller K, Kellison I et al. (2007). Abnormal affective startle modulation in individuals with psychogenic [corrected] movement disorder. Mov Disord 22 (9): 1265–1271.

Shibasaki H, Hallett M (2006). What is the Bereitschaftspotential? Clin Neurophysiol 117 (11): 2341–2356.

Stins JF, Kempe CL, Hagenaars MA et al. (2015). Attention and postural control in patients with conversion paresis. J Psychosom Res 78 (3): 249–254.

Strasburger H, Waldvogel B (2015). Sight and blindness in the same person: gating in the visual system. Psych J 4 (4): 178–185.

Terada K, Ikeda A, Van Ness PC et al. (1995). Presence of Bereitschaftspotential preceding psychogenic myoclonus: clinical application of jerk-locked back averaging. J Neurol Neurosurg Psychiatry 58: 745–747.

Thompson PD, Colebatch JG, Brown P et al. (1992). Voluntary stimulus-sensitive jerks and jumps mimicking myoclonus or pathological startle syndromes. Mov Disord 7 (3): 257–262.

Tiihonen J, Kuikka J, Viinamaki H et al. (1995). Altered cerebral blood flow during hysterical paresthesia. Biol Psychiatry 37 (2): 134–135.

Towle VL, Sutcliffe E, Sokol S (1985). Diagnosing functional visual deficits with the P300 component of the visual evoked potential. Arch Ophthalmol 103 (1): 47–50.

van der Salm SM, Tijssen MA, Koelman JH et al. (2012). The bereitschaftspotential in jerky movement disorders. J Neurol Neurosurg Psychiatry 83 (12): 1162–1167.

Voon V, Brezing C, Gallea C et al. (2010a). Emotional stimuli and motor conversion disorder. Brain 133 (Pt 5): 1526–1536.

Voon V, Gallea C, Hattori N et al. (2010b). The involuntary nature of conversion disorder. Neurology 74: 223–228.

Voon V, Brezing C, Gallea C et al. (2011). Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder. Mov Disord 26 (13): 2396–2403.

Vuilleumier P, Chicherio C, Assal F et al. (2001). Functional neuroanatomical correlates of hysterical sensorimotor loss. Brain 124 (Pt 6): 1077–1090.

Waldvogel B, Ullrich A, Strasburger H (2007). Sighted and blind in one person: a case report and conclusions on the psychoneurobiology of vision. Nervenarzt 78 (11): 1303–1309.

Wolfsegger T, Pischinger B, Topakian R (2013). Objectification of psychogenic postural instability by trunk sway analysis. J Neurol Sci 334 (1–2): 14–17.

Yoneda T, Fukuda K, Nishimura M et al. (2013). A case of functional (psychogenic) monocular hemianopia analyzed by measurement of hemifield visual evoked potentials. Case Rep Ophthalmol 4 (3): 283–286.

Zeuner KE, Shoge RO, Goldstein SR et al. (2003). Accelerometry to distinguish psychogenic from essential or parkinsonian tremor. Neurology 61 (4): 548–550.