Paula Muhr

The Biologically Vulnerable Brain – Emerging Neuroimaging Research on the Roles of Early-Life Trauma, Genetics, and Epigenetics in Functional Neurological Disorder

Historical Views on Hysteria Patients' Vulnerability

Characterised by a baffling array of heterogeneous somatic symptoms, such as paralysis, seizures, tremors, blindness, muteness, and loss of sensation, hysteria has since antiquity been considered a medical mystery. Because no undisputed organic cause had ever been established for its diverse symptoms, over the centuries, hysteria patients were often dismissed as simulators (Charcot, 1889, p. 14). The early medical theories that gave the disorder its name causally linked hysteria to the wandering womb (Micale, 1995, p. 19). These theories were influentially opposed by the late-nineteenth-century neurologist J.-M. Charcot. Using photography and other visualisation methods to investigate hysterical symptoms, Charcot conjectured that hysteria was caused by a localised brain dysfunction (Charcot, 1889; Muhr, 2022, chap. 1). He argued that this brain dysfunction, which he termed functional lesion, was triggered by adverse external events, such as physical injuries (i. e., traumas),[1] negative emotions, and various organic diseases. Charcot thereby insisted that external events could trigger the functional lesion, thus causing the onset of hysterical symptoms, only in vulnerable individuals who had inherited a latent neurophysiological defect from their ancestors (Charcot, 1889, p. 85). And whereas Charcot posited a distinct neurological mechanism through which external events led to the formation of a functional brain lesion in those vulnerable to hysteria, he did not specify the nature of this innate neuropathic vulnerability (Muhr, 2022, sec. 1.3.2). According to Charcot, hysterical symptoms were potentially curable, but the inherited neurobiological vulnerability to hysteria was not, leaving the patients prone to recurring symptoms.

Charcot's views on hysteria were later challenged by his former pupil Sigmund Freud. Freud claimed that not some hereditary neurobiological vulnerability but

1 Regarding Charcot's physical understanding of trauma, see Muhr (2022, p. 163). For a detailed history of the concept of trauma, see Leys (2000).

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

instead psychologically challenging external events (i.e., traumas) solely "determine the pathology of hysteria" (Breuer & Freud, 2001, p. 4). He thus transformed hysteria from an inherited brain disease – as Charcot had defined it – into a purely psychogenic disorder caused by emotionally charged memories of past events. In the process, Freud redefined trauma as a psychological concept whose content was highly subjective (Muhr, 2022, p. 213). Trauma thus came to denote emotionally distressing impressions of any, even a seemingly trivial event, whose psychologically damaging effect was specific to the individual and the context in which it occurred. Freud further hypothesised that the psychological process he termed conversion facilitated the transformation of traumatic memories into somatic hysterical symptoms that served as symbols of those memories. This psychogenic definition of hysteria, which was officially renamed conversion disorder, dominated medicine in the twentieth century (Micale, 1995, p. 28). But by the end of the twentieth century, Freud's theories fell out of favour. As a result, hysteria patients once again came to be seen as malingerers (Muhr, 2022, sec. 2.2.3). Hysteria was thus increasingly avoided as a diagnosis, leading to its apparent disappearance as a medical phenomenon. In fact, the current view in the humanities is that hysteria no longer exists (Micale, 1995, p. 29; Scull, 2009).

Yet, recent epidemiological studies have shown that hysterical symptoms are common in present-day neurological clinics (Stone et al., 2008, p. 13). Moreover, since the late 1990s, hysteria has gradually re-emerged as the object of systematic medical research into the neurophysiological basis of its varied symptoms. This research uses state-of-the-art neuroimaging techniques. These include functional magnetic resonance imaging (fMRI) – which enables non-invasive mapping of brain activity (Muhr, 2022) – and lately also quantitative structural neuroimaging methods, such as voxel-based morphometry (VBM), which characterise microstructural changes in brain anatomy through statistical analyses of magnetic resonance imaging (MRI) scans (Bègue et al., 2019). These imaging techniques enable researchers to experimentally link hysterical symptoms, which were until recently viewed as symbolic manifestations of psychological traumas, to anatomically localisable disturbances of brain function and/or structure.

As I have argued elsewhere (Muhr, 2022, chap. 2), fMRI-based research has been instrumental in the medical reframing of hysteria, now renamed functional neurological disorder (FND), from a purely psychological disorder into one that arises from a still not fully understood brain dysfunction. In the past two decades, the neuroimaging research into hysteria/FND has focused on searching for the disorder's underlying neurophysiological mechanisms while largely avoiding posing questions about the symptoms' potential aetiological factors and proc-

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

esses (Muhr, 2022, chap. 4).[2] However, since 2020, this situation has started to shift with the publication of three pioneering neuroimaging studies that have attempted to experimentally link FND patients' aberrant functional or structural brain patterns to genetic or epigenetic factors, on the one hand, and to early-life adverse experiences, on the other hand (Spagnolo et al., 2020; Diez et al., 2021; Jungilligens et al., 2022). In doing so, these studies have re-introduced the aetiologically intoned concept of neurobiological vulnerability into the current neuroimaging research on FND.

Approaching these pioneering studies from the perspective of science and technology studies and, more specifically, drawing on Bruno Latour, this chapter discusses the studies' epistemic import "by paying close attention to the details of scientific practice" (Latour, 1999, p. 24). I will thereby argue that the studies' authors are refashioning and expanding the concept of neurobiological vulnerability to FND in potentially productive ways. Through a close reading of the three studies, I hope to show that their authors operate with the concept of neurobiological vulnerability that is neither fixed and deterministic (Pitts-Taylor, 2019) nor simplistic and implicitly pathologising (Filipe et al., 2021). Although by its very definition, it is primarily expected to be localisable in the brain, neurobiological vulnerability, understood here as the pathological susceptibility to developing FND symptoms under the influence of environmental challenges, is experimentally framed in these studies as multifactorial, dynamic, and processual. As we will see, the studies discussed here neither search for fixed (epi)genetic biomarkers of FND nor do they aim to identify single risk factors or probabilistically assess risk scores (Filipe et al., 2021). Instead, they deploy tailor-made experimental setups to explore complex aetiological mechanisms and "biosocial loops" (Chiapperino & Paneni, 2022) through which genetic predispositions, environmental influences, and epigenetic processes interact to give rise to neurobiological vulnerability to FND.[3] But before I turn to the individual studies to make this point, we first need to examine how these studies both build upon and expand the current medical research into FND.

2 For the analysis of two earlier fMRI studies on the role of adverse memories in FND, see Muhr (2022, sec. 4.3.2).

3 In epigenetic research into disease aetiologies, biosocial loops designate "the looping effects between (material and social) environments and biology, past experiences and future predispositions, as well as nature and nurture in the production of disease" (Chiapperino & Paneni, 2022, p. 2).

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

Stress, Trauma-Induced Neuroplasticity and Vulnerability to Developing FND

Since, historically, adverse life events were thought to either trigger or directly cause hysteria, it may seem surprising that, at first, neuroimaging research avoided explicitly addressing their potential role in this disorder (Muhr, 2022, p. 457). But such choices become more comprehensible if we consider that, in the early 2000s, as this research started to consolidate, hysteria was regarded as a contentious disorder and often equated with malingering. Against this backdrop, it seems logical that, initially, the fMRI research focused on showing that hysterical symptoms are underpinned by distinctly different neural activity than malingering and on generating neuroimaging evidence that patients had no voluntary control over their symptoms (Muhr, 2022, chap. 4). Moreover, the research-based focus on hysterical symptoms' underlying neurophysiological mechanisms was aligned with the broader medical and diagnostic reframing of hysteria as a neurological disease. In the earlier versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the dominant classification system in psychiatry, the presence of antecedent stressors was necessary for diagnosing hysteria/conversion disorder (APA, 1994, p. 457). Yet, after several influential medical studies revealed that a significant proportion of hysteria patients lack identifiable precipitating stressors (Stone & Edwards, 2011), the current version of the manual, the DSM-5, dispensed with this diagnostic requirement (APA, 2013, p. 320). In doing so, the DSM-5 effectively decoupled FND from a presumed psychogenic aetiology.

But despite this diagnostic excision, the potential aetiological relevance of stressors has once again started to gain ground in the research context in the late 2010s. On the one hand, a systematic review of multiple recent studies has shown that, while not all patients report precipitating psychological stressors, the frequency of adverse events experienced during childhood and adulthood is significantly higher among FND patients than in healthy subjects or patients with other psychiatric disorders (Ludwig et al., 2018). Although it does not prove causality, the statistically significant association between stressful events and FND indicates that these events might be aetiologically relevant in some patients. Moreover, in line with Charcot's views, one recent study found an association between the onset of FND and a preceding adverse physical event, such as a minor injury or illness, thus expanding the concept of precipitating stressors to include not just psychological but also physical factors (Pareés et al., 2014). Taken together, these findings raise the question of why some individuals develop FND symptoms without exposure to any apparent distal or proximal traumas, some in

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

response to seemingly minor difficulties or physical injuries, whereas others experience multiple adverse events without falling ill.

On the other hand, a growing number of fMRI studies have demonstrated that FND patients exhibit a dysregulation in the neural circuitries that are involved in the physiological response to acute stress (Muhr, 2023, pp. 285–288). Because they were conducted on patients with diverse symptoms and used a variety of experimental paradigms for stress induction, each study implicated different neural regions and posited disparate neurophysiological mechanisms. But despite such inconsistencies, all studies found that FND patients have impaired neurophysiological processing of negative emotions, which makes them susceptible to adverse effects of psychologically threatening situations. In short, FND patients appear to be neurophysiologically vulnerable to various forms of stress, which perpetuate and aggravate their symptoms.

Concurrently, at a more general level, an important conceptual impulse for the neuroimaging research on vulnerability to stress in FND was delivered by the intensifying medical investigation of other stress-related disorders (e. g., anxiety, depression, and posttraumatic stress disorder) over the past two decades. In the latter context, heterogeneous patients' clinically determined impaired stress reactions have been increasingly aetiologically explained in terms of the stress-diathesis model. According to this model, exposure to severe early-life stressors produces "a cascade of physiological and neurohumoral reactions that alter brain-development trajectories, setting the stage for the (later) emergence of psychiatric symptoms in genetically susceptible individuals" (Teicher et al., 2016, p. 652). The implication is that, in individuals with a genetic predisposition, different types of childhood traumas, ranging from physical abuse to emotional neglect, first lead to aberrant epigenetic changes – e. g., over-expression of stress-related genes.[4] Next, through not yet understood complex neuromolecular mechanisms, the over-expressed genes then induce pathological neuroplastic modifications in the individuals' brain structures and functions. The resulting neuroplastic modifications, in turn, make these individuals neurobiologically vulnerable to even mild stressors, which can trigger the onset of illness.[5] In this model, stress refers to any environmental challenge an individual can cope with at the neurophysiological and behavioural levels. By contrast, trauma designates the stressors that induce pathological neuroplastic changes, thus effectively damaging the brain (Richter-Levin & Sandi, 2021).

4 In current medical research, genetic predisposition is defined as the presence of gene variants in an individual's DNA sequence. Conversely, epigenetic changes refer to processes, such as DNA methylation and histone modifications, that, without modifying the DNA sequence, control which genes are expressed and which are not (Deichmann, 2016).

5 For a detailed account of neural plasticity, see von Bernhardi et al. (2017).

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

Drawing on such a broadly defined stress-diathesis model, the authors of three recent neuroimaging studies developed the 'proposition' (Latour, 1999, p. 141) that a dynamic combination of mutually interacting genetic, epigenetic, neuromolecular, neuroplastic, and environmental factors underpins the production of neurobiological vulnerability to developing FND in some patients. According to Latour, propositions are not fixed, declarative statements about "mute (research) objects" but "occasions for interaction" (1999, p. 141). Propositions allow scientists to bring different phenomena of interest into novel relations to one another in order "to modify their definitions over the course of an event," e. g., a neuroimaging experiment. In the following three sections, I will examine how the authors of the three neuroimaging studies articulated their initial proposition about the FND patients' neurobiological vulnerability through their specific experimental setups. As defined by Latour (1999, p. 142), the articulation of propositions is understood here to comprise all experimental interventions that jointly enable the emergence of new scientific insights. Having traced the experimental emergence of the new insights into neurobiological vulnerability to FND, I will conclude the chapter by discussing the broader implications of these insights for patients.

Since my focus here is on the articulation of neurobiological vulnerability in neuroimaging research into FND, I will address psychosocial aspects of FND only to the extent that will allow me to examine their experimental operationalisation in the case studies at the centre of my analysis. My approach here is aligned with Chiapperino and Paneni (2022), who argue for developing more sophisticated methods for dissecting the environmental and social factors in epigenetically informed research while, at the same time, they acknowledge that some level of reduction of complex biosocial phenomena is unavoidable in experimental sciences.[6]

Relating Aberrant Brain Connectivity to Early-Life Trauma and Genetic Polymorphism

In a study published in 2020, Spagnolo et al. set out to examine if, as suggested by the stress-diathesis model, genetic factors, both directly and in interaction with childhood trauma, modulate the vulnerability to developing motor symptoms in FND patients. To this end, they recruited 69 patients with motor symptoms that ranged from tremor over gait problems to paralysis. Because of the symptoms'

6 For the humanities-based criticism of different aspects of reductionism in epigenetic research, see Pickersgill et al. (2013), Meloni (2014), Pitts-Taylor (2019), Filipe et al. (2021), and Dupras (2023).

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

heterogeneity and the fact that the ongoing research into other stress-related disorders has failed to causally link these disorders to single dysfunctional gene variants, Spagnolo et al. posited that FND was likely a polygenic disorder "modulated by multiple genes of small effect" (2020, p. 814). However, due to the small sample size, they could not conduct an exploratory genome-wide association study of the entire DNA sequence needed to identify all potentially contributing gene variants. Instead, they used a hypothesis-driven candidate gene approach to narrow their search to a set of a priori specified genes.

In choosing their candidate genes, Spagnolo et al. focused on articulating their proposition about the role of genetics in FND patients' neurobiological vulnerability to stress. Their choice was informed by the earlier fMRI studies that revealed multiple stress response dysfunctions in FND patients at the neural level. Arguing that the FND-related neural dysfunctions underpinning aberrant stress responses were comparable to those of other stress-related disorders, Spagnolo et al. selected 14 genes which previous studies had linked to other stress-related disorders (2020, p. 815). These genes, e.g. TPH2, control the biosynthesis of particular neurotransmitters, such as serotonin (5-HT), which, in turn, coordinate the brain's response to acute and chronic stress. Drawing on previous research into the activity of these genes, Spagnolo et al. further limited their analysis to 18 specific locations at which functionally relevant genetic variations, so-called single-nucleotide polymorphisms (SNP), are known to occur on the preselected genes.

Apart from genotyping the DNA samples extracted from the patients' blood to identify the type and location of gene variants, the researchers also assessed the patients' salient clinical features. These included the age of FND onset, symptom severity, and the intensity of comorbid depression and anxiety symptoms. To identify the patients' exposure to childhood trauma, Spagnolo et al. applied the Childhood Trauma Questionnaire (CTQ), which is widely used in psychological research. This standardised retrospective self-report screening tool quantifies five subtypes of childhood trauma: emotional, physical, and sexual abuse, and emotional and physical neglect (Bernstein et al., 1994). The CTQ measures the frequency of childhood exposure to traumatic events without registering any information about the context in which these events occurred or the affected individual's subjective evaluation of the experienced trauma. It results in separate scores for each trauma subtype, which range from no exposure to extreme exposure. Using the CTQ total scores, calculated by adding up the five subtype scores, Spagnolo et al. (2020, p. 816) established that 53% of their patients had experienced some level of childhood trauma.

Next, to examine how the gene variants influenced the aberrant neural patterns underpinning the patients' symptoms, Spagnolo et al. collected resting-state fMRI data for a subgroup of 38 patients. Resting-state fMRI is a neuro-

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

imaging method for evaluating the patterns of intrinsic synchronous activity across widely distributed brain areas – called functional connectivity networks – while subjects are not engaged in any external cognitive tasks but merely rest as their brain activity is measured (Bijsterbosch et al., 2017; Muhr, 2022, sec. 4.4.1). Once collected, resting-state fMRI data can be submitted to different types of statistical connectivity analyses. Aiming to articulate the FND patients' vulnerability to stress, Spagnolo et al. focused on examining alterations in the neural circuitry connecting the amygdala and the frontal cortex since its dysfunction had previously been "associated with hyperarousal and impaired emotion regulation" (2020, p. 816). Hence, they additionally recruited 38 healthy control subjects and performed a so-called seed-based analysis of fMRI data (Muhr, 2022, pp. 500–501) to determine how the amygdala-frontal cortex functional connectivity differed between patients and healthy controls.

Having thus obtained fMRI connectivity maps, Spagnolo et al. conducted multiple statistical analyses that allowed them to explore possible associations across the genetic, clinical, and fMRI measurements. First, they established that from the 14 candidate genes, only a particular polymorphism of the TPH2 gene correlated with a clinical feature of FND symptoms – the presence of this gene variant was associated with an earlier age of the symptom onset (Spagnolo et al., 2020, p. 817). Moreover, the concurrent presence of this genetic variant and early-life trauma correlated with the patients' increased symptom severity. Further, Spagnolo et al. found that patients with the TPH2 variant exhibited significantly decreased amygdala-frontal cortex resting-state connectivity compared to either patients without the mutation or healthy subjects (2020, p. 819). This difference in the connectivity pattern was independent of the cumulative childhood trauma exposure and thus directly associated with the TPH2 variant. Drawing their findings together, Spagnolo et al. conjectured that the TPH2 gene variant possibly resulted in dysfunctional serotonergic neurotransmission, thus making the carriers of this genetic variant innately vulnerable to stress (2020, p. 819). Both directly and in interaction with early-life trauma, the TPH2 gene variant seems to alter serotonin levels and thus facilitate the pathological neuroplastic alterations in the brain circuitries that coordinate the stress response.

Crucially, Spagnolo et al. provided a preliminary empirical indication that apart from functioning as a predisposing risk factor for developing FND symptoms, the TPH2 gene variant might also amplify the neurophysiological damage caused by childhood trauma through a particular neuromolecular mechanism. Admittedly, their findings were limited to identifying the potential role of a single genetic polymorphism in a disorder that would probably "manifest only when the net effect of possibly hundreds of gene variants causes a system-level failure" (Spagnolo et al., 2020, p. 820). Furthermore, their experimental embedding of patients' early-life traumatic experiences was reduced to the total scores of ex-

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

posure frequencies. Yet despite these limitations, the methodologically innovative aspect of their study was that Spagnolo et al. went beyond the mere risk prediction in genetic terms. Instead, they attempted to experimentally articulate FND patients' vulnerability to stress as a product of specific non-linear interactions across genetic (TPH2 polymorphism), neurochemical (serotonin), neurofunctional (aberrant amygdala connectivity), and environmental (childhood trauma) factors. It was the first study of this kind in FND research, laying the ground for others that followed.

Linking Trauma-Related Changes in Functional Brain Architecture to Gene Expression Profiles

In their 2021 study, Diez et al. developed a different approach to experimentally articulating the potential interplay of genetic and environmental factors in the aetiology of FDN patients' neurobiological vulnerability. They, too, collected resting-state fMRI data for 30 FND patients with mixed motor symptoms and for 21 control subjects. Moreover, they also used the CTQ to identify the exposure frequency to five subtypes of childhood trauma in their study participants. However, the control subjects in this study were not healthy subjects but patients with clinical depression. And compared to Spagnolo et al., Diez et al. used a different method to analyse the fMRI data and a different way to integrate the neuroimaging and genetic data.

Unlike Spagnolo et al., who deployed the seed-based analysis to assess functional connectivity between the predefined brain regions of interest, Diez et al. opted for two types of computationally more sophisticated graph-theoretical analyses. These statistical analyses allowed them to characterise their patients' brain-wide resting-state network architectures. First, Diez et al. computed the weight-degree connectivity maps that measure the level of influence of each region on the rest of the brain. Additionally, they performed a link-level connectivity analysis that quantifies "connectivity strength relationships across brain areas" (Diez et al., 2021, p. 3818).

For each patient group separately, Diez et al. correlated the thus obtained connectivity maps to the CTQ scores to examine how each of the five subtypes of childhood trauma modulated the FND patients' functional brain architectures. The decision to separately analyse each subtype was motivated by the recent research finding that different trauma subtypes "may have specific biological consequences" (Diez et al., 2021, p. 3818). The analysis showed that in the FND patients, the physical abuse and, to a lesser extent, physical neglect scores correlated with increased weight-degree connectivity in the limbic (amygdala, hip-

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

pocampus), paralimbic and cognitive control areas, as well as the sensorimotor and visual cortices (Diez et al., 2021, p. 3822). In other words, early-life exposure to physical abuse and neglect appeared to produce a widespread topological reorganisation of the functional brain architecture in these subjects, thus making them vulnerable to developing FND symptoms at a later age. Other subtypes of childhood trauma – sexual and emotional abuse or emotional neglect – did not have statistically significant correlations with either type of connectivity map, although, as pointed out by Diez et al. (2021, p. 3826), these negative findings could have been due to the modest sample size. Moreover, the link-level maps revealed that in the FND patients, the physical abuse scores correlated with the strength of the amygdala and insula coupling to the motor cortices, suggesting that this subtype of trauma "may predispose the central nervous system in some individuals for the development of functional motor symptoms" (Diez et al., 2021, p. 3824). Importantly, none of these trauma-related neuroplastic changes in functional connectivity was seen in the depression patients with a comparable level of childhood physical abuse or neglect.

In the next step, Diez et al. combined their fMRI maps with genetic data to explore "molecular mechanisms underlying individual differences in network connectivity" between FND and depression patients (2021, p. 3818). But unlike Spagnolo et al., Diez et al. did not search for structural variations in patients' genomes. Instead, they used a novel epigenetic approach to integrate their fMRI maps with brain-wide gene expression profiles. Such profiles provide a more direct measure of gene function than genotyping as they "quantify the transcriptional activity of thousands of genes across many different anatomical locations" (Fornito et al., 2019, p. 25). Whereas, until recently, gene expression variations across brain regions could only be quantified post-mortem, this changed in 2019 with the publication of the Allen Human Brain Atlas (AHBA). The AHBA is a publicly available database comprising genome-wide expression values "for over 20,000 genes quantified across 3702 different anatomical locations and in six different brains" (Fornito et al., 2019, p. 35). Using this atlas, Diez et al. could relate their patients' fMRI connectivity maps to spatial variations in expressions of over 20,000 genes.

To achieve this, Diez et al. compared the FND patients' physical abuse weighted-degree connectivity maps to the maps of regional gene expression profiles from the AHBA and computationally assessed their spatial similarity.[7] Genes with sufficiently similar spatial distribution to the patients' connectivity

7 It is important to note that assessing spatial similarity between the study-specific brain maps and the maps of regional gene expression profiles from the AHBA is far from straightforward, since there are different ways in which expression profiles can be processed. For details of this highly complex multistage computational process, which is currently not standardised, see Arnatkeviciute et al. (2019) and Diez et al. (2021, p. 3819).

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

patterns were deemed functionally relevant and submitted to a gene-set enrichment analysis (Subramanian et al., 2005). This statistical analysis allowed Diez et al. to divide the overrepresented genes into three functional clusters that, based on the previously published research, are associated with specific biological processes. Diez et al. thus conjectured that genes known to be implicated in neuronal morphogenesis were overexpressed in the FND patients' limbic and paralimbic areas, whereas genes associated with neural development and locomotory behaviour were overrepresented in the sensorimotor regions (2021, p. 3824). Finally, Diez et al. used the AHBA to perform an additional hypothesis-driven analysis by testing if the five preselected candidate genes, which had been aetiologically implicated in other stress-related disorders, were also overexpressed in the FND patients. The analysis disclosed that the BDNF gene, which is "important for neuronal development, neurogenesis, and memory functions" (Diez et al., 2021, p. 3824), was overexpressed in the FND patients' limbic and paralimbic brain areas, which play crucial roles in emotion processing.

In sum, the combined use of different gene expression analyses allowed Diez et al. to attempt to explain trauma-related reorganisation of functional brain networks in FND patients in terms of distinct epigenetically-driven neuromolecular processes, thus shifting the focus from the search for gene variants to gene activity. By deploying the newly developed gene expression brain atlas, Diez et al. could also go a step further than Spagnolo et al. and, instead of focusing on aberrant connectivity between predefined neural regions, explore how the brain-wide changes in functional architecture relate to regionally different expression profiles of thousands of gene with varied functions. Moreover, as we have seen, the complexity of their experimental articulation of FND patients' vulnerability to stress was further enhanced by their decision to separately examine potentially distinct neurophysiological effects of different subtypes of childhood traumas. Yet, similarly to Spagnolo et al., in this study, the experimental operationalisation of early-life trauma remained limited to reductive proxy measures of the frequency scores.

Associating Trauma-Related Changes in Regional Brain Volumes to Diachronic Gene Expressions

In a study published in 2022, Jungilligens et al. devised yet another way of experimentally articulating the aetiology of neurobiological vulnerability to adverse life experiences in FND patients. Unlike the authors of the two previous studies, Jungilligens et al. focused on a single symptom, recruiting 20 FND patients diagnosed with functional seizures but no control subjects. Moreover,

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

instead of screening the patients only for childhood traumas, the researchers aimed to identify potentially traumatic experiences across the patients' lifespans. For this purpose, they used a standardised self-report questionnaire called the Traumatic Experiences Checklist (TEC). The TEC categorises traumatic experiences into six subtypes: emotional neglect, emotional abuse, physical abuse, threat to life, sexual abuse, and sexual harassment (Nijenhuis et al., 2002). Unlike the CTQ, the TEC assesses the age of the trauma onset and relation to the perpetrator, and it quantifies the affected individual's perceived trauma severity on a scale from none to extreme. Using additional questionnaires, the researchers also quantified the duration and self-reported severity of functional seizures in their patients.

Similarly to the Diez et al. study, Jungilligens et al. relied on the AHBA to explore the role of genetic influences on the aberrant neuroplastic changes in their patients. But, unlike the previous two studies, instead of collecting functional MRI data, Jungilligens et al. opted for a quantitative structural MRI method called voxel-based morphometry (VBM). Using this method, they generated statistical maps that characterised regional microanatomical differences in grey matter volumes across the patients' brains (Jungilligens et al., 2022, p. 3). Having computed these maps, the researchers correlated them to the patients' symptom severity scores and the reported magnitudes of different trauma subtypes to explore potential relations across these measures. The analyses showed that the symptom severity was associated with reduced volumes of the brain regions comprising the salience network, which is "implicated in affective experiences and attention" (Jungilligens et al., 2022, p. 7). Moreover, emotional neglect and sexual trauma scores correlated with lower grey matter volumes of the amygdala and insula, respectively.[8]

Lastly, the researchers turned to "identifying genetic pathways dually implicated in the association of volumetric grey matter variations with symptom severity and trauma burden" (Jungilligens et al., 2022, p. 2). To do so, they first computed the spatial similarity between the patients' statistical brain maps – derived by correlating grey matter volumes to symptom severity and different trauma subtypes – and the gene expression profiles from the AHBA. But instead of analysing over 20,000 genes mapped in the AHBA, Jungilligens et al. focused only on 2382 genes known to have significantly higher expression in the brain than in other organs. Like Diez et al., they also performed a gene-enrichment analysis that allowed them to make inferences about the function of the thus identified gene sets. The analysis revealed that the grey matter maps which were dually related to sexual trauma and symptom severity had a statistically significant overexpression

8 Jungilligens et al. merged TEC's subtypes of sexual abuse and sexual harassment into a single subtype they termed 'sexual trauma' (2022, p. 3).

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

of 22 genes associated with "serotonin, oxytocin, (nor)epinephrine (e.g., noradrenalin), and opioid receptor signaling" (Jungilligens et al., 2022, p. 7). As emphasised by the researchers, these overrepresented genes are involved in the stress-related signalling pathways, whose dysfunction had been linked by multiple studies to "affective vulnerabilities to everyday events" (Jungilligens et al., 2022, p. 8).

Additionally, Jungilligens et al. conducted one more gene attribution analysis using the so-called Specific Expression Analysis tool. This statistical tool enabled them to explore during which neurodevelopmental period each of the 22 identified genes was most likely to influence the formation of a particular brain region. According to this analysis, the over-expressed genes impacted the development of the FND patients' cortical structures from the neonatal period to young adulthood and the maturation of their amygdalas during adolescence and young adulthood (Jungilligens et al., 2022, p. 8).

With this latter analysis, Jungilligens et al. opened up a new research perspective on FND. Besides examining the underlying neuromolecular mechanisms through which genetic factors and life stressors interact to induce pathological neuroplastic changes that underpin the FND patients' vulnerability to subsequent stressors, Jungilligens et al. were the first to explore potential differences in the timing of such changes across different brain regions. They thus framed their search for the aetiology of the FND patients' neurobiological vulnerability in distinctly diachronic and processual terms, taking into account not just childhood traumas but also the effects of adverse life experiences during early adulthood on FND patients' neurodevelopment. And although Jungilligens et al. used a standardised questionnaire to operationalise their patients' traumatic experiences in terms of quantitative scores, it can be argued that the perceived severity of trauma is a more nuanced proxy than the frequency of exposure.

Complicating the Picture: Articulating Neurobiological Vulnerability as a Multifactorial and Dynamic Process

The three neuroimaging studies discussed in this chapter were the first to empirically explore the potential aetiological links between hysteria/FND patients' aberrant patterns of brain functions and structure, on the one hand, and patients' adverse life experiences and genetic and epigenetic factors, on the other hand. These pioneering studies are indicative of the emerging new focus on aetiological approaches within the current neuroimaging research into FND. At a superficial glance, it may appear that these studies merely used state-of-the-art technologies

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

(from fMRI and VBM to genotyping and gene expression measurements) to rehash discarded nineteenth-century theories about the hysteria patients' innate neurobiological vulnerability. Yet, my analysis has aimed to show that this was not the case.

First, although the findings of these studies are preliminary and tentative, they are epistemically relevant as they go beyond simply identifying various risk factors or postulating potential (epi)genetic biomarkers of FND. Instead, they provide new insights into the neuromolecular and developmental mechanisms through which heterogeneous biological and environmental factors may produce neurobiological vulnerability to FND by disrupting an individual's biological stress processing.

Second, I argue that more than their specific preliminary findings, the most innovative aspect of these studies is the development of novel, exploratory approaches to experimentally articulating FND patients' neurobiological vulnerability. There were significant methodological differences across the studies. These included which aspect of the FND patients' underlying brain disturbance to measure (seed-based connectivity, global functional architecture, or regional alterations in grey-matter volume), whether to examine genetic or epigenetic factors, and which standardised questionnaires to use to screen for traumatic life experiences. But despite these differences, all three studies articulated FND patients' neurological vulnerability in distinctly dynamic terms – as a multifactorial process that entails complex, non-linear interactions between inherited genetic variations, neuroanatomically specific epigenetic changes, potentially distinct effects of multiple subtypes of early-life traumas, and repeated exposures to different types of stressors. In these studies, vulnerability is not only conceptualised as both innate and acquired, but the focus is placed on elucidating the processual relations between these two mutually interacting aspects of vulnerability.

Yet, this is not to say that the studies discussed here are without limitations. Significantly, none of these studies has dealt with the specific content of the self-reported traumas, thus effectively reducing the patients' lived experiences to standardised quantitative scores of trauma frequency or severity. In doing so, they failed to address how the adverse experiences were embedded into broader sociocultural contexts or to examine the subjective, symbolic meanings that particular stressors might have had for different individuals. As suggested by Freud, such contextual psychosocial factors could be argued to modulate in nontrivial ways the impact that otherwise seemingly comparable stressors have on an individual. Instead, in our case studies, the decontextualised stressors were of interest only inasmuch as their neurophysiologically damaging effects, operationalised through quantitative scores of trauma frequency and severity, were retrospectively measurable in terms of correlated aberrant neural structure or

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

function and the associated epigenetic changes. Such neurobiological framing of vulnerability that disregards patients' individual differences and focuses solely on identifying shared neural, genetic, and epigenetic mechanisms and, as we have seen, relies on a mutual interlinking of multiple statistical analyses may be considered by some to be unduly reductive (Dupras, 2023).

However, I propose a different interpretation. In line with Chiapperino and Paneni, who call for a methodological complexification in the "ways of studying the biological and social factors producing diseases" (2022, p. 5), I think that future neuroimaging research should find a way to experimentally address FND patients' individual, context-specific experiences of trauma. This could perhaps be achieved through detailed interview techniques or by developing tailor-made questionnaires. Also, because most of the patients diagnosed with FND are women (APA, 2013), another thus far neglected aspect that future studies need to examine is whether there are gender-specific differences in how traumatic experiences relate to epigenetically modulated neuroplastic changes.

Nevertheless, I argue that, despite its limitations, the current neurobiological reframing of vulnerability pioneered by the three studies discussed above is not just epistemically productive in that it produces novel medical insights, but is also, in a broader sense, affirmative for FND patients. According to earlier medical framing, hysteria patients' vulnerability to adverse life events was viewed either as a shameful psychological weakness or as a feigned behaviour (APA, 1994, p. 446; Muhr 2022, sec. 2.2.3). By contrast, the current reframing of vulnerability as a genuine neurophysiological phenomenon arising from a dynamic interplay between one's biological makeup and a diachronic influence of multiple environmental factors shifts the blame away from patients for their impaired ability to cope with stress. Defined in such terms, vulnerability is neither an exaggerated attention-seeking behaviour nor a purportedly shameful character flaw and, most importantly, it is not a fixed innate property of an individual. Furthermore, there is a glimmer of optimism in this reframing. After all, if the neurophysiological vulnerability to FND is partly acquired through trauma-induced neuroplastic changes, the implication is that, once we understand the mechanisms of this acquisition, we might learn how to reverse at least some of its effects. Should this transpire, not just diverse FND symptoms but also the underlying neurophysiological vulnerability to developing these symptoms, which Charcot had regarded as a fixed predisposition, could one day perhaps become treatable.

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

References

American Psychiatric Association (APA) (1994). Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association.

American Psychiatric Association (APA) (2013). Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association.

Arnatkeviciute, A., Fulcher, B. D., & Fornito, A. (2019). A Practical Guide to Linking Brain-wide Gene Expression and Neuroimaging Data. In Neuroimage, 189 (pp. 353–367).

Bègue, I., Adams, A., Stone, J., & Perez, D. L. (2019). Structural Alterations in Functional Neurological Disorder and Related Conditions: A Software and Hardware Problem? In NeuroImage: Clinical, 22 (101798) (pp. 1–18).

Bernstein, D. P., Fink, L., Handelsman, L, Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., & Ruggiero, J. (1994). Initial Reliability and Validity of a New Retrospective Measure of Child Abuse and Neglect. In American Journal of Psychiatry, 151 (pp. 1132–1136).

Bijsterbosch, J., Smith, S. M., & Beckmann, C. F. (2017). Introduction to Resting State fMRI Functional Connectivity. Oxford: Oxford University Press.

Breuer, J., & Freud, S. (2001). Studies on Hysteria (1893–1895). Vol. 2 of S. Freud. Standard Edition of the Complete Psychological Works of Sigmund Freud. 24 vols. Translated and edited by J. Strachey. London: Vintage.

Charcot, J.-M. (1889). Clinical Lectures on the Diseases of the Nervous System, Delivered at the Infirmary of La Salpêtrière. Vol. 3. Translated by T. Savill. London: New Sydenham Society.

Chiapperino, L., & Paneni, F. (2022). Why Epigenetics is (not) a Biosocial Science and Why That Matters. In Clinical Epigenetics, 14, (pp. 1–6).

Deichmann, U. (2016). Epigenetics: The Origins and Evolution of a Fashionable Topic. Developmental Biology, 416 (pp. 249–254).

Diez, I., Larson, A. G., Nakhate, V., Dunn, E. C., Fricchione, G. L., Nicholson, T. R., Sepulcre, J., & Perez, D. L. (2021). Early-life Trauma Endophenotypes and Brain Circuit-Gene Expression Relationships in Functional Neurological (Conversion) Disorder. In Molecular Psychiatry, 26 (pp. 3817–3828).

Dupras, C. (2023). Being against Reductionism regarding Epigenetics. In Epigenetics Communications, 3 (pp. 1–4). Available at: https://doi.org/10.1186/s43682-023-00020-6 (31.01.2024).

Filipe, A. M., Lloyd, S., & Larivée, A. (2021). Troubling Neurobiological Vulnerability: Psychiatric Risk and the Adverse Milieu in Environmental Epigenetics Research. In Frontiers in Sociology, 6 (635986) (pp. 1–13).

Fornito, A., Arnatkeviciute, A., & Fulcher, B. (2019). Bridging the Gap between Transcriptome and Connectome. In Trends in Cognitive Sciences, 23 (pp. 34–50).

Jungilligens, J., Popkirov, S., Perez, D. L., & Diez, I. (2022). Linking Gene Expression Patterns and Brain Morphometry to Trauma and Symptom Severity in Patients with Functional Seizures. In Psychiatry Research: Neuroimaging, 326 (111533) (pp. 1–11).

Latour, B. (1999). Pandora's Hope: Essays on the Reality of Science Studies. Cambridge, MA: Harvard University Press.

Leys, R. (2000). Trauma: A Genealogy. Chicago: University of Chicago Press.

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

Ludwig, L., Pasman, J. A., Nicholson, T., Aybek, S., David, A. S., Tuck, S., Kanaan, R. A., Roelofs, K., Carson, A., & Stone, J. (2018). Stressful Life Events and Maltreatment in Conversion (Functional Neurological) Disorder: Systematic Review and Meta-analysis of Case-Control Studies. In Lancet Psychiatry, 5 (pp. 307–320).

Meloni, M. (2014). The Social Brain Meets the Reactive Genome: Neuroscience, Epigenetics and the New Social Biology. In Frontiers in Human Neuroscience, 8 (309) (pp. 1–12), doi:10.3389/fnhum.2014.00309.

Micale, M. S. (1995). Approaching Hysteria: Disease and its Interpretations. Princeton, NJ: Princeton University Press.

Muhr, P. (2022). From Photography to fMRI: Epistemic Functions of Images in Medical Research on Hysteria. Bielefeld: transcript.

Muhr, P. (2023). Tracing Hysteria's Recent Trajectory: From a Crisis for Neurology to a New Scientific Object in Neuroimaging Research. In J. Engelschalt, J. Lemberg, A. Maibaum, A. Rothenhäusler, & M. Wiegand (eds.), Wissenskrisen–Krisenwissen: Zum Umgang mit Krisenzuständen in und durch Wissenschaft und Technik (pp. 269–293). Bielefeld: transcript.

Nijenhuis, E. R. S., Hart, O. van der, & Kruger, K. (2002). The Psychometric Characteristics of the Traumatic Experiences Checklist (TEC): First Findings among Psychiatric Outpatients. In Clinical Psychology and Psychotherapy, 9 (pp. 200–210).

Pareés, I., Kojovic, M., Pires, C., Rubio-Agusti, I., Saifee, T. A., Sadnicka, A., Kassavetis, P., Macerollo, A., Bhatia, K. P., Carson, A., Stone, J., & Edwards, M. J. (2014). Physical Precipitating Factors in Functional Movement Disorders. In Journal of the Neurological Sciences, 338 (pp. 174–177).

Pickersgill, M., Niewöhner, J., Müller, R., Martin, P., & Cunningham-Burley, S. (2013). Mapping the New Molecular Landscape: Social Dimensions of Epigenetics. In New Genetics and Society, 32 (pp. 429–447).

Pitts-Taylor, V. (2019). Neurobiologically Poor? Brain Phenotypes, Inequality, and Biosocial Determinism. In Science, Technology, & Human Values, 44 (pp. 660–685).

Richter-Levin, G., & Sandi, C. (2021). Title: Labels Matter: Is it Stress or is it Trauma? In Translational Psychiatry, 11 (pp. 1–9).

Scull, A. (2009). Hysteria: The Biography. Oxford: Oxford University Press.

Spagnolo, P. A., Norato, G., Maurer, C. W., Goldman, D., Hodgkinson, C., Horovitz, S., & Hallett, M. (2020). Effects of TPH2 Gene Variation and Childhood Trauma on the Clinical and Circuit-Level Phenotype of Functional Movement Disorders. In Journal of Neurology, Neurosurgery & Psychiatry, 91 (pp. 814–821).

Stone, J., & Edwards, M. J. (2011). How 'Psychogenic' are Psychogenic Movement Disorders? In Movement Disorders, 26 (pp. 1787–1788).

Stone, J., Hewett, R., Carson, A., Warlow, C., & Sharpe, M. (2008). The 'Disappearance' of Hysteria: Historical Mystery or Illusion? In Journal of the Royal Society of Medicine, 101 (pp. 12–18).

Subramanian, A., Tamayo, P., Mootha, V. K., Mukherjee, S., Ebert, B. L., Gillette, M. A., Paulovich, A., Pomeroy, S. L., Golub, T. R., Lander, E. S., & Mesirov, J. P. (2005). Gene Set Enrichment Analysis: A Knowledge-based Approach for Interpreting Genome-wide Expression Profiles. In Proceedings of the National Academy of Sciences, 102 (pp. 15545–15550).

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The Effects of Childhood Maltreatment on Brain Structure, Function and Connectivity. In Nature Reviews Neuroscience, 17 (pp. 652–666).

Von Bernhardi, R., Eugenín von Bernhardi, L., & Eugenín, J. (2017). What is Neural Plasticity? In R. von Bernhardi, J. Eugenín, & K. Muller (eds.), The Plastic Brain: Advances in Experimental Medicine and Biology (pp. 1–15). Cham: Springer.

ISBN Print: 9783847117049 – ISBN E-Lib: 9783737017046