



REVIEW ARTICLE

# Conversion disorder/functional neurological disorder – a narrative review on current research into its pathological mechanism



J. Ratcliff<sup>a,\*</sup>, C. van der Feltz-Cornelis<sup>b</sup>

<sup>a</sup> Hull York Medical School, University of Hull, Hull, United Kingdom

<sup>b</sup> Department of Health Sciences, University of York, York, United Kingdom

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## Abstract

**Background and objectives:** Conversion disorder/functional neurological disorder (CD/FND) can be a chronic disorder and has an unknown pathology. This review explored the current level of research and understanding the origin of CD/FND pathology.

**Methods:** This narrative review collated relevant papers and articles identified by a search in both Scopus and PubMed. Systematic reviews and observational articles focusing on inflammation and childhood trauma were included. Articles that were not in English, case reports, or that included participants from military background, were excluded.

**Results:** Overall 54 papers were included from an initial search number of 5264. 34 of these articles were identifying and discussing new trends and theories related to the pathophysiology while the remaining 20 were defining the current knowledge of CD/FND.

There is no definitively known pathophysiology of FND, with several noted categories of involved being immune system, inflammation and neural changes. Each system and mechanism could either be seen as a direct mechanism of action or an indirect effect from a further unknown mechanism of action. Additionally, there seems to be a lack of coherency between these different proposed theories, with little information bringing them together. Further research may explore whether or not inflammation plays a direct role in the pathophysiology of the disorder, and if a difference in the symptoms is dictated by different inflammatory markers.

**Conclusion:** Overall this narrative review identified and postulated different mechanisms for the pathology of CD/FND while also discovering where new research should focus.

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\* Corresponding author.

E-mail address: [jono.rat23@gmail.com](mailto:jono.rat23@gmail.com) (J. Ratcliff).

## Background

Conversion disorder (CD) or functional neurological disorder (FND), as defined in DSM-5,<sup>1</sup> can be a disorder with large and long-term impact on functioning and is not currently explained by organic disease.<sup>2</sup> CD and FND is a condition that affect voluntary motor or sensory functioning of the patient.<sup>3,4</sup> This condition affects patients in multiple ways, ranging from but not limited to; gait disturbances, muscle weakness, tremor, anaesthesia, blindness, pseudoseizures, paraplegia, paralysis, deafness, psychogenic non-epileptic seizures and aphasia.<sup>5,6</sup> With prevalence reported to varying degrees of 30–60% of neurology outpatients to have FND in the UK in studies over the last two decades,<sup>8–10</sup> more recent studies found that 6% of neurological outpatients have FND, with incidence in adults roughly 4–12 per 100,000.<sup>7</sup> In children, a 12 month review of FND in the UK and Ireland found an incidence of 1.3/100,000, with the most common symptoms being motor weakness and abnormal movements<sup>11</sup>; and an older study in Australia found an incidence between 2.3 and 4.2/100,000.<sup>12</sup>

The disorder is diagnosed if there is one symptom that affects motor or sensory functioning causing significant deficit or distress to normal everyday functioning, where there is no organic cause and the symptom is not explained by another psychological or physiological condition.<sup>13</sup> For DSM-5 diagnosis, the occurrence of a stressor is no longer a necessary requirement.<sup>1</sup>

The research that is currently available focuses mainly on the confounding factors and comorbidities of the CD/FND patients. For instance, there is a link between childhood trauma, stressful events and developing CD/FND. There have been reports of symptom onset being marked by stressor life events,<sup>15</sup> and physical, mental and sexual abuse throughout patients' childhood,<sup>6</sup> with emotional and sexual abuse recorded to be a more significant predictor of CD/FND.<sup>14</sup> Although, the childhood trauma is not limited to abuse, there is also evidence that life events exposed to a child increase susceptibility to CD/FND in adulthood. Events such as; parental separation, parental divorce, neglect, family conflict, bullying, maternal or paternal illness, migration and even change of school are all examples of antecedent life events which have been reported by families in relation to CD/FND.<sup>17,18</sup> CD/FND is not the only condition that has been linked to adverse events during childhood. For example, chronic fatigue, which is often thought of as a medically unexplained symptom (MUS), has been shown to correlate with adverse events during childhood as well,<sup>17</sup> and so have anxiety and depressive disorder.<sup>20</sup> There is a correlation amongst characteristics of CD/FND patients such as; female gender, being uneducated, lower socioeconomic status, younger age and from a rural population, minimal medical or psychological knowledge, with these patients being over represented in a standard CD/FND population.<sup>8,18,21,22</sup> Currently, the literature around FND has well investigated comorbidities and confounding factors. Examples of comorbidities would include 'significantly' higher levels of child abuse and adverse events throughout childhood in FND patients when compared to healthy controls.<sup>17,18,21,23</sup> Additionally, an association exists with other psychiatric disorders and conditions including

anxiety, dissociative disorder, post-traumatic stress disorder and depression.<sup>11,16,23</sup>

Treating conversion disorder has had limited success, with a common method of treatment being anti-depressants, talking therapies, such as cognitive behavioural therapy,<sup>24</sup> and hypnosis although, best results are multidisciplinary.<sup>17,18,19,21,23</sup> As with many conditions treatment of children and adolescents are different, there has been research that investigates 'restrained rehabilitation' which is a physical therapy that aims to use favoured activities to drive the rehabilitation of less favoured activities. This means withholding the therapy that would allow resumption of favoured activities until those necessary movements that are harder to motivate for have been completed.<sup>25</sup> Understanding the pathology of the various symptoms would allow treatments to be more successful and reliable, as both medication and 'restrained rehabilitation' are not completely successful often with both having limited and highly varied results. For example, a longitudinal study found worse treatment outcomes in CD/FND patients with adverse childhood experiences compared to CD/FND patients without such experiences.<sup>26</sup>

There has been an increasing amount of research on the effects of chronic low-grade inflammation and functional neurological symptoms in an attempt to investigate the ill-defined mechanism of these symptoms. Certain psychiatric disorders, such as major depressive disorder and bipolar disorder, could have an inflammatory component combined with other pathophysiological processes, although the mechanism is not known.<sup>27</sup> One plausible cause could be due to cell activation from inflammatory markers.<sup>28</sup> Additionally, since cases of depression are a lot higher in those patients who are ill, who also have a confounding inflammation, it could be assumed that inflammation could exacerbate depression and other mental illness, including CD/FND.<sup>28</sup> Furthermore, there is an association between increased stressors and increased mental illness, for instance, chronic marital problems will enhance the vulnerability for depression and uncontrollable events like deaths in the family are powerful triggers for depression.<sup>29</sup>

The possibility of inflammation playing a role in the pathophysiology of this disease could be an answer to how trauma and adverse events have such a detrimental effect on the health of an adult. It is commonly known that stress can induce inflammation,<sup>30–33</sup> by causing imbalances to the homeostatic mechanism, ultimately causing the release of glucocorticoids via the hypothalamic-pituitary-adrenal axis. These stressors can be caused by physiological stimuli, such as infection or temperature changes and by psychological pressures, like adverse events.<sup>33</sup> Therefore, by extension, since stress is caused by adverse events it would not be unreasonable to assume that adverse events could cause inflammation as well.

The aim of this narrative review is to:

- Collate the current research to ascertain the present level of understanding of CD/FND with a primary focus on inflammation, including other topics if they appear relevant with relation to inflammation.
- Discern where the lack of research lies, reviewing which aspect of CD/FND should be investigated.

## Methods

An initial search strain was used on both PubMed and Scopus, which allowed relevant articles written since or in 2000 to be selected. Other articles were found from references and citations within these initial articles, or were suggested by experts. The narrative articles found make up a large proportion of the sources in this review. The search strain and relevant results are shown in [Table 1](#).

Articles that focused on refugees or other specific groups such as veterans were also excluded, as these groups often covered more complex psychopathologies such as post traumatic stress disorder that was a result of trauma during adulthood as opposed to adverse events in childhood. Titles with epilepsy as a keyword were excluded, as were case reports. Beyond these criteria, articles were further excluded based on relevance pertaining to the research question. Papers were further excluded by key words, such as ‘conversion disorder’, ‘adult’ and ‘adolescent’. With these papers having to be written or translated to English, articles and reviews were prioritised.

The remaining articles were reviewed and assessed on relevance and overall quality. Generally, most papers were included if 2 out of 4 topics were investigated and discussed. The four general topics being: chronic low-grade inflammation, FND, childhood trauma or adverse events and activation or action of the immune system.

## Results

A total of 54 articles were found of which 20 were found to be reviews of FND or CD. With the remaining 34 referring to either inflammation, FND or other relevant information or relationships that could be of note. These studies can be seen in [fig. 1](#). The findings are discussed below.

### Chronic low-grade inflammation and CD/FND

There are numerous ways to investigate inflammation in patients. When it comes to evaluating chronic low-grade inflammation, high-sensitivity C reactive protein (hsCRP) is often measured to give a direct reading of inflammation and immune system activation. CRP concentration readings are measures of pathological processes which stimulate CRP synthesis. Increased CRP concentrations can be due to infections, trauma or inflammation.<sup>34</sup>

Groups of children and adolescences who have CD/FND have been shown to have elevated CRP scores which can indicate inflammation.<sup>6</sup> In one study there was no connection between the elevated CRP scores and other factors, such as age or pubertal status.<sup>6</sup> All values of over 10mg/L were still included even though that this indicates a biological pathology and chronic disease; other studies have excluded these readings as they suggest inflammation that is not low-grade and instead a significant pathology, this means that some of the patients who had a higher reading may have inflammation from other causes. Although this was a relatively small study of only 79 participants it was found that if the patients had either experienced maltreatment or who currently suffered from anxiety, they were more likely to have a higher hsCRP score. Indicating that inflammation

is somehow involved in the pathophysiology of these symptoms and disorders, while also having an involvement with either external stress from trauma like maltreatment or anxiety. It would be important to note that the relationship between anxiety and a higher CRP concentration was not a significant result, yet the maltreatment relationship was significant ( $p=0.05$ ). The trauma and maltreatment during childhood was well recorded range from abuse to house fires and bullying, a further finding was that physical ill-health did not contribute to CRP readings but mental-ill health, like an anxiety disorder, did contribute to CRP readings.

This study only showed two thirds of participants have an elevated CRP reading. This emphasises the complexity of the condition as if it was a simple pathology where inflammation was the one and only cause, you would expect a much higher majority of the patients with FND to have an elevated CRP reading. However, since only two thirds of patients had elevated CRP levels, it indicates a more complicated process is the underlying cause. Potentially meaning that there are multiple strains of CD/FND each with different causes or that inflammation is only one stage in the pathology of CD/FND.

In this study, 4 theories of causes are outlined: (1) autonomic modulation of peripheral immune system towards an imbalance in the inflammatory state, (2) activity of glucocorticoids on the brain's glial cells, (3) experiencing dependent gluconeogenesis in response to stress and (4) elevated CRP readings due to changes in the gut microbiota. Although this study, found correlations between a higher hsCRP score and CD/FND, it did not investigate other inflammatory markers.<sup>6</sup>

An additional study investigated different inflammatory markers including TNF- $\alpha$ , IL-6, IL-1 $\beta$  and hsCRP against different symptoms experienced by CD/FND patients.<sup>35</sup> Unlike the previously mentioned study it did not find a significant difference between symptoms and elevated hsCRP, instead finding that different symptoms, such as musculoskeletal, gastrointestinal and general, were marked by different inflammatory markers. Raised hsCRP concentrations were most commonly found in patients who were experiencing motor symptoms, such as paralysis or weakness. This demonstrates the potential for different mechanisms within different symptom categories of CD/FND as it opens the idea that different symptoms could be influenced by different inflammatory factors or by different processes all together. Another find from this piece of research was that there was no correlation between number of symptoms and hsCRP concentration. In a way, further complicating the potential mechanism as it does not seem to be as simple as concentration X high would cause symptom Y.

There would appear to be a difference in the prominence of inflammatory markers amongst children and teenagers, who have experienced abuse. Although these patients, who had experienced abuse during childhood, at the time of the research did not have CD/FND, they were recorded to have a marked increase in TNF- $\alpha$ . The patients who have experienced abuse had a raised hsCRP compared to the healthy control group, showing that the process of abuse and adverse life events in children is linked to increased inflammatory markers. However, in this particular paper there was no indication about how the inflammatory markers would be increased from abuse, and how the inflammatory markers

**Table 1** Search string and results.

Search strain	Database	Number of results
“conversion disorder”	Scopus	3634
“inflammation” AND “conversion disorder” OR “functional neurological disorder”	Scopus	15
“inflammation” AND “conversion disorder” OR “functional neurological disorder” AND “stress”	Scopus	2
“chronic low-grade inflammation” AND “immune system”	Scopus	145
“chronic low-grade inflammation” AND “immune system” AND “functional neurological” OR “conversion disorder”	Scopus	0
“conversion disorder” OR “inflammation” AND “conversion disorder” OR “functional neurological disorder” OR “inflammation” AND “conversion disorder” OR “functional neurological disorder” AND “stress” OR “chronic low-grade inflammation” AND “immune system” OR “chronic low-grade inflammation” AND “immune system” AND “functional neurological” OR “conversion disorder”	Scopus	3780
“Conversion disorder”	PubMed	3200
“inflammation” AND “conversion disorder” OR “functional neurological disorder”	PubMed	113
“inflammation” AND “conversion disorder” OR “functional neurological disorder” AND “stress”	PubMed	19
“chronic low-grade inflammation” AND “immune system”	PubMed	96
“conversion disorder” OR “inflammation” AND “conversion disorder” OR “functional neurological disorder” OR “inflammation” AND “conversion disorder” OR “functional neurological disorder” AND “stress” OR “chronic low-grade inflammation” AND “immune system” OR “chronic low-grade inflammation” AND “immune system” AND “functional neurological” OR “conversion disorder”	PubMed	3345

would possibly affect the nervous system to instigate the symptoms of CD/FND at a later age.<sup>36</sup>

Furthermore, TNF- $\alpha$  could be used to track the progression of CD/FND, as it has been shown to change concentration as the symptoms and disorder progresses.<sup>36</sup> However, this data set did not search the healthy controls or the patients for childhood abuse, as abuse can cause long term inflammation similar to CD/FND but not lead to the symptoms or condition. This should be further investigated in future research. If hsCRP is specific to musculoskeletal symptoms from inflammation related to adverse events in childhood, it could mean a more specific and targeted treatment could be brought out that only had to work on certain symptoms rather than focussing on all aspects of CD/FND.<sup>36</sup>

### Neural changes and CD/FND

The aforementioned theories hypothesised from Kozłowska<sup>5</sup> indicated that there was a possible pathology of CD/FND that involved changes in activity on the brain's glial cells. While glial cells are considered a form of innate immune cells, the changes noted in glial cells are one of many examples that indicate neural anomalies.

Upregulation of sympathetic nervous system and down-regulation of parasympathetic nervous system would cause an inflammatory state in the body. The vagus nerve, a

part of the parasympathetic nervous system, has multiple anti-inflammatory effects; most notably the role it plays in peripheral inflammation. When there is peripheral inflammation, the vagus nerve will be stimulated by interleukins and other inflammatory mediators such as IL-6, TNF- $\alpha$  and IL-1, consequently this causes the vagus nerve to stimulate the adrenal glands to release glucocorticoids, which suppress inflammation, therefore returning the body to a normal homeostasis.<sup>37</sup> If the parasympathetic nervous system is out of balance with the sympathetic, it would cause a decrease in parasympathetic functions and an increase in sympathetic functions, resulting in peripheral inflammation that cannot be ‘switched off’.

This dysregulation of autonomic nervous system has been well recorded in this population. For example, children with CD/FND or functional neurological symptoms have a greater heart rate at both baseline and during cognitive and emotional activation,<sup>38</sup> which shows that there is a general imbalance towards sympathetic nervous activation.<sup>39</sup> The sympathetic nervous system is key in regulating and activating an immune response, having both direct and indirect actions on immunological cells, pathways, blood flow and perhaps most importantly proinflammatory peptide release and production. Meaning that an overactive sympathetic nervous system can lead to an increase release and production of proinflammatory peptides leading to inflammation.<sup>39</sup>

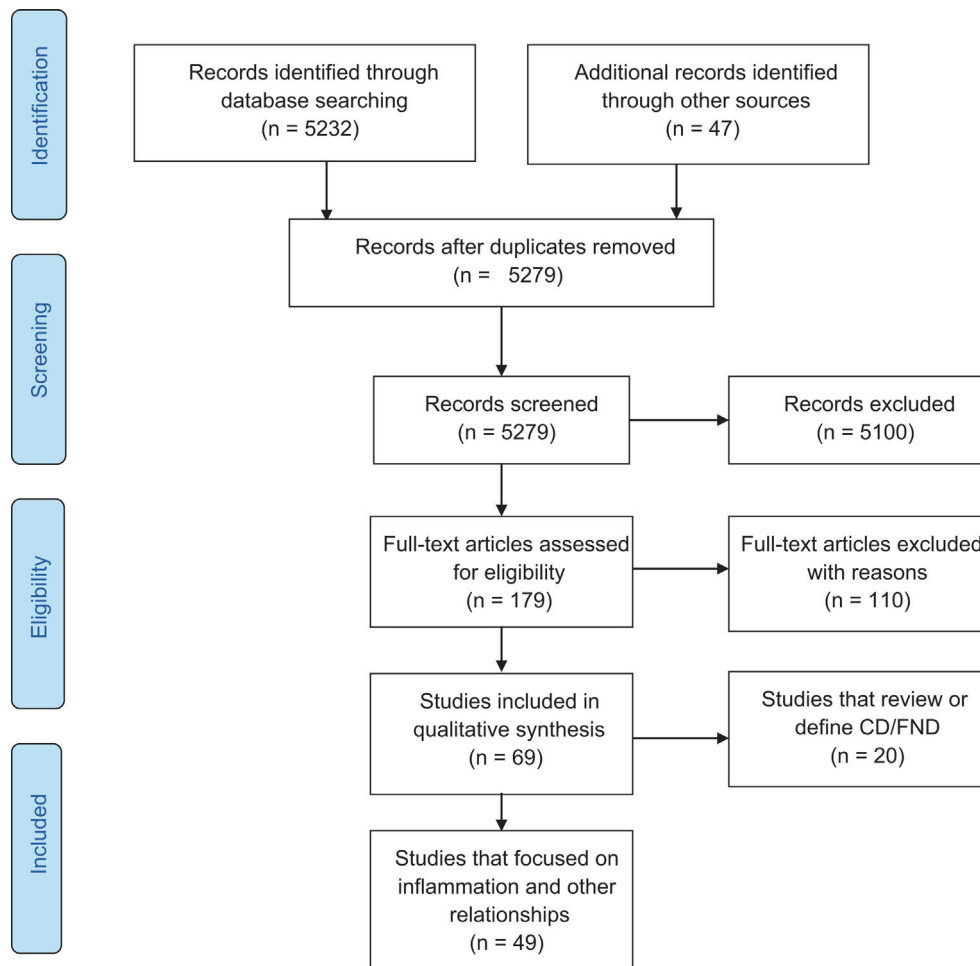


Figure 1 PRISMA 2009 flow diagram.

Karadag et al. imaged the brains of 50 CD/FND patients and compared them to healthy volunteers. It was found that the choroid, a network of blood vessels that cover both the eye and the brain, has degenerated and lost mass, in the CD/FND group. The neurodegeneration of some of the layers in the choroid could be the main pathology itself or the indirect effect of a different process. However, loss of the choroid could be due to inflammation or neurodegeneration in general, much like in Alzheimer's and multiple sclerosis.<sup>40</sup> It was also found that this change can be measured in order to track progression, much like the amount of TNF- $\alpha$  in the patients' blood. These two results can be used to track the stage of the disease and could be used in future research to better understand the pathophysiology of CD/FND.<sup>40</sup>

One systematic review collated research that tracked mental illness and childhood trauma. Not only did they find increased inflammatory markers in the patients who had been abused, but also changes in protein methylation patterns in the brain.<sup>41</sup> These noted changes in proteins caused by changes in the HPA axis could be one of the potential mechanisms that results in CD/FND. Although the patients involved in the study did not have symptoms measured there was no mention or indication they had CD/FND or any functional neurological symptoms the theory could still apply, as there is a known correlation between inflammation and

childhood abuse and adverse events, and so should be further investigated with patients who have FND, to see if there is a relevant correlation. Medically unexplained symptoms, which CD/FND is part of, have been shown to have varying but noticeable changes in HPA activation, however, there has not been enough distinct research on this specific topic for a conclusive definitive relationship to be noted.<sup>42</sup>

Furthermore, a systematic review discovered that childhood stress or trauma primed microglia,<sup>43</sup> a neuronal tissue macrophage which resides in the central nervous system, which can lead to subsequent stress in adulthood.<sup>44</sup> This theory would explain the trend of patients who have experienced trauma and adverse events during childhood, who developed CD/FND later in life as an adult. As noted in the review, if the priming could be prevented, then the disease would never progress to CD/FND or the symptoms. Aside from the overall mechanism being unclear this poses its own unique challenges as it would involve finding children at risk from adverse events, child abuse or childhood trauma. Although, if a therapy was developed that would reverse the priming of the microglia it could be used as a potential preventive treatment. However, there would need to be a substantial amount of research done to investigate the underlying mechanism beforehand.

In addition to these changes in neurones, glia and the brain, there is also evidence that brain derived neurotrophin factor (BDNF) changes in CD/FND. It has been found that while it is elevated in epilepsy, it is decreased in CD/FND.<sup>44</sup> Changes in BDNF have been shown to be recurrent throughout psychiatric illnesses. The role of BDNF, a specialised neuropeptide, is mainly involved with the development and maintenance of neurones. However, it is believed to have some paracrine and autocrine function within its role in supporting sensory neurones.<sup>46,5</sup> Paracrine signalling is mediated by cell-secreted factors that act on neighbouring cells and tissues in a close vicinity, whereas autocrine signalling are cell secretions that act on the cell they were secreted from.<sup>46</sup> Perhaps the decreased serum concentrations of BDNF cause changes in affected sensory neurones, causing paraesthesia and therefore changes in sensation. Although this is an unexplored area with a minimal amount of research investigating a direct relationship. Results from investigations in rodents have shown that stress-induced inflammation has knock-on effects, one of them being the suppression of BDNF. This is thought to be one of the effects of stress-induced inflammation, the others include, decreased neurogenesis, increase apoptosis and increased neuronal damage.<sup>47</sup>

A further point of interest in the pathophysiology of CD/FND is the involvement of the limbic system, which is the main processor of emotions. It would appear that when compared to healthy volunteers who had been age and gender matched to the CD/FND group, it was found that CD/FND patients had greater functional connectivity between the right amygdala and right supplementary motor area during both neutral vs fearful stimuli and neutral vs happy stimuli. This could help explain the relationship between adverse events in adulthood and sudden onset of symptoms, or how external stress or life events seem to coincide with exacerbation of symptoms. Although this paper had a very small sample size of 32 participants, 16 healthy controls and 16 CD/FND patients, it should be repeated with more patients.<sup>48</sup> Furthermore, while it is an interesting discovery, it leaves more questions to be answered as it does not explain why this change occurs, or explain the pathophysiology for people without adverse life events on the onset of symptoms.

Further supporting this growing evidence that there are noted changes in the limbic system and sensorimotor networks, one study imaged 64 patients with functional movement disorders (FMD), a subset of movement symptoms that is still under the CD/FND 'umbrella', finding numerous structural changes and abnormalities when compared to 64 healthy controls.<sup>49</sup> While there was no difference noted between the two groups in terms of sex, age or education level, there was notable differences in grey matter volume. FMD patients had greater grey matter volume compared to healthy controls in the left putamen, left caudate, left cerebellum, left parahippocampal gyrus, left fusiform gyrus and the bilateral thalami. However, the study did not detect any white matter or grey matter differences overall, meaning that the white and grey matter volume changes were leaving the total grey and white matter volume unchanged.<sup>49</sup> Whether these changes in grey matter volume are a result of the disorder or as a cause is unknown currently. This particular sample did not show any discrepancy between

the healthy control and FMD patient in terms of adverse events or childhood trauma, while further not investigating any inflammation or inflammatory factors, leaving it unclear whether or not inflammation is playing a role in these structural changes. These noted differences have been in support of other fMRI imaging studies where connectivity between the right temporo-parietal junction and right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area, and right insula have been decreased.<sup>50</sup> Further demonstrating the widespread changes that are either an effect of CD/FND or the pathology that causes the disorder.

It is important to take note of the complexity of the pathology of this disorder. Even if there are neural changes, it cannot be noted without the obvious interplay from other recorded changes in physiology, such as the changes in the immune system and the HPA axis.

### HPA and immunological changes in FND

Activity of glucocorticoids on the brain's glial cells is another of the proposed theories. Glial cells and microglial cells are a heterogeneous group of innate immune cells that are heavily involved in regulating and modulating the central nervous system (CNS).<sup>33, 51</sup> They have a key role in surveying the brain and its surrounding environment, making them very sensitive to assorted changes.<sup>52</sup> Glucocorticoids are a vast group of proteins that are essential in homeostasis, signalling and general regulation of most bodily processes. Slightest changes in the concentration and type of glucocorticoids can have detrimental effects with a lot of diseases being caused by glucocorticoid changes, such as multiple sclerosis and dementia.<sup>52</sup> Additionally, an increase in concentration of glucocorticoids can be just as severe as a decrease. Meaning that any subtle change in glucocorticoids, either an increase or a decrease, could be responsible for the pathophysiology of CD/FND. Furthermore, concentrations of glucocorticoids are intrinsically involved with the immune system and cause various different effects, for instance: T cell migration back into secondary lymphoid organs,<sup>52</sup> T cell apoptosis<sup>53</sup> and repressed production of pro-inflammatory cytokines.<sup>54</sup> Glial cells have been found to have large levels of glucocorticoid receptors (GR) on their surface,<sup>55</sup> showing how susceptible to glucocorticoid levels they are. This close relationship between the immune system and the autonomic nervous system could explain the link between inflammation and CD/FND. The neuroendocrine system is intrinsic in controlling inflammation in both the CNS and further-a-field, and with the glial cells being highly sensitive to changes in the hypothalamic-pituitary adrenal axis (HPA), the main producer of glucocorticoids, this could mean that glial cells are involved in the pathophysiology of CD/FND.<sup>33</sup> However, there has not been any research that directly investigates these links between glucocorticoids, glial cells, the HPA and FND.

A previously mentioned study by Kozłowska theorised that one of the causes of CD/FND could be autonomic nervous system modulating the peripheral immune response towards an inflammatory state. This is further supported as stress causes changes in both the parasympathetic and sympathetic nervous system. For instance, IL-8 is an interleukin

that is directly involved in the regulation of local pro-inflammatory responses during chronic inflammation that is upregulated during psychological stress.<sup>56</sup> Additionally, people in lower socioeconomic backgrounds have a higher risk of elevated IL-6, which is thought to link low socioeconomic backgrounds to coronary artery disease.<sup>57</sup> As a final example, corticotropin releasing hormone (CRH) is integral in the stress response. Where CRH was released from sympathetic neurones which locally activated components of the innate immune system, such as mast cells.<sup>58</sup>

As seen above there is a lot of focus on the interplay between the immune system and nervous system, which as previously discussed is a potential mechanism for CD/FND pathophysiology. A meta-analysis tracked the progression of mental illness linked with childhood trauma, there was a significant association between childhood trauma and increased immune activation. This meta-analysis also discovered the potential that each type of trauma could impact the heterogeneity in the findings.<sup>36</sup> Like prior papers, unfortunately this data set merely includes mental illness and does not include any direct patients with CD/FND, although due to the link between childhood trauma, CD/FND and inflammation it could still apply or at least be the focus for new research projects with a focus on CD/FND.

Moreover, one 2017 study discovered that there is a hyperarousal stress state in motor symptom FND. This was shown by measuring HPA biomarker and autonomous nervous system biomarker, cortisol and amylase.<sup>59</sup> While introducing the idea of a hyperarousal stress state in CD/FND patients it seems that there is also further evidence that adverse life events are linked with CD/FND, although not a causal relationship, adverse events may still be involved in the pathophysiology of CD/FND.<sup>60</sup>

Although, the idea of stress levels and HPA activation is debated in the pathology of CD/FND, there are varying results on whether or not there is a difference in stress levels between patients and controls. For instance, a study conducted in 2015 sampled the blood of 33 CD/FND patients and 33 sex-matched controls to find that there is no significant difference in circulating cortisol.<sup>61</sup> This further muddies the water on the involvement of the HPA and whether stress is a factor. It may be that cortisol is not the part of the HPA pathway that is the effector of the main changes or that its involvement changes as the disorder progresses. Also it may have to do with the way cortisol was measured. Any way this is a focus for future research.

## Discussion

The current level of research suggests a correlation between inflammation and adverse childhood events, with links between inflammation and CD/FND. However, interestingly there seems to be trends in CD/FND symptoms where only certain symptoms are caused by certain inflammatory factors. This potential trend really increases the complexity of the pathophysiology and by extension, increases the scope for potential treatments as well. For instance, if it turns out that certain inflammatory factors have their own associated symptoms and one patient experiences symptoms that are both from different pathophysiologies like gastrointestinal and neuromuscular. They would require different

and specific treatments, resulting in a complex and tailored treatment plan. Furthermore, it is possible that all the inflammatory markers and their prospective increases are a result of a more complex unknown biological process.

Additionally, there are questions to be answered surrounding how adverse events cause varying degrees of inflammation, with there not being a full link between adverse events in childhood and CD/FND, as not all people who have had trauma in their childhood develop CD/FND, and not all CD/FND patients experienced trauma. Indicating that adverse events in childhood are perhaps an environmental catalyst of sorts that cause the pathophysiology of CD/FND.

Finally, there seems to be a collection of proteins and structures that seem to be involved in the overall pathogenesis of FND, including BDNF, inflammatory factors, and the limbic system. Currently, there is no direct relationship between all these different factors with no explanation how they are involved in the pathophysiology, or even if they are directly involved or merely a change that occurs because of different processes having knock-on effects.

## Limitations

This review has multiple limitations:

The first being the number of articles found. The initial searches uncovered more than 5000 articles, however the focus on inflammation, adverse events in childhood, and CD/FND narrowed the number of relevant studies down greatly. Whilst this may be an indication that this domain so far has not yet been widely explored in CD/FND, some of the exclusion criteria might have prevented research pertaining to the research focus from being included.

There was a general lack of directly relevant research that encompassed inflammation, adverse events in childhood, and CD/FND and inflammation.

Which went that often papers had to be read that did not include some of the relevant topics, which, although it can be useful to increase the general knowledge level, in some situations does put into question the relevance of these articles, and how well translated the research within them is to this review and general topic. Nevertheless, for this review, only relevant material was covered.

Another limitation was that this review did not include case reports or reports about specific groups of patients, such as refugees, rural villages in Asia or groups from the military. There was a concern that this would increase the variability too much, as there would be different adverse events, and if groups from the military were included it would limit the ability to assess adverse events in childhood, instead of PTSD based trauma in adulthood.

## Future research

Overall, there is a gap in the research currently about pathophysiology of CD/FND, although there is increasing research in the interplay between the immune system and central nervous system. However, this is not a definite pathophysiology and instead, an emerging idea. CD/FND, the specific involvement of the immune system and adverse childhood

events are yet to be simultaneously investigated in a rigorous study, instead of often only two of those ideas being investigated at once. Research has investigated more innate pathways such as inflammation pathways, yet currently there is not an explanation on how the inflammation could impact the patient in such a way to result in these symptoms.

There has been research that has investigated the effects of extrinsic stress, such as psychological stress and its effect on gut microbiota.<sup>61</sup> Intestinal microbiota is thought to influence brain chemistry and behaviour independently of both the nervous system and inflammation, meaning that certain microbiota that are in a dysbiotic relationship with the human host could potentially, contribute to psychiatric disorders. This research, although focused on mice, does show that changing microbiota increased hippocampal expression of BDNF, while having varied effects on exploratory behaviour. Therefore should be further investigated in humans, specifically with a underlying gastrointestinal pathology with a psychiatric disorder, namely FND.<sup>62</sup> Microbiome 'health' and quality in the gut has been shown to have some impact on psychiatric disorders such as depression in humans, meaning a healthier diet can decrease depression. However this is only applied to people who can improve their diet further, diet being another factor in a multifactorial condition.<sup>63</sup>

A further example of this is how, if two genetically identical mice with different microbiota can have highly varied inflammatory responses, this perhaps notes the significance microbiota has on the body and its integral functions. Further studies should be carried out to see the potential impacts different microbiota can have on inflammatory and neurological processes in humans.<sup>64,65</sup>

There is an emerging idea that depression and other psychiatric conditions are impacted by certain gram-negative bacteria in the gut, which in turn create an inflammatory process. The lipopolysaccharide fragments the bacteria are thought to interact with toll-like receptors, which in turn released inflammatory mediators such as TNF- $\alpha$ . This could be the start of the inflammatory cascade that causes the chronic-low grade inflammation found in FND and other psychiatric conditions. Although, like many aspects of research, this must be further investigated both in FND but also other psychiatric conditions.<sup>66</sup>

In the future, a further review should be conducted that would include more widespread searches, perhaps including a search strain about inflammation alone, while also including different sections on different demographics, as noted differences in CD/FND could perhaps be documented between different demographics which would aid in the understanding of FND.

Future research will need to address further questions that are currently unanswered by present research. For instance:

- Does inflammation play a direct role in the pathophysiology of the disorder or is it a by-product from another mechanism, such as immune cell activation?
- There seems to be a significance in different levels of inflammatory markers with associated symptoms, is there an overall difference in the symptoms created by the various inflammatory proteins?

- Could the wide array of symptoms found among the patient cohort of functional neurological disorders be due to various different concentrations and mixes of different inflammatory markers, and if so, what would that mean for diagnosing and treating CD/FND as a whole?
- Are there multiple strains of CD/FND each with its own unique pathophysiology, one being related to inflammation, HPA and another neuronal changes, if this is the case where does childhood trauma and stressful life events fit into the overall pathophysiology of these disorders that make up CD/FND as a whole?

All of these potential research questions would lead to very interesting and exciting advances in the overall pathophysiology and understanding of FND.

## Ethical considerations

Ethical approval was not necessary for this narrative review.

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## Conflict of interest

CVDFC is member of the Editorial Board of the journal. The European Journal of Psychiatry has rigorous operational standards in place to ensure that this does not interfere with journal policies regarding independent review and Editorial decision. JR has no conflicts of interests to declare.

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