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Neuroimaging studies in patients with psychogenic non-epileptic seizures: A systematic meta-review

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ABSTRACT

Psychogenic Non-epileptic Seizures (PNES) are 'medically unexplained' seizure-like episodes which superficially resemble epileptic seizures but which are not caused by epileptiform discharges in the brain. While many experts see PNES disorder as a multifactorial biopsychosocial condition, little is known about the neurobiological processes which may predispose, precipitate and/or perpetuate PNES symptomology. This systematic meta-review advances our knowledge and understanding of the neurobiological correlates of PNES by providing an up-to-date assessment of neuroimaging studies performed on individuals with PNES. Although the results presented appear inconclusive, they are consistent with an association between structural and functional brain abnormalities and PNES. These findings have implications for the way in which we think about this "medically unexplained" disorder and how we communicate the diagnosis to patients. However, it is also evident that neuroimaging studies in this area suffer from a number of significant limitations and future larger studies will need to better address these if we are to improve our understanding of the neurobiological correlates of predisposition to and/or manifestation of PNES.

1. Introduction

Psychogenic Non-epileptic Seizures (PNES)[1] are episodic functional neurological symptoms which superficially resemble epileptic seizures but which are not caused by epileptic discharges in the brain (LaFrance et al., 2013). Current medical nosologies class most PNES episodes as a manifestation of conversion/somatoform (DSM 5) or dissociative disorder (ICD-10) without providing any additional insights into the likely neurobiological underpinnings of the disorder (American Psychiatric Association, 2013; World Health Organization, 1992). In fact, the traditional dualistic approach to the understanding of functional disorders such as PNES has only provided psychoanalytic/psychodynamic perspectives, characterizing these disorders as "medically unexplained", and while a host of studies have provided insights into the psychosocial characteristics of PNES (Brown and Reuber, 2016a; Reuber et al., 2007; Wiseman and Reuber, 2015), the biological underpinnings of this disorder have received much less attention.

This is in spite of the fact that many experts see PNES as a biopsychosocial condition (Reuber et al., 2007; Reuber, 2009) and that patients find it difficult to understand how a physical problem such as a seizure could be caused by "purely" psychological processes or emotional problems. As a result, patients often feel misunderstood, dismissed and stigmatized when they are presented with a psychological model of their disorder (Thompson et al., 2009). In fact, patients may reject their PNES diagnosis altogether due to their subjectively physical seizure experiences on the one hand and their dualistic concept of their condition on the other (Rawlings and Reuber, 2016). One could argue that the relative lack of understanding of PNES from a biological perspective does not only hinder our understanding but also has significant implications for the way in which diagnosis is communicated to patients (Green et al., 2004). However, over the last two decades, researchers have begun to employ novel neuroimaging techniques to investigate the neurobiological correlates of PNES. Like other mental health conditions which are not categorised as "medically unexplained", we may now be getting closer to providing a neurobiological perspective which may help to improve our understanding of how

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[1] While the authors have concerns with adopting the term psychogenic non-epileptic seizures (PNES), this was done because this was the most commonly used term in the scientific literature presented in this review. However, defining this condition as 'psychogenic' necessarily implies a purely psychological mechanism underlying non-epileptic seizures. While the psychological aspects of conversion are very helpful to our understanding and treatment of functional neurological disorders such as PNES, it is not clear if they are always necessary or indeed sufficient for the development or maintenance of this condition. Alternative biological explanations of PNES may provide important additional information, which when presented, should be given due consideration.

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neurobiological changes could play a part in the aetiology and maintenance of this disorder.

Although neuroimaging studies focusing on PNES have been summarised previously (Allendorfer and Szaflarski, 2014; Asadi-Pooya, 2015; Baslet, 2011; Perez et al., 2015; Sundararajan et al., 2016), most previous reviews were not systematic and may have missed important studies in this area. In addition, no previous review has sought to uncover convergent neuroimaging findings in patients with PNES to better determine the neurobiological correlates of this condition. To that end, this systematic meta-review provides an up-to-date synthesis and quantification of both structural and functional neuroimaging studies performed on individuals with PNES. Having summarised the research in this area, we provide a critical appraisal of each methodological approach from which the conclusions where derived. This may better inform future research and current theoretical models.

2. Method

2.1. Literature search

The literature search for this review was closed on the 2nd of May 2017. The search terms used to identify relevant publications were 'dissociative seizure*' OR 'non-epileptic attack disorder' OR 'non-epileptic seizure*' OR 'psychogenic non-epileptic seizure*' OR 'conversion seizure*' OR 'pseudoseizure*', AND 'MRI' OR 'fMRI' OR 'imaging' OR 'neuroimaging' in the Web of Science core collection (1960–May 2017; 189), ovid Medline (1960 to May 2017; 209), and Psychinfo (1960 to May Week 1 2017; 392). Our initial literature search identified a total of 790 publications. After a multistage selection process 17 empirical publications were retained and form the basis of this review (Fig. 1).

2.2. Quality assessment of studies

Due to the absence of a suitable rating system specific to studies in this area, a bespoke rating system was employed. This rating system is similar to one used recently by Brown and Reuber (2016a) and was adapted with neuroimaging of patients with PNES specifically in mind. The ratings are based on the proportion of "yes" responses to the following criteria; 1) video-EEG confirmed PNES diagnosis; 2) comparison groups matched for age and gender; 3) patients with mixed diagnosis (PNES plus epilepsy) excluded from the PNES group. If not, was this group compared to a PNES group free of a mixed diagnosis (PNES with no epilepsy); 4) co-existing psychiatric conditions excluded from the PNES group; 5) other central nervous system pathologies excluded from the PNES group; 6) other functional neurological disorders excluded from the PNES group; 7) effects of medication controlled for; 8) image acquisition and analysis discussed in sufficient detail to allow for study replication. The final item relates to sample size. Studies with group sizes ≥ 50 were rated as good, studies with group sizes between16 and 49 were rated as moderate, and studies with group sizes ≤ 15 received a poor rating.

The overall rating was based on the summation of "yes" responses to items 1–8 in addition to weighted scores for sample size. Each item was assigned a score of 0.1 for yes and 0.0 for no, with the exception of sample size (item 9) which was given the score of 0.0 for poor, 0.1 for moderate and 0.2 for good. Therefore, the highest possible rating was 1.0. In addition, studies that reported on the prevalence of brain abnormalities in PNES groups relating to lesions, tumours, evidence of stroke, cysts etcetera were given a score of 0.1 for item 5 (other central nervous system pathologies excluded from the PNES group). It was not deemed appropriate to mark these down when the presence of neurological/CNS pathologies was the primary focus of these studies. In cases in which it was unclear whether or not a study met any of the items described above or where only some of the participants but not all met these criteria, a score of 0.0 was allocated. These ratings were then used to assess the overall quality of the respective research methodology from which the conclusions were derived. Studies with ratings ≥ 0.8 (based on yes item response, score of 0.8 out of 1.0) were rated as high quality. Studies with ratings between 0.5 and 0.7 were rated as moderate and those with ratings between 0.2 and 0.4 were rated as poor.

2.3. Meta-analyses

Nine of the seventeen studies included in this review were eligible for inclusion in our meta-analysis (Table 1). Given that a number of different neuroimaging approaches were used and in order to identify which brain regions were most consistently implicated in PNES across these studies, we conducted a coordinate-based Activation Likelihood Estimation (ALE) meta-analysis using GingerAle 2.3.6 (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012).

This method is capable of integrating findings from multiple imaging modalities and to identify converging brain areas across different experiments/different contrasts and statistically determines whether the convergent brain areas or clusters reported are greater than expected by chance. All available coordinates were transformed from MNI space to Talairach space using icbm2tal transform (Laird et al., 2010; Lancaster et al., 2007) provided by brainmap.org (Eickhoff, 2014). Given that this was an exploratory analysis, and as noted by Eickhoff et al. (2012) both uncorrected p values and FDR corrected thresholds are not always optimal, we opted for a less conservative correction by implementing cluster-level inference. This threshold algorithm uses a "cluster-forming threshold" with an uncorrected p value of 0.001 as the cluster-forming threshold with a cluster-level inference of 0.05 with 1000 permutations, as recommended by brainmap.org. Mango (v 4.0) was used to view the threshold maps and the ALE results were superimposed on the high-resolution standard anatomical brain image provided by brainmap.org (Colin_tlrc.nii).

Given that all of the imaging studies entered into our meta-analysis involved group comparisons, we summed the number of PNES patients and the number of participants in the comparison groups to quantify the number of participants in each study. Where studies came from the same research group and used the same participants (Ding et al., 2014; Li et al., 2014, 2015) we subsumed these participants into a single group of coordinate results in order to avoid any overestimation of these participants in the results. Three different meta-analyses were conducted. The first analysis combined both structural and functional findings from all nine studies. The second analyses focused solely on studies reporting functional connectivity patterns in PNES patients compared to healthy controls. The third and final analysis focused solely on imaging studies reporting structural brain differences between PNES patients and controls. All reported foci (MNI or Talairach coordinates) from these publications entered the ALE analysis. In the results, brain areas within $\pm$ 5 mm^3 of any significant cluster above the corrected p value threshold are also reported.

3. Results/discussion

The results of this review have been divided into three sections. The first section describes the results of the quality assessment. The second section is sub-divided into the different neuroimaging modalities used in which limitations are discussed and future directions proposed. The third section outlines the results of the meta-analyses.

3.1. Quality assessment results and imaging methods

Of the seventeen studies assessed, none were rated as high quality, fourteen were of moderate quality, and three were rated as poor. Eleven (65%) were case control studies and six (35%) adopted a retrospective methodology. Sample sizes were considered good in three (17.6%), moderate in nine (53%) and poor in five studies (29.4%). All studies included both male and female participants, all over the age of 16. Across all seventeen studies the median total sample size was 38 (range