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Resting-state networks and dissociation in psychogenic non-epileptic seizures

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ABSTRACT

Objective: Psychogenic non-epileptic seizures (PNES) are epilepsy-like episodes which have an emotional rather than organic origin. Although PNES have often been related to the process of dissociation, the psychopathology is still poorly understood. To elucidate underlying mechanisms, the current study applied independent component analysis (ICA) on resting-state fMRI to investigate alterations within four relevant networks, associated with executive, fronto-parietal, sensorimotor, and default mode activation, and within a visual network to examine specificity of between-group differences.
Methods: Twenty-one patients with PNES without psychiatric or neurologic comorbidities and twenty-seven healthy controls underwent resting-state functional MR imaging at 3.0T (Philips Achieva). Additional neuropsychological testing included Raven's Matrices test and dissociation questionnaires. ICA with dual regression was used to identify resting-state networks in all participants, and spatial maps of the networks of interest were compared between patients and healthy controls.
Results: Patients displayed higher dissociation scores, lower cognitive performance and increased contribution of the orbitofrontal, insular and subcallosal cortex in the fronto-parietal network; the cingulate and insular cortex in the executive control network; the cingulate gyrus, superior parietal lobe, pre- and postcentral gyri and supplemental motor cortex in the sensorimotor network; and the precuneus and (para-) cingulate gyri in the default-mode network. The connectivity strengths within these regions of interest significantly correlated with dissociation scores. No between-group differences were found within the visual network, which was examined to determine specificity of between-group differences.
Conclusions: PNES patients displayed abnormalities in several resting-state networks that provide neuronal correlates for an underlying dissociation mechanism.

1. Objectives of the study and background

Psychogenic non-epileptic seizures (PNES) are seizures which are assumed to be caused by emotional, rather than organic factors (Bodde et al., 2009a). PNES account for as much as 20% of the definitive diagnoses among patients referred to tertiary epilepsy centres for untreatable epilepsy (Lesser, 1996). The commonly occurring initial misdiagnosis of PNES as epilepsy has serious consequences for the patients, as it results in unnecessary anti-convulsant treatment and delay of appropriate psychological therapy. In addition, erroneous treatment for intractable epilepsy is expensive, and as such, affects societal costs (Martin et al., 1998). Increased understanding and awareness of the pathological

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mechanism and predisposition factors are crucial to facilitate accurate diagnosis and treatment of PNES, preventing burden for both patient and economy.

Patients with PNES are often considered to experience a seizure during an episode of severe dissociation, i.e. an episode of altered conscious functioning caused by disrupted connections between thoughts, memories, feelings, and sense of identity (Stone et al., 2005; Bodde et al., 2009b). In addition, patients with PNES often demonstrate dissociative symptoms (Goldstein and Mellers, 2006), increased dissociation tendency (Alper et al., 1997; Bowman and Coons, 2000; Prueter et al., 2002) and high hypnotisability (Dienes et al., 2009), and have dissociative disorders in over 90% of the cases (Bowman and Markand, 1996), which strongly suggest that dissociation underlies the psychopathology of PNES. Accordingly, the DSM-IV-TR and ICD-10 classifications of PNES as conversion disorder and dissociative disorder, respectively, are still matter of debate (Brown et al., 2007).

The function of dissociation is probably to avoid confrontation with painful or unendurable emotions, which might explain why patients with PNES have difficulties in reporting emotional causes or circumstances of their symptoms (Mellers, 2005; Reuber et al., 2011). Therefore, more objective physiological measures may provide more information about the aetiology of PNES and the underlying process of dissociation than psychological self-report instruments (Baslet, 2011). Neuroimaging methods such as functional MRI can be sensitive to detect changes in the processing of information and emotion by patients with pathological conditions, including dissociative conditions such as PNES (Veltman et al., 2005; Felmingham et al., 2008; Bagshaw and Cavanna, 2013; Van der Kruijs et al., 2014).

In specific, functional connectivity analyses are useful to examine alterations in interaction between brain regions. In our previous fMRI study we adopted functional connectivity analyses in order to examine altered information processes in a pilot population of patients with PNES (Van der Kruijs et al., 2012). However, in that study we focused on pre-defined regions of interest and therefore needed a priori assumptions. In order to investigate whole-brain networks in patients with PNES, and without making a priori assumptions, the current study examines functional MRI of brain networks that are activated during resting state using a robust data-driven approach, independent component analysis (ICA) (Beckmann et al., 2005; Calhoun et al., 2009). ICA is employed in this study to decompose resting-state fMRI data of patients with PNES and matched healthy controls into a set of statistically maximally independent functional networks. The resting-state networks that are identified are compared with a highly robust set of resting-state networks described by Smith et al. (2009). Smith et al. demonstrated that brain regions that are functionally related also interact during "rest", and identified ten resting-state networks associated with specific functions. We focused on four networks which are of specific relevance with regard to the trait of dissociation. The resting-state network associated with *executive control* covers several medial-frontal areas, including the anterior cingulate and paracingulate cortex, and is regarded relevant for its function in action-inhibition, emotion, and perception-somesthesis-pain. The *fronto-parietal* network covers insular regions and is as such also associated with perception-somesthesis-pain. The *sensorimotor* network includes the supplementary motor area, sensorimotor cortex, and secondary somatosensory cortex, and is involved with action-execution and perception-somesthesis. The *default mode* network, known from task-fMRI to be typically active during rest, covers the precuneal, posterior cingulate and ventromedial frontal cortex, and is selected for its possible function in self-reflection and self-awareness (Gusnard et al., 2001; Schneider et al., 2008). To examine the specificity of changes identified in these networks, we also include a resting-state network which is unlikely to be affected by PNES, namely the *visual* network which covers the visual areas in the occipital lobe.

1.1. Aims of the study

Our first aim is to examine alterations in resting-state networks that may underlie PNES psychopathology, comparing adult patients with PNES with matched healthy control subjects. The second goal of the study is to investigate the association of altered resting-state connectivity with indices of dissociation.

2. Materials and methods

2.1. Participants

The inclusion of the study population was according to the same criteria as have been described in a previous paper (Van der Kruijs et al., 2012), in which we report on seed-based functional connectivity analyses on a subset (11 patients with PNES and 12 healthy controls) of the current study population. In short, patients were recruited from the outpatient epilepsy clinic of the tertiary referral centre Kempenhaeghe. Patients with a confirmed diagnosis of PNES were screened by their treatment team (consisting of clinical psychologist and neurologist) before study inclusion, which occurred on the absence of psychiatric comorbidity (e.g. mood and anxiety disorders, schizophrenia and psychosis, and cluster B personality disorders), determined through extensive psychological assessment and examination of anamnestic information, which was provided by the patients themselves and often also by family members. Individuals with neurological comorbidities (e.g. epilepsy) and malingering patients were not included. At moment of inclusion and during investigation, none of the patients used antiepileptic medication. Healthy controls were recruited by advertisement. All participants gave written informed consent to participate in the investigation, which received ethical approval by the Medical Ethical Committee of Maastricht University (ref. 10-3-045) and was carried out in accordance with the 7th revision of the Declaration of Helsinki.

2.2. Questionnaires and neuropsychological investigation

All participants completed the Raven's Progressive Matrices Test (Raven et al., 1998, updated 2003), which indicates global cognitive performance. We obtained completed dissociation scales (Dissociation Questionnaire (DIS-Q), Dissociative Experiences Scale (DES), and the Somatoform Dissociation Questionnaire (SDQ-20) (Sno, 2004)) from 20 patients with PNES and 27 healthy controls, as one patient did not complete the questionnaires. All questionnaires are often used to examine dissociation tendencies of patients with PNES (Kuyk et al., 1999; Reuber et al., 2003; Ito et al., 2009).

2.3. MRI acquisition

MRI imaging was performed at the epilepsy centre Kempenhaeghe using a 3.0-T unit equipped with an 8-channel head coil (Philips Achieva, Philips Medical Systems, Best, The Netherlands). The scan protocol for structural MRI consisted of a T1-weighted 3D turbo field echo with the following parameters: Repetition time (TR) 8.2 ms, echo time (TE) 3.7 ms, inversion time (TI) 1022 ms, flip angle 8°, matrix 240 × 240, field of view (FOV) 256 × 256 × 180 mm^3, and 1 mm adjacent coronal slices.

Functional MRI data were acquired using a whole-brain single-shot multi-slice blood oxygen level-dependent (BOLD) echo-planar imaging (EPI) sequence with the following parameters: TR 2 s, TE