



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 pre-cuneus 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.

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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

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(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

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 mm³, 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

35 ms, flip angle 90°, voxel size $2 \times 2 \times 4 \text{ mm}^3$, matrix 128×128 , 32 contiguous slices per volume, 195 volumes per acquisition. During the resting state fMRI session, the subjects were instructed to think of nothing in particular. A total of 2 resting-state fMRI sessions was performed per participant, with an interval of 15 min (Van der Kruijs et al., 2012).

2.4. Imaging analysis

Resting state fMRI analysis was performed using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC; FMRIB's Software Library, <http://fsl.fmrib.ox.ac.uk/fsl>). Individual preprocessing comprised motion correction performed using FMRIB's Linear Image Registration Tool (MCFLIRT), brain extraction, spatial smoothing with a Gaussian kernel of full-width-at-half-maximum (FWHM) of 5 mm, high-pass temporal filtering at 100 s (0.01 Hz), intensity normalization, and affine registration to the Montreal Neurological Institute 152 standard space template. The preprocessing also consisted of removal of the first 6 s (3 volumes) from each time series to ensure magnetization equilibrium. The absolute head motion (mean) was below 1.9 mm for all subjects across both the sessions, and not significantly different between patients and controls. As a result, the preprocessed functional data contained 192 time-points for each subject per session. The preprocessed data were temporally concatenated across subjects and sessions to create a single 4D data set. This way, the data points of both resting-state fMRI sessions were taken into consideration for computing the independent components. This single 4D data set was then decomposed into spatio-temporal components that represent large-scale patterns of co-activating voxels that are consistent over subjects, taking into consideration the statistically independent sources of variation in the fMRI signal (Beckmann et al., 2005). MELODIC's probabilistic group ICA was used and identified 33 independent components using automatic model-order estimation. From these, we objectively identified the 5 components (Fig. 1) based on spatial cross-correlation with a minimum Spearman's correlation of 0.32 ($p < 0.05$) corresponding to the maps of the resting-state networks associated with executive functioning, fronto-parietal activation, sensorimotor functioning, default mode activation and visual functioning (Smith et al., 2009) using templates from <http://fsl.fmrib.ox.ac.uk/analysis/brainmap+rsns/>, and overlap was also confirmed by visual inspection.

Subsequently, the pooled functional networks (i.e. controls and patients) were mapped to the subject level using the dual regression approach (Filippini et al., 2009). The motivation to perform a pooled analysis of both controls and patients is i) to increase reliability by using a larger subject sample, and ii), since the major ICA components, as indexed by Smith et al. (2009), can be identified in a very robust manner over a large heterogeneous sample of subjects, it is reasonable to assume that these major networks are also present in controls and patients.

Firstly, the full set of group-ICA spatial maps was used in a linear model fit (spatial regression) against the separate fMRI data sets, this creates matrices describing temporal dynamics for each component and subject. Secondly, these time course matrices were used in a linear model fit (temporal regression) against the corresponding fMRI data set to estimate individual subject spatial maps. Thirdly, the different independent component maps were concatenated across subjects into single 4D files (one per original ICA map, with the fourth dimension corresponding to subject identification).

Next, the maps were tested voxel-wise for statistically significant differences between the patient and control group using nonparametric permutation testing (5000 permutations) using FSL's randomize tool. This yielded spatial maps characterizing the group differences. Lastly, these spatial maps were thresholded based on an alternative hypothesis test by fitting a Gaussian/gamma mixture model to the distribution of voxel intensities within spatial maps and controlling the local false discovery rate at $p < 0.05$ to yield multiple-comparisons corrected group difference maps (Beckmann et al., 2005).

The temporal weight of an independent component in a particular voxel is ideally the correspondence of a voxel's time-course to the time signature of the resting-state network under investigation, and can be interpreted as a measure of functional connectivity with the component under investigation. In order to reveal a potential relationship between the weight of the independent components that differ significantly across patients and controls and known clinical (psychological) parameters, the following procedure was carried out. ROIs were drawn on the independent component maps in the networks where significant differences in the functional connectivity between the patients and controls were found (i.e. the aforementioned spatial maps). The weight of the independent components in both the sessions was averaged across these ROIs to produce mean connectivity values for

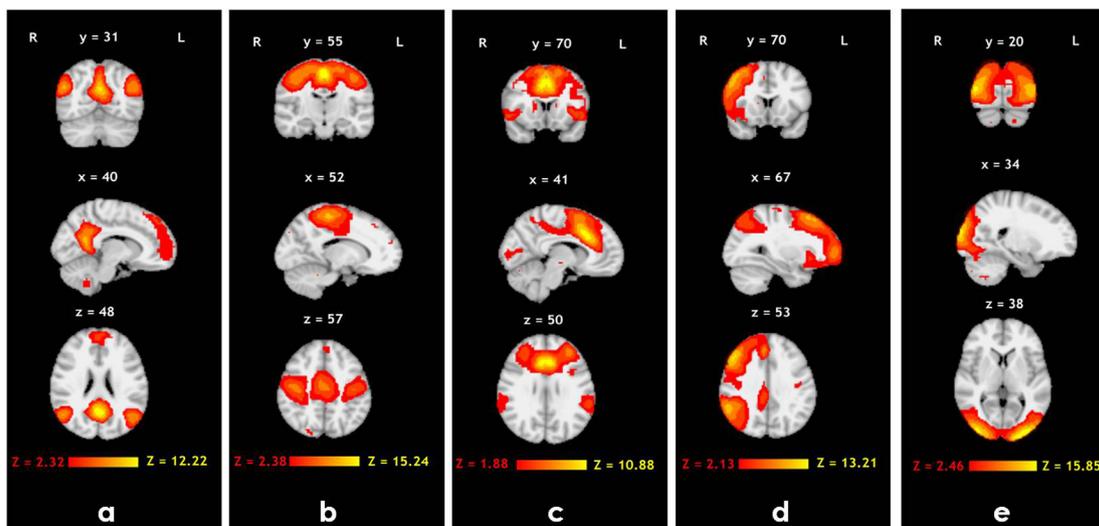


Fig. 1. The five networks which cross-correlated well with the primary functional networks identified by Smith et al. [2] for default mode (a), sensorimotor (b), executive (c), frontoparietal (d), and visual functioning (e). Coordinates (x y z) refer to MNI space.

each patient and control, which could then be correlated with clinical parameters.

2.5. Statistical analysis

Statistical data analysis was performed in SPSS (PASW Statistics 18.0, Chicago: SPSS Inc.). Descriptive statistics of clinical and neuropsychological variables were obtained, and Mann–Whitney *U*-tests were performed to examine differences between patients with PNES and controls. Additionally, correlation coefficients between regional variations in functional connectivity with neuropsychological scores were obtained using the non-parametric Spearman rank correlation test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical and neuropsychological assessment

Twenty-eight patients with PNES and 30 healthy volunteers were enrolled in the study. All structural MRI scans were interpreted for incidental findings by an experienced neuroradiologist. Ten participants had to be excluded from the MRI analyses: Four patients with PNES did not complete the study, two patients showed large cysts on MRI, one patient had parahippocampal gliosis, and three healthy controls demonstrated callosal white matter abnormalities, unclear contouring of the ventricles, and periventricular heterotopia on MRI. The other subjects did not have clinical significant MRI abnormalities. The final analysis included 27 healthy volunteers (21 females, 6 males, age 36 ± 12 y) and 21 patients with PNES (13 females, 8 males, age 34 ± 12 y, number of seizures in previous month 12.3 ± 34.1 , disease duration 5.7 ± 6.7 y). Gender and age were not statistically different between both groups ($p > 0.25$). According to the classifications of Abubakr et al. (2003), PNES were classified as episodes of major motor symptoms (during which patients are often unresponsive) in 7 patients, as episodes of unresponsiveness without major motor symptoms in 12 patients, and as the two types of PNES episodes combined in 2 patients. The patients demonstrated significantly higher dissociation tendency on all dissociation questionnaires; the DES (1.7 ± 1.27 vs 0.6 ± 0.58 [ctrl], $p < 0.001$), DISQ (1.6 ± 0.38 vs 1.4 ± 0.22 , $p = 0.007$), and SDQ-20 (28.0 ± 6.80 vs 21.5 ± 4.74 , $p < 0.001$), and significantly lower performance on the Raven's Progressive Matrices test (Raven nr correct: 46 ± 7 vs 51 ± 5 , $p = 0.017$), as assessed with Mann–Whitney *U* tests.

All patients with PNES had a scheduled consult with their psychotherapist directly after the scanning session, to evaluate whether the patients experienced tension, anxiety or recall of memories during the procedure, and to examine whether dissociative phenomena took place. Also, all patients were instructed to use the alarm button in case of aversive feelings. However, none of the patients used the alarm button or reported negative experiences after the scanning session. There were also no indications of pathological dissociative experiences during the scanning sessions. However, since we have no systematic data on what the patients experienced in the scanner, we cannot be certain that minor dissociation or anxiety did not occur.

3.2. Imaging analysis

Pooled probabilistic group ICA identified 33 components. Of these, we selected 5 components for further analysis based on neuroanatomical correspondence with the consistently identified resting-state networks described in the literature (Smith et al., 2009). Based on the regions involved, these networks have been associated

with fronto-parietal activation, executive control, sensorimotor functioning, default-mode activation and visual functioning.

Compared to healthy controls, patients with PNES showed increased coactivation of the orbitofrontal, insular and subcallosal cortex in the resting-state network associated with fronto-parietal activation; the cingulate and insular cortex in the resting-state network associated with executive control; the cingulate gyrus, superior parietal lobe, pre- and postcentral gyri and supplemental motor cortex in the resting-state network associated with sensorimotor functioning; and the precuneus and (para-) cingulate gyri in the default-mode network. On the other hand, patients with PNES showed relatively decreased coactivation of the orbitofrontal cortex in the resting-state network associated with executive control, and of the precuneus in the resting-state network associated with sensorimotor functioning (Fig. 2). There were no significant differences between patients and controls in the resting-state network associated with visual functioning.

3.3. Correlation analyses

The connectivity values within the areas of significant between-group differences were all significantly correlated with all dissociation scales within both groups (patients and controls) combined (Table 1). Within the healthy control group, significant correlations were found between connectivity strengths within the executive control network and DES scores ($\rho = 0.43$, $p = 0.024$), and connectivity strengths within the sensorimotor network and DISQ scores ($\rho = 0.45$, $p = 0.020$) and SDQ scores ($\rho = 0.55$, $p = 0.003$). Other correlations within both groups separately showed similar trends with regards to the combined group regarding direction of correlation, but did not yield statistical significance ($p > 0.080$).

Correlations were positive between dissociation scores and functional connectivity values within areas where patients showed higher connectivity than controls, and negative between dissociation scores and connectivity values within areas where patients showed lower connectivity. Fig. 3 illustrates these findings by showing the relationship between connectivity values within the executive functioning network and scores on the Dissociative Experiences Scale. Correlations with results on the Raven's Matrices test were only significant for the connectivity values within the default mode network and the sensorimotor network, in opposite directions as found with dissociation scores. No significant correlations between disease duration and connectivity strengths were found ($p > 0.174$).

4. Discussion

4.1. Main findings

Using a data-driven approach, we have shown that patients with PNES have an increased coactivation of several regions in the resting-state networks associated with fronto-parietal activation, executive control, sensorimotor functioning, and the default mode. Decreases in network contribution were identified within the networks associated with executive control and sensorimotor functioning. The connectivity values within the regions of interest were significantly correlated with dissociation scores. No differences were found for the control resting state network associated with visual functioning, which confirms that visual behaviour is most likely not affected by PNES or dissociation.

4.2. Resting-state networks and dissociation in PNES

The alterations identified in the resting-state networks could all contribute to the process of dissociation in patients with PNES in a

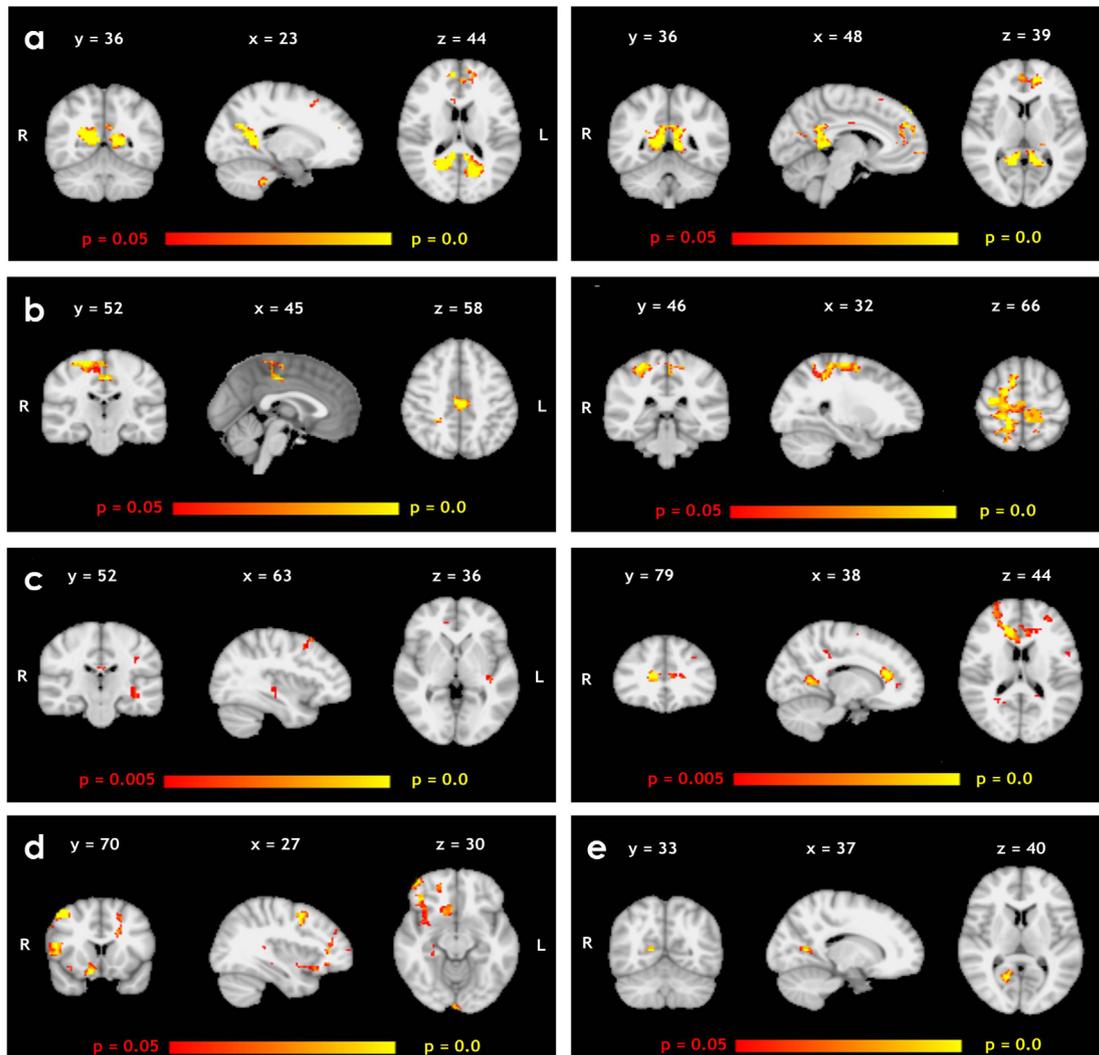


Fig. 2. Regions of increased network contribution in patients within the networks for default mode (a), sensorimotor (b), executive (c), and frontoparietal (d), and regions of decreased network contribution in patients within the sensorimotor network (e). In order to aid visualisation, a stronger p -value has been selected in figure 2c.

distinctive way (see Fig. 4 for a schematic overview). The fronto-parietal network corresponds strongly to perception, somesthesia, and pain (Smith et al., 2009); alterations in this network may be associated with the observation that self-generated movements are not voluntary. In particular altered connectivity of the insula, as was found within this network, has been related to impairments in

Table 1

Spearman's correlation coefficients between functional connectivity values in aberrant regions (ROIs), dissociation scores, and scores on Raven's Progressive Matrices Test.

	DES total score	DISQ total score	SDQ total score	Raven nr. correct
<i>Patients > Controls</i>				
Fronto-parietal network	0.40**	0.34*	0.58**	-0.18
Default mode network	0.38**	0.35*	0.56**	-0.38**
Sensorimotor network	0.41**	0.38**	0.47**	-0.10
Executive control	0.54**	0.39**	0.47**	-0.19
Visual network	N/A	N/A	N/A	N/A
<i>Controls > Patients</i>				
Sensorimotor network	-0.39**	-0.29*	-0.43**	0.30*

* $p < 0.050$ and ** $p < 0.010$.

Correlations coefficients are shown for regions in which patients with PNES showed relatively increased (Patients > Controls) and decreased (Controls > Patients) network contribution.

conscious error perception (Klein et al., 2013). Impaired error awareness may prevent patients with PNES to recognize incorrect (dissociative) behaviour and to adjust future behaviour, as has been suggested in other psychiatric conditions, e.g. schizophrenia (Mathalon et al., 2002), autism spectrum disorder (Vlamings et al., 2008; Sokhadze et al., 2010) and ADHD (Schachar et al., 2004; Wiersma et al., 2009).

Similar conclusions can be drawn from the abnormalities located in the sensorimotor network, the primary functions of which, next to motor preparation, also are perception, somesthesia, and pain. The abnormalities associated with PNES found in this network, especially within the cingulate gyrus, might be related to altered (motor) response selection (Devinsky et al., 1995).

The network for executive control also covers perception-somesthesia-pain, as well as action-inhibition and emotion; alterations in this network might contribute to the manifestation of emotional triggers as motor symptoms. As both the insular and cingulate cortex show abnormal functional connectivity in this network, this behaviour might be explained from impaired action selection and/or decreased response-inhibition (Devinsky et al., 1995; Klein et al., 2013).

The default-mode network has been linked to self-referential or introspectively oriented mental activity (Gusnard et al., 2001;

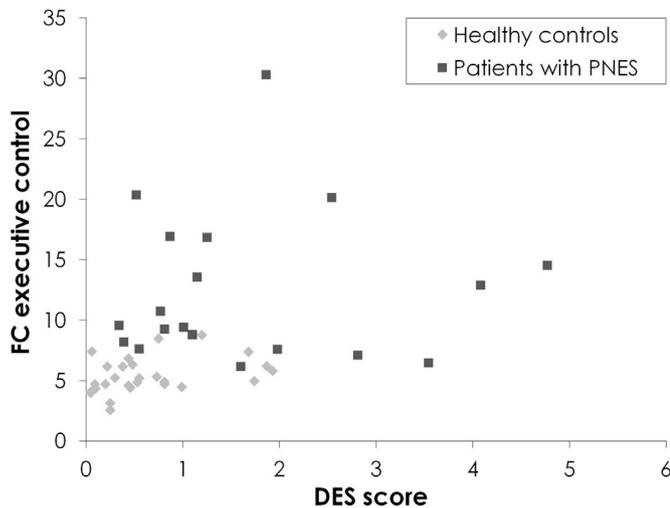


Fig. 3. Scatter plot of functional connectivity values in the aberrant regions of the executive functioning network and DES scores in the whole population ($r = 0.54$, $p < 0.001$).

Schneider et al., 2008). It has also been related to the sense that one controls one's own actions and self-reflection processes, which is important for motor intentions and subsequent action monitoring (Tsakiris et al., 2010; Cavanna and Trimble, 2006; Cavanna, 2007). These findings suggest that abnormalities in the default mode network in patients with PNES could reflect abnormal coping styles (e.g. dissociation) and lack of motor control. Furthermore, studies employing neuroimaging techniques indicate the default mode network to play a central role in sustaining consciousness (Demertzi et al., 2013). This network may be important for the specific alterations of consciousness, in addition to dissociative experiences, that have been identified in patients with PNES (Ali et al., 2010).

Previous research also suggests altered connectivity of the precuneus within the default mode network to be of influence in maintaining hypnosis (Pyka et al., 2011). Since hypnosis is an

altered state of consciousness in the same spectrum as dissociation, these findings might explain the increased coactivation of the precuneus found in patients with PNES.

Besides significant correlations between functional connectivity and dissociation scales, we also identified an association between global cognitive functioning as assessed with the Raven's Progressive Matrices Test and functional connectivity values within the sensorimotor and default mode networks. However, only one of them was significant at the $p < 0.01$ level, whereas most other networks showed no significant correlation, suggesting that the aberrations in resting-state networks of patients with PNES are likely to be caused by other factors than intelligence. However, other factors besides dissociation, e.g. anxiety, may also contribute to the observed network alterations.

The results of this study are consistent with previous findings in a pilot study which was based on a priori assumptions, in which we identified higher functional connectivity values between regions in the frontal, parietal, and limbic cortices in patients with PNES, e.g. between the insula and the precentral sulcus (involved in motor preparation) (Van der Kruijs et al., 2012). Due to the data-driven approach in the current study, the search window of potential abnormal brain regions was increased to include the whole brain. As the current study located abnormal network function in regions beyond the abnormal regions found in the pilot study (e.g. the precuneus), the current study provides a completer picture of the implications of PNES and dissociation on brain function. Our findings are also coherent with alterations in functional connectivity that have been identified in other populations with functional symptoms: between the motor cortex and posterior cingulate cortex, precuneus and ventromedial prefrontal cortex in conversion paralysis (Cojan et al., 2009), between the supplementary motor cortex and the amygdala in conversion disorder (Voon et al., 2010), between the prefrontal and sensorimotor cortices in conversion paralysis (De Lange et al., 2010), between supplementary motor and dorsolateral prefrontal cortices in conversion disorder (Voon et al., 2011). Also, altered topological properties of whole-brain networks as increased clustering coefficient, but also increased path length and decreased connection strength have been reported in PNES (Ding et al., 2013).

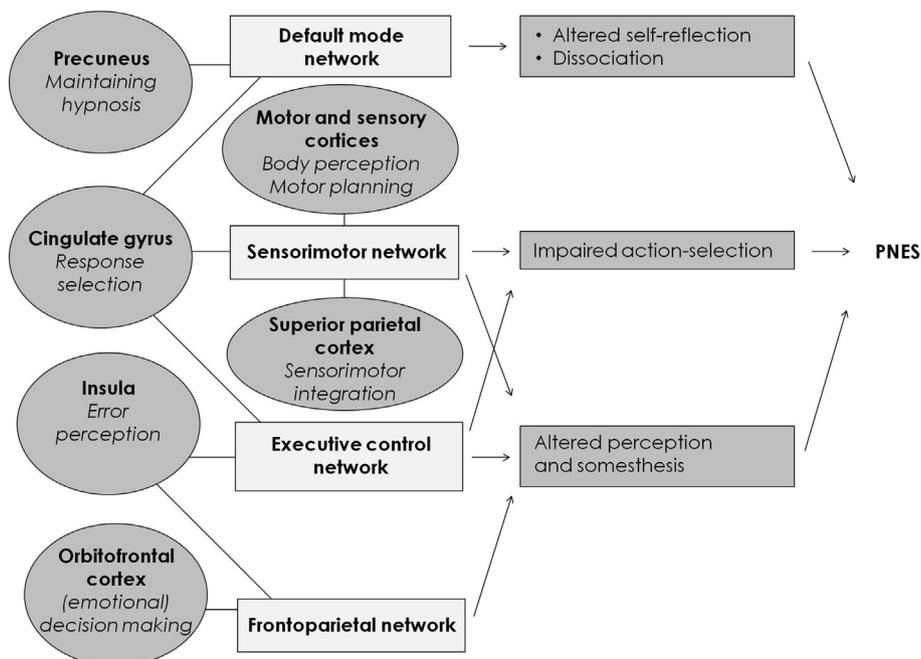


Fig. 4. Schematic representation of the investigated resting-state networks and their potential contributions to the occurrence of PNES.

These findings suggest that brain networks in patients with PNES lack optimal information-integration abilities, which is possibly reflected in the abnormal coping style of these patients.

4.3. Limitations and future considerations

One drawback of our study was that significant correlations between connectivity strengths and dissociation scores were obtained within both groups (patients and healthy controls) combined. There is a risk that these correlations are explicable by group differences in connectivity strengths and dissociation scores (Kriegeskorte et al., 2009). However, all within-group correlation analyses displayed similar, though not always significant outcomes, which is indicative of the robustness of the findings. The lack of statistical significance is possibly due to the relatively small group sizes.

Another difficulty was the inability to disentangle the effects of PNES and dissociation, because most included patients had both PNES and high dissociation scores, and not enough healthy controls demonstrated high dissociation scores to be able to split groups based on dissociation scores. Future studies should focus on dissociation scores at moment of inclusion, although ethical considerations may complicate the handling of such criteria. Moreover, the causal direction of the relationship between dissociation and brain network alterations is not known. In addition, the dissociation scales which are currently available and which were used in this study only measure dissociation as a trait, not as a state. Future studies could focus on patients who do not show increased dissociation tendencies, but who may dissociate during PNES episodes.

Furthermore, the current study, though preliminary in nature, yields promising steps towards an objective diagnosis of PNES using functional MRI. However, at present, the technique should only be used to supply complementary information for the current clinical practice, in which video-electroencephalography procedures are considered the gold standard for differential diagnosis between epilepsy and PNES (Eddy and Cavanna, 2014). Future longitudinal studies are warranted to investigate these issues.

Future studies are also needed to investigate whether a structural substrate for the resting network abnormalities can be found. Diffusion tensor imaging (DTI) and voxel-based morphometry are examples of techniques which could be useful to examine the microstructural integrity of the brain. Additionally, molecular and/or “imaging genetics” studies might yield more insight into the underlying molecular mechanism of the observed differences in resting-state functionality.

5. Conclusion

Abnormalities in resting-state networks associated with frontoparietal activation, executive control, sensorimotor functioning, and default-mode activation have been identified in patients with PNES. Significant correlations suggest the network alterations to be related to the process of dissociation. The changes in resting-state networks could contribute to the underlying dissociation mechanism in various ways.

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Contributors

Authors Van der Kruijs, Bodde, Lazeron, Vonck, Boon, Cluitmans, Backes, Hofman, Aldenkamp and Jansen designed the study and wrote the protocol.

Author Van der Kruijs managed the literature searches and analyses.

Authors Van der Kruijs, Bodde and Jansen collected the data.

Authors Jagannathan, Besseling and Jansen undertook the image analysis, author Van der Kruijs undertook the statistical analysis and wrote the first draft of the manuscript.

All authors contributed to and have approved the final manuscript.

Conflicts of interests

None of the authors has conflicts of interest to declare.

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