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Cortical thickness, surface area and folding in patients with psychogenic nonepileptic seizures

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Summary
Objective: To determine cortical thickness (CTh), cortical surface area (CSA), curvature and sulcal depth (SD) in patients with psychogenic nonepileptic seizures (PNES).
Methods: Freesurfer software was used to identify differences between active and control group in Cth, CSA, curvature, and SD. Neuropsychological tests intending to document possible frontal lobe deficit were applied.
Results: We included 37 patients with PNES (age 37.3 ± 13.8; female/male 31/6; age of disease onset 26.1 ± 10.6; age of disease duration 11.1 ± 11.1), and 37 healthy controls (age 38.4; ±12.7; female/male 26/11). No difference in CSA and curvature was detected between groups. Patients with PNES had increased CTh in the left insula, left and right medial-orbitofrontal, and left lateral-orbitofrontal, and decreased CTh in the left and right precentral, right enthorinal, and right lateral-occipital region than healthy controls. SD was increased at the level of the left and right insula, right rostral anterior cingulate, right posterior cingulate, and left cuneus, and reduced at the level of the right and left medial-orbitofrontal sulci in patients with PNES compared to healthy controls.
Conclusion: Individuals with PNES display a distinct profile of changes in CTh, in association with increase in SD in both insula as compared to controls. Our results may contribute to the understanding of the neurobiological background of PNES. Further research, to include replication of the findings and directed to understand the role of insula is needed.

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Introduction

The International League Against Epilepsy (ILAE) has identified psychogenic nonepileptic seizures (PNES) as one of the 10 key neuropsychiatric issues associated with epilepsy (Kerr et al., 2011). The accurate diagnosis of PNES is essential, as misdiagnosis of PNES leads to inappropriate treatment of presumed epilepsy with significant consequences. The most reliable diagosis of PNES, in addition to good clinical data, relies on the habitual event being recorded on video EEG (vEEG) (LaFrance et al., 2013). Although classical psychiatric theory explains PNES in the context of psychological and psychodynamic models, preliminary data from recent neuroimaging studies argue for the presence of impairment in motor conceptualization or abnormal limbic-motor interaction (Voon et al., 2010). The results of resting-state functional MRI results in PNES patients show abnormal, strong functional connectivity between the insula and precentral sulcus. This provides a possible neurophysiological correlate where emotions can influence executive control, resulting in altered motor function (van der Krujis et al., 2012).

Disease-related cortical volume and cortical thickness measures have been employed to better understand the underlying pathophysiology in temporal lobe epilepsy (Keller and Roberts, 2008). In addition, these data were used in explore the role of frequently used antiepileptic drugs. The authors showed that the use of sodium valproate is associated with parietal lobe thinning, reduced total brain volume, and reduced white matter volume (Pardoe et al., 2013). Both morphologic whole-brain MRI measurements, voxel-based morphometry (VBM) (Ashburner and Friston, 2000), and *Freesurfer* analysis (Fischl and Dale, 2000), have been used in epilepsy patients. VBM and cortical thickness on *Freesurfer* were analysed in a single study of subjects with PNES. The authors showed abnormal cortical atrophy of the motor and premotor regions in the right hemisphere and the cerebellum bilaterally, in addition to significant association between increasing depression scores and atrophy involving the premotor regions. Nevertheless, the authors acknowledged the sample size (20 patients) as the major weakness of the study (Labate et al., 2012).

Several other brain morphometric measurement methods are currently available. Cortical volume is the composite of cortical surface area and thickness. Recent work has illustrated that both are highly heritable but genetically unrelated (Panizzon et al., 2009). Some authors have found distinct results when analysing patterns of cortical surface area reduction and neocortical thinning in temporal lobe epilepsy patients (Alhusaini et al., 2012). Studies of the morphology of the cortical surface (variability of folding patterns) have provided sufficient results to deserve the interest of scientific audience (Mangin et al., 2010). Studying the morphologic patterns of the inferior surface of the temporal lobe in healthy controls and patients with temporal lobe epilepsy, authors have described ''simplified'' and unbroken collateral sulcus as the predominant sulcal pattern. They suggest that these may be an indicator of neurodevelpomental abnormality associated with this condition (Kim et al., 2008). The single published morphometric study on PNES studied to date did not publish data on cortical surface area, and morphology of the cortical surface (Labate et al., 2012).

There is a strong case for further exploration of the morphometric abnormalities in patients with PNES. Our aim was to examine, by comparing PNES patients to healthy control subjects, several parameters of cortical anatomy in patients with PNES; including cortical thickness, cortical surface area, and cortical folding (curvature and sulcal depth) that may contribute to PNES pathophysiology. In addition, we investigated the association between clinical parameters and neuropsychological assessment measures and data from morphometric analysis.

Materials and methods

Patients and controls

Patients were recruited from a cohort of 564 subjects who underwent video-EEG telemetry at the Epilepsy Center, Neurology Clinic, Clinical Center of Serbia in the period between June 2010 and December 2013. Indications for telemetry included: differential diagnosis, epileptic syndrome definition and presurgical evaluation.

The diagnosis of definite PNES was made when: (a) patients with indicative clinical history had spontaneous seizures recorded during vEEG or habitual attacks provoked by a subcutaneous administration of saline solution while under vEEG; (b) all recorded seizures were considered habitual by seizure witnesses, and (c) epileptiform interictal discharges and ictal EEG that correlates with clinical event were not registered. All PNES patients underwent the protocol routinely used for patients with epilepsy (brain MRI and neuropsychological assessment). Only patients with diagnosis of definitive PNES were included in the analysis.

PNES were classified according to their resemblance to epileptic seizures during telemetry: (1) dialeptic-like-loss of consciousness without motor phenomena; (2) astatic-like-loss of consciousness and muscle tone with fall; (3) motor—different motor phenomena; and (4) multiple. A control group ($n = 37$) was identified among staff of the Neurology Clinic, Clinical Center of Serbia, and students from the Medical School, University of Belgrade with no previous history of neurological and psychiatric diseases. Neurological examination were normal in all patients and control subjects. The research was performed in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the Ethics Committee on Human Research of the Clinical Centre of Serbia. Written informed consents were obtained from every patient and control subject.

Image acquisition

All control and PNES subjects MR examinations were performed using Philips Achieva 1.5 T using an 8-channeled head coil. T1W-3D-FFE sequences (TR = 25 ms, TE = 5 ms, FA = 30°, matrix 256×256, slice thickness 1 mm, slice gap 1 mm, sagital plane) were used for analysis. The imaging protocol also contained T1 W and T2 W and FLAIR sequences in the axial plane in order to exclude the presence of gross pathology. 3D-T1 W images were transferred to a MacBookPro workstation and converted to NifTI (Neuroimaging Informatics Technology Initiative) format using MRIcron