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SHORT COMMUNICATION

# Cerebro-cerebellar functional connectivity profile of an epilepsy patient with periventricular nodular heterotopia

Santarnecci Emiliano<sup>a,\*</sup>, Vatti Giampaolo<sup>a</sup>, Marino Daniela<sup>a</sup>, Polizzotto Nicola<sup>b</sup>, Cerase Alfonso<sup>a</sup>, Rocchi Raffaele<sup>a</sup>, Rossi Alessandro<sup>a</sup>

<sup>a</sup> Department of Neurological, Neurosurgical and Behavioral Sciences, University of Siena, Siena, Italy

<sup>b</sup> Department of Psychiatry, University of Pittsburgh, PA, USA

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## KEYWORDS

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**Summary** Periventricular nodular heterotopia (PNH) is a rare malformation of cortical development often associated with drug resistant focal onset epilepsy. The link between nodules and neocortex have been demonstrated with depth electrodes investigations showing that seizures may arise from both structures. In the last years fMRI resting-state (fMRI-RS) have received a surge in interest due to its capability to track non-invasively physiological and pathological relevant differences in brain network organization. We performed a cerebro-cerebellar voxel-wise and region-of-interest resting state fMRI (RS-fMRI) functional connectivity analysis in a seizure-free epilepsy patient with a PNH in the right temporal horn. Our finding confirms a spontaneous synchronization between PNH and its surrounding cortex, specifically in the inferior temporal, fusiform and occipital gyrus. We also found a significant connectivity with bilateral cerebellum, more intense and widespread on the PNH cerebellar contralateral lobule. RS-fMRI confirmed its potential as a promising tool for non-invasive mapping of cortical and subcortical brain functional organization.

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## Introduction

Periventricular nodular heterotopia (PNH) is a rare malformation of cortical development. Patients may suffer from drug resistant epilepsy with features of temporal lobe onset

(Aghakhani et al., 2005). Surgical treatment may lead to unsatisfactory results unless resective strategies include heterotopic nodules as well as large parts of overlying neocortex (Sisodiya, 2000; Tassi et al., 2005). SEEG studies indeed showed that seizure may arise from periventricular nodules, neocortex or simultaneously from both structures (Aghakhani et al., 2005; Valton et al., 2008).

In the last years fMRI resting-state (fMRI-RS) received a surge in interest because of its capability to track physiological and pathological relevant differences in brain network

\* Corresponding author at: Policlinico "Le Scotte", Viale Bracci, 2, Siena 53100, Italy. Tel.: +39 3382149984; fax: +39 0577270260.

E-mail address: [emilianosantarnecci@gmail.com](mailto:emilianosantarnecci@gmail.com) (S. Emiliano).

organization (Fox and Raichle, 2007). This method has been recently applied to a patient with epilepsy, a surgical candidate, demonstrating the presence of a functional link between nodule and overlying cortex (Archer et al., 2010). In this view, due to its high spatial resolution and the possibility to capture deep brain structures activity, fMRI-RS could be a promising non-invasive tool to investigate both local and widespread cerebral network organization in neuronal migration disorders like periventricular nodular heterotopia.

With this report we extend results previously observed (Archer et al., 2010) using a voxel-wise and region-of-interest fMRI-RS analysis to map both cortico-cortical and cortico-cerebellar functional connectivity in a seizure-free epileptic patient with a PNH.

## Methods

A 39-year-old right handed man was evaluated at our department because of the occurrence, a few months before, of two generalized tonic-clonic seizures (GTCS). A detailed clinical history revealed infrequent partial seizures characterized by rising epigastric sensation and oral automatisms since adolescence without language impairment. MRI imaging disclosed a single gray matter sub-hepndymal nodule in the temporal horn of the right lateral ventricle. EEG showed right temporal epileptiform discharges with phase reversal at the mid temporal lead. The patient was diagnosed as having right temporal lobe epilepsy and started on Oxcarbazepine 1200 mg bid achieving immediate and complete seizure control. We acquired a complete anatomical set of images (T1 and T2-weighted, Inversion Recovery-IR and Fluid Attenuated Inversion Recovery-FLAIR) and an fMRI session during rest condition (TR 2500 ms, 200 scans, TE 40 ms, 23 slices, 1 mm gap, total scanning length 8 min) on a Philips Intera 1.5 T Scanner. In order to better delineate the PH nodule we used a  $128 \times 128$  resolution matrix allowing to obtain an isotropic resampled voxel size of  $2 \text{ mm}^3$ . Patient was instructed to keep the eyes closed, to avoid falling asleep without focusing on any particular thought during fMRI acquisition. Functional images underwent the following preprocessing steps using SPM8 software (Statistical Parametric Mapping; <http://www.fil.ion.ucl.ac.uk/spm/>) after having discarded the first five volumes to allow steady-state magnetization: slice timing, realigning to T1-weighted image and reslicing to correct for head motion, nonlinear normalization to the Montreal Neurological Institute template brain, smoothing with an isotropic Gaussian kernel (full-width at half-maximum, 6 mm). Structural images were coregistered to functional images and subsequently segmented using the SPM unified segmentation routine. The white matter and cerebrospinal fluid masks were used for removal of spurious variance. Linear trends were removed to reduce the influence of the rising temperature of the MRI Scanner. All functional volumes underwent band pass filter at  $0.01 \text{ Hz} < f < 0.08 \text{ Hz}$  in order to reduce low-frequency drift and physiological high-frequency respiratory and cardiac noise.

PNH were manually traced using MRICro software (<http://www.cabiatl.com/mricro>). The nodule Region of Interest (ROI) was added to an anatomical atlas (Anatomical Automatic Labeling Atlas, composed by 90 cerebral and

26 cerebellar ROI) (Tzourio-Mazoyer et al., 2002). To ensure the independence of the heterotopic nodule from other surrounding anatomical structures, we subtracted the nodule ROI mask of hippocampus, precuneus, cuneus, parahippocampal, lingual and fusiform gyri from the nodule ROI mask. Then we extracted average time series of Blood Oxygenation Level Dependant (BOLD) signal from the 117 ROI and calculated normalized pairwise connectivity metrics, using Pearson product-moment correlation coefficient. All the within-subject ROI-to-ROI pairwise connectivity metrics were fitted into a general linear model with a  $p < .05$  False Discovery Rate (FDR) correction for multiple comparisons (Fig. 1).

## Results

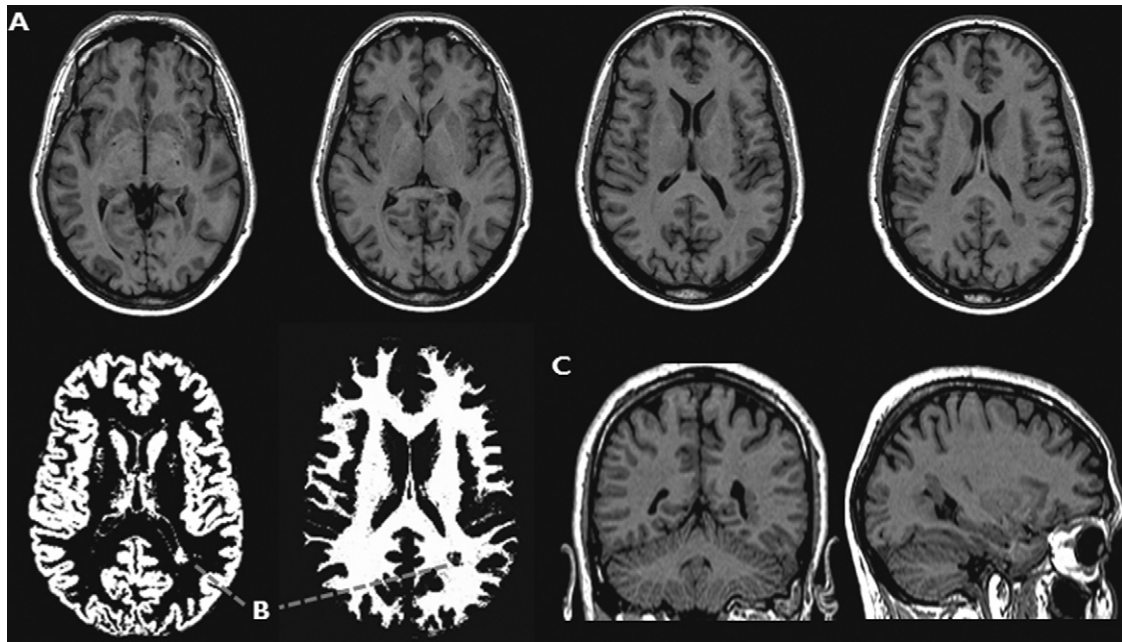
For illustrative purpose we mapped the voxel-wise connectivity profile (not-threshold correlation coefficient) of the PNH onto a Population-Average, Landmark- and Surface-based cerebral and cerebellar surface in SPM space (PALS-B12) (Fig. 2A). Strongest nodule connections involve bilateral cerebellar areas and homolateral inferior temporal, occipital and middle frontal gyrus.

Whole cerebro-cerebellum analysis indicated that the PNH displayed a statistically significant connectivity with right Inferior Temporal Gyrus ( $T=3.4$ ; uncorrected  $p < 0.000662$ ; FDR=0.0193), right Fusiform Gyrus ( $T=3.28$ ; uncorrected  $p < 0.001046$ ; FDR=0.024), right Inferior Occipital Gyrus ( $T=3.32$ ; uncorrected  $p < 0.000318$ ; FDR=0.0194), right CRUS I ( $T=3.54$ ; uncorrected  $p < 0.000398$ ; FDR=0.0194), and left CRUS I ( $T=3.48$ ; uncorrected  $p < 0.000502$ ; FDR=0.0188), and CRUS II ( $T=3.43$ ; uncorrected  $p < 0.000612$ ; FDR=0.0183).

A thresholded version of the connectivity map showing the significant clusters of connectivity and their corresponding Brodmann and cerebellum areas is shown in Fig. 2B.

## Discussion

Our findings confirm and extend previously observed results with a similar approach (Archer et al., 2010) showing spontaneous synchronization between PNH and overlying cortex, specifically inferior temporal, fusiform and occipital gyri. The demonstration of functional connection between nodules and neocortical areas gives a further explanation of both seizure semiology and unsatisfactory surgical results (Aghakhani et al., 2005; Sisodiya, 2000). Stereo EEG studies already showed that seizure may arise simultaneously from nodules and overlying cortex, while in a single case, a seizure onset within the nodule with later spreading to neocortex and hippocampus was clearly demonstrated (Scherer et al., 2005). The link between heterotopic neurons and neocortex pertains not only to seizures circuitry but may also be active in physiological functions. fMRI studies demonstrated heterotopic nodule and neocortex co-activation during motor task (Draganski et al., 2004), while several other studies showed that heterotopic neurons can be activated during different tasks including language (Scherer et al., 2005; Vitali et al., 2008). Future research should be addressed to evaluate the pattern of functional connectivity in patients with multiple nodules having different size and

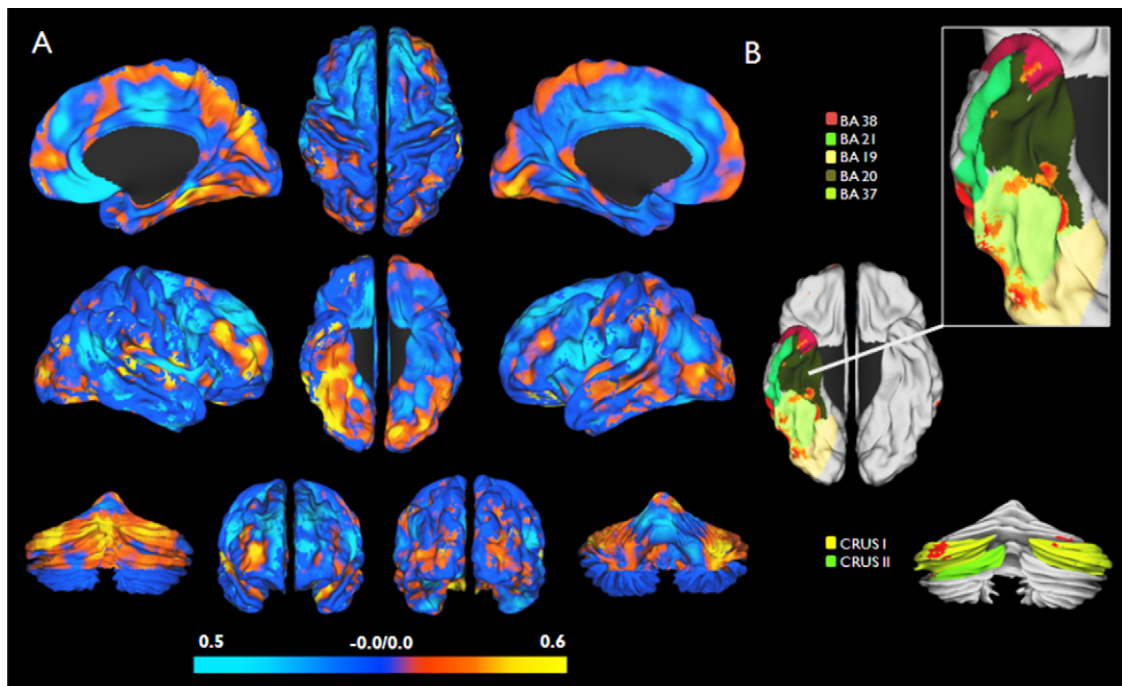


**Figure 1** Axial (A), coronal and sagittal (C) T1-weighted images highlighting the position and extension of right periventricular nodular heterotopia. The gray and white matter masks show the nodule correct classification into gray matter (B). Images are shown in neurological convention.

location. In this way, diffusion tensor imaging and tractography could be also useful to unveil preferential anatomical pathways that could corroborate functional findings.

Functional connection between PNH and cerebellar hemispheres has not been previously reported. Here we found

a bilateral participation of cerebellar lobules in a functional network of a heterotopic nodule, with a larger cluster of connected voxels in the contralateral lobule. Such results are not surprising and could be explained by existing preferential crossed pathways connecting cerebellum and



**Figure 2** Voxel-wise functional connectivity profile of the right temporal horn PNH. Panel A shows a not-thresholded cerebrocerebellar map (Pearson correlation coefficient). Panel B reports a thresholded version of the map at  $p < 0.05$  (FDR multiple comparisons correction) with Brodmann and cerebellar areas overlay for significant clusters. Images are shown in neurological convention.

neocortex that probably constitute the basis of the well-known phenomenon of crossed cerebellar diaschisis. Some limitations however need to be highlighted. RS-fMRI studies cannot estimate the direction of functional connection, moreover the demonstration of a cortical network do not necessarily imply that the different areas are involved in the same function. This topic can best be addressed using RS-fMRI as a complementary tool to task-fMRI experiments (Janszky et al., 2003).

In conclusion, resting state fMRI analysis is a profitable non-invasive tool for assessing the connectivity profile of PNH, otherwise difficult to be explored with standard approach like scalp EEG. Moreover, PNH-cerebellum connectivity is a new and intriguing finding considering that cerebellar deep brain stimulation has been recently proposed as a possible treatment for drug-resistant epilepsy patients (Fountas et al., 2010).

### Conflict of interest statement

None of the authors has any conflict of interest to disclose.

### Ethical approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this article is consistent with those guidelines.

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