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Default mode network alterations during language task performance in children with benign epilepsy with centrotemporal spikes (BECTS)

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ABSTRACT

Benign epilepsy with centrotemporal spikes (BECTS) is the most common idiopathic epileptic disorder in children. Besides reported cognitive deficits, functional alterations mostly in the reorganization of language areas have also been described. In several publications, it has been reported that activation of the default mode network (DMN) can be reduced or altered in different neuropsychiatric and neurological disorders in adults. Whether this also holds true for children with epilepsy has so far not been clarified.

To determine the functional activation of the DMN in children with BECTS, 20 patients and 16 healthy controls were examined using functional magnetic resonance imaging (fMRI), while a sentence generation task and a reading task were applied in a block design manner. To study the default mode network and the functional alterations between groups, an independent component analysis (ICA) was computed and further analyzed using SPM5.

Compared with controls, children with BECTS showed not only significantly less activation of the DMN during the rest condition but also less deactivation during cognitive effort. This was most apparent in the precuneus, a key region of the DMN, while subjects were generating sentences.

From these findings, we hypothesize that children with BECTS show a functional deficit that is reflected by alterations in the DMN.

1. Introduction

Neuroimaging studies suggest that brain networks involving the posterior cingulate cortex/precuneus and medial prefrontal regions, having a reciprocal relationship to task positive activation, are deactivated during task performance and activated during rest [1–5]. The expression of a "default mode network" (DMN) was first introduced by Raichle and colleagues and describes a state of alert, awake but not actively goal-directed behavior [3]. Some authors describe the DMN as a brain activity supporting self-referential behavior such as autobiographical memory, introspection, theory of mind, and empathy [2,6–8]. The DMN is a baseline activity of the brain, which is consistent within and across subjects [9,10] and which also has a strong anatomical overlap when studied during rest and during different cognitive task performances in adults [11]. The architecture of the DMN varies during the course of life [12]. In newborns and infants, different results have been published [13–16]. The most recent article by Gao and colleagues describes the DMN mainly evolving in the first year of life [17]. In adolescence, functional connectivity of anterior and posterior nodes of the DMN becomes stronger [18], and task-induced deactivation increases with age [19]. On the other hand, functional connectivity weakens during the process of aging [20].

In pathological states, alterations of the DMN architecture and modified connectivity have been described [21]. Of all psychiatric and neurological diseases, Alzheimer's disease has been especially extensively studied. It has been shown that the degree of deactivation during cognitive demand and functional connectivity between the anterior and posterior nodes of the DMN are predictive not only for the development but also for the course of Alzheimer's disease [22]. Moreover, in various disorders of the CNS, such as attention deficit/hyperactivity disorder, depression, autism, schizophrenia, mild cognitive impairment, and posttraumatic stress disorder, altered DMN functionality has been reported (for a review, see [21]).

In adults with epilepsy, including focal and generalized epilepsies, several results have been published showing, e.g., decreased functional connectivity in mesial temporal lobe epilepsy (mTLE) with a strong relation to right or left hippocampal sclerosis and to the duration of epilepsy [23]. In a combined fMRI and DTI study in patients with mTLE, decreased functional connectivity in the DMN was shown to be a consequence of decreased density in DTI combined with a degeneration of

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structural connectivity [24]. Decreased resting state activity and interictal epileptiform discharge-related deactivation in the posterior cingulate, precuneus, and frontal and parietal lobes in patients with TLE but not in patients with extra-TLE have been described [25]. In adults with idiopathic generalized epilepsy, reduced functional network connectivity was seen between anterior and posterior cortical seed regions, which were correlated with seizure duration [26].

In pediatric epilepsy, few data are available so far. A recent study showed reduced connectivity in children with nonlesional temporal lobe epilepsy and suggested that interictal epileptiform activity affects connectivity in different networks [27]. Epileptiform activity in children with continuous spikes and waves during slow sleep (CSWS) was associated with a decreased blood oxygenation level-dependent (BOLD) effect in structures that are part of the DMN [28].

Since children with epilepsy are often affected by cognitive deficits and learning and behavioral problems, it is crucial to acquire a greater understanding of the underlying pathophysiological mechanisms. Previous literature showed not only a reduced behavioral language performance in children with BECTS but also a atypical functional pattern of language areas [29]. In our previous article [30], results of functional magnetic resonance imaging (fMRI) confirmed a bilateral activation pattern in these patients in contrast to healthy controls. In the present study, we investigated the same cohort and hypothesized an altered reactivity of the DMN in patients compared with controls. Since the precuneus, a region which comprises the posterior and dorsal medial parietal lobe, has often been cited as being a crucial part of the DMN [31] in terms of maintaining functional and structural connections to other areas [32,33], we focused especially on this anatomical region in the subsequent analyses.

2. Materials and methods

2.1. Participants

Twenty-seven children with a diagnosis of BECTS (13 girls and 14 boys), with age ranging between seven and a half and 13.11 years ($M = 10.0$, $SD = 1.7$) and with ($N = 13$, six girls and seven boys) or without antiepileptic treatment ($N = 14$), were included. Exclusion criteria were no clear diagnosis of BECTS or any other epileptiform activity; any parenchymal pathology; other neurological disorders such as cerebral palsy, brain tumor, and neurometabolic diseases; and mental retardation. For more detailed patient information, we refer to one of our previous publications [30]. All participants and their parents gave written informed consent.

Nineteen healthy children (six girls and 13 boys) who volunteered for the study, with age ranging between eight and 13.3 years ($M = 10.9$, $SD = 1.6$), were included as a control group. Exclusion criteria were epileptiform discharges in EEG or any history of epilepsy, developmental delay, and neurological or psychiatric disorders. There was no statistically significant difference for gender and age between the groups.

In order to ensure equalized cognitive status in the two groups, a neuropsychological examination was administered to each child by using the German version of the Wechsler Intelligence Scale for Children (WISC-IV) [34]. The mean IQ of both groups was within the normal range (patients: $M = 104.7$, $SD = 15.6$; controls: $M = 110.0$, $SD = 7.6$) and did not differ significantly ($t\,(43) = -1.355$; $p = 0.183$).

2.2. fMRI tasks

To study differences in brain activation during two language tasks between the children with BECTS and healthy controls, functional magnetic resonance imaging (fMRI) was applied. The children were familiarized with both tasks outside the scanner to ensure a silent task performance with minimal head and mouth movement. All tasks were programmed using E-Prime software (version 1.1.3, Psychology Software Tools). To test expressive and receptive language aspects, the two following paradigms were applied:

> *Silent reading of word-pairs*: The children were asked to silently read two words (e.g., “restaurant–elephant”). Seventeen patients (eight girls and nine boys) and 11 controls (three girls and eight boys) completed the task with movement parameters below the cutoff of 4 mm of translation and 2° of rotation and contributed therefore to the final statistical analysis.
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> *Silent generation of simple sentences* (subject–verb–complement): For 5000 ms, a noun was presented on the screen, and the children had to silently build simple sentences (e.g., “banana”: “I like bananas”). Twenty subjects in the group with epilepsy (nine girls and 11 boys) and 16 children from the healthy control group (six girls and 10 boys) completed the task with movement parameters below the chosen cutoff.

In both tasks, one block of activation contained five stimuli and lasted for 25,000 ms followed by a rest condition of 25,000 ms where the children had to fixate on a cross. Tasks consisted of five blocks of rest condition and four blocks of activation in alteration.

2.3. Image acquisition

Brain imaging data were obtained with a 3.0-T MRI system (Magnetom VERIO, Siemens Healthcare, Erlangen, Germany) and a standard head coil. First, an anatomical image for registration purposes was acquired (sagittal T1-weighted 3D high resolution magnetization-prepared rapid gradient echo (MPRAGE) sequence with $TI = 1000$ ms, providing an isotropic spatial resolution of $1 \times 1 \times 1$ mm^3). For functional images, echo-planar imaging (EPI) sequences were applied ($TR = 2500$ ms, $TE = 28$ ms, 38 slices with a slice thickness of 3 mm and a matrix size of 76×76, $FOV = 228$ mm, voxel size $= 3 \times 3 \times 3$ mm^3). For both tasks, 94 volumes with a total scan time of 235 s and slices positioned parallel to the AC–PC line were recorded.

2.4. Data management and analysis

Data were preprocessed and analyzed using the statistical parametric mapping software package (SPM5) implemented in MATLAB (version 6.5.1, 2003; MathWorks, Inc., Natick, MA, USA). Because of equilibration effects, the first four volumes were excluded from analysis, yielding 90 volumes. Sessions were subjected to standard preprocessing procedures [35] including realignment with second mode movement correction, coregistration to the structural T1-weighted image, normalization to the standard MNI template, and smoothing with a 9-mm isotropic 3-dimensional Gaussian filter. To define the contrast of interest and the model design, the smoothed images were subjected to a first-level analysis. To remove residual variance, movement parameters extracted from the realignment step were included as additional covariates. To identify language-associated brain activation, the rest condition of the fMRI paradigm was subtracted from the performance condition in each subject. To extract group effects, these contrast images were submitted to a two-sample t-test and explored with an uncorrected threshold of $p = 0.001$ and a cluster size of 10 voxels. For detailed information about statistical analysis, see [30].

2.5. Independent component analysis (ICA)

After preprocessing in SPM5, the smoothed images of each subject were inserted into an overall ICA to decompose fMRI data into spatially independent patterns and time courses by using the GIFT toolbox [36]. The number of components was estimated using the minimum description length (MDL) criterion [37]. Minimum description length estimated 21 components ($M = 20.91$, $SD = 4.3$) for the task *silent generation of*