



Cortical arousal in children and adolescents with functional neurological symptoms during the auditory oddball task



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ABSTRACT

Objective: Stress, pain, injury, and psychological trauma all induce arousal-mediated changes in brain network organization. The associated, high level of arousal may disrupt motor-sensory processing and result in aberrant patterns of motor function, including functional neurological symptoms. We used the auditory oddball paradigm to assess cortical arousal in children and adolescents with functional neurological symptom disorder.

Method: Electroencephalogram (EEG) data was collected in fifty-seven children and adolescents (41 girls; 16 boys, aged 8.5–18 years) with acute functional neurological symptoms and age- sex- matched controls during a conventional auditory oddball task. The high-resolution fragmentary decomposition technique was used to analyse the amplitude of event-related potentials (ERPs) to target tones at midline sites (Fz, Cz, and Pz).

Results: Compared to age- and sex-matched controls, and across all three midline sites, children and adolescents with functional neurological symptoms showed increased amplitude of all ERP components (P50, N100, P200, N200, and P300) (t-value range 2.28–8.20; p value-range 0.023 to <0.001) to the emotionally-neutral auditory stimulus.

Conclusions: Our findings add to a growing literature indicating that a baseline state of high arousal may be a precondition for generating functional neurological symptoms, a finding that helps explain why a range of psychological and physiological stressors can trigger functional neurological symptoms in some patients. Interventions that target cortical arousal may be central to the treatment of paediatric patients with functional neurological symptom disorder.

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Abbreviations: EEG, electroencephalogram; ERP, event-related potential; GMP, generic mass potential; PFC, Prefrontal cortex; dlPFC, Dorsolateral prefrontal cortex.

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1. Introduction

Children and adolescents with functional neurological symptom disorder present with a complex array of neurological symptoms that are triggered by stress, pain, injury, or psychological trauma. Accumulating data from brain-imaging studies suggest that during states of high arousal, emotion-processing regions interfere with motor-sensory processing regions, altering patterns of connectivity and motor control (Vuilleumier and Cojan, 2011; Voon et al., 2011; Voon, 2014; Aybek et al., 2014). Because states of high arousal impair higher-order

cognitive- and motor-executive regions in the frontal cortex, there is a loss of integrative capacity that is the foundation of abstract thought and the basis for the preparation and execution of voluntary movements; automatic, emotionally driven motor responses are consequently strengthened³ (Jackson, 1884; Arnsten, 2015). Event-related potentials (ERPs) have been successfully used in a range of psychiatric disorders for spatiotemporal analysis of brain activation during perceptual and cognitive processing following presentation of a novel stimulus. In this study, we utilized the auditory oddball task with a cohort of children and adolescents with functional neurological symptom disorder, along with age- and sex- matched controls, to assess brain activation to an auditory stimulus.

The ERP waveform elicited via the auditory oddball task yields a number of positive (denoted by P) and negative (denoted by N) wave components: P50, N100, P200, N200, and P300 in response to novel stimuli (see *Text Box 1* for details). ERP amplitude reflects the extent of neural activation, with amplitude increasing with arousal (Polich, 2003) mediated by the hypothalamic-pituitary-adrenal (HPA) axis and brain catecholaminergic systems (Sumich et al., 2014; Soltani and Knight, 2000). Increased amplitude of wave components in response to novel stimuli has been found in clinical conditions characterized by increased arousal: children with high trait anxiety (N100) (Hogan et al., 2007) and adults with clinical and subclinical depression (N100, N200 and N300) (Shagass and Roemer, 1992; Ogura et al., 1991; Bruder et al., 2001; Sumich et al., 2006). By contrast, decreased amplitude of wave components (P300) has been found in monkeys with lesions of the septal area and locus coeruleus (Picton, 1992)—areas involved in the brain's stress response (Arnsten, 2015; Reis et al., 2011).

In our research program with children and adolescents with functional neurological symptom disorder, we have previously found that these patients are characterized by excessive activation of brain-body arousal systems and by a shift from cognitive/integrative processing to emotion/motor-sensory processing. First, in a study using a facial emotion-identification task, patients from the current cohort demonstrated faster reaction times than controls, (Kozłowska et al., 2013a) suggesting increased motor readiness with concomitant activation of the motor and sympathetic systems. Second, in a study assessing integrative capacity within narratives (Kozłowska et al., 2011) and in a study assessing cognitive function, (Kozłowska et al., 2015a) patients demonstrated difficulties in integrating autobiographical information and also decreased performance on cognitive tasks dependent on prefrontal cortex (PFC) function. Third, in a study assessing autonomic regulation, patients showed higher baseline autonomic arousal—indexed by increased resting heart rate and decreased heart rate variability—suggesting activation of the sympathetic system and downregulation of the restorative vagus (Kozłowska et al., 2015b). Studies with adult patients, though sparse, also demonstrate upregulation of the HPA axis, the autonomic nervous system, and neural systems mediating arousal (Vuilleumier and Cojan, 2011; Lader and Sartorius, 1968; Horvath et al., 1980; Seignourel et al., 2007; Bakvis et al., 2009a; Bakvis et al., 2009b; Kanaan et al., 2007; Ponnusamy et al., 2011; Voon et al., 2010).

Taken together, the above data suggest that cortical arousal in children and adolescents with functional neurological symptom disorder may be increased and may be measurable through the conventional auditory oddball task. In this context, the prime hypothesis for this study was that children and adolescents with functional neurological symptom disorder (vs. controls) would, because of their presumed state of high arousal, show increased amplitude in all ERP components—P50,

N100, P200, N200, P3a and P3b—at midline frontal cortical sites (Fz, Cz, and Pz).

2. Materials and methods

2.1. Participants

Fifty-seven children and adolescents with functional neurological symptom disorder (41 girls; 16 boys) aged 8.5–18 years were recruited between August 16, 2006, and August 16, 2010, from a paediatric tertiary-care hospital in New South Wales, Australia, and took part in a series of studies (Kozłowska et al., 2013a; Kozłowska et al., 2011; Kozłowska et al., 2015a; Kozłowska and Williams, 2010). Because data for the auditory oddball were missing for seven patients, seven other patients matched for age and sex—recruited during August 17, 2010, to April 31, 2014—replaced the 7 patients for whom there was no data, yielding 41 girls and 16 boys aged 8.43–18 years (mean: 13.46 years, SD: 2.14). At the time of testing, all patients were experiencing functional neurological symptoms (defined by DSM-IV-TR) (American Psychiatric, 2000); that is, testing occurred while they were experiencing motor-sensory symptoms or during a period of time when their non-epileptic seizures were occurring. Testing was typically completed soon after the clinical assessment, while the children were medication free.

The children with functional neurological disorder had presented with one or more symptoms (mean: 2.42, range: 1–7)—sensory symptoms (54% of patients, $n = 31$), motor symptoms (68%, $n = 39$), non-epileptic seizures (56%, $n = 32$)—that were sufficiently disabling to require hospital treatment in 96% (55/57) of cases. Most of the children/adolescents—with the exception of 8 outliers (all relatively chronic)—had acute presentations with functional neurological symptoms ranging from 2 days to six months (median, 1.5 months). The small chronic group ($n = 8$) was made up primarily of older adolescents whose symptoms had been present for 8–24 months, with a mean of 14 months and a median of 12 months. Structural abnormalities of the brain or skull had been excluded by neurological examination combined with clinical electroencephalogram (EEG) reviewed by a paediatric neurologist in 61% (35/57) patients and brain imaging in 82% (47/57) patients (17 had computerised axial tomography [CT] and 43 had magnetic resonance imaging [MRI])—all of which were normal.

On clinical assessment, using DSM-IV-TR criteria, 54% (34/57) of patients were diagnosed with comorbid anxiety, 17% (8/57) with depression, 11% (6/57) with a dissociative disorder NOS, and 7% (4/57) with a behavioural disorder. In addition, 61% (35/57) had comorbid medically unexplained pain, and 58% (33/57) had comorbid nonspecific somatic symptoms: 18% (10/57) with nausea, 37% (21/57) with dizziness, 25% (14/57) with breathlessness, and 30% (17/57) with fatigue. Antecedent life events were documented using a structured clinical interview at assessment combined with a checklist and were reported by all families (range: 1–10, mean: 5) (see Table 1). Additional demographic information is provided in Table 1.

The same battery of tests was administered to the 57 age- and sex-matched healthy controls. The study was approved by the Sydney Children's Hospital Network Ethics Committee. Written informed consent was obtained from all patients and their parents. Details on the recruitment protocols, screening for inclusion and exclusion criteria, assessment for organic pathology, and other aspects of clinical characteristics have been reported previously (Kozłowska et al., 2013a; Kozłowska et al., 2011; Kozłowska et al., 2015a; Kozłowska and Williams, 2010).

2.2. EEG acquisition

A QuickCap (Neuroscan) was used to acquire EEG data from the cephalic sites (10–10 International system) during the auditory oddball task. Several non-cephalic sites that are required for EEG data

³ In the psychiatric literature this destabilization the brain system away from a state of integrative capacity in the context of stress, pain, fatigue, injury, or psychological trauma has been termed dissociation (Janet, 1889) Janet P. *L'Automatisme psychologique*. Paris: Alcan; 1889.

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