



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.

Table 1
Demographics and life events reported by families (n = 57).

	Number	Percent
Life event		
Family conflict	36	63%
Precipitating physical illness or accident	30	53%
Bullying	25	44%
Maternal mental illness	21	37%
Loss of a close other via separation	20	35%
Loss of a close other via death	19	33%
Paternal mental illness	14	25%
Maternal physical illness	13	23%
Paternal physical illness	11	19%
Domestic violence	10	18%
Physical abuse	6	11%
Custody battle	4	7%
Sexual abuse	4	7%
Neglect	4	7%
Socioeconomic status of families		
Unemployed	1	2%
Blue collar	12	21%
White collar	24	42%
Professional	29	50%
Intelligence quotient		
Borderline (IQ 70–79)	4	7%
Average (IQ 80–119)	42	73%
Superior (IQ 120+)	11	20%

processing were additionally recorded: VPVA and VPVB vertical electrooculogram (EOG); HPHL and HNHR horizontal electrooculogram (EOG); and A1 and A2 electrodes on each mastoid process (bone behind the ear). Skin resistance was kept at <5 Ohms. Scalp and EOG potentials were amplified and digitized continuously by a system (NuAmps, SCAN 4.3) having a frequency response from DC to 100 Hz (above which attenuating by 40 dB per decade), a sampling rate of 500 Hz, and a 22-bit resolution digitization. Correction for eyeblink artifact was carried out on the 26 cephalic sites using a technique based on Gratton et al. (1983) using the recorded EOG data. Artifact correction included rejection of any epoch that had a voltage level above 100 μV on at least 3 channels—if >50% of the epochs were rejected the data was deemed unusable.

2.3. Procedure

All participants were presented with auditory stimuli binaurally, via headphones. A series of high-frequency tones (target tones with a frequency of 1000 Hz) and low-frequency tones (background tones of 500 Hz) were presented at 75 decibels. Stimuli lasted for 50 ms, with an inter-stimulus interval of 1 s. Tone rise and fall time was 5 ms. Participants were required to ignore the low-pitched background tones and respond—press a button with the index finger of each hand—to target tones. All participants are given a brief practice session to clarify the distinction between target and background stimuli. Speed and accuracy of response are stressed equally in the task instructions. Two hundred eighty background tones and 60 target tones were presented in a quasi-random order, with the only constraint being that two targets could not appear consecutively. Task duration was approximately 6 min.

2.4. Sites for data analysis

Data was analysed for the midline sites Fz, Cz, and Pz, areas identified in previous studies as most informative in assessing arousal (Polich, 2003; Sumich et al., 2014; O'Malley et al., 2003; Pop-Jordanova, 2011; Schupp et al., 2012).

2.5. Behavioural data analysis

Independent t-tests were used to analyse group differences in reaction speed, reaction time variability, false alarms, omission errors and accuracy.

2.6. Single-trial ERP analysis

P50, N100, P200, N200, P3a and P3b components of the late ERP complex were identified in single-trial ERP recordings using single-trial ERP analysis with the high-resolution fragmentary decomposition technique (FD) (see Fig. 1) (Melkonian et al., 2001; Melkonian et al., 2003). The FD method builds on conventional single-trial screening procedures (Ford et al., 1994; Lange et al., 1997). Whereas the former utilize a single predefined template, (Ford et al., 1994; Lange et al., 1997) FD uses adjustable templates for each component (see Melkonian et al., 2001 for a complete description of the methodology) (Melkonian et al., 2001). The template is based on the model of ERP component in the form

$$e(t) = \kappa bud [(t-\psi)/\rho],$$

where

$$bud(x) = \frac{1}{\sqrt{2\pi}} \left(e^{-(x-1)^2/2} - e^{-(x+1)^2/2} \right) \text{ at } x \geq 0 \text{ and } 0 \text{ at } x < 0$$

is standard generic mass potential (GMP), and κ , ρ , and ψ are GMP parameters. Importantly, the FD method allows the P3a and P3b components to be analysed independently, this is a significant methodological improvement from previous late positive complex decomposition methods (Melkonian et al., 2001; Melkonian et al., 2003).

Decomposition of single-trial ERP into event-related components

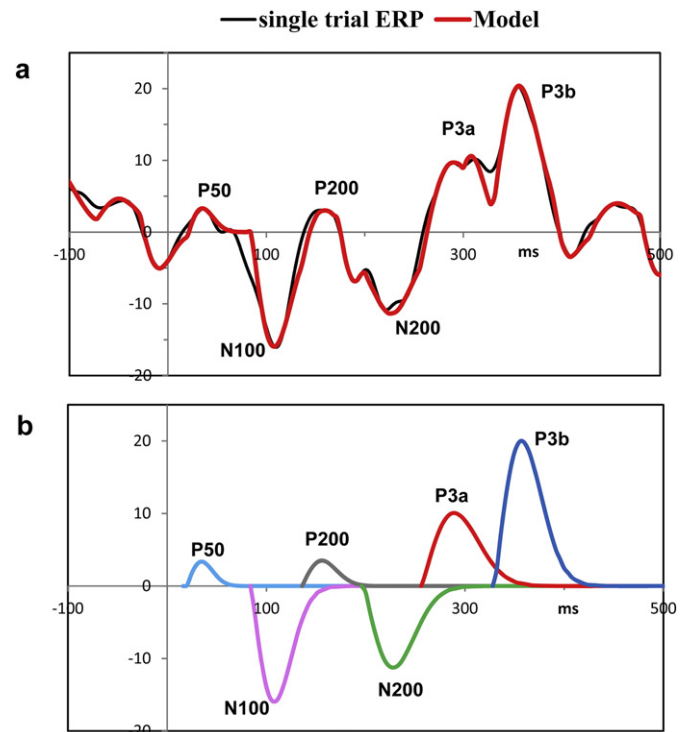


Fig. 1. Panel a illustrates the typical result of the single trial ERP decomposition. Panel b illustrates separate ERP components.

Table 2
Windows for ERP component identification.

	Peak amplitude (A, μV)		Peak latency (L, s)		Shape parameter (ρ , s)	
	Min	Max	Min	Max	Min	Max
P50	2.0	45	0.02	0.075	0.008	0.04
N100	−45	−2	0.08	0.120	0.008	0.05
P200	2	45	0.16	0.220	0.008	0.05
N200	−45	−2	0.18	0.235	0.008	0.05
P3a	2	45	0.24	0.299	0.008	0.05
P3b	2	45	0.3	0.36	0.008	0.05

Given the identified GMP, the measures employed to characterize the ERP component are the peak amplitude A, peak latency L, and shape parameter ρ . The A and L are conventional parameters, while ρ is a new parameter that characterizes the shape of the identified component. Parameter estimation is performed automatically by specially designed software that measures A, L, and ρ parameters of each peaking waveform detected in the single-trial segment from 100 to 600 ms. Given parameters of identified waveform, the windows from the Table 2 are used to determine whether the waveform belongs to the set of the P50, N100, P200, N200, P3a and P3b late ERP components.

The patient and control groups were compared using the amplitude and latency parameters of identified components. Due to a non-Gaussian character of frequency distributions of the parameters of the late ERP components, (Melkonian et al., 2001) conventional parametric estimates have been validated using non-parametric Mann-Whitney *U* test for inter-group comparisons. Procedures of ensemble averaging were applied to selected groups of single-trial ERPs. An explicit analysis of single-trial variability of ERP components included estimation of the missing responses.

2.7. Post hoc analyses

To run post hoc analyses to look at the possible contribution of pain, anxiety, depression, stress and arousal to amplitude increases, a composite amplitude score—the sum total of absolute amplitude values at P50, N100, P200, N200, P3a and P3b at Fz, Cz and Pz—was computed for each individual. In analyses within the patient group, we ran a *t*-test to compare composite amplitude scores in the subgroup of patients with pain to those without pain and we also ran correlations between the composite amplitude score, DASS scores (total DASS score, anxiety

sub-score, depression sub-score and stress sub-score) and arousal measures (heart rate variability [HRV] indexed by RMSSD-HRV, root mean squared successive differences of the interbeat intervals measured in ms^2 ; heart rate [HR] measured in beats per minute; and skin conductance [SC] measured in $\mu S/s$). In between-group analyses we ran a general linear analysis comparing the composite amplitude scores between the patient and control groups with the three indices of arousal—heart rate variability heart rate and skin conductance as separate covariates.

3. Results

3.1. Behavioural data

All patients—41 girls and 16 boys aged 8.43 to 18 years—and 57 age- and sex-matched controls had ERP data. There were no differences between patient and controls groups regarding reaction speed, reaction time variability, false alarms, omission errors and accuracy. There were also no differences regarding the percentage of single trials for ERP components, with the exception of the P50 component, where the percentage of single trials was higher in the patient group ($\chi^2 = 6.6155$, $df = 2$, $p = 0.036598$). A Pearson's correlation between number of trials and amplitude was not significant, and tended in the opposite direction (Pearson's correlation = -0.604 , $p = 0.085$).

3.2. ERP amplitude

The amplitude of all ERP components was increased across the three midline sites Fz, Cz, and Pz in the patient group vs. controls (see Table 3 and Fig. 2). At all sites, the degree of amplitude increases in P3a and P3b were equal. Post hoc analyses of latency showed no between-group differences.

3.3. Post hoc analyses

Post hoc analyses suggested that pain, anxiety, depression, stress and arousal did not account for amplitude increases in the patient group. The *t*-tests comparing composite amplitude scores in the subgroup of patients with pain to those without pain were not significant ($t(44) = -0.914$, $p = 0.366$). The correlation analysis of composite amplitude score with DASS scores and measures of arousal were not significant at the $p < 0.05$ level. The between-group general linear analyses with the three indices of arousal—heart rate variability (HRV), heart

Table 3
Group differences in ERP amplitudes between participants with functional neurological symptoms and controls.

EEG site and wave component	Conversion group (mean, (SE))	Control group (mean, (SE))	t (df)	p-Value	Cohen's d effect size
Fz					
P50	10.985 (± 0.22)	10.202 (± 0.21)	2.58(2798)	0.010	0.10
N100	−11.359 (± 0.23)	−10.294 (± 0.22)	3.40(2532)	0.001	0.14
P200	11.215 (± 0.21)	10.299 (± 0.19)	3.23(3054)	0.001	0.12
N200	−11.513 (± 0.23)	−10.498 (± 0.21)	3.21(2621)	0.001	0.13
P3a	10.709 (± 0.26)	9.471 (± 0.22)	3.65(2049)	<0.001	0.16
P3b	12.093 (± 0.23)	11.37 (± 0.22)	2.28(3031)	0.023	0.08
Cz					
P50	10.645(± 0.21)	9.823(± 0.22)	2.76(2705)	0.006	0.11
N100	−11.783(± 0.23)	−10.289(± 0.23)	4.57(2708)	<0.001	0.18
P200	11.064(± 0.21)	10.264(± 0.22)	2.64(2932)	0.008	0.10
N200	−11.772(± 0.25)	−10.655(± 0.23)	3.32(2651)	0.001	0.13
P3a	11.506(± 0.26)	10.443(± 0.23)	3.09(2536)	0.002	0.12
P3b	12.011(± 0.24)	10.656(± 0.21)	4.33(3051)	<0.001	0.16
Pz					
P50	11.807 (± 0.23)	10.481 (± 0.25)	3.93(2614)	<0.001	0.15
N100	−12.908 (± 0.25)	−10.946 (± 0.25)	5.54(2507)	<0.001	0.22
P200	11.765 (± 0.23)	9.777 (± 0.23)	6.17(2572)	<0.001	0.24
N200	−12.978 (± 0.23)	−10.290(± 0.23)	8.20(2760)	<0.001	0.31
P3a	12.808(± 0.26)	10.262(± 0.24)	7.25(2471)	<0.001	0.29
P3b	13.671(± 0.23)	11.156(± 0.22)	7.82(3290)	<0.001	0.27

57 vs 57 subjects, Pz cortical site

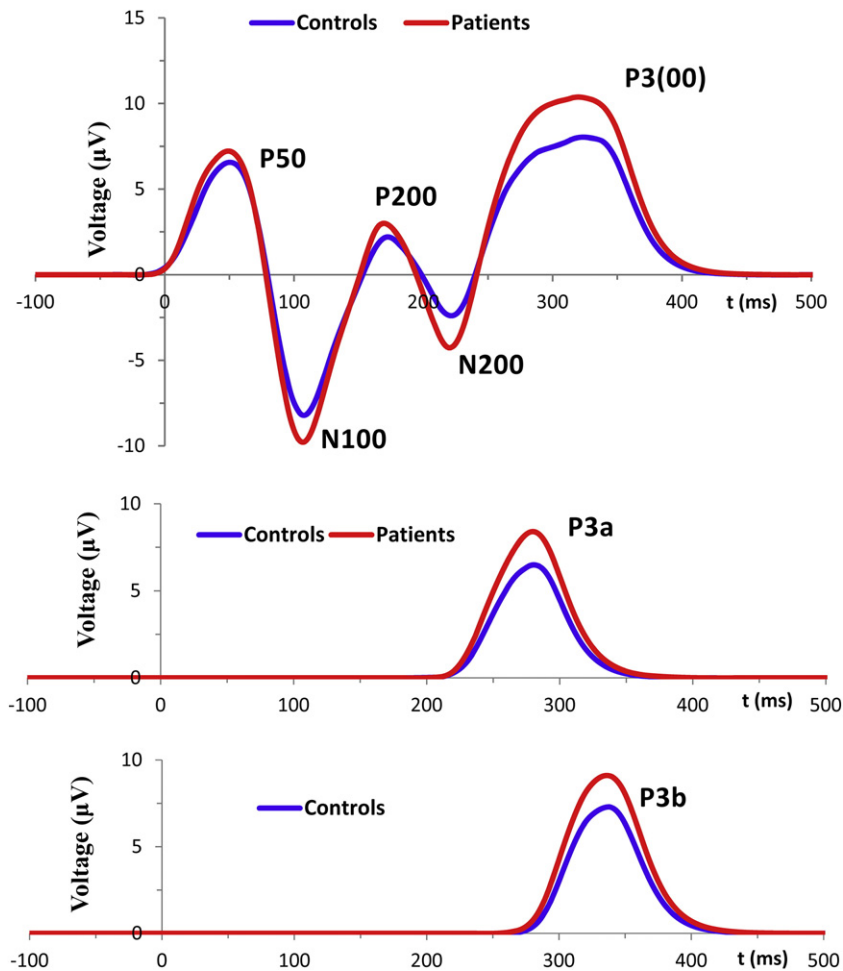


Fig. 2. Group differences between participants with functional neurological symptoms and controls on single trial ERP analysis at the Pz cortical site.

rate (HR) and skin conductance (SC) as separate covariates—remained significant even when the covariates were controlled for (see Table 4). The only significant correlation at the $p < 0.05$ level was that between pain and HR (Pearson Correlation = 0.273, $p = 0.048$). The result was not significant with a Bonferroni correction for multiple comparisons with a significance level of $p < 0.006$.

4. Discussion

This study used ERPs to assess brain activation during perceptual and cognitive processing in children and adolescents with functional neurological symptom disorder during an auditory oddball task. We found an increase, compared to controls, in the amplitude of all ERP components across the three midline sites (Fz, Cz, and Pz). The equal increases in P3a and P3b amplitude in the patient group across all three sites suggested that children and adolescents with functional

neurological symptoms had maintained coordination between frontal and posterior generators. Given that elevations in ERP amplitudes reflect activation of brain catecholaminergic systems (Sumich et al., 2014) and that midline sites are most sensitive to increases of cortical arousal, (Sumich et al., 2014; O'Malley et al., 2003; Pop-Jordanova, 2011; Schupp et al., 2012) we interpret our findings of increased ERP amplitude in children and adolescents with functional neurological symptoms as reflecting a generalized cortical-arousal response.

Taylor (1986) proposed that children present with functional neurological symptom disorder when faced with intolerable predicaments for which all apparent solutions are blocked (Taylor, 1986). Intolerable predicaments involve exposure to uncontrollable stress and result in the activation of the stress response (Arnsten, 2015; Chrousos, 2009). In line with this conception, the children and adolescents in this cohort presented in the context of chronic relational stress (Kozłowska et al., 2011) and with cumulative, antecedent adverse life events (Kozłowska et al., 2011).

Table 4

Role of arousal in amplitude increases in patients with functional neurological symptom disorder vs. controls.

ERP amplitude increases in the auditory oddball task						
Measure	Mean value patient group	Mean value control group	F	df	p-Value	Eta squared effect size
ERP composite amplitude	78.73	61.29	6.181	1, 89	0.015	0.065
ERP composite amplitude (HRV as covariate)	78.73	61.29	5.985	1, 86	0.016	0.065
ERP composite amplitude (HR as a covariate)	78.73	61.29	6.764	1, 84	0.001	0.075
ERP composite amplitude (SC as covariate)	78.73	61.29	7.062	1, 83	0.009	0.078

Although previous studies with the same cohort demonstrated increased peripheral arousal, increased motor readiness to emotional signals, and impairments in cognitive functions mediated by the PFC, the current study looks at cortical functioning more directly and indicates a generalized activation of cortical arousal systems.

A recent review by Arnsten (2015) describes the cascade of neural changes that occur in the face of acute, uncontrollable stress (Arnsten, 2015). The amygdala activates noradrenergic neurons of the locus coeruleus, which increase their firing rates and, in turn, release large concentrations of norepinephrine, which engages lower-affinity β -adrenergic receptors that change network organization. Further, via its wide-ranging projections, the locus coeruleus mediates a generalized excitatory effect throughout the brain. Of special relevance is the PFC, where catecholamines activate dopaminergic 'salience' neurons—neurons that respond to both aversive and rewarding events—resulting in an increase of dopamine release in the dorsolateral prefrontal cortex (dlPFC) and a stress-induced impairment of PFC function. In women, oestrogen accentuates the activation of the locus coeruleus and the action of catecholamines, (Arnsten, 2015) thereby increasing the vulnerability of postpubertal females to stress exposure and stress-related disorders, including functional neurological symptom disorder (Sigurdardottir and Olafsson, 1998; Kozłowska et al., 2007; Ani et al., 2013).

The final outcome of the above cascade of stress-induced changes is a brain-wide network reconfiguration (Hermans et al., 2011). Acute stress switches control from reflective dlPFC circuits (cognitive/integrative processing) to more reflexive subcortical circuits (emotion/motor-sensory processing). Network reorganization involves increased responsiveness and connectivity between the cortical (fronto-insular, dorsal anterior cingulate, inferotemporal, and temporoparietal) and subcortical (amygdala, thalamus, hypothalamus, and midbrain) regions that define the salience network—a network that functions to prep the body for action (Hermans et al., 2011). Following activation of the salience network, the anterior cingulate, via its connections with motor regions (midcingulate cortex, supplementary motor cortex, and other motor areas), facilitates a motor response (Menon and Uddin, 2010). Because functional neurological symptom disorder also involves reorganization of neural networks—and, in particular, increased connectivity between emotion-processing and motor-sensory regions (Vuilleumier and Cojan, 2011; Aybek et al., 2014; Voon et al., 2010; van der Kruis et al., 2012)—it is possible that functional neurological symptoms emerge when aberrant motor responses are incidentally co-opted in the process of the network reorganization that occurs with activation of the brain's stress systems.

Our finding that subjective anxiety, depression, stress and did not explain amplitude increases was not surprising. It has long been known that subjective experiences do not correlate well with measures of behavioural and physiological responses (LeDoux and Pine, 2016) and in previous studies with this cohort we have likewise found a lack of correlation between subjective anxiety, depression and stress and physiological measures (Kozłowska et al., 2013a; Kozłowska et al., 2015b). The lack of correlation between amplitude increases and different measures of arousal (indexed by HRV, HR and SC) is consistent with Berntson's concept of autonomic space (Berntson et al., 1991; Berntson et al., 1993). Berntson highlighted that autonomic patterns of response can involve reciprocal, independent, or even coactive changes in autonomic branches. The concept was subsequently extended by both by Janig and Habler, (Janig and Habler, 2000) who emphasized the existence of many subsystems within the sympathetic system, and by Porges, (Porges, 1995; Porges, 2011) who proposed that mammals have two independent sources of cardiac vagal input (known as Polyvagal Theory) rather than a single source. In this context, although patients with functional neurological symptom disorder show increased arousal in all these components of the brain-body arousal system, the mechanisms mediating changes in each component function independently, and the relationship between components is not linear. Finally, the finding that amplitude increases did not differ in patients with subject pain versus those without pain, was interesting. In the resting state,

subjective pain is associated with increases in activation in the amygdala, insula and medial prefrontal cortex (Apkarian et al., 2011; Vachon-Presseau et al., 2016). The medial prefrontal cortex encodes both the intensity of subjective pain (Apkarian et al., 2011; Vachon-Presseau et al., 2016) and it modulates cardiovascular responses (Gianaros et al., 2004). Our finding of a correlation between pain and heart rate may be reflective this overlap of functions within the medial prefrontal cortex. However, our data suggests that amplitude increases caused by the auditory stimulus were independent to any resting state changes in cortical activation modulated by pain.

Our emphasis on arousal in the aetiology of functional neurological symptoms disorder comes from our clinical work and ongoing research with paediatric patients presenting with acute functional neurological symptoms. In the adult literature, the findings on arousal are mixed. Along the same lines as our group, some researchers emphasize the important role of arousal, activation of affective representations by subcortical structures such as the amygdala, and disruption of motor functions by aberrant activation or connectivity of emotion-processing regions (Vuilleumier and Cojan, 2011; Aybek et al., 2014; Kanaan et al., 2007;

Text Box 2

Clinical outcomes of the 57 children/adolescents with functional neurological symptom disorder following the multimodal treatment intervention {Kozłowska et al., 2012 #2150; Kozłowska et al., 2013a, 2013b #2151} (follow-up for a minimum of 2.5 years).

Outcome	Number	Percentage
Fully recovered	33	58%
Range 2 weeks to 5 years		
Time to recovery (median) = 6 months		
Time to recovery (mean) = 11.42 months (mean value is inflated by five outliers whose recovered times were 36, 43, 48, 58 and 60 months respectively). Two children with hemiparesis and hemi sensory loss recovered motor function (and returned to school) in 3 and 9 months respectively, but full (sensory) recovery occurred at 18 and 58 months respectively.		
Relapsing in the context of new stress but well in-between (attending school or working)	11	19%
Relapses became shorter over time as the children/adolescents and their families got better at managing stress and at managing the episodes.		
Chronic conversion symptoms (non-epileptic events)	1	3.5%
Conversion disorder transformed into a different chronic illness	11	19%
Chronic pain (n = 3)		
Chronic pain, fatigue, anxiety and depression (n = 3)		
Chronic and debilitating anxiety (n = 1)		
Chronic anxiety and behavioural disorder (n = 1)		
Eating disorder (n = 1)		
Factitious presentations (n = 1)		
Borderline personality disorder and severe family conflict (n = 1)		
Lost to follow up	1	2%
Discharge against medical advice following a child protection notification (n = 1)		

Voon et al., 2010). Studies with more chronic patients, however, have not replicated findings of increased arousal (van der Kruis et al., 2012; Bryant and Das, 2012). In addition, on certain neurobiological models—namely, the “Bayesian account of ‘hysteria’” (p3495) (Edwards et al., 2012)—subcortical affective factors are not necessary for the production of functional motor-sensory symptoms; these models highlight, instead, the role of attention, aberrant sensory-motor expectations, and belief-driven processes. The differences in arousal between adults with acute vs. chronic functional neurological symptoms may depend upon priming. In acute presentations, high arousal may be necessary to enable reconfiguration of brain networks into new patterns of organization, and generation of de novo functional neurological symptoms. In chronic presentations, other stimuli—in the absence of high arousal—may be sufficient to enable reactivation of existent networks, and the triggering or perpetuation of previously experienced functional neurological symptoms.

Our study has a number of limitations. First, as typical in paediatric practice, our sample consisted largely of children and adolescents with multiple functional neurological symptoms, making subdivision into symptom-pure groups impossible. Second, as also typical in paediatric practice, the majority of the children and adolescents had comorbid psychiatric disorders, most frequently anxiety. The availability of an anxiety comparison group would potentially have been useful to tease apart the potential contribution of anxiety. Third, our sample consisted largely of children and adolescents who had acute functional neurological symptoms that were treated actively soon after presentation (Kozłowska et al., 2012; Kozłowska et al., 2013b) and, in the majority of cases, with excellent outcomes (see Text Box 2). Our data may not be directly applicable to adults, whose presentations are more likely to be chronic and may be complicated by mechanisms involved in priming, conditioning, and learned associations. Fourth, because our cohort came from around the state of NSW, large distances precluded us from being unable to retest them in the laboratory after recovery to identify whether the functional shift characterized by increased ERP amplitudes normalized after the resolution of symptoms. In this context we have no data on whether elevated ERP amplitudes normalized with the resolution of symptoms. Fifth, although the study sample is relatively large for this difficult-to-recruit patient population, it is small from a statistical perspective. Sixth, although the effect sizes for our results are small, they are consistent across all ERP components, suggesting a generalized baseline activation of cortical arousal during a task that was carried out in a safe neutral context and that was devoid of any emotional saliency. They are also consistent with other studies with this cohort that have likewise suggested a state of increased arousal and motor reactivity (Kozłowska et al., 2013a; Kozłowska et al., 2015b). Exposure to emotionally salient threat cues would be expected to result in more significant cortical arousal, higher ERP amplitudes and larger effect sizes (Vuilleumier and Cojan, 2011; Voon et al., 2011; Voon, 2014; Aybek et al., 2014; Kanaan et al., 2007). Finally, we are unclear as to the potential significance of the greater percentage of target tones for the P50 component available for the patient group. The finding did not reflect more effective peak detection as a function of increased P50 amplitude. If not coincidental it is possible that the greater percentage of P50 target tones could reflect increased activity in the salience network along with increased pre-attentive, automatic sound processing in the auditory cortex.

Despite the above limitations, our results have important implications for theoretical models of functional neurological symptom disorder and for treatment. This study adds to a growing literature indicating that states of high arousal may be a precondition for generating functional neurological symptoms. The brain-body stress systems—the HPA axis, the autonomic nervous system, the immune-inflammatory system, and brain systems underpinning pain, arousal, and emotional states—are interconnected and form part of a larger integrated system. Activation of any single part of the system, whether by stress, pain, injury, or psychological trauma, can trigger the body's stress response, resulting in a cascade of stress-induced changes in the brain, with the endpoint of brain-wide network reorganization. Future

neurophysiological studies in child/adolescent and adult patients—and, in particular, studies that utilize threat cues that have emotional saliency for the individual—are needed to ascertain the soundness of the ideas presented in this article. Future studies will also need to delineate the different subgroups of patients as reflected by acute vs. chronic patterns of presentation. Pending the resolution of such questions, if arousal is necessary for the generation of acute functional neurological symptoms, then interventions that help patients downregulate arousal may be centrally important in order to break aberrant patterns of functional activation and connectivity, and to shift brain networks back to health.

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Text Box 1

‘Of the ERP components elicited via the auditory oddball task, the N100 and P300 are the most, and the P50, P200 and N200 the least, studied. The P50 and N100 are understood to reflect neural sensory gating mechanisms that filter out redundant stimuli (Witten et al., 2014). The N100 component is generated from two sites: the posterior auditory cortex appears to provide a “fast and coarse” preattentive stimulus analysis that functions to determine which novel auditory stimuli enter awareness (an aspect of stimulus processing that may be crucial for activation of innate defense responses in the face of impending danger) (Jaaskelainen et al., 2004); and the anterior auditory cortex appears to provide a subsequent attentional analysis detailing the characteristics of the stimulus (Jaaskelainen et al., 2004). The P200 and N200 are understood to reflect basic sensory processing—termed lower-level processing—of the stimulus. The P200 is modulated by stimulus characteristics and by cognitive and task demands, and is generated in associative auditory temporal regions (Portella et al., 2012; Ferreira-Santos et al., 2012). The N200 is associated with discrimination and classification of the stimulus (Portella et al., 2012; Sumich et al., 2008) and has multiple subcomponents, with different generators (Patel and Azzam, 2005). The P300 is made of two separate wave forms, the P3a and P3b, whose activity reflects coordinated activities in the prefrontal and posterior cortical areas during attention switching and updating of task sets in working memory (Meares et al., 2005).

The P3a peaks 60–80 ms earlier than the P3b, and new methodologies—the fragmentary decomposition method—enable both components to be studied independently (Melkonian et al., 2003). Novel stimuli evoke the anteriorly distributed P3a associated with the orienting reflex and the automatic allocation of attention (Sumich et al., 2014; Volpe et al., 2007). In the conventional auditory oddball, the P3a is elicited by a specific, anticipated “target” or “background” stimuli that occur unpredictably within an experimental session (Comerchero and Polich, 1999). P3a generators are localized in cingulate, frontal and right parietal areas, and temporo-occipital regions (Volpe et al., 2007). The posteriorly distributed P3b reflects effortful, higher-level processing involving attention orientation and working memory (updating changes in the environment and response modulation) (Sumich et al., 2014; Portella et al., 2012). P3b generators are localized in bilateral frontal, parietal, limbic, cingulate and temporo-occipital regions (Volpe et al., 2007).

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