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ORIGINAL CONTRIBUTION

Abnormal neural responses to emotional stimuli in children with primary monosymptomatic nocturnal enuresis

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Abstract
Nocturnal enuresis (NE) is a common disorder in school-aged children that has been reported to affect nearly 10% of 7-year-old children and affects both the children and their families. Previous studies have shown that the risk of psychosocial difficulties in children with enuresis is elevated. Thus, children with NE may experience negative effects on psychosocial health or emotion processing. Therefore, the aim of this study was to investigate the potential disturbance in emotional processing in children with NE using functional magnetic resonance imaging (fMRI). In this work, we used fMRI and an affective picture task to evaluate brain response changes in children with NE. Two groups, one consisting of 22 children with primary monosymptomatic NE and one with 23 healthy controls, were scanned using fMRI. Compared to the healthy subjects, children with NE mainly showed increased activation when viewing negative vs. neutral pictures in the bilateral medial superior frontal gyrus that extended to the anterior cingulate cortex. Our results demonstrated that children with primary monosymptomatic NE showed abnormal neural responses to emotional stimuli and overactivation in the medial prefrontal and anterior cingulate cortices suggested that children with primary monosymptomatic NE may be hypersensitive in their sensory perception of negative pictures.

Keywords Nocturnal enuresis · fMRI · Emotion · Brain

Introduction

Nocturnal enuresis (NE) involves involuntary voiding during sleep and is a common developmental disorder that affects 15–20% of 5-year-old children [26]. The prevalence of NE was 12.4% for boys and 6.5% for girls among 6- to 13-year-old schoolchildren in Turkey [28]. According to the International Children's Continence Society, NE without other lower urinary tract (LUT) symptoms (nocturia excluded) and without bladder dysfunction is defined as monosymptomatic NE [2, 23], which is further subdivided according to its onset: secondary enuresis is reserved for children who have had a previous dry period of > 6 months, whereas primary monosymptomatic nocturnal enuresis (PMNE) is defined as no period of established urinary continence for more than 6 months [2, 23]. NE has important negative effects on performance and self-image in these children [32], with quality of life, depression, and sleep quality scores suggesting worse health in children with NE [34]. Children with primary NE have been found to show higher rates of generalized anxiety disorder, school phobia, panic disorder, social anxiety, and separation anxiety than healthy children

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[27]. Epidemiological investigation also suggested that neuropsychiatric conditions (e.g., anxiety, depression, and obsessive behaviour) were more prevalent in NE patients than in age-matched healthy controls [15]. These studies reveal an increased risk of psychosocial difficulties in children with enuresis. Thus, NE may have negative effects on psychosocial health or emotion processing.

In our previous work using functional magnetic resonance imaging (fMRI), we reported that the bilateral inferior frontal gyri, right superior and middle frontal gyri, right inferior parietal lobe, bilateral cingulate gyri, and insula showed reduced activation during a response inhibition task [19] and that spontaneous brain activity was altered in the left inferior frontal gyrus and medial frontal gyrus during the resting state in children with PMNE [20]. Children with PMNE were also found to have microstructural abnormalities in the thalamus, medial frontal gyrus, anterior cingulate cortex (ACC) and insular cortex [21], as well as neurochemical abnormalities in the prefrontal cortex (PFC) and pons [41]. These previous studies indicated that the lateral and medial PFC (mPFC), ACC, thalamus, and insular cortex display functional and structural abnormalities related to the control of micturition [13, 14]. On the other hand, the PFC, ACC, and insular cortex all participate in emotional processing [1, 25, 36]. NE may induce stress and depression and may negatively affect emotion. In our other work, young adults with histories of childhood NE showed increased activation of the temporoparietal junction, bilateral dorsolateral PFC, and bilateral ACC in the negative pictures minus neutral pictures condition compared with controls [36]. Equit et al. [10] reported that children with NE showed more intense responses to positive and negative pictures than controls in the frontal region, as measured by event-related potentials. However, these results require further validation due to limited sample size.

In the present study, we speculated that children with PMNE may have emotional problems and would show different responses to emotional stimuli. Furthermore, some overlap may exist between brain areas that show different responses to emotion and those that control micturition, such as the PFC and ACC. Therefore, we investigated brain responses to emotional stimuli in children with PMNE using fMRI and affective picture stimuli.

Materials and methods

Ethics statement

The East China Normal University Committee on Human Research (Project no. HR2015/03011) approved the study. Each participant involved in our study signed an informed consent form approved by the committee.

Subjects

A total of 22 children with PMNE (7–12 years old) who were outpatients at Shanghai Children's Medical Center and who were diagnosed by senior doctors were included. We also used advertisements to recruit 23 healthy children from Shanghai who were matched for age, gender and general educational level (Table 1). The children with PMNE wet their beds during the night at least twice per week for three consecutive months but did not wet their clothes during the daytime. Their symptoms had not been interrupted for more than 6 months or were not caused by any related diseases or medicine. The healthy controls had not wet their bed since they were 5 years of age. Children with any other neurological or psychiatric diseases, internal implant metals, or claustrophobia were excluded prior to MR scanning.

Table 1 Demographic and clinical characteristics of the sample

Measures	PMNE group ($n=22$)	Healthy group ($n=23$)	p value
Age (years), mean ± SD	9.45 ± 1.56	9.39 ± 1.31	0.89
Gender (male/female)	9/13	10/13	
Years of education, mean ± SD	3.36 ± 1.46	3.20 ± 1.35	0.63
CDI scores, mean ± SD	4.71 ± 3.07	3.95 ± 3.74	0.28
SASC scores, mean ± SD	4.07 ± 2.27	3.85 ± 2.78	0.80
Bed-wetting frequency (per week), mean ± SD	4.65 ± 2.06	N/A	
Number of patients never waking up for voluntary voiding	10 ($n=22$)	N/A	

Some behavioural and clinical data were collected incompletely as follows: the number of patients who completed the CDI and SASC was 14; one healthy child did not complete the CDI scale; and one patient did not confirm his bed-wetting frequency per week

PMNE primary monosymptomatic nocturnal enuresis, *CDI* Children's Depression Inventory, *SASC* Social Anxiety Scale for Children

Measures of depressive and anxiety symptoms

Patients and controls were all right-handed. The potential depressive and social anxiety symptoms of the participants were assessed using the Children's Depression Inventory (CDI) [8] and the Social Anxiety Scale for Children (SASC) [18], respectively.

fMRI paradigm

The affective picture task included 60 affective pictures from the Chinese Affective Picture System [3] (30 negative and 30 neutral) that were presented to evoke neutral or negative emotions in the participants over a total duration of approximately 6 min. Pictures associated with bloodiness, violence, and snakes were excluded to avoid any adverse influence on the children. The two types of pictures were significantly different in valence ($valence_{negative} = 2.71 \pm 0.23$, mean ± SD; $valence_{neutral} = 5.42 \pm 0.17$, mean ± SD; $t_{1,45} = -0.51$, $p < 0.001$) and arousal ($arousal_{negative} = 4.65 \pm 0.56$, mean ± SD; $arousal_{neutral} = 4.21 \pm 0.27$, mean ± SD; $t_{1,45} = 3.89$, $p < 0.001$). The experimental paradigm consisted of ten blocks presented in a pseudo-randomized order, with each block containing six pictures (either all neutral or all negative) and each picture being displayed for 4 s (Fig. 1). A fixation cross was presented in the centre of the screen for 10 s during the resting period.

All stimuli were presented using a SAMRTEC SA-9900 system (Shenzhen Sinorad Medical Electronics Inc., Shenzhen city, China), which is a professional fMRI stimulus presentation system that can achieve synchronization between stimuli presentation and scanning.

fMRI image acquisition

The MRI data were collected at the Shanghai Key Laboratory of Magnetic Resonance (East China Normal University, Shanghai, China) using a 3.0 T scanner (Siemens, Erlangen, Germany). Custom-fit foam pads were placed around the children's heads to minimize motion during scanning. Functional MRI data were acquired during the task using a T_2^*-weighed gradient-echo echo-planar-imaging (EPI) sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, field of view (FOV) = 220 × 220 mm^2, matrix size = 64 × 64, slice thickness = 3 mm, number of axial slices = 32, number of volumes = 175, and voxel size 3.4 × 3.4 × 4 mm^3). For within-subject registration, structural scans were obtained using a high-resolution, T1-weighted and three-dimensional magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence with the following parameters: TR = 1900 ms, TE = 3.42 ms, inversion time = 900 ms, FOV = 240 × 240 mm^2, acquisition matrix = 256 × 256, slice thickness = 1 mm, and 192 slices with voxel size 1 × 1 × 1 mm^3.

fMRI image analysis

Functional images were preprocessed and analysed with the Data Processing Assistant for Resting-State fMRI (DPARSF; http://rfmri.org/DPARSF) and statistical parametric mapping (SPM; http://www.fil.ion.ucl.ac.uk/spm/software/spm) software. In the preprocessing step, for each participant, the first ten volumes (20 s) of functional data were discarded to allow the person and the scanner to reach equilibrium, during which period the subjects were asked to look at a fixation cross. Then, the functional scans were corrected for differences in slice timing and for motion. Maximum movement of each of the 45 children was less than 2 mm or 2°. To spatially normalize the fMRI data, individual structural images were co-registered to their respective mean functional images; segmented into grey matter, white matter and cerebrospinal fluid; and then both the structural and functional images were normalized to MNI (Montreal Neurological Institute) space based on these segmentation parameters using the DARTEL (Diffeomorphic Anatomical Registration using Exponential Lie Algebra) tool implemented in DPARSF. The tissue probability template used for segmentation was created by the Template-O-Matic toolbox (https://irc.cchmc.org/software/tom.php) according to the

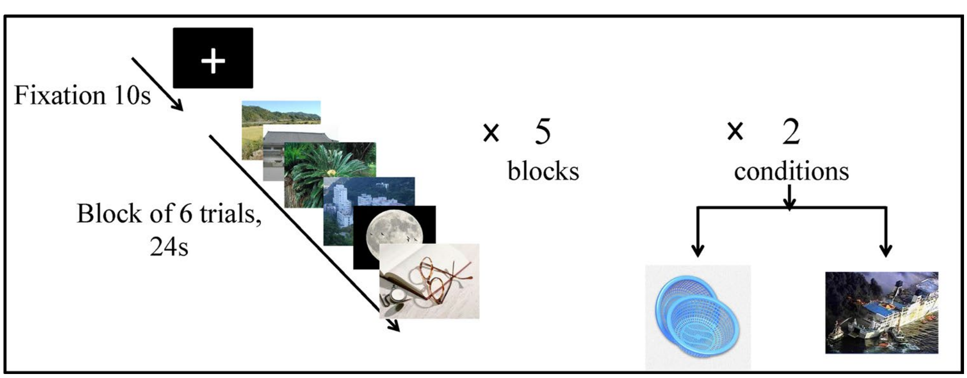

Fig. 1 The sample blocks in the affective picture task are shown. Participants were presented neutral or negative pictures (24 s) and rest (10 s) blocks. Each task block had six pictures

age and gender of the sample. The normalized functional volumes were spatially smoothed using a 6-mm isotropic Gaussian kernel (full width at half-maximum).

In the first-level (within-subject) analysis, the preprocessed data for each participant were modelled on the basis of the general linear model within each voxel of the whole brain by modelling the different conditions (emotional valence: negative and neutral) using SPM. The regressor (experimental block) was convolved using SPM's default haemodynamic response function with time derivatives. Additionally, the six realignment motion regressors were included as nuisance variables. The resulting contrast images (negative vs. rest, neutral vs. rest, and negative vs. neutral) were entered into the second-level group analysis.

Whole-brain one-sample *t* tests were conducted for both groups for the negative vs. neutral contrast to analyse the activation of the emotion network in response to the task. In addition, the group × condition interaction [patients (negative – neutral) – controls (negative – neutral)] was tested in both directions using a factorial analysis of variance (SPM 'flexible factorial' model). Age and gender were included as covariates of no interest. All the statistical results reported reached cluster-level $p < 0.05$, with family-wise error (FWE) correction (surpassing a peak level $p < 0.001$ initial voxel threshold). Within the clusters observed in the group × emotion interaction effect, the mean activation values were extracted for each contrast to perform post hoc tests using the SPSS software.

Results

As seen in Table 2, the within-group analysis showed that both groups demonstrated activation or deactivation in emotion-related brain areas, including the amygdala, medial frontal lobe, and middle temporal lobe, when the subjects were processing negative effects. The between-group analysis showed that the group × emotion interaction effect was significant in the medial superior frontal gyrus and extended to the ACC, as seen in Table 2 and Fig. 2. The children with PMNE showed increased activation in the clusters compared to that in the controls during the negative > neutral contrast. The questionnaires (CDI and SASC) showed that none of the participants suffered from depressive or anxiety disorders, while the scores on both scales were slightly higher in patients than in the healthy children.

Discussion

To the best of our knowledge, this is the first study using fMRI to investigate brain responses to emotional picture stimuli in enuretic children, and we found that children with PMNE differed from healthy controls in the way they processed emotion. Furthermore, compared to the healthy subjects, children with PMNE mainly showed increased activation in the bilateral mPFC, which extended to the ACC, in the negative pictures minus neutral pictures condition. Negative emotional stimuli activate a broad network of brain regions, including the mPFC and ACC. The ACC and mPFC have been reported to be involved in appraisal and expression of negative emotion, and these regions play regulatory roles related to limbic system involvement in generating emotional responses [11]. A review of the positron emission tomography and fMRI literature indicated that the mPFC was found to be activated in many emotion tasks, both with and without cognitive demand, and had a general role in emotional processing, and the ACC was found to be involved in emotional recall/imagery and emotional tasks with cognitive demand [24]. Saunders et al. [29] proposed that conflict was emotive, thereby integrating perspectives from affective science and cognitive neuroscience on the mPFC. In light of this, children with PMNE showed higher activation in the mPFC and ACC; this finding suggested that when these children view negative pictures, the stimuli may trigger a negatively valenced affective state, and the degree of this aversive experience motivates the upregulation of cognitive control to avoid further negative experiences [29].

The mPFC and ACC are involved in emotional disorders, such as anxiety and depression disorders. Anxious youth have been found to exhibit reduced activation in the mPFC and ACC relative to healthy controls [7]. Compared to healthy subjects, individuals with generalized social anxiety disorder demonstrated reduced regional cerebral metabolic rates of glucose uptake within the ACC and ventral mPFC pretreatment at baseline [12]. A voxel-based morphometry study found that the dorsal medial frontal cortex was anticorrelated with greater levels of depression, and in males, greater levels of depression were associated with reduced dorsal medial prefrontal volumes [9]. In our study, children with PMNE had slightly higher scores on the SASC than the control children, but this difference was not significant. In addition, children with PMNE showed higher activation in the mPFC and ACC, suggesting that these patients may be more sensitive to negative stimuli, though this sensitivity did not reach the level of anxiety disorder. Several recent studies have focused on behavioural disorders and impaired quality of life in children and adolescents with urinary incontinence, reporting that enuresis has negative emotional and social effects on children [22, 30]. Neuropsychiatric conditions were found to be more prevalent in NE patients, and quality of life scores were significantly lower in the NE group than in the HC group [15]. A large-sample prospective study with a community-based sample of children followed from age 3 years to age 9 years found that significant age 3 predictors of developing primary enuresis by age 9 included childhood

Table 2 Within-group and between-group differences in the negative > neutral condition

Brain areas	*T*/*F* value	Number of voxels	MNI coordinates (*X Y Z*)			p_{FWE} value (cluster level)
PMNE group						
Left middle temporal and occipital gyri	10.41	892	−54	−63	6	0.000
Right middle temporal and occipital gyri	8.07	680	51	−60	12	0.000
Right inferior and middle frontal gyri	5.72	66	45	21	21	0.019
Bilateral medial frontal gyri	5.66	60	−6	51	24	0.028
Left amygdala and parahippocampal gyrus	5.33	49	−27	−6	−21	0.050
Left fusiform gyri	5.22	65	−42	−51	−18	0.021
Left inferior parietal and supramarginal gyri	−8.09	415	−36	−54	33	0.000
Left middle temporal gyrus	−6.38	52	−60	−48	−12	0.048
Bilateral cingulate gyrus	−5.89	231	0	−30	30	0.000
Right inferior parietal and supramarginal gyri	−5.88	357	42	−48	39	0.000
Bilateral precuneus	−5.37	104	−6	−72	39	0.002
Left inferior frontal gyri	−5.27	97	−45	48	9	0.003
Healthy group						
Bilateral middle occipital gyri	9.51	2509	−48	−69	6	0.000
Bilateral fusiform gyri	9.44		45	−48	−21	
Right inferior occipital gyri	8.35		39	−78	−9	
Bilateral inferior temporal gyri	7.90		−42	−69	−3	
Right parahippocampal gyrus	7.77		39	−36	−18	
Bilateral middle temporal gyri	7.53		−39	−72	12	
Midbrain	6.40		12	21	−15	
Right superior and inferior parietal lobule	6.61	85	−27	−51	54	0.006
Left amygdala and parahippocampus	6.29	140	−21	−6	−21	0.000
Right middle temporal gyrus	5.71	79	54	0	−21	0.009
Right superior parietal lobule	5.37	64	27	−60	54	0.022
Left middle temporal gyrus	5.25	73	−48	0	−15	0.013
Right inferior parietal and supramarginal gyri	−7.86	474	45	−54	42	0.000
Left inferior parietal and supramarginal gyri	−7.38	505	−51	−48	39	0.000
Right middle frontal gyri	−6.96	138	39	15	45	0.000
Right middle and inferior temporal gyri	−6.70	94	60	−33	18	0.004
Left precuneus	−6.23	100	−9	−66	24	0.003
Left middle and superior frontal gyri	−5.75	219	−39	51	3	0.000
Left medial and middle frontal gyri	−5.73	245	9	36	30	0.000
Left middle and inferior temporal gyri	−5.48	61	−60	−30	−12	0.027
Bilateral cingulate cortex and precuneus	−5.08	213	−3	30	39	0.000
Right middle and superior frontal gyri	−4.08	58	33	45	3	0.032
PMNE group > heathy group						
Medial superior frontal gyrus extending to the anterior cingulate gyrus	17.36	51	−18	45	24	0.045

x, *y*, and *z* correspond to the peak-activated voxel coordinates; in the second column

PMNE primary monosymptomatic nocturnal enuresis

The within-group results are represented as *t* values, and the group effect is reported as an *F* value. All the results reported reached cluster level $p < 0.05$, with family-wise error (FWE) correction for voxels surpassing a $p < 0.001$ initial voxel threshold

anxiety and low positive affectivity, maternal history of anxiety, and low authoritative parenting, indicating that primary enuresis shows both strong antecedent and prospective associations with psychopathology [17]. The literature suggests that clinicians should not overlook the effects of enuresis on psychosocial development and the relationship with psychopathology.

Activity in the ACC and mPFC has been reported in many bladder experiments, and these brain regions are within the pathway of the model of lower urinary tract control via

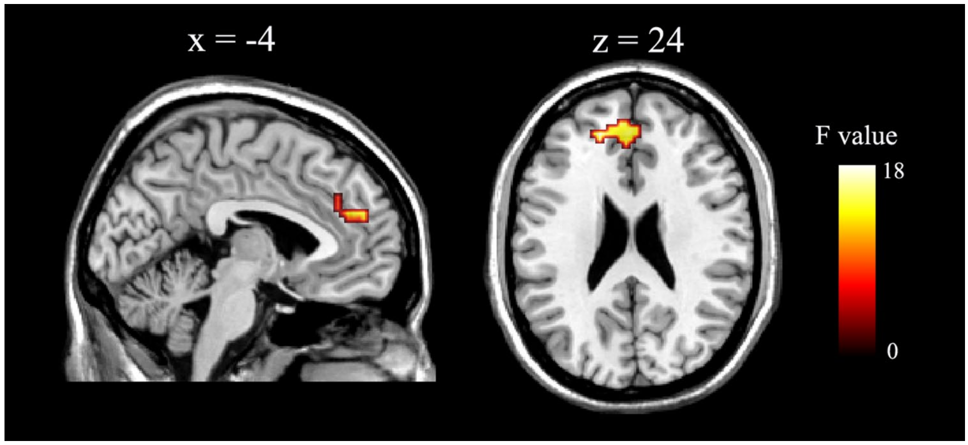

Fig. 2 Brain activation map comparing children with PMNE to healthy children when viewing negative vs. neutral pictures

higher brain centres [13, 14]. The ACC, PFC, and insula are likely concerned with the modulation of continence and micturition control and the cognition involved in bladder sensations [16]. Previous literature related to bladder control suggested that the mPFC is associated with the decision to void or not [4, 5, 13]. In fact, the PFC is critical for executive function and emotion regulation and is involved in controlling micturition. The PFC undergoes considerable maturation during childhood [5, 33] and is particularly vulnerable to lesions due to its protracted developmental course [31]. Our previous studies demonstrated that functional and structural abnormalities in the mPFC and ACC are associated with PMNE [19–21], indicating developmental delays or abnormalities in these areas. Children with PMNE showed abnormal neural responses to emotional stimuli in the mPFC and ACC in the present study, which may be primarily due to developmental delays or abnormalities in these brain areas. On the other hand, higher activation in the mPFC and ACC in children with PMNE may also be secondary effects of long-term bed-wetting. Children with PMNE often experience social and emotional distress, such as fear of being discovered by others and feeling unable to sleep at a friend's house. The symptom of wetting might result in chronic stress, which would have a negative effect on emotion states and may lead to changes in the neural pathways of emotional processing. The children with PMNE had experienced NE many times, which may have caused them to be hypersensitive to negative events, such as negative emotional pictures. Stress is associated with cognitive and emotional dysfunction, and chronic stress has been reported to alter neural activity in the mPFC during retrieval of extinction [39]. Acute and chronic stresses are thought to influence extinction and alter the structure and function of the mPFC [38]. The exact relationship between bed-wetting and abnormal neural responses to emotional stimuli in children with PMNE remain unclear. These phenomena are not independent and may interact with and influence one another; for example, children with PMNE may exhibit developmental delays and local brain dysfunction, which would induce bed-wetting and affect emotional processing, with bed-wetting then inducing long-term stress and emotional problems, which alter the structure and function of the mPFC and increase the risk for a variety of psychological disorders. In the future, more studies are needed to further clarify the relationship between bed-wetting and emotional problems.

Our results were consistent with those of the previously mentioned event-related potentials study, as that study also found that children with NE exhibited more intense responses to positive and negative pictures than controls [10]. In our previous study, young adults with histories of childhood NE showed increased activation in the temporo-parietal junction, bilateral dorsolateral PFC, and bilateral ACC in the negative pictures minus neutral pictures condition compared to controls [37]. The young adults with histories of childhood NE showed similar responses to those of the children with PMNE, but the brain areas were not exactly the same. Possible reasons for these differences may be as follows: (1) the brains of children are in development and change with age, and the brain regions of emotional processing also change over time [40]; and (2) different negative pictures were used in the two studies, and considering the tolerance of children, negative images that induced high levels of horror or nausea were excluded in the experiment with children, while those involving adults included pictures of this nature. Young adults with histories of childhood NE showed increased activation to emotional stimuli, even if the NE resolved as they grew up. Our research suggested that we need to pay more attention to the mental health of children with enuresis and that it is necessary to conduct appropriate psychological interventions and treatments.

Our research sheds light on the study of abnormal emotional processing in children with PMNE. In fact, children with nonmonosymptomatic NE had even higher scores for behavioural problems when compared with PMNE [35, 42]. The presence of behavioural and emotional symptoms impacts treatment of the dysfunction, as well as the self-esteem of patients and caregivers. Thus, childhood NE should be managed carefully and comprehensively to prevent the development of more serious behavioural problems in the future. The PIN-Q, a cross-cultural continence-specific paediatric quality-of-life measurement tool, is recommended to measure the emotional impact of urinary incontinence on a child [2, 6]. Enuresis may have other potential behavioural and psychological effects, and a full child psychiatric assessment and physical examination would be helpful in future research. Furthermore, more studies are needed to assess the link between bed-wetting and emotional problems, and larger samples and different subtypes of enuresis are needed to validate the results. Longitudinal studies of emotional processing in NE patients with/without successful treatment of incontinence would also be useful for investigating the interaction between emotional problems and enuresis. In addition, the present study focused on brain responses to neutral and negative emotion pictures in children with PMNE, and the neural processing of positive emotion pictures also requires further study.

Conclusions

In summary, our results showed that children with PMNE showed abnormal neural responses to emotional stimuli. Bed-wetting during childhood negatively affects children, and this may lead to increased activation in the mPFC and ACC when viewing negative vs. neutral pictures. This overactivation suggested that children with PMNE may be hypersensitive in their sensory perception of negative pictures, and thus the emotional impact must be managed carefully and comprehensively to prevent the development of more serious behavioural problems in the future.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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