Minireview *Highlight article*

Pathogenesis and brain functional imaging in nocturnal enuresis: A review

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Impact statement

Nocturnal enuresis is a common and distressing developmental disease, while the etiology and pathogenesis of nocturnal enuresis remain unclear. Currently, nocturnal enuresis is generally considered a multifactorial disease associated with a complex interaction of somatic, psychosocial, and environmental factors. A variety of postulations have been proposed to explain the occurrence and progression of nocturnal enuresis. In recent decades, the introduction of functional neuroimaging technologies has provided new approaches for uncovering the mechanisms underlying nocturnal enuresis. The relevant studies have indicated that nocturnal enuresis is associated with functional and structural alterations of the brain. In this review, we briefly summarized the popular hypotheses regarding the pathogenesis of nocturnal enuresis and the current progress of functional neuroimaging studies in examining the underlying mechanisms.

Abstract

Nocturnal enuresis is a common and distressing developmental disease, which may cause various degrees of psychosocial stress and impairment to self-esteem in affected children as well as agitation to their parents or caregivers. Nevertheless, the etiology and pathogenesis of nocturnal enuresis are not understood. Currently, nocturnal enuresis is generally considered a multifactorial disease associated with a complex interaction of somatic, psychosocial, and environmental factors. A variety of postulations have been proposed to explain the occurrence and progression of nocturnal enuresis, including hereditary aberration, abnormal circadian rhythm of antidiuretic hormone secretion during sleep, bladder dysfunction, abnormal sleep, difficulties in arousal, neuropsychological disorders, and maturational delays of the brain. In recent decades, the introduction of functional neuroimaging technologies has provided new approaches for uncovering the mechanisms underlying nocturnal enuresis. The main neuroimaging modalities have included brain morphometry based on structural magnetic resonance imaging (MRI), task-based and event-related functional MRI (fMRI), and resting-state fMRI. The relevant studies have indicated that nocturnal enuresis is associated with functional and structural alterations of the brain. In this review, we briefly summarized the popular hypotheses regarding the pathogenesis of nocturnal enuresis and the current progress of functional neuroimaging studies in examining the underlying mechanisms thereof.

Keywords: Enuresis, nocturnal enuresis, brain functional imaging, functional magnetic resonance imaging, resting state, pathogenesis

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Introduction

Nocturnal enuresis, also known as nightly bedwetting, is defined as the continuous, nocturnal, and involuntary voiding of urine during sleep that is associated with normal daytime urination beyond the age of 5 years old.[1] Nocturnal enuresis has a long-standing history, which was first documented in the Papyrus of Ebers around 1500 BC.[2] Nocturnal enuresis is a common and distressing developmental disease affecting approximately 15%–20% of 5-year-old children and nearly 2% of young adults.[3] Furthermore, the prevalence of nocturnal enuresis has been reported to be 12.4% for boys and 6.5% for girls among 6 to 13-year-old school-age children.[4] After the age of 7 years old, nocturnal enuresis can be spontaneously cured at a rate of 15% annually; however, some patients remain affected even beyond the age of 16 years old.[5] According to the diagnostic criteria of the International Children's Continence Society, nocturnal enuresis without additional lower urinary tract symptoms or a history of bladder dysfunction can be diagnosed as nocturnal enuresis.[6,7] Based on the clinical onset, nocturnal enuresis can be further categorized into two forms, primary and secondary. Primary nocturnal enuresis is identified as no period of established urinary continence

for more than 6 months, and secondary nocturnal enuresis is identified as a previous period of established urinary continence for more than 6 months.[6,7]

Nocturnal enuresis usually causes various degrees of psychosocial stress and impairment to the self-esteem of affected children and agitation to their parents or caregivers.[1,8] Additionally, since nocturnal enuresis often poses adverse effects on performance and self-image in affected children,[9] it can further lead to depression, social maladjustments, and impaired sleep quality. These comorbidities can have a significant impact on the psychosocial health, emotional well-being, social life, and individual quality of life.[4,10] In fact, as reported in literature, pediatric patients with nocturnal enuresis exhibit a higher incidence of neuropsychiatric disorders, such as social anxiety, panic disorder, school phobia, depression, obsessive behaviors, and separation anxiety than their non-enuretic peers.[11,12]

The etiology and pathogenesis of nocturnal enuresis is not fully understood. Currently, nocturnal enuresis is generally considered a multifactorial disease associated with a complex interaction of somatic, psychosocial, and environmental factors. Until now, a variety of hypotheses have been proposed to explain this phenomenon and include hereditary aberration, detrusor overactivity, vasopressin circadian rhythm, nocturnal polyuria or reduced secretion of antidiuretic hormone during sleep, disturbance in renal sodium handling, abnormal sleep, difficulties in waking, stress, neurological or psychological disorders, and maturational delays of the brain.[1,13–20] In recent decades, the introduction of functional neuroimaging technologies has provided new approaches for studying neuropsychological diseases. The relevant studies have indicated that nocturnal enuresis is associated with functional and structural alterations of the brain.[21–26] In this review, we briefly summarized the pathogenic hypotheses underlying nocturnal enuresis and the main findings of functional neuroimaging studies documented in the existing literature.

Search strategy and selection criteria

We conducted a systematic literature review of the Medline and PubMed databases using the search terms of "(nocturnal enuresis OR enuresis) AND functional neuroimaging," "(nocturnal enuresis OR enuresis) AND brain function," "(nocturnal enuresis OR enuresis) AND functional MRI," "(nocturnal enuresis OR enuresis) AND functional," and "(nocturnal enuresis OR enuresis) AND pathogenesis." We reviewed all evidence for functional neuroimaging studies in patients with nocturnal enuresis. Only articles published in English were considered.

Pathogenesis of enuresis

Although the definite pathogenetic mechanisms of nocturnal enuresis remain unclear, there have been several theoretical hypotheses based on clinical and experimental evidence.

Hereditary factors and genetic aberrations

During the last three decades, numerous studies have investigated the role of hereditary factors in the etiology of nocturnal enuresis. The earliest study dates back to the 1930s; however, formal molecular genetic studies have been performed since the 1990s. Gontard *et al*. postulated that hereditary factors are the most predominant in the pathogenesis of nocturnal enuresis; however, somatic and psychosocial environmental features also have important regulatory functions.[27] Furthermore, some studies have indicated that nocturnal enuresis is inherited with an autosomal dominant pattern and a penetrance rate of 90%. Meanwhile, one-third of all cases are sporadic and without a definitive familial history. Several genetic loci associated with nocturnal enuresis have been identified, including genes located on chromosomes 13q13–q14.3 (*ENUR1*), 12q (*ENUR2*), 22q11 (*ENUR3*), and 8q (*ENUR4*). Nevertheless, there may be other undetected candidate loci that still need to be discovered. In 1995, Eiberg and colleagues first mapped the dominant inherited nocturnal enuresis (*ENUR1*) gene to chromosome 13q.[28] They performed an exclusion analysis in approximately three hundred DNA markers, and chromosome segments 5q and 13q (*ESD*, *D13S1*) were further identified via linkage analyses. Eventually, linkage analyses in three families confirmed that the gene responsible for nocturnal enuresis is located on chromosome 13q13–q14.3, which was consistent with the locations of the flanking markers D13S1 (13q13) and ESD (13q14.1–14.2) .[28] Subsequently, *ENUR2∼4* genes were accurately localized on chromosomes.[29] Although these genes have been found to be clearly associated with familial nocturnal enuresis, there is no specific correlation between different genotypes and clinical phenotypes, which may be complicated or disrupted by complex environmental influences. Additionally, a variety of single nucleotide polymorphisms may contribute to the occurrence of nocturnal enuresis. In 2019, Ece and coworkers found that the urine level of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) was increased in patients with nocturnal enuresis. Despite this observation, polymorphisms in the *BDNF* and *NGF* genes did not make a significant contribution to the development of nocturnal enuresis.[30] Recently, Balat *et al*. tested the polymorphisms in the *KCNJ10* gene in 97 children with nocturnal enuresis and 100 non-enuretic controls, and found that promoter polymorphism may play a role in potassium excretion, suggesting the *KCNJ10* gene may be involved in the pathogenesis of nocturnal enuresis.[31] Although many genetic variants have been identified, there are few studies that have combined genetic alterations and functional imaging abnormalities. This concept will be elucidated in later sections.

Abnormal circadian rhythm of antidiuretic hormone secretion

Antidiuretic hormones are thought to decrease urine production and increase bladder distention; however, this hypothesis is not generally accepted.[19] Serum antidiuretic hormone levels in healthy subjects increase during

nighttime as a response to bladder distension with the reduction of urine production.[32] This circadian rhythm in antidiuretic hormone secretion may be altered in children with nocturnal enuresis.[33,34] The overproduced urine exceeds bladder capacity and leads to enuresis.[35] This phenomenon, however, has been denied in another study.[36] Fatouh *et al*. found that the circadian rhythm was reversed in 71.7% of children with nocturnal enuresis ($n = 99$; age, 6–18 years), and there were significant differences in morning and evening antidiuretic hormone levels between patients with a reversed rhythm, those with a normal rhythm and with non-enuretic controls.[19] It is worth noting that not every child with nocturnal enuresis has nocturnal polyuria, and not every child with nocturnal polyuria responds to desmopressin treatment. As reported, approximately 20–60% of children with nocturnal enuresis are desmopressin-resistant.[17] Therefore, the abnormal circadian rhythm of antidiuretic hormone secretion is an important factor that should be considered in the pathogenesis of nocturnal enuresis even though it may only have clinical significance in a subset of affected children.

Bladder dysfunction or disturbance in bladder control

It is well accepted that there are no abnormalities in the anatomical bladder capacity of children with nocturnal enuresis.[37] However, bladder dysfunction may be involved in the etiology of nocturnal enuresis. The average physiological bladder capacity is approximately 60 ml at birth and increases with age at a rate of ~30 ml/year, reaching the maximum at the age of 12.[37] Previously, the voiding and bladder volume was considered to be normal in children with nocturnal enuresis.[17] However, increasing evidence indicates that an isolated decrease of functional bladder capacity during nighttime may be one cause of enuresis, despite the fact that the expected bladder capacity is normal at daytime.[38] Some studies have concluded that nocturnal voided volumes are significantly reduced compared to daytime voided volumes in children with nocturnal enuresis.[38,39] Additionally, Hagstroem *et al*. found there was no significant difference in the frequency of incomplete micturitions as well as in the post-void residual volume between polyuric and nonpolyuric children during enuresis episodes.[40] Another theory proposes that bladder dysfunction in nocturnal enuresis may be caused by detrusor over-activity, and some investigators postulate that children with nocturnal enuresis may have defects in detrusor inhibition.[41]

Sleep-arousal disorder

Children with nocturnal enuresis share the common feature that they are difficult to wake up, which leads to the assumption that nocturnal enuresis may be caused by the absence of arousal. However, this hypothesis has been questioned as there is no definitive evidence proving that children have to pass through a phase of nocturia to acquire night-time continence.[17] Additionally, electroencephalogram studies during sleep have not identified an increase in deep-sleep phase in affected children.[42,43] Despite these doubts, Dhondt *et al*. found that children with nocturnal enuresis have higher sleep fragmentation and periodic limb movements in sleep than non-enuretic controls, strongly suggesting that nocturnal enuresis may be associated with sleep disorders.[44] Coincidentally, Van Herzeele and colleagues also noted that treatment with desmopressin can decrease periodic limb movements during sleep and prolong the first undisturbed sleep period in children with nocturnal enuresis.[45] Overall, the correlation between the sleep-arousal cycle and nocturnal enuresis is not yet clear.

Neuropsychological factors

Neuropsychological disturbances represent an important factor affecting the progression of nocturnal enuresis and in turn, nocturnal enuresis is often accompanied by anxiety, depression, and inferiority.[46] The causal relationship between these items seems to be a pseudo-proposition. Based on existing evidence, neuropsychological disorders can aggravate the severity of nocturnal enuresis, while children with strong self-confidence are usually rapidly cured.[47] Furthermore, Van Herzeele *et al*. proposed that nocturnal enuresis and psychological disorders may share a common central nervous pathway based on the coexistence of these problems.[48]

Maturational delays of the central nervous system

Global central nervous system maturation delay is considered to be another contributor to nocturnal enuresis, and neuroelectrophysiological evidence also supports this hypothesis. Given that arousal and the micturition reflex are both mediated by nuclei in the brainstem, Freitag *et al*. evaluated the brainstem deficits underlying nocturnal enuresis by measuring evoked potentials (brainstem auditory evoked potential, visual evoked potential, event-related late acoustic-evoked potential [P300]), and the pre-pulse inhibition of the startle reflex. They found that the inter-peak latencies I–III and I–V of the brainstem auditory evoked potential were increased, supporting the hypothesis of an arousal deficit mediated by delayed maturation of brainstem function.[49] Iscan and coinvestigators also found that the P300 latency in the enuretic group was significantly prolonged compared to non-enuretic controls, indicating there was a maturational delay of the central nervous system.[50] A Turkish group investigated the brainstem integrity in children with nocturnal enuresis using auditory brainstem responses, blink reflex, and exteroceptive suppression of the masseter muscle, and found that there were brainstem dysfunctions based on S2 duration time changes.[51]

Brain functional imaging in nocturnal enuresis

In recent decades, magnetic resonance imaging (MRI) techniques, including structural MRI, task-based blood oxygen level-dependent functional MRI (BOLD fMRI), resting-state fMRI, diffusion-weighted MRI, and magnetic resonance spectroscopy (MRS) have provided a noninvasive

approach to investigate the functional and structural changes in patients with nocturnal enuresis.

Brain morphometry based on structural MRI

Voxel-based morphometry is an advanced MRI technique that allows the investigation of focal alterations in brain anatomical volume using parametric mapping. After drawing regions of interest (ROIs) on structural MRI, the volumes of the whole brain or grey matter sub-regions can be computed and compared between patients and controls. As early as in 2012, Yu *et al*. measured cognitive functions and assessed gray matter density variations using voxel-based morphometry in 75 children with nocturnal enuresis. Their findings showed that the intelligence quotient was normal in affected children while the memory and attention functions were impaired. Structural analysis also revealed decreased gray matter density in the right dorsolateral prefrontal cortex and the left cerebellum in the nocturnal enuresis group compared to normal controls.[23] In 2017, this research group further investigated the relationship between genetic polymorphisms and gray matter volume in pediatric patients with nocturnal enuresis.[1] Their study enrolled 104 children with nocturnal enuresis (range, 9.1–11.9 years; median, 10.4 years) and 107 age-matched non-enuretic controls (range, 9.0–11.8 years; median, 10.1 years), which were stratified based on the 616 C/G polymorphism in the *DRD4* gene. For the measurement of gray matter volumes, high-resolution T1-weighted structural images were collected and voxel-based morphometric analysis was performed by normalizing each brain to the standard stereotaxic space of the Montreal Neurological Institute (MNI) template. The results indicated that C-allele carriers in the nocturnal enuresis group had significantly decreased gray matter volumes in the thalamus compared with the GG homozygote patients.[1] On the contrary, in 2018, Wang *et al*. compared the gray matter volumes and gyrification indices (reflecting the absolute values of mean curvature of the cerebral cortical surface) between nocturnal enuresis group ($n = 26$) and non-enuretic controls ($n = 28$) using voxel-based morphometry and surface-based morphometry. In this study, whole-brain gray matter volume analysis revealed significantly increased gray matter volumes in the supplementary motor area and medial prefrontal cortex in the nocturnal enuresis group when compared to controls, while gyrification indices were significantly suppressed in the right precuneus in patients with nocturnal enuresis.[52] Additionally, Lei *et al*. evaluated cerebral structural alterations in pediatric patients ($n = 26$) with nocturnal enuresis using diffusion tensor imaging (DTI) and found that nocturnal enuresis was associated with a decrease in fractional anisotropy and an increase in mean diffusivity in the thalamus. They also noted that the mean diffusivity increased in the frontal lobe, the anterior cingulate cortex, and the insula. It is noteworthy that the thalamus can regulate both urine storage and awakening from sleep, while the latter cerebral areas are all involved in controlling micturition.[22] Despite these promising preliminary results, it is not possible to reach a consistent conclusion and further studies are warranted.

Task-based fMRI and event-related fMRI

fMRI is a burgeoning neuroimaging method developed for identifying regional and time-varying changes in cerebral metabolism. Functional MRI can detect the altered neural activity by identifying the following signals: local cerebral blood flow (CBF) and oxygenation concentration (BOLD). CBF can be measured by perfusion-weighted MRI (needing an injection of contrast agent) or non-invasively by arterial spin labeling, however, the use of this method is limited due to low sensitivity, long acquisition time, and hypersensitivity to motion.[53] BOLD fMRI identifies signals in the magnetic field surrounding the erythrocytes, depending on the oxygenation state of the hemoglobin. Although hemoglobin is diamagnetic and indistinguishable from cerebral parenchyma, completely deoxygenated hemoglobin has four unpaired electrons and is highly paramagnetic. It is based on this property by which local signals in the magnetic field depend on the hemoglobin concentration.[54]Task-based fMRI is a neuroimaging modality used for examining neuroanatomical and functional changes evoked by tasks performed during image acquisition. Event-related fMRI allows for the evaluation of hemodynamic changes in response to transient brain activation evoked by various sensory, motor, and cognitive events.[55] In 2011, Yu's group assessed the working memory and corresponding activation of cerebral regions in children ($n = 13$) with nocturnal enuresis and age-matched non-enuretic controls ($n = 15$). Although the intelligence quotient was normal, the memory/caution factor was significantly lower in the nocturnal enuresis group, and event-related fMRI revealed remarkable attenuation of activity in the left posterior cerebellar lobes.[25] In 2017, this research group investigated changes in whole-brain cerebral metabolic rate of oxygen ($CMRO_2$), cerebral blood flow (CBF), and oxygen extraction fraction (OEF) in children with nocturnal enuresis, and they noted that whole-brain $CMRO_2$ and OEF values were increased in nocturnal enuresis patients even though there was no significant difference in CBF. The authors speculated that elevated OEF levels are important for maintaining oxygen supply in children with nocturnal enuresis, and these patients may be more susceptible to hypoxia. Additionally, the increased OEF levels were positively correlated with the difficulty of arousal from sleep.[56] Zhang *et al*. used fMRI in combination with an n-back task to investigate cerebral functional abnormalities specifically related to working memory in pediatric patients with nocturnal enuresis. They found the right precentral gyrus and the right inferior parietal lobule extending to the postcentral gyrus exhibited reduced activation during the n-back task. Furthermore, patients showed suppressed cerebral activation in the task-positive network, increased task-related cerebral deactivation during a working memory task, and longer response times. These findings strongly suggest that nocturnal enuresis is associated with working memory dysfunction.[57] Another study adopted fMRI in combination with a Go/NoGo task and revealed that nocturnal enuresis patients exhibited significantly prolonged response times. Moreover, the cerebral regions with reduced activation

during motor response inhibition included the bilateral inferior frontal gyri, bilateral cingulate gyri, right inferior parietal lobe, right superior and middle frontal gyri, and insula.[24] As children with nocturnal enuresis usually experience adverse effects on psychosocial health or emotion processing, some studies evaluated the potential disturbance in emotional processing in nocturnal enuresis using fMRI and an affective picture task. Children with nocturnal enuresis were hypersensitive in the sensory perception of negative pictures, manifesting as increased activation in the medial prefrontal and anterior cingulate cortices.[4] Due to the lack of specific tasks, fMRI cannot provide comprehensive information for explaining the alterations of cerebral functions in children with nocturnal enuresis.

Resting-state fMRI and brain network connectivity

Resting-state fMRI was first introduced by Biswal in 1995,[58] and has since been widely used in both healthy subjects and patients with various neurological, psychological, and psychiatric diseases. Unlike task-based fMRI, resting-state fMRI does not require subjects to perform any specific task, and rather the low-frequency oscillations of BOLD signals can reflect spontaneous neural activities. When intracerebral neurons are activated, the hemodynamic response is characterized by more blood supplied by the feeding arteries, and the regional CBF and oxygen supply increases.[59] As a result, the oxyhemoglobin and deoxyhemoglobin levels will be reflected on fMRI as BOLD signals, which is the theoretical basis for constructing brain functional topographical maps.[60] Resting-state fMRI is also based on BOLD signal fluctuation, which is similar to task-based or event-related fMRI; however, resting-state fMRI focuses on the spontaneous alterations of BOLD signals. Imaging data is acquired via a dedicated scan sequence, in which subjects are instructed to maintain a resting state.[61] As resting-state fMRI does not need any active tasks, its application has been growing rapidly during the past decades, especially in patients with neuropsychological diseases. The use of resting-state fMRI in patients with nocturnal enuresis has a relatively short history. In 2012, Lei *et al*. analyzed spontaneous brain activities associated with nocturnal enuresis using resting-state fMRI, and the data were analyzed using statistical parametric mapping. They found that children with nocturnal enuresis showed significantly different amplitudes of low-frequency fluctuation (ALFF) and regional homogeneity (REHO) in the left inferior frontal gyrus, medial frontal gyrus, and left midbrain.[62] Theoretically, the medial frontal gyrus and the inferior frontal gyrus may affect the decision-making for urination, and the midbrain may be involved in the internal signal transmission within the brain network for bladder control. Therefore, the authors speculated that nocturnal enuresis might be attributed to the developmental delay of these brain regions.[62] Subsequently, they also performed a connectome-scale assessment of brain functional connectivity in children with nocturnal enuresis, and found a remarkably decreased clustering coefficient and global/local efficiency, as well as an increased characteristic path length, compared to healthy controls. To be specific, nocturnal enuresis was associated with a decreased nodal efficiency in the bilateral cuneus, bilateral calcarine sulcus, bilateral lingual gyri, and right superior temporal gyrus, suggesting that brain network alterations may impair the global communication and integration functions.[26] Yu's research group assessed the potential correlation between intelligence functions and whole-brain functional connectivity in children with nocturnal enuresis. This work revealed that cerebello-thalamo-frontal circuit aberrations may be an important pathway in the development and exacerbation of attention impairment in nocturnal enuresis.[21] In a study mentioned in the previous section,[1] the authors also noted that the functional connectivity density in the thalamus was decreased in *DRD4* 616 C/G patients with nocturnal enuresis, while *DRD4* 616 C/C controls exhibited elevated functional connectivity density in the posterior cingulate cortex. Overall, the analysis methods of resting-state fMRI data are variable. In addition to the ALFF analysis and ReHo analysis mentioned above, there are functional integration methods for identifying neural networks such as functional connectivity density analysis, seed-based functional connectivity analysis, independent component analysis, and graph analysis.[63] Jiang and colleagues analyzed the resting-state fMRI data via the degree centrality (DC) and voxel-mirrored homotopic connectivity (VMHC) approaches. They found that the DC values of the nocturnal enuresis group were significantly reduced in the anterior cingulate cortex, superior left temporal gyrus, medial frontal gyrus, and posterior cerebellar lobe, and the VMHC values were decreased in the anterior cingulate cortex and the cerebellar lobe.[64] Their findings may facilitate the explanation of the correlation between nocturnal enuresis and psychological symptoms of attention, control, and memory deficits. Subsequently, they performed another study with regard to the DC of key cerebral areas of attention networks in nocturnal enuresis, in which pediatric patients showed remarkable attention deficits and the DC values were reduced in the right inferior parietal sulcus, temporoparietal junction, right frontal eye field, left angular gyrus, and left inferior parietal sulcus.[65] Therefore, dysfunctions in these cortices may be responsible for the impaired attention in children with nocturnal enuresis. Recently, this group also found that the ALFF values were increased in the bilateral medial prefrontal cortex, left inferior temporal gyrus, and anterior cerebellum lobe, but decreased in the left middle temporal gyrus in the children with attention deficit hyperactivity disorder (ADHD). Nevertheless, in children with nocturnal enuresis, the ALFF value was increased in the left inferior parietal lobule compared to controls.[66] There was no overlap in abnormal brain functional regions between ADHD and nocturnal enuresis patients. Some studies have aimed to uncover the neuropathological mechanisms of nocturnal enuresis by combining the ALFF, ReHo, and seed-based functional connectivity analyses.[67] These groups found that the ALFF value was reduced in the left medial orbital superior frontal gyrus, and the ReHo value was increased in the left superior occipital gyrus. When the left thalamus was set as the seed, the functional connectivity to the left medial superior frontal gyrus was significantly decreased

in children with nocturnal enuresis. Based on the existing literature, most of the evidence seems to support the view that the thalamus is a pivotal area involved in the pathogenesis of nocturnal enuresis.[1,22,67] In the latest study, Zhang *et al*. investigated the functional connectivity between the thalamus and other brain regions, and noted that four brain regions had a decreased connection efficiency with the thalamus, including the frontal lobe, parietal lobe, precentral gyrus, and cerebellum posterior lobe.[68] Dysfunctions in these areas may be associated with an arousal disorder and may lead to nocturnal enuresis. It should be noted that resting-state fMRI also has limitations, and the most important issue is the test-retest reproducibility and inter-subject variability. Therefore, more evidence from larger cohorts in different centers may help the fieldget closer to an authentic conclusion.

Future research directions

Overall, functional neuroimaging studies on nocturnal enuresis remain limited, and their findings are generally inconsistent due to the variation in neuroimaging modalitiesand study designs used. All the existing evidence is from cross-sectional studies, and there are no longitudinal observations. As is well-accepted, nocturnal enuresis can be spontaneously cured in most children after the age of seven, but a few children may remain affected even after the age of 16. In these two groups with a distinctly different prognosis, researchers can perform prospectively controlled clinical observations, in which the functional neuroimaging parameters before and after remission of nocturnal enuresis can be compared. Additionally, although current resting-state fMRI results exhibit certain positive findings, the test-retest reproducibility still needs further validation. Moreover, little is known about the specific function of brain regions in the context of nocturnal enuresis, the significance of resting-state fMRI findings in general (especially, aberrations in brain connectome) remains unclear, and the underlying neuropathological mechanisms have not been well clarified. In the future, studies should focus on the correlation between functional neuroimaging alterations and mainstream hypotheses regarding the pathogenesis of nocturnal enuresis.

AUTHORS' CONTRIBUTIONS

All authors participated in the design, interpretation of the studies, analysis of the data, and review of the manuscript. JD drafted the manuscript.

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