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ORIGINAL CONTRIBUTION

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The role of abnormal neural oscillations in the pathophysiology of co-occurring Tourette syndrome and attention-deficit/hyperactivity disorder

Abstract *Objective* To examine the role of aberrant neural oscillatory activity in the pathophysiology of co-occurring Tourette Syndrome (TS) and Attention-Deficit/Hyperactivity Disorder (ADHD). *Method* Neural oscillations refer to periodic variations in the recording of neural activity. The temporal synchronization of oscillations represents a mechanism of neural communication implicated in normal brain functioning as well as psychopathology. We reviewed physiological, imaging, and neuropsychological evidence that tics and symptoms of ADHD may result from abnormal oscillatory activity in the brain. *Results* Structural and functional abnormalities in the cortical–striatal–thalamo–cortical circuits may result in the disruption of oscillatory activity within the basal ganglia of individuals with TS and lead to transient hyperpolarization of selected thalamocortical regions. Extended to TS plus ADHD this or similar mechanisms, in turn, would lead to the dysrhythmia of particular vulnerable cortical regions and give rise to various deficits in motor control (TS + ADHD) as well as impulsivity and attention (ADHD). Compensatory systems within the prefrontal cortex could be activated and trained to modulate the misguided striatal and thalamocortical oscillations. *Conclusions* Although it is highly likely that abnormal neural oscillations have a prominent role in co-occurrence of TS + ADHD, its final relevance in this case deserves further differentiated research (i.e. oscillatory networks disentangled from other neuropsychiatric disorders).

Key words Tourette syndrome – Attention-Deficit/Hyperactivity Disorder – oscillations – thalamocortical dysrhythmia

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Introduction

Rhythmic variations and synchronization of neuronal activity at the levels of cells and networks represent a mechanism of neural communication that subserves perception [98], cognitive function [127], motor coordination [110] and even consciousness [69]. At the same time, abnormalities in oscillatory communication are implicated in various forms of pathology including epilepsy [122], movement disorders [51], schizophrenia [124] and dementia [56]. Emerging anatomical and neurophysiological data have led to a set of hypotheses regarding the role of aberrant neural oscillations in the pathogenesis of Tourette Syndrome (TS) [67]. Specifically, the disruption of oscillatory activity within the basal ganglia may lead to transient hyperpolarization of selected thalamocortical regions, which, in turn, would lead to the ectopic activation of selected cortical pyramidal neurons. It was also proposed that compensatory systems within the prefrontal cortex could adaptively modulate the misguided striatal and thalamocortical oscillations. In this paper, we examine whether the neural oscillations model formulated by Leckman and colleagues could be relevant to understanding the co-occurrence of TS and Attention-Deficit/Hyperactivity Disorder (ADHD).

TS is diagnosed if motor and phonic tics, that can vary in their number, anatomic location, frequency, intensity, and complexity, are present for at least 1 year [64]. ADHD is a heterogeneous disorder of inattention, impulsivity, and hyperactivity which significantly impairs adaptive functioning [10, 99, 104]. Both disorders are characterized by childhood onset, excessive motor activity, and abnormalities in the cortical–striatal–thalamo–cortical (CSTC) circuits. Studies of clinically referred samples reveal that 60–90% of children and adolescents with TS also have ADHD [34, 117]. The co-occurrence of TS and ADHD is somewhat lower in community ascertained samples and ranges from 20% to 50% [62, 111]. When present in children with TS, co-occurring ADHD is associated with family dysfunction, social maladjustment and academic problems [100, 120].

The question of whether co-occurring TS and ADHD represent a combination of two independent pathologies, a separate nosologic entity manifested by both tics and ADHD, or a phenotype subgroup of one of the two major clinical forms has been an area of active research [5, 97, 130]. Based on the findings from a genetic family study, Pauls and colleagues suggested that ADHD that precedes the onset of tics may be etiologically independent from TS and the later onset ADHD may be a secondary manifestation of TS [88]. It was also suggested that ADHD without tics and ADHD co-occurring with TS are different phenomenologically, with the later being a more severe condition than the former [118]. Neurophysiological studies reported reduced intracortical inhibition and shortened cortical silent period in children with TS and ADHD, lending evidence to the additive effect of the deficient inhibitory control of the motor function [79]. A recent electrophysiological study suggested that early event-related theta activity may be a psychophysiological marker of co-occurrence of TS and ADHD [130] while increased spontaneous theta activity is related to ADHD-only.

Neural circuit model of TS

Similarly to other movement disorders, TS vulnerability has been associated with basal ganglia dysfunction [76]. Animal studies suggest that tics and stereotypies are likely to arise from the imbalance in the metabolic activity between medium spiny neurons in the striosomes and matrix compartments of the striatum [21, 108]. The disruption of the neuronal activity in the sensorimotor globus pallidus was associated with the occurrence of stereotypies in non-human primates [43], which suggests that this area of the globus pallidus may be associated with the impaired suppression of unwanted movement in TS. The sensorimotor system modulated by the basal ganglia is also involved in habit formation and in the performance of routine behaviors [57, 108], which has led to a conceptualization that tics often arise from a heightened and selective sensitivity to environmental cues from within the body or from the outside world [66].

In agreement with this view, neuroimaging data have revealed abnormalities in the CSTC structure and function. In the largest structural MRI study to date, basal ganglia volumes were examined in 154 children and adults with TS and 130 matched healthy controls [93]. The volumes of the caudate nucleus were decreased in all participants with TS and the volumes of the putamen and globus pallidus were decreased in adults with TS, but not in children. This result is consistent with a study of monozygotic twins in which more severely affected co-twins had smaller caudate nucleus volumes [53]. Because tics tend to improve by early adulthood in most cases, the smaller lenticular nuclei may reflect a neuroregulatory predisposition to continuing or worsening of tics into adulthood. A recent study showed that reduced caudate volumes in childhood predicted persistence and severity of tics in adults with TS [11]. Peterson and colleagues also reported that prefrontal and orbital frontal cortical volumes were larger in children and smaller in adults with TS and that the presence of ADHD was associated at a trend level of significance with the larger cerebral volumes and with smaller ventricular volumes [92]. Similarly, a disproportional increase in white matter volume in the right frontal lobe was associated with TS and reduced frontal lobe volumes were associated with ADHD in a controlled study of 11 boys with TS and 14 boys with TS and ADHD [40, 95].

In a series of studies utilizing positron emission tomography (PET) in 18 adults with TS, Braun and colleagues reported decreased activity in the basal ganglia regions and abnormal coupling between limbic and motor areas [17, 18, 55]. This abnormal communication between mostly parallel but integrative CSTC circuits [45] may be manifested in symptoms of co-occurring psychiatric disorders, including ADHD in individuals with TS. A recent PET study identified a paralimbic network consisting of anterior cingulate and insular cortex, supplementary motor area and parietal operculum, which were activated before tic onset and possibly responsible for the experience of sensory premonitory urges [13]. By contrast, the onset of motor or vocal tics was associated with activation in sensorimotor areas including superior parietal lobule bilaterally and cerebellum. Taken together with the finding of altered pre-motor EEG activity [59, 102, 104] and impaired sensorimotor gating [26, 121] in

TS, Bohlhalter and colleagues concluded that internally generated tics (probably associated with an urge) may be associated with the limbic overdrive of the motor system. A recent study with transcranial magnetic stimulation showed that the voluntary motor drive in TS is not increased but motor inhibition is reduced [47]. In a functional MRI study with 21 adults, tic suppression was associated with bilateral deactivation of putamen, globus pallidus, and thalamus, but increased activation in right caudate and right mid-frontal cortex [91]. This pattern of neural activity was inversely correlated with tic severity. A well-documented reduced activation in subjects with ADHD during motor inhibition [38, 105], suggests that the presence of ADHD in TS may be associated with difficulty suppressing tics and possibly with greater levels of tic severity.

The prevailing theory concerning the pathophysiology of TS is that there is an increased activity of the inhibitory direct pathway connecting the basal ganglia striatal input to its output in the internal globus pallidum (GPi) and decreased activity in the indirect pathway via the external globus pallidum (GPe) and subthalamic nucleus STN. The net effect of this imbalance between the pathways is to reduce the firing rate of inhibitory neurons in GPi that project to important premotor structures, such as the thalamus. Disinhibition of premotor centers provides the anatomical basis for the emergence of tics [1, 102]. According to this hypothesis, each tic corresponds to the activity of a discrete set of striatal neurons, possibly within striatal matrisomes [77].

The neural activity between the functionally related areas of the basal ganglia and the cortex during learning [16, 87] and performance [41] of habitual behavior is a highly dynamic process, working on-line simultaneously in multiple neural ensembles, contexts and time-scales [44]. The neural activity in these pathways is modulated by the reciprocally interconnected cortical and thalamic inputs. Abnormalities of intracortical inhibition in patients with TS revealed by transcranial magnetic imaging studies [42, 79], suggest abnormal cortical function in TS, which may be primary or secondary to basal ganglia or thalamic abnormalities. The components of the frontal cortex that mediate motor behavior, cognition, and motivation are reflected in the organizations and physiology of the CSTC circuits and comprise a series of parallel pathways [2]. Recent anatomical evidence from primates suggest that the neural networks within the parallel pathways can move information across functional circuits and the thalamo–cortico–thalamic projections may play a critical role in integrating information across functional circuits [45].

Neuropsychological studies

Both TS and ADHD could be associated with deficient performance on visual-motor integration tasks such as Bender–Gesalt Test and the Beery Visual–Motor Integration Test when compared to normative data or normal controls [20, 113]. Additionally, fine-motor coordination deficits in TS subjects have been demonstrated on both the grooved pegboard and Purdue Pegboard tests [12, 14, 15, 113]. These findings of visual–motor integration and fine-motor skill deficits in individuals with TS helped pinpoint the caudate nucleus, basal ganglia and fronto–corticostriatal circuits as the neuroanatomical region of interest in TS research [65]. Poor performance on the neuropsychological measures of procedural learning [61, 74, 75], further implicated a dysfunction of the striatal learning system in TS.

The neuropsychology of TS has also focused on deficits in executive functioning, a broad domain covering planning, goal directed behavior, inhibitory controls, attention and self-regulation [90]. Early studies in adults with TS found evidence of executive deficits [14, 30]. However, these studies did not screen participants adequately for comorbid disorders such as OCD and ADHD which are associated independently with impairments on executive tasks [28, 115]. Several studies with children and adolescents with TS reported that deficits in executive functioning were attributable to comorbid conditions [85, 100, 128]. However, recent reports suggested that TS might be characterized by a selective deficit in behavioral inhibition, the ability to suppress an activated response and avoid interference, which is often operationalized by neuropsychological tasks such as the Go-No/Go and the Stroop [6, 31]. Furthermore, considering that response inhibition may encompass multiple constructs [83], some measures may be more sensitive than the others to deficits in response inhibition in TS. For example, no inhibitory impairment has been reported in children with uncomplicated TS using the Stroop test [84] or a negative priming task [85]. By contrast, the adolescents with TS differed significantly from the control group on the Sentence Completion task and on the Flanker task [36] as well as on the Go-No/Go task [82]. Taken together with the extensive literature documenting executive functioning deficits in ADHD [25], it is likely that the impairment in response inhibition in subjects with comorbid TS and ADHD is conferred by the presence of ADHD. However, the heterogeneity of neuropsychological deficits, including impaired delay aversion, poor working memory, and increased intra-individual response variability, suggests a possibility of multiple unique as well as shared pathways in the pathophysiology of ADHD [4, 116].

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Aberrant neural oscillations

Neural oscillations refer to periodic variations in the recording of neural activity. Abnormalities of oscillatory synchronization have been associated with various neuropsychiatric disorders, but most notably basal ganglia disorders [70, 71, 112]. Selectively distributed oscillatory systems of the brain exist as resonant communication networks through large populations of neurons, which work in parallel and are interwoven with sensory, motor, cognitive and emotional functions [24]. Recent advances in basal ganglia research [44] and the observation that the electrical activity in globus pallidus seen in dystonia and tic disorders is similar to that in Parkinson's disease [52, 130] lead to a hypothesis that one or more of these oscillatory processes are aberrant in TS [67]. This hypothesis is consistent with the recent finding of a doubling of the density and number of the GABAergic projection neurons in the GPi in a postmortem study of three subjects with severe TS [58]. By contrast, the number of fast-spiking neurons, identified by their immunoreactivity for the calcium-binding protein parvalbumin, was reduced in the striatum, caudate and putamen. These cellular abnormalities would allow clusters of medium spiny neurons within the somatotopic areas associated with tics to become disengaged from the high-voltage spindle oscillations and to become relatively autonomous, giving rise to tics.

The cerebral cortex uses fast-spiking neurons to exert powerful feed-forward inhibition upon the striatum [94], suggesting that this inhibitory system with its ensuing oscillatory activity may be used to suppress and filter out of consciousness unattended patterns of activity. Hence, it is possible that the disruption of the basal ganglia oscillations may interfere with the efficient recruitment of the frontostriatal structures involved in suppression of unwanted movement and cognitions [67]. In addition, the same postmortem study [58] revealed the 120% increase in the parvalbumin-positive GABAergic projection neurons in the globus pallidus internus in the three patients with severe TS. The functional consequences of this increase are as yet unclear, but it is possible that this increase could led to the lower than normal neuronal discharges (approximately 40 Hz) similar to that described in patients with dystonia [131]. These slow and irregular discharges would transiently hyperpolarize their target thalamocortical neurons causing them to reset the phase and transiently increase the amplitude of high-frequency membrane potential oscillations (20–80 Hz) [89], which in turn would lead to the aberrant activation of a selected pattern of cortical pyramidal neurons and the overt perception of premonitory urges and tics. If the dysrhythmia of particular cortical regions may underlie the generation of corresponding symptoms it is possible to assume that the inattention and impulsivity of the ADHD would reflect aberrant oscillations in the various vulnerable regions of the prefrontal cortex.

Based on physiological evidence as well as magnetoencephalographic (MEG) whole head recordings, it was proposed that a single mechanism involving the thalamocortical reentry loop, thalamocortical dysrhythmia, may be responsible for a variety of neuropsychiatric symptoms. At the thalamic cellular level, this mechanism is evidenced by a state of membrane hyperpolarization accompanied by the low-threshold calcium spike bursts [54, 72, 119]. The presence of thalamic cell hyperpolarization is brought about by either excess inhibition or disfacilitation, which, in the case of TS, may be caused by abnormal activity in the globus pallidus. At the level of MEG recording, thalamocortical dysrhythmia is characterized by increased low-frequency theta rhythmicity, in conjunction with a widespread and marked increase of coherence among high- and low-frequency oscillations [71]. Remarkably, a recent study revealed a significantly elevated theta power and increased coherence between low and high frequency oscillations in 11 adult subjects with TS compared to 9 normal controls, providing initial evidence for thalamocortical dysrhythmia in TS [81].

Some of the EEG findings in ADHD reveal abnormal patterns of slow and high frequency oscillations that are reminiscent of thalamocortical dysrhythmia. In fact, the most consistent finding in children and adults with ADHD is the increased theta activity [19, 29, 33, 48] and higher theta-to-beta ratios [39, 80]. ADHD patients also exhibit increased level of event-related gamma amplitudes [129]. Studies of EEG coherence in children with ADHD revealed consistent differences from healthy controls, suggesting reduced cortical differentiation and specialization in ADHD [7]. Children with ADHD revealed elevated intrahemispheric coherence at shorter inter-electrode distances in the theta band and reduced lateral coherence in the theta and alpha bands. At longer inter-electrode distances, ADHD children had lower intrahemispheric coherence alpha coherence than healthy controls [8]. Provided that ADHD is likely to involve multiple pathophysiologies, it is possible that the mechanisms of thalamocortical dysrhythmia, operating in TS, may also lead to the abnormal neural oscillations observed in the scalp EEG recordings of ADHD.

Of particular relevance to this review is a recent report of multisecond oscillations in the periodic structure of Eriksen Flanker task reaction time data obtained from 24 boys with ADHD and 18 age-matched comparison boys [27]. Reaction time variability in ADHD differed from control subjects, particularly at a modal frequency around 0.05 Hz (once per 20 s). Furthermore, these oscillations in reaction time were suppressed by double-blind methylphenidate and were unaffected by double-blind placebo. Intriguingly, the modulation of ultraslow, multisecond oscillations by dopamine in the basal ganglia has been reported in animal studies. Low frequency oscillations (2–60 s and longer) were observed in single-unit activity and local field potentials recorded in the external segment of the globus pallidus and the subthalamic nucleus from awake, locally anesthetized and immobilized rats [106, 107]. These oscillations were sensitive to systemically injected dopamine agonists. Castellanos and colleagues speculated that the increased power of multisecond oscillations in ADHD reaction time data represents a catecholaminergic deficit in the ability to appropriately modulate such oscillations in neuronal activity. Further circumstantial evidence for this speculation was obtained in a study of slow BOLD fMRI fluctuations at 0.1 Hz (once per 10 s) in three healthy volunteers and one adult with ADHD [3]. The low frequency oscillations were observed in the posterior inferior vermis of the cerebellum, and were reduced by administration of methylphenidate. Interestingly, ADHD was associated with anatomical deficits in cerebellum [9, 23]. The cerebellum, particularly the midline regions, is involved in directing motor system oscillations by way of projections to intralaminar thalamus and pedunculopontine nucleus. As a result, the vermis could provide behavioral state-dependent modulation of the sensorimotor gating regions in the basal ganglia [63]. The presence of 10–25 Hz synchronous oscillations electrically linking the cerebellum with primary motor cortex and primary somatosensory cortex was documented during motor task performance in primates [35]. In addition, oscillations of the olivocerebellar system are likely to also play a role in the temporal control of movement execution including tics [60].

Frontal lobe compensation

It is possible that compensatory systems within the prefrontal cortex could be activated to modulate the misguided striatal and thalamocortical oscillations. A common feature of TS and ADHD is that both disorders improve with age, with symptomatic improvement by adolescence occurring in 40% of children with ADHD [73] and 80% of children with TS [68, 86]. This symptomatic improvement is likely to be associated with increased functional capacity of the frontal cortical regions subserved by an increased myelinization of prefrontal regions [108] and compensatory increased postnatal generation of inhibitory interneurons [37, 78].

Serrien and colleagues [114] found increased EEG coherence in the alpha frequency band range during both voluntary tic suppression and the suppression of voluntary movements during a Go-No/Go task. The alpha frequency band (8–12 Hz) was included in the analyses because activity in this band preferentially reflect the regulation of cognitive driven functions [126] and captures motor inhibition as well as motor excitation [50]. The alpha coherence during tic suppression was most pronounced in the right prefrontal cortex, the mesofrontal cortex and in sensorimotor and motor cortices. These results are similar to the results of a functional MRI study of tic supression [91], which revealed that increased activity in the right frontal cortex was associated with increased activity in the right caudate nucleus, and increased activity in the right caudate nucleus in turn was associated with greater decreases in activity of the globus pallidus, the putamen, and the thalamus during tic suppression.

The brain areas that are activated during tic suppression are nearly identical to those involved in response inhibition which involve various regions of the prefrontal cortex [96] as well as subcortical areas [49]. We speculate that frontal abnormalities such as those seen in ADHD might limit an individual's ability to mobilize this inhibitory system [22]. By contrast, prefrontal hypertrophy [92] as well as changes in other structures, including the corpus callosum [95, 125], could be seen as adaptive changes in individuals who are able to successfully regulate their tics.

Conclusion

We reviewed selected physiological, imaging and neuropsychological studies in support of the association between abnormal neural oscillations in the pathophysiology of TS. It is possible that abnormal oscillations in the basal ganglia and thalamus that are responsible for the generation of tics may also lead to dysrhythmic activity in the cortical regions involved in motor inhibition and cognitive control. These deficits, in turn, would result in ADHD symptoms. There is also initial evidence that momentary lapses in attention and increased reaction time variability that are observed in ADHD may

stem from abnormal oscillatory activity in the basal ganglia. Finally, successful compensatory mobilization of prefrontal areas involved in response inhibition may be a factor in reduction of tics and ADHD symptoms by early adulthood. It is possible that optimization of temporal synchronization of brain oscillations as seen in neurofeedback training [46] and methylphenidate trials [32] may be responsible for the reduction of ADHD symptoms as well as the tics [123].

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