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Effects of age on motor excitability measures from children and adolescents with Tourette syndrome

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ABSTRACT

Tourette syndrome (TS) is a neurological disorder characterised by vocal and motor tics. It is associated with cortical–striatal–thalamic–cortical circuit [CSTC] dysfunction and hyper-excitability of cortical motor regions. TS follows a developmental time course, in which tics often become increasingly more controlled during adolescence. Importantly, however, a substantial minority of patients continue to have debilitating tics into adulthood. This indicates that there may be important differences between adult TS patients and children and adolescents with the disorder. We use TMS to examine cortical motor excitability in a sample of children, adolescents and young adults with TS. We demonstrate that, in contrast to studies of adult patients, resting motor threshold and the variability of MEP responses are increased in children with TS, while the gain of motor excitability in reduced. Importantly, we demonstrate that these differences normalise with age over adolescence. We conclude that these effects are likely due to a developmental delay in the maturation of key brain networks in TS, consistent with recent brain imaging studies of structural and functional brain connectivity. Importantly, these findings suggest that the alterations in brain network structure and function associated with TS may be quite different in children and adult patients with the condition.

1. Introduction

Tourette syndrome (TS) is a neurological disorder that lies at the extreme of the tic disorder spectrum and is characterised by the presence of chronic vocal and motor tics (Cohena et al., 2013). Tics are involuntary, repetitive, stereotyped behaviours that occur with a limited duration, often many times in a single day (Cohena et al., 2013). TS is highly heritable, is more often seen in males than females (~4:1), and affects approximately 1% of individuals aged 5–18 years (Cohena et al., 2013).

Importantly, TS often follows a developmental time course in which tics become increasingly more controlled during adolescence in many individuals. TS first presents during early childhood (~4–7 years) and the severity of tics follow a remitting pattern with increasing age. Tic severity is often maximal between 11 and 14 years with tics decreasing by early adulthood (Cohena et al., 2013). This suggests that the majority of individuals with TS appear to develop a means of controlling and effectively suppressing their tics by early adulthood, however a substantial minority (~20–30%) continue to have debilitating tics into adulthood, with symptoms becoming more severe in some cases and resistant to treatment (Cohena et al., 2013).

While the neurobiological basis of TS remains unclear, it is generally acknowledged that cortical–striatal–thalamic–cortical circuits [CSTC] are dysfunctional in TS, with subsets of striatal projection neurons becoming active within inappropriate contexts, resulting in the disinhibition of thalamo-cortical projections (Albin and Mink, 2006) and hyper-excitability of cortical motor regions (Gilbert et al., 2004; Orth et al., 2008; Heise et al., 2010) that in turn lead to the occurrence of tics (Bohlhalter et al., 2006). In particular, TS has been associated with dysfunctional signalling of the neuromodulator dopamine (DA) (Buse et al., 2013), which is linked to mechanisms of reinforcement learning (Schultz, 1997), and the neurotransmitter GABA (Ramamoorthi and Lin, 2011; Clarke et al., 2012). Dysfunctional signalling of DA and GABA may each contribute to impairment in TS in the operation of the cortical–striatal–thalamic–cortical [CSTC] brain circuits that are

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implicated in motor learning, particularly habit formation, and the selection of actions according to behavioural context (Albin and Mink, 2006; Graybiel, 2008).

Alterations in cortical excitability and physiological inhibition have previously been studied using brain stimulation (e.g., transcranial magnetic stimulation [TMS]) techniques (for review see Orth, 2009). TMS can be used to stimulate the primary motor cortex and induce a measurable motor evoked potential [MEP] in a targeted muscle; it is therefore a useful tool to non-invasively measure corticospinal excitability [CSE], both at rest and during the execution of behaviour. Several different measurements can be obtained using TMS in order to quantify different aspects of CSE. Key studies in TS have examined resting and active motor threshold for each individual, TMS recruitment curves, and the peak-to-peak amplitude of the MEP at different time points during movement preparation.

Motor threshold is defined as the minimum intensity of stimulation required to reliably induces an MEP of a specific amplitude in a target muscle, either at rest (resting motor threshold [RMT]), or when the muscle is partly activated (active motor threshold [AMT]). A key theoretical construct is the 'gain' in CSE. This can be defined as the rate at which CSE increases. This construct can be operationsalised in several ways but is most often measured as the slope of the TMS recruitment curve or the rate at which MEPs increase in amplitude ahead of a volitional movement. TMS recruitment curves are assessed by using a stimulus-response TMS technique, where the intensity of TMS is systematically increased from RMT in order to measure the intrinsic capability of the motor cortex to ramp up global excitability in the resting muscle (which we will refer to as the 'gain' of motor excitability). Gain of motor excitability can also be measured during the preparation of a volitional movement in a resting muscle, where the TMS intensity is not altered, but the time in which the TMS pulse is given is altered. Typically, the closer to onset of the movement, the greater the MEP amplitude signalling that gains are made in motor excitability during movement preparation.

Two key findings are as follows: First, motor threshold values do not differ in individuals with TS relative to matched controls (Orth, 2009) (c.f. reference (Orth and Rothwell, 2009)). Importantly, it is suggested that equivalent RMTs in TS patients and controls indicates that neural populations recruited by TMS at threshold are in the same state in both samples (Orth, 2009).

Second, a number of studies have demonstrated that the gain of motor cortical excitability is reduced in individuals with TS. This is the case for both TMS-induced increases in motor excitability (i.e., TMS recruitment curves) (Orth et al., 2008; Draper et al., 2014) and gains in motor excitability during motor preparation, immediately preceding the execution of volitional movements (Heise et al., 2010; Draper et al., 2015). Importantly, the gain in cortical excitability is thought to depend upon the distribution of excitability within the population of corticospinal neurons (i.e., recruitment of neurons with different levels of excitability): thus it is concluded that a shallower gain function in TS reflects a reduction in the spread of excitability within this population (Orth, 2009).

Importantly, the relationship between individual TMS measurement values and tic severity scores in TS has been examined, however the evidence is rather mixed. Orth and colleagues reported, in a study of adults with TS, that the individual slope values for TMS recruitment curves were positively associated with some measures of complex, phonic, and finger tics (Heise et al., 2010). By contrast, they reported that clinical tic rating scales (i.e., the Yale Global Tic Severity Scale [YGTSS] (Leckman et al., 1989)) and other video measures (e.g., the Modified Rush Video Scale (Goetz et al., 1999)) were not associated with tic severity.

It is important to note that the majority of studies investigating cortical excitability and physiological inhibition in TS using TMS techniques have been conducted in *adults* with TS and must therefore be interpreted with some caution for the following reasons. First, TS is a disorder of childhood onset that typically follows a developmental time course in which in the majority of individuals, tics are absent or relatively mild by early adulthood. Adults with TS can be viewed therefore as unrepresentative of the more general TS population (i.e. children and adolescents with the disorder), but may nevertheless constitute an important group in which the clinical phenotype is stable and the compensatory plastic changes thought to bring about increased control over tic severity during adolescence (Jackson et al., 2011) have either failed to occur or have been ineffective. Second, brain imaging studies have consistently demonstrated that while there are widespread alterations in brain structure and function associated with TS (for review see Plessen et al., 2009), these effects differ quite markedly for adult and child samples, and have often been diametrically opposite (Plessen et al., 2009). Given the above, it is important to investigate whether the findings demonstrated in TMS studies investigating cortical excitability and physiological inhibition in adults with TS are replicated in children and adolescents with TS.

In this study we examine core measures, namely: resting motor threshold; TMS recruitment curves; and motor excitability during the preparation of volitional movements, in a sample of children, adolescents and young adults with TS compared to a sample of age- and gender matched typically developing individuals. We demonstrate that, consistent with previous studies of adult TS patients, children and adolescents with TS exhibit reduced gain in motor excitability when indexed by TMS recruitment (IO) curves and ahead of volitional movements. However, and in direct contrast to studies of adult patients, we show that: RMT is significantly different (higher) in children and adolescents with TS compared to age-matched controls; that differences in RMT vary with age and are most pronounced in the youngest individuals and absent in young adults (18 years or older); that TMS-induced MEP responses are more variable in children and adolescents with TS relative to controls; and, that individual measures of motor gain function are inversely related to motor tic severity scores, indicating that reduced gain values are associated with increased tic severity. The results are interpreted as consistent with the view that there may be a delay in the development of the structure and function of brain networks in TS that contributes to the occurrence of tics but which may normalise with age during adolescence in the majority of individuals with TS.

2. Method

2.1. Participants

17 adolescents and young adults with Tourette Syndrome (TS) were recruited to take part in two TMS studies (age range = 11.9–21.6 years, mean = 16.47 years ± 3.17, 3 females). The sum of motor and phonic tic scores ranged from 3 to 44, mean = 22.6 ± 11.7. Participants in the TS Group suffered from additional co-morbidities besides TS. Three had an additional diagnosis of OCD, one had ADHD and three participants were diagnosed with ASD. See Table 1 for additional details of tic scores, co-morbidities and medication.

For ethical reasons (all of the TS group were in full time education) we could not ask those children on medication to come off their medication for the purposes of this study. Accordingly, we conducted several stepwise regression analyses to determine whether medication status, having first accounted for age differences, predicted any of the core dependent measures (i.e., motor threshold, TMS recruitment curve slopes, or gain in motor excitability (slope)) prior to volitional movements. These analyses revealed