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Procedural learning in Tourette syndrome, ADHD, and comorbid Tourette-ADHD: Evidence from a probabilistic sequence learning task

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ABSTRACT

Procedural memory, which is rooted in the basal ganglia, plays an important role in the implicit learning of motor and cognitive skills. Few studies have examined procedural learning in either Tourette syndrome (TS) or Attention Deficit Hyperactivity Disorder (ADHD), despite basal ganglia abnormalities in both of these neurodevelopmental disorders. We aimed to assess procedural learning in children with TS (n = 13), ADHD (n = 22), and comorbid TS-ADHD (n = 20), as well as in typically developing children (n = 21). Procedural learning was measured with a well-studied implicit probabilistic sequence learning task, the alternating serial reaction time task. All four groups showed evidence of sequence learning, and moreover did not differ from each other in sequence learning. This result, from the first study to examine procedural memory across TS, ADHD and comorbid TS-ADHD, is consistent with previous findings of intact procedural learning of sequences in both TS and ADHD. In contrast, some studies have found impaired procedural learning of non-sequential probabilistic categories in TS. This suggests that sequence learning may be spared in TS and ADHD, while at least some other forms of learning in procedural memory are impaired, at least in TS. Our findings indicate that disorders associated with basal ganglia abnormalities do not necessarily show procedural learning deficits, and provide a possible path for more effective diagnostic tools, and educational and training programs.

1. Introduction

Tourette syndrome (TS) and Attention Deficit Hyperactivity Disorder (ADHD) are both neurodevelopmental disorders associated with frontal and basal ganglia abnormalities (Arnsten & Rubia, 2012; Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Robertson, 2015b). These disorders, which are often comorbid with each other (Denckla, 2006; Robertson, 2015a), are characterized by behavioral symptoms such as compulsions, tics, and impulsive actions (Robertson, 2015a). It has been suggested that the frontal/basal-ganglia abnormalities may lead to procedural memory abnormalities in both disorders (Goodman, Marsh, Peterson, & Packard, 2014; Kéri, Szlobodnyik, Benedek, Janka, & Gádoros, 2002).

Despite these links between procedural memory and both disorders, few studies have examined procedural learning in either TS or ADHD. Moreover, these have yielded mixed results (Channon, Pratt, & Robertson, 2003; Kéri et al., 2002; Marsh et al., 2004). There has been even less work examining procedural learning (or other cognitive functions) in comorbid TS-ADHD – despite the fact that 60% of children with TS also have ADHD (Denckla, 2006). Here we attempt to address these gaps and inconsistencies by testing four groups of age- and sex-matched children – with TS, ADHD, TS-ADHD, and typically

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developing children – on the same well-studied implicit probabilistic sequence learning task.

1.1. The disorders

TS is a developmental disorder characterized by multiple motor tics and at least one vocal tic, which are not explained by medications or another medical condition (American Psychiatric Association, 2013). The prevalence of the disorder appears to be in the range of 0.85–1% (American Psychiatric Association, 2013; Robertson, 2015a). TS is associated with both structural and functional abnormalities of the basal ganglia and frontal cortex, and their connecting circuits (Goodman et al., 2014; Müller-Vahl et al., 2009; Tremblay, Worbe, Thobois, Sgambato-Faure, & Féger, 2015). The tics appear to be caused by disturbances of the basal ganglia and closely connected regions of cortex, especially motor and cognitive regions of frontal cortex (Albin & Mink, 2006; Müller-Vahl et al., 2014). In particular, they may be caused by enhanced excitability in the direct relative to the indirect striatal pathway (Maia & Frank, 2011). It has been suggested, that basal ganglia hyperactivity in TS is associated not only with tics and impulsivity, but also with alterations of the related cognitive systems, such as procedural memory (Goodman et al., 2014; Kéri et al., 2002).

ADHD is a developmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity, with a prevalence of about 5–10% in school-age children (American Psychiatric Association, 2013; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Similarly to TS, fronto-striatal networks are compromised in ADHD (Arnsten & Rubia, 2012), including the basal ganglia and inferior prefrontal cortex, as well as its connections to striatal as well as cerebellar and parietal regions. The heterogeneous neural alterations in ADHD have been linked to impairments in a wide range of cognitive functions, from perception to learning (Arnsten & Rubia, 2012; Kóbor et al., 2015; Sjöwall, Roth, Lindqvist, & Thorell, 2013).

The majority of children with TS (88%) have comorbidities, which can affect cognitive, social, and academic outcomes of TS (Robertson, 2015a). ADHD is perhaps the most frequent comorbid disorder, occurring in about 60% of individuals with TS (Denckla, 2006). There are significant anatomical and neurobehavioral differences between children with TS-ADHD and those with just TS or just ADHD. For example, the basal ganglia, right prefrontal cortex, and rostral corpus callosum appear to be smaller in children with comorbid TS-ADHD than in children with TS only (Denckla, 2006; Robertson, 2015a). We are not aware of studies that directly compare anatomical differences in TS-ADHD and ADHD.

1.2. Procedural memory in TS and ADHD

This implicit memory system involves a network of interconnected brain structures rooted in frontal/basal-ganglia circuits (Cleeremans, Destrebecqz, & Boyer, 1998; Doyon et al., 2009; Eichenbaum, 2012; Song, Howard, & Howard, 2007a; Ullman, 2004, 2016). We use the term procedural memory to refer to a particular brain system that underlies implicit memory, rather than implicit memory more generally, which is subserved by other systems as well (Squire, 2004; Ullman, 2004). The procedural system underlies the implicit learning and processing of a wide range of perceptual-motor and cognitive skills, including navigation, sequences, rules, and categories. The basal ganglia play a critical role in the learning and consolidation of these new skills, whereas frontal regions (in particular premotor and related regions) may be more important for processing skills after they have been automatized (Sefcsik et al., 2011; Stillman et al., 2013). The system may be specialized for learning to predict, perhaps especially probabilistic outcomes – for example the next item in a sequence or the output of a rule. Learning in the system requires practice, which seems to eventually result in rapid and automatic processing of skills and knowledge. For a more computational approach, which emphasizes implicit learning processes rather than the above described brain system, please see the review of Reber (2013). In the current paper, our focus is on procedural memory, and not implicit learning more generally.

Few studies have examined procedural memory in TS. We are aware of three published studies probing learning in this system, two of which found impairments. Kéri et al. (2002) reported impaired learning in children with TS in a study employing the weather prediction task. Moreover, this impairment in learning was positively associated with TS symptom severity. In the weather prediction task participants learn probabilistic associations between simple visual stimuli and their outcomes (good or bad weather). The task has been shown to depend on procedural memory brain structures (Knowlton, Ramus, & Squire, 1992; Poldrack & Foerde, 2008), though declarative memory also appears to play a role, especially in earlier stages of learning (Newell, Lagnado, & Shanks, 2007; Speekenbrink, Channon, & Shanks, 2008). Another study examining learning with the weather prediction task also found impaired learning, both in children and adults with TS (Marsh et al., 2004).

In contrast, Channon et al. (2003) observed intact sequence learning in children with TS on the serial reaction time (SRT) task, which depends on procedural memory (Janacsek, Shattuck, Lum, Tagliatelli, & Ullman, in preparation; Lum, Conti-Ramsden, Morgan, & Ullman, 2014; Lum, Ullman, & Conti-Ramsden, 2013; Nissen & Bullemer, 1987). It has been suggested that sequence learning may be a distinct procedural memory function (Hsu & Bishop, 2014; Krishnan, Watkins, & Bishop, 2016), since sequence learning might dissociate from other types of procedural learning in other developmental disorders (Hsu & Bishop, 2014; Kemény & Lukács, 2010; Krishnan et al., 2016). Thus, sequence learning may warrant further investigation in TS.

We are also aware of two studies examining the processing of knowledge that has previously been learned in procedural memory, that is, of already established knowledge. One study found that children with TS were faster (but not more accurate) than TD children at producing past tense forms that are posited to be combined (walk + -ed, rick + -ed) by the mental grammar, but not those that appear to be retrieved from (*dug*) or processed in (*splung*) associative lexical memory (Walenski, Mostofsky, & Ullman, 2007). Since independent evidence suggests that rule-governed combinatorial aspects of grammar, across syntax, morphology and phonology, are learned and processed in procedural memory (Ullman, 2004, 2016), it was suggested that the observed pattern reflects speeded processing of knowledge learned in procedural memory more generally, that is, of both linguistic and non-linguistic knowledge. Indeed, the same participants were faster (but not more accurate) than controls at naming manipulated objects such as *hammer* (which involve learned motor skill knowledge), but not non-manipulated objects such as *elephant* (Walenski et al., 2007). A second study found evidence for speeded combination in children with TS in phonology, in a non-word repetition task, and also attributed it to fast processing in procedural memory (Dye, Walenski, Mostofsky, & Ullman, 2016). These findings are also consistent with the possibility that sequence-based knowledge in procedural memory in both language and non-language domains (Krishnan et al., 2016) may remain unimpaired in TS.

The literature examining procedural memory in ADHD is sparser. We are aware of two studies examining procedural learning in ADHD in children or adolescents (Barnes, Howard, Howard, Kenealy, & Vaidya, 2010; Karatekin, White, & Bingham, 2009) and two in adults (Adi-Japha, Fox, & Karni, 2011; Pedersen & Ohrmann, 2012). One study, which examined sequence learning with the SRT task, found evidence of intact procedural learning in adolescents with ADHD (Karatekin et al., 2009). Another study found that children with ADHD showed similar performance at early and later stages of sequence learning in the ASRT task, but altered performance at a middle stage (Barnes et al., 2010). In adults with ADHD, one study of sequence learning with the SRT task found intact learning (Pedersen & Ohrmann, 2012). Another study, of finger sequence learning in women with ADHD, found normal initial learning, but