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Cognitive flexibility and its electrophysiological correlates in Gilles de la Tourette syndrome

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ABSTRACT

Motor symptoms in Gilles de la Tourette syndrome (GTS) have been related to changes in frontostriatal brain networks. These changes may also give rise to alterations in cognitive flexibility. However, conclusive evidence for altered cognitive flexibility in patients with GTS is still lacking. Here, we meta-analyzed data from 20 neuropsychological studies that investigated cognitive flexibility in GTS using the Wisconsin Card Sorting Test (WCST). Results revealed medium-sized GTS-related performance deficits, which were significantly modulated by age: Whilst being substantial in children and adolescents with GTS, WCST deficits seem to dissolve in adult patients with GTS. This age-related normalization of WCST performance might result from the compensatory recruitment of cognitive control in adult patients with GTS. We addressed this possibility by examining neural correlates of proactive and reactive cognitive control in an event-related potential (ERP) study. We analyzed cue- and target-locked ERPs from 23 adult patients with GTS and 26 matched controls who completed a computerized version of the WCST. Compared to controls, patients with GTS showed a marked increase in parietal cue-locked P3 activity, indicating enhanced proactive cognitive control. We conclude that the additional recruitment of proactive cognitive control might ensure flexible cognitive functioning in adult patients with GTS.

1. Introduction

Approximately one percent of school-aged children show a combination of motor and vocal tics that is commonly referred to as Gilles de la Tourette syndrome (GTS; Robertson, 2008). Many of these children continue to have tics as adults, although often with decreased severity (Pappertet al., 2003). Tics in GTS have been attributed to alterations in the basal ganglia and the associated frontostriatal circuits (Mink, 2001). In accordance with this notion, imaging studies have revealed reduced gray matter volume in the basal ganglia of both children and adults with GTS, as well as structural changes in areas of the frontal cortex (Plessen et al., 2009). Frontal cortical changes are not restricted to motor and premotor regions but also extend to the prefrontal cortex (Müller-Vahl et al., 2009). The prefrontal cortex is connected with the basal ganglia via frontostriatal circuits that are thought to be critical for efficient executive functioning (Frank et al., 2001; Hazy et al., 2007; Monchi et al., 2006; Owen, 2004; Robbins and Cools, 2014). It thus appears plausible to assume that GTS is not only associated with motor symptoms (i.e., with tics) but also with deficits in the domain of executive functioning (Eddy et al., 2012).

One central aspect of executive functioning is cognitive flexibility (Miyake et al., 2000). Cognitive flexibility has been variably defined: Some authors conceptualize cognitive flexibility as a well-delimited mental ability while others think of it more as a property of the cognitive system or a metacognitive state (Ionescu, 2012). Here, we adopt an operational definition according to which cognitive flexibility refers to the cognitive processes that allow for the efficient adaptation of goal-directed behavior to changing environmental demands (Garcia-Garcia et al., 2010).

A number of neuropsychological tests have been developed for the assessment of cognitive flexibility, the most popular of which is the Wisconsin Card Sorting Test (WCST; Berg, 1948; Grant and Berg, 1948; Heaton et al., 1993). On the WCST, participants are required to sort cards and to use the experimenter's feedback to shift between different sorting rules. The analysis of WCST performance typically focusses on the number of completed categories and an index of perseverative tendencies (i.e., number/percentage of perseverative errors/responses). Performance on the WCST appears to be sensitive to prefrontal lobe

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damage (Demakis, 2003; Milner, 1963) as well as to lesions (Eslinger and Grattan, 1993) and deep brain stimulation (Jahanshahi et al., 2000; Jahanshahi et al., 2014; Pillon et al., 2006) of the basal ganglia. In addition, cognitive inflexibility on the WCST has been observed in a number of neurological and psychiatric conditions that are associated with frontostriatal dysfunction, including Parkinson's disease (Kudlicka et al., 2011; Lange et al., 2016c), dystonia (Lange et al., 2016b, 2016d), and obsessive-compulsive disorder (OCD; Shin et al., 2014).

With respect to GTS, Eddy et al. (2009) conducted a review of the studies that analyzed performance on the WCST. They reported that the majority of studies did not find pronounced WCST performance deficits in patients with GTS. However, this lack of evidence for GTS-related impairment on the WCST may not be taken as evidence for intact WCST performance in these patients (Altman and Bland, 1995). Low statistical power due to small sample sizes in individual studies poses a problem to many research areas including neuropsychology (Bezeau and Graves, 2001; Demakis, 2006). This implies that, even in the presence of relevant WCST performance deficits in the population of patients with GTS, these deficits may often go undetected in individual studies. The meta-analytical aggregation of evidence across multiple neuropsychological studies allows overcoming this limitation.

In the following, we present a meta-analysis that aimed at obtaining a reliable effect-size estimate for potential WCST deficits in patients with GTS. In addition, this meta-analytical approach enabled us to investigate whether the extent of GTS-related alterations in WCST performance is moderated by patient characteristics such as age and gender. Following the description of this meta-analysis, we present an event-related potential (ERP) study that we conducted to examine the electrophysiological correlates of WCST performance in patients with GTS. In this study, we analyzed the ERP waveforms evoked by stimuli in a computerized version of the WCST. This approach allowed us to further elucidate the neural underpinnings of WCST performance in patients with GTS. Specifically, we were able to investigate whether patients with GTS differ from healthy control participants with regard to the neural correlates of the cognitive control processes that they recruit while performing the WCST. Hence, our two studies complement each other in providing (a) a powerful test of potential GTS-related WCST performance deficits (meta-analysis) and (b) an in-depth analysis of the mechanisms that underlie WCST performance in patients with GTS (ERP study).

2. Meta-analytic evidence for impaired WCST performance in GTS

2.1. Methods

A systematic literature review was conducted in April 2015 and updated in July 2017 using the databases PubMed, ScienceDirect, PsychInfo, and Scopus as well as Google Scholar. In a first step, we screened the results of a Google-Scholar search involving the combination of the keywords "Tourette" and "Wisconsin Card Sorting Test" (2345 hits). We then looked for studies that did not explicitly mention the term "Wisconsin Card Sorting Test", but that involved the keyword "Tourette" as well as either "Card Sort"; "Card Sorting"; "WCST"; or "MCST" (952 hits). When screening these 3297 records for eligibility; we excluded a record as soon as we were able to determine that it does not fulfill all the inclusion criteria of our meta-analysis (see Fig. 1). The following inclusion criteria were applied:

1) The study had to administer a standard version of the WCST to a sample of patients with GTS. This implies that studies reporting WCST data from single patients with GTS were not considered.

2) The study had to involve WCST performance data from a sample of healthy control participants or it had to report standard scores that describe the performance of patients with GTS in comparison to normative data.

3) The study had to report data for at least one of the best-established WCST measures (i.e., number of completed categories, percent/number of perseverative errors/responses) at a level of detail that allows for the calculation of effect sizes (i.e., test statistic, means and standard deviations, or descriptive data (median, range, interquartile range) that allow estimating means and standard deviations according to the procedure described by Wan et al., 2014).

When the title of a record did not allow determining that one of these criteria was not fulfilled, we screened the abstract. When the abstract did not allow excluding the record, we accessed the full text. After screening the potentially eligible full texts, we retained 20 records that fulfilled the criteria listed above. We repeated the same procedure using the databases PubMed, ScienceDirect, PsychInfo, and Scopus, but theses searches did not render any additional studies to be included.

Hence, we performed our meta-analysis on 20 studies reporting WCST performance data from patients with GTS. Fourteen studies involved a direct comparison between patients with GTS and healthy controls, whereas the other six studies reported standard scores based on normative data. For the studies comparing patients with GTS and healthy controls, the *t*-statistic for the between-group comparison was calculated using the two-sample *t*-test provided by GraphPad QuickCalcs (http://www.graphpad.com/quickcalcs/ttest1/). For the studies reporting standard scores, the *t*-statistic was obtained by computing a one-sample *t*-test (http://www.graphpad.com/quickcalcs/oneSampleT1/) comparing the mean standard score in the patient sample to the mean in the normative sample.

Effect sizes (Cohen's *d*) and their confidence intervals were calculated from *t*-statistics using the syntaxes provided by Wuensch (2012). Effect sizes were transformed such that more positive values indicate more pronounced deficits in patients with GTS. When a study involved more than one group of patients with GTS, data were pooled across groups. For studies without a control group, control group size was imputed with the average control group size of all other studies.

When provided, we extracted the data for two measures of WCST performance from each study: the number of completed categories and a measure of perseveration (i.e., percent/number of perseverative errors/responses). When more than one measure of perseveration was reported (e.g., the number of perseverative errors and the number of perseverative responses, Sung and Park, 2000), only the number of perseverative errors was extracted as measure of perseveration for the particular study. Mean effect sizes and confidence intervals for both WCST measures were calculated using the random-effects model syntax provided by Field and Gillett (2010). Heterogeneity of effect sizes was examined using Cochran's Q and the I^2 index (Higgins et al., 2003). In addition, we tested whether effect sizes were moderated by sample characteristics (i.e., age and gender). Potential moderating effects were examined using weighted multiple regression analysis (Field and Gillett, 2010) with age (children/adolescents vs. adults) as a categorical predictor and gender (i.e., the proportion of female participants in the patient sample) as a continuous predictor. We decided to treat age as categorical predictor because the distribution of mean age across the studies was clearly bimodal. Eleven studies reported a mean age ranging from 9 to 13 years, whereas eight studies reported a mean age ranging from 29 to 41 years. One study (Matsuda et al., 2012) that included adolescent and adult participants (mean age = 18 years) was excluded from the analysis of the moderating effect of age. The Kendall's tau rank correlation between effect sizes and their standard errors was calculated to evaluate potential publication bias (Rothstein et al., 2005).

2.2. Results

Table 1 provides an overview of the 20 studies that were included in our meta-analysis on WCST performance in patients with GTS. Effect sizes and the corresponding confidence intervals for the individual studies are displayed in Fig. 2. Table 2 presents the results of the meta-analysis across these studies. Overall, GTS was associated with significant performance deficits on the WCST. Patients with GTS