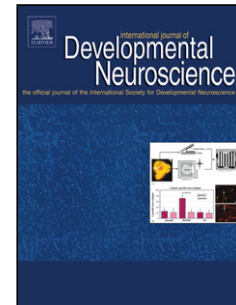# Accepted Manuscript

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Title: Electrophysiological correlates of reinforcement learning in young people with Tourette syndrome with and without co-occurring ADHD symptoms

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Abstract

Altered reinforcement learning is implicated in the causes of Tourette syndrome (TS) and attention-deficit/hyperactivity disorder (ADHD). TS and ADHD frequently co-occur but how this affects reinforcement learning has not been investigated. We examined the ability of young people with TS (n = 18), TS+ADHD (N = 17), ADHD (n = 13) and typically developing controls (n = 20) to learn and reverse stimulus-response (S-R) associations based on positive and negative reinforcement feedback. We used a 2 (TS-yes, TS-no) x 2 (ADHD-yes, ADHD-no) factorial design to assess the effects of TS, ADHD, and their interaction on behavioural (accuracy, RT) and event-related potential (stimulus-locked P3, feedback-locked P2, feedback-related negativity, FRN) indices of learning and reversing the S-R associations. TS was associated with intact learning and reversal performance and largely typical ERP amplitudes. ADHD was associated with lower accuracy during S-R learning and impaired reversal learning (significantly reduced accuracy and a trend for smaller P3 amplitude). The results indicate that co-occurring ADHD symptoms impair reversal learning in TS+ADHD. The implications of these findings for behavioural tic therapies are discussed.

Abbreviations

TS, Tourette syndrome; ADHD, attention-deficit/hyperactivity disorder; TS+ADHD, Tourette syndrome and co-occurring ADHD; EEG, electro-encephalography; ERP, event-related potential; FRN, feedback-related negativity; HRT, habit-reversal therapy

Keywords: Tourette syndrome, ADHD, reinforcement learning, comorbidity, event-related potentials, electrophysiology

1. Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterised by chronic motor and phonic tics, i.e. involuntary and repetitive movements and sounds (American Psychiatric Association, 2013). A large proportion of young people with TS have co-occurring symptoms of attention-deficit/hyperactivity disorder (ADHD) (Freeman, 2007; Hirschtritt et al., 2015), a neurodevelopmental disorder characterised by inappropriate and impairing symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2013). Young people with TS and co-occurring ADHD (TS+ADHD) have worse functional outcomes (Conelea et al., 2011; Debes et al., 2010) and experience less success with behavioural tic therapies (McGuire et al., 2014) than young people with TS without ADHD but the mechanisms underlying these effects are not known.

Reinforcement learning, the ability to learn and modify behaviours based on their association with positive and negative outcomes, has been implicated in the causes of TS and ADHD. This ability relies on dopaminergic transmission in cortico-striato-thalamo-cortical (CSTC) circuitry (Kehagia et al., 2010; Maia & Frank, 2011). In TS, it has been proposed that excessive striatal dopamine leads to inappropriate hyper-learning of associations between sensory stimuli and motor responses, resulting in tic 'habits' that are difficult to break (Leckman & Riddle, 2000; Maia & Frank, 2011). Findings of increased dopamine transmission in unmedicated patients with TS (recently reviewed in Buse et al., 2013) and the successful amelioration of tics with dopamine antagonist medications (Lombroso et al., 1995; Sallee et al., 1997) support this proposal. Further, experimental work has found that unmedicated adults with TS show enhanced habit-learning performance and impaired learning from punishments (Delorme et al., 2015; Palminteri et al., 2009; 2011) compared with those on medication, and these effects are positively associated with tic severity and atypical white matter in CSTC circuitry (Delorme et al., 2015). These findings indicate that

learned associations are more ingrained (hyper-learned) when individuals with TS are not on dopamine-reducing antagonist medication, and that this hyper-learning is associated with more severe tics and greater atypicality in the CSTC neural circuitry that is proposed to underlie both tic generation and dopamine-driven reinforcement learning. This pattern of findings therefore supports the proposal that excessive dopamine in CSTC circuitry leads to tics via over-active reinforcement learning. However, others have reported poorer habit-learning performance (Kéri et al., 2002; Marsh et al., 2004) or typical learning profiles (Channon et al., 2006; Crawford et al., 2005) in TS. Mixed findings of intact (Channon et al., 2004; Cirino et al., 2000; Ozonoff & Jensen, 1999) or impaired (Eddy & Cavanna, 2014) learning performance on the Wisconsin Card Sorting Test have also been reported in TS, although this task places considerable demands on cognitive processes other than reinforcement learning, including planning and working memory, which limits the interpretability of these findings. Of note, few of these studies adequately controlled for the influence of co-occurring symptomatology, including ADHD, and so further work is needed to fully test the proposed link between reinforcement learning mechanisms and tics.

Impaired reinforcement learning is central to several models of ADHD, all of which propose dopaminergic abnormalities in CSTC pathways (Johansen et al., 2009; Sagvolden et al., 2005; Sonuga-Barke, 2003; Tripp & Wickens, 2008). In support of this, treatment with methylphenidate, which increases dopaminergic activity in CSTC circuits, reduces ADHD symptoms, and reinforcement learning is impaired in unmedicated cases (Frank et al., 2007; Thoma et al., 2015; but see Luman et al., 2009; 2014) but normalises with methylphenidate (Frank et al., 2007). There is also evidence of impaired reversal or modification of learned stimulus-response (S-R) associations in ADHD (Itami & Uno, 2002) and abnormal neural processing of reinforcement information during learning, as indicated by atypical amplitudes of the feedback-related negativity (FRN; Miltner et al., 1997) and feedback-locked P2 (van

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Meel et al., 2005) event-related (ERP) components (Hauser et al., 2014; Thoma et al., 2015; Umemoto et al., 2014). FRN and feedback-locked P2 amplitudes typically decrease during a learning episode, likely reflecting decreasing reliance on external performance-related feedback as a new behaviour becomes consolidated (Eppinger et al., 2009; Holroyd & Coles, 2002; Groen et al., 2008; Shephard et al., 2014). These decreases are absent in young people with ADHD (Groen et al., 2008), suggesting they have difficulty learning a new behaviour and consequently rely on external performance feedback for longer than unaffected controls. This pattern of findings suggests that, at least in some individuals with ADHD, the ability to learn and modify behaviours by reinforcement as well as neural processing of reinforcement information is impaired in the absence of dopamine-agonist medication.

Considering the evidence for altered reinforcement learning in TS and ADHD, research is needed to examine the profile of this neurocognitive function in TS+ADHD. Measuring the impact of co-occurring ADHD on the ability to modify learned behaviours in TS may be particularly important. This ability may play a key role in the modification of tics in behavioural therapies such as Habit-Reversal Therapy (HRT; Azrin & Nunn, 1973), which trains individuals to break associations between sensory cues and tic responses and learn to replace tics with non-tic actions or sounds.

In this study we investigated the ability to learn and modify behaviours by reinforcement in young people with TS, TS+ADHD, ADHD, and typically developing controls. Participants learned to associate visual stimuli with left/right hand responses using positive and negative feedback, and then reversed those S-R associations following an unexpected change in reinforcement contingencies. EEG was recorded throughout task performance to investigate neural correlates of learning and reversing behaviours. We used this task previously in typically developing individuals and found that amplitude of the stimulus-locked P3, which in the context of S-R learning is thought to reflect how strongly an

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association has been consolidated (Rose et al., 2001; Shephard et al., 2014), and performance accuracy increased with initial learning, decreased following reversal, and increased once more as participants re-learned the reversed S-R associations (Shephard et al., 2014). Amplitude of the FRN decreased with initial learning, increased during reversal, and decreased with re-learning of the reversed associations (Shephard et al., 2014), which is consistent with changes in reliance on feedback information as the behaviours were consolidated. In the current study we used a 2 (TS-yes, TS-no) x 2 (ADHD-yes, ADHD-no) factorial design to investigate the effects of TS, ADHD, and their interaction on these indices of learning and reversing S-R associations. We also analysed amplitude of the feedback-locked P2 given previous findings of diminished learning-related changes in this component in ADHD (Groen et al., 2008).

We predicted that TS would be associated with hyper-learning of the S-R associations indexed by greater increases in accuracy and P3 amplitude and greater decreases in P2 and FRN amplitude during initial learning of the associations in those with TS (TS-yes) than those without (TS-no). We further predicted that TS would be associated with difficulty breaking those learned behaviours, reflected in greater decreases in accuracy and P3 amplitude and greater increases in P2/FRN amplitude in TS-yes than TS-no during reversal. We predicted that ADHD would be associated with impairments in learning and reversing the S-R associations, reflected in smaller changes in accuracy and amplitude of the P3 and P2/FRN during S-R acquisition in ADHD-yes, and greater decreases in accuracy and amplitude of the P3 and larger increases in P2/FRN amplitude in ADHD-yes during reversal. Based on previous work on other cognitive functions in TS+ADHD (Greimel et al., 2011; Roessner et al., 2007; Shephard et al., 2015), we hypothesised that TS- and ADHD- related reinforcement learning atypicalities would be additive in TS+ADHD. This would be indicated by a lack of interactions between the TS-present and ADHD-present group factors.

2. Method

2.1 Participants

Sixty-eight 9-17 year-olds with TS (n=18), ADHD (n=13), TS+ADHD (n=17), or typical development (n=20, Control group) took part in this study. Participants had normal or corrected-to-normal vision and were free from neurological conditions such as epilepsy. Young people with TS, TS+ADHD and ADHD were recruited from Nottinghamshire and Lincolnshire Child and Adolescent Mental Health Services (CAMHS) and Tourette's Action support groups. Typically developing participants were recruited from Nottinghamshire primary and secondary schools. Ethical approval for the study was obtained from University and NHS Research Ethics Committees and Research and Development departments of Nottinghamshire and Lincolnshire NHS trusts. In accordance with the Declaration of Helsinki, parental written informed consent with child's written assent was obtained for 9-15 year-olds; 16-17 year-olds provided written informed consent.

Consultant psychiatrists or paediatricians provided information on existing clinical diagnoses of TS, TS+ADHD and ADHD, as well as other co-occurring conditions. The Development and Well-Being Assessment (DAWBA, Goodman et al., 2000) was used to confirm diagnoses and obtain further information on clinical or sub-clinical co-occurring symptomatology. The following co-occurring conditions were reported. TS: obsessive-compulsive disorder (OCD) (3), obsessive-compulsive behaviours (5), depression (3), anorexia (1), anxiety disorder (1); TS+ADHD: OCD (2), oppositional defiant disorder (ODD) (5), anxiety disorder (2), dyslexia (1); ADHD: ODD (5), conduct disorder (2), dyslexia (1), dyspraxia (1). Young people with actual or possible diagnoses of an autism spectrum disorder (ASD) or learning disability, or who had IQs less than 70 on the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) were excluded from the study due to the likelihood that these conditions would interfere with reinforcement learning processes (D'Cruz et al.,

2014) and/or the ability to follow experimental instructions. The following combinations of medications were being received. TS: Clonidine (2), Fluoxetine + Clonidine (1), Aripiprazole (1), Citalopram (1); TS+ADHD: Clonidine + methylphenidate (1), methylphenidate (1), Aripiprazole (2), Fluoxetine (1); ADHD: methylphenidate (8), Atomoxetine (1), methylphenidate + Atomoxetine (1). Methylphenidate was withdrawn 24 hours prior to testing. All other medications were continued, leaving 5 participants with TS, 4 participants with TS+ADHD, and 2 participants with ADHD on non-stimulant medication when testing was conducted.

Tic severity (past week) was assessed using the Motor, Phonic and Total (Motor+Phonic) scores from the Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). ADHD symptom severity (past 6 months) was measured with the ADHD Index from the parent-rated Conners Rating Scale Revised (CPRS-R; Conners et al., 1998) and the Hyperactivity scale from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Participants were assigned to clinical groups based on clinical diagnoses and scores on these measures. Thirty-five participants had a clinical diagnosis of TS or chronic motor tics. Of these, 10 participants also held a diagnosis of ADHD and were assigned to the TS+ADHD group. A further 7 participants with TS scored above-threshold for clinically significant symptoms on the ADHD rating scales (CPRS-R ADHD Index scores >/= 60; SDQ Hyperactivity scores >/= 7) and had a high predicted probability of having ADHD on the DAWBA (combined-type n=5, predominantly inattentive-type n=2) and were also assigned to the TS+ADHD group (n=17). The remaining 18 participants with TS formed the TS group; these young people did not have a diagnosis of ADHD and their scores on ADHD rating scales were below clinical thresholds. Thirteen participants held a diagnosis of ADHD combined-type with no co-occurring tics and were assigned to the ADHD group. Typically developing control participants were screened for symptoms of neurodevelopmental disorders

with the DAWBA and symptom rating scales. The groups were matched on age (+/- 8 months), gender, handedness, and socioeconomic status (SES) (+/- 1 classification on the Office of National Statistics Socio-Economic Classification system, Rose & Pevalin, 2003). The participant demographics and symptom profiles are shown in Table 1.

2.2 Learning and reversal task

Participants completed a computerised reinforcement-based learning and reversal task (see Shephard et al., 2014) during EEG recording. Briefly, participants learned to associate four visual stimuli (cartoon characters) with left- or right- hand button presses (two stimuli per hand) by trial and error using performance feedback. Feedback was valid, that is, not probabilistic, on all trials. Stimulus-response (S-R) mappings were counterbalanced across participants. Three blocks of trials were presented for participants to acquire the S-R mappings. In a fourth block, the mappings reversed unexpectedly and participants used feedback to re-learn the reversed mappings. Finally, a fifth block of trials was presented in which participants consolidated the reversed mappings. Every task block contained 48 trials. Each S-R mapping was presented 12 times in random order in every block. Participants were instructed to find out which button-press they should make for each character and were awarded one point for every correct response; the number of points won was displayed at the end of each trial block.

Table 1

Summary of clinical and socio-demographic characteristics for each participant group. Group means are presented with standard deviations in parentheses.

	TS (n = 18)	TS+ADHD (n = 17)	ADHD (n = 13)	Control (n = 20)	Group differences
Age (months)	158.1 (33.3)	148.2 (33.9)	168.5 (32.9)	156.3 (34.8)	n/s
Gender (% males)	77.8	94.1	92.3	80.0	n/s
Handedness (% right handed)	83.3	88.2	92.3	85.0	n/s
SES	2.1 (1.4)	1.8 (1.2)	2.1 (1.4)	1.5 (1.1)	n/s
IQ	111.2 (11.8)	110.1 (10.2)	96.3 (15.6)	112.6 (11.2)	ADHD < TS/TS+ADHD/ Controls *
Motor tic severity (YGTSS Motor)	13.6 (7.5)	12.2 (7.8)	---	---	TS = TS+ADHD (n/s)
Phonic tic severity (YGTSS Phonic)	5.5 (5.8)	19.1 (8.9)	---	---	TS < TS+ADHD**
Total tic severity (YGTSS Total)	19.1 (11.8)	28.1 (11.3)	---	---	TS < TS+ADHD*
CPRS-R ADHD Index[a]	54.0 (9.0)	71.4 (9.2)	76.1 (16.0)	47.6 (6.5)	TS+ADHD/ADHD > TS/Controls**
SDQ Hyperactivity	4.6 (3.1)	5.9 (3.1)	8.3 (2.0)	2.6 (2.6)	ADHD > TS/Controls** TS+ADHD > Controls**

* = significant at the $p < .05$ level. ** = significant at the $p < .01$ level. [a] Scores above 60 on the CPRS-R ADHD scale are considered to be clinically significant.

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2.3 Behavioural measures of learning performance

Learning performance was assessed using the variables accuracy, defined as the percentage of correct trials in each learning block (1-5) and RT, the median response time (ms) for correct trials in each block. Participants with scores 2.5 SD outside of the group mean on these measures were considered to be outliers.

2.4 Electrophysiological recording

Electroencephalography was recorded continuously during task performance from 128 Ag/AgCl scalp electrodes placed according to the 5-20 system (Oostenveld & Praamstra, 2001) using a Biosemi Active II recording system (Biosemi, Amsterdam, the Netherlands). The data were referenced online to the common mode sense electrode located to the left of Cz on the scalp and sampled at 512Hz. Flat sintered Ag/AgCl electrodes were placed on the inner orbital ridge and outer canthus of each eye and the left and right mastoids to record ocular and non-ocular artefacts. Electrode offsets were kept below 50KΩ throughout.

2.5 Electrophysiological measures of learning

EEG data were processed offline using Brain Vision Analyzer version 2.3 (Brain Products, Munich, Germany). Flat or noisy channels were removed before re-referencing to the average reference and filtering with 0.5Hz high-pass, 30Hz low-pass, notch 50Hz Butterworth 24dB/Oct filters. Independent Components Analysis (ICA) was used to identify and remove ocular artefacts from the data. Following ICA the data were segmented into learning blocks (1-5). Within each learning block, stimulus- and feedback- locked epochs were created by segmenting the data in time from -200ms to +1000ms around stimulus and feedback onset respectively. Epochs with amplitudes +/- 90μv were rejected. The remaining

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epochs were baseline corrected using the -200 to 0 ms period before stimulus/feedback onset and averaged to create stimulus- and feedback- locked ERPs. Only epochs in which a correct response was made were included in averages. Participants with fewer than 15 artefact-free correct trials were excluded.

Electrophysiological measures of learning were the stimulus-locked P3 and the feedback-locked P2 and FRN components. To facilitate measurement of the FRN and following previous research (Umemoto et al., 2014), the data used for feedback-locked processing were filtered with a 20Hz low-pass Butterworth 24dB/Oct filter after ICA. Following parameters used in previous research and inspection of grand and individual averages, the components were identified as follows: P3, the most positive peak within 300-600ms post-stimulus at Pz; P2: the most positive peak within 170-250ms post-feedback at Fz; FRN: the most negative peak within 200-400ms post-feedback at FCz. Peak amplitude, defined as the mean of +/- 30ms around peak amplitude, was used to measure the P3. Peak-to-peak measures were used for the feedback-locked components. The P2 was measured with respect to the preceding N1 (most negative peak within 70-180ms post-feedback). The FRN was measured with respect to the preceding positive peak, the P2. Participants with amplitudes greater than 2.5 SD outside of the group mean were considered outliers.

2.6 Statistical analysis

To test the hypothesis that TS is associated with enhanced learning and ADHD is associated with impaired learning, behavioural (accuracy, RT) and electrophysiological (P3, P2, FRN) measures from the acquisition phase of the task (blocks 1-3) were subjected to 2 x 2 factorial ANCOVA models. The between-groups factors were TS-present with the levels TS-yes and TS-no, and ADHD-present with the levels ADHD-yes and ADHD-no. Block (task blocks 1-3) was included as a repeated, within-subjects measure. To test the hypothesis

that both TS and ADHD are associated with impaired reversal learning, behavioural and electrophysiological measures from the reversal phase of the task (blocks 3-5) were subjected to 2 x 2 factorial ANCOVA models as described above. Greenhouse-Geisser corrections for violations of sphericity were applied where appropriate. Significant main effects of block were further investigated using repeated contrasts between successive learning blocks (blocks 1-2, 2-3, 3-4, 4-5) with Sidak correction applied to control for multiple comparisons. Significant main effects of TS-present and ADHD-present and interactions between these factors and block were further investigated with planned pairwise contrasts with Sidak correction applied. Covariates in the models were age, due to previous findings that learning and reversing S-R associations improves with age (Shephard et al., 2014), and IQ due to group differences in IQ (ADHD < TS, TS+ADHD, controls; table 1). IQ was non-significant in all models and was therefore removed as a covariate.

We conducted a set of correlational analyses to further understand how behavioural and ERP markers of learning were related to each other in the whole sample, and how tic and ADHD symptoms were related to these measures of learning in the TS-yes and ADHD-yes groups respectively. Pearson correlation coefficients were computed between accuracy and amplitudes of the stimulus-locked P3 and the feedback-locked P2 and FRN in blocks 1 and 4, the blocks in which the most learning and modification of learned behaviours occurs, in all participants. Within participants with TS-yes (TS, TS+ADHD), Pearson correlation coefficients were computed between YGTSS total tic severity (motor+phonic tics) and learning measures (accuracy, RT, and amplitudes of the P3, P2 and FRN) in blocks 1 and 4. Within participants with ADHD-yes (ADHD, TS+ADHD), Pearson correlations coefficients were computed between these learning measures in blocks 1 and 4 and CPRS-R ADHD Index scores. The effects of age were partialled out in all correlations.

3. Results

3.1 Behavioural learning performance

One participant with TS, one participant with TS+ADHD, and one control participant produced outlying scores on performance measures and were excluded from all analyses. Thus, analyses of behavioural learning performance were conducted on a final sample of 17 TS, 16 TS+ADHD, 13 ADHD and 19 controls.

3.1.1 Acquisition phase

Factorial ANCOVAs revealed that accuracy tended to increase across the first three task blocks (F (1.7, 99.7) = 2.87, p = .07, η^2 = .046), indicating all participants gradually learned the S-R mappings in the acquisition phase (figure 1). RT did not change significantly with learning block (p > .6) (figure 1). The ADHD-present factor had a significant effect on accuracy (F (1, 60) = 10.84, p = .002, η^2 = .153), with lower accuracy in ADHD-yes than ADHD-no across the acquisition phase of the task (figure 1). There was no effect of ADHD-present on RT (p > .8). The effect of TS-present, TS-present*ADHD-present interaction, and interactions between group factors and block were non-significant (all p > .1). There were significant main effects of age on accuracy (F (1, 60) = 5.17, p = .03, η^2 = .079) and RT (F (1, 60) = 4.11, p = .05, η^2 = .064).

[FIGURE 1 HERE]

3.1.2 Reversal phase

There were significant main effects of block on accuracy (F (1.7, 103.6) = 4.49, p = .02, η^2 = .070) and RT (F (2, 120) = 7.16, p = .001, η^2 = .107) in the reversal phase (blocks 3 to 5). Across participants, accuracy decreased (p = .01) and RT increased (p = .004) in the

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reversal block (block 4) compared with the preceding learning block (block 3) (figure 1). There was a trend for accuracy to increase (p = .07) with the consolidation of the reversed mappings in block 5 compared with block 4. There was a significant main effect of ADHD-present on accuracy (F (1, 60) = 20.30, p < .001, η^2 = .253); participants with ADHD-yes had significantly lower accuracy across the reversal phase than ADHD-no. This effect was qualified by a significant interaction between ADHD-present and block (F (1.7, 103.6) = 6.74, p = .003, η^2 = .103). To further investigate this interaction, accuracy was compared between blocks 3, 4 and 5 at each level of the ADHD factor (ADHD-yes, ADHD-no). This analysis revealed that all participants showed significant decreases in accuracy with reversal (block 3 versus block 4; ADHD-yes: p = .001; ADHD-no: p = .004) and increases in accuracy in the consolidation block (block 4 versus block 5; ADHD-yes: p < .001; ADHD-no: p = .004) but participants with ADHD-yes also showed significantly lower accuracy in block 5 compared with the pre-reversal block 3 (p = .001) whereas participants with ADHD-no showed no such difference (p > .7). This indicates that participants with ADHD were unable to regain the level of accuracy they had achieved prior to the reversal of the S-R mappings (figure 1). There was no effect of ADHD-present on RT (p > .5). The effect of TS-present, TS-present*ADHD-present interaction, and interactions between remaining group factors and block were non-significant for accuracy and RT (all p > .1). Age had a significant effect on accuracy (F (1, 60) = 11.35, p = .001, η^2 = .159) and RT (F (1, 60) = 8.63, p = .005, η^2 = .126) but did not interact with Block.

3.2 Electrophysiological measures of learning

One participant with TS+ADHD and three participants with ADHD had fewer than 15 artefact-free correct trials and were excluded from ERP analysis. Additionally, one control participant produced outlying amplitudes for the P3 and was excluded from analysis of this

component. One participant with ADHD produced outlying amplitudes for the P2 and FRN and was excluded from analysis of these components. After these exclusions, analysis of the P3 was conducted on 17 TS, 15 TS+ADHD, 10 ADHD and 18 controls; analysis of the feedback-locked P2 and FRN was conducted on 17 TS, 15 TS+ADHD, 9 ADHD, and 19 controls.

3.2.1 Acquisition phase

Group means for amplitudes of the P3, feedback-locked P2 and FRN are plotted by learning block in figure 2; grand average waveforms for these components are presented in figures 3-5. There were significant main effects of block on amplitude of the feedback-locked P2 ($F (1.5, 83.0) = 3.79$, $p = .04$, $\eta^2 = .064$) and FRN ($F (1.7, 93.3) = 6.58$, $p = .004$, $\eta^2 = .107$) (figures 2, 4, 5). Further investigation of these main effects with repeated contrasts between successive learning blocks revealed that P2 amplitude significantly decreased across blocks 1 to 2 ($p = .02$) but not blocks 2 to 3 ($p > .3$), while FRN amplitude tended to decrease across blocks 1 to 2 ($p = .08$) and significantly decreased across blocks 2 to 3 ($p = .03$). Amplitude of the P3 did not change with learning block in the acquisition phase ($p > .15$) (figures 2-3). The effects of TS-present and ADHD-present, interactions between the group factors, and interactions between group factors and block were non-significant in the acquisition phase (all $p > .15$). Age had a significant effect on amplitude of the P2 ($F (1, 55) = 27.31$, $p < .001$, $\eta^2 = .332$) and FRN ($F (1, 55) = 13.31$, $p = .001$, $\eta^2 = .195$) but did not interact with Block.

[FIGURES 2-5 HERE]

3.2.2 Reversal phase

Amplitudes of the P3, feedback-locked P2, and FRN did not change with block in the reversal phase (all p > .2) (figures 2-5). The ADHD-present factor had a trend-level effect on amplitude of the P3 across the reversal phase with a medium effect size (F (1, 55) = 3.32, p = .07, η^2 = .057), reflecting smaller P3 amplitudes in ADHD-yes than ADHD-no (figures 2-3). There was a trend-level TS-present*ADHD-present interaction for the feedback-locked P2, with a medium effect size (F (1, 55) = 3.49. p = .07, η^2 = .060). While this effect did not quite reach statistical significance, we cautiously conducted follow-up analysis due to the medium effect size and relevance to our study hypotheses. Planned pairwise contrasts were conducted to compare the levels of each factor and revealed that within ADHD-no, participants with TS-yes (TS group) had significantly smaller P2 amplitudes than participants with TS-no (control group) (p = .01) (figures 2, 4). Further, within TS-yes, participants with ADHD-no (TS group) had significantly smaller P2 amplitudes than participants with ADHD-yes (TS+ADHD group) (p = .02) (figures 2, 4). This pattern of effects indicates smaller P2 amplitudes in the TS group than control and TS+ADHD groups, although the initial interaction did not reach the p<.05 threshold and so the effect must be interpreted with this in mind. There were no other main effects of group, interactions between the group factors, or interactions between group factors and block (all p > .1). Age had a significant effect on amplitude of the P3 (F (1, 55) = 3.93, p = .05, η^2 = .067), P2 (F (1, 55) = 19.38, p < .001, η^2 = .261), and FRN (F (1, 55) = 10.05, p = .002, η^2 = .154) but did not interact with block.

3.3 Relationships between behavioural and electrophysiological measures

In all participants, amplitude of the FRN was significantly positively correlated with accuracy in block 1 (r (57) = .255, p = .05, r^2 = .065) and block 4 (r (57) = .491, p < .001, r^2 = .241), indicating that participants with the highest accuracy during acquisition and reversal of

the S-R associations had the smallest (least negative) FRN. Relationships between accuracy and amplitudes of the stimulus-locked P3 and feedback-locked P2 were non-significant (all p > .2).

3.4 Relationships between symptomatology and learning

There were no significant relationships between tic severity and learning measures in participants with TS-yes (all p > .15). However, in participants with ADHD-yes (ADHD, TS+ADHD), ADHD severity was significantly positively correlated with amplitude of the feedback-locked P2 in block 1 (r (18) = .462, p = .04, r^2 = .213) and significantly negatively correlated with FRN amplitude in blocks 1 (r (18) = -.479, p = .03, r^2 = .229) and 4 (r (18) = -.457, p = .04, r^2 = .209), indicating that young people with the most severe ADHD symptoms displayed the largest amplitudes of the feedback-related components at these challenging points in learning and reversing the S-R associations. The remaining correlations between ADHD severity and learning measures were non-significant.

4. Discussion

The current study investigated disturbances in learning and modifying behaviours by reinforcement in young people with TS, TS+ADHD and ADHD in comparison with typically developing young people. The effects of TS, ADHD, and their interaction on behavioural and ERP correlates of learning and reversing S-R associations were investigated using a factorial approach. Before discussing these effects, it is worth noting that the task elicited the expected learning- and reversal-related changes in behaviour and ERPs in this sample. Participants' accuracy increased as they learned the S-R associations in the acquisition phase (blocks 1-3), although this did not quite reach the significance threshold of .05. Concurrently, amplitudes of the feedback-locked P2 and FRN decreased significantly, likely reflecting decreasing

reliance on feedback information as the participants learned the mappings. Performance (accuracy, RT) was impaired by the requirement to reverse the S-R associations in block 4, but improved as the reversed mappings were re-learned in block 5. Consistent with our previous study (Shephard et al., 2014), participants achieving the highest accuracy in the first acquisition block and in the reversal block (block 4) had the smallest FRN amplitudes, which might reflect less reliance on feedback in these "fast learners".

4.1 TS-related effects on reinforcement learning

In contrast to our hypothesis and previous findings in adults with TS (Delorme et al., 2015; Palminteri et al., 2009; 2011), there was no effect of TS on behavioural or ERP measures of learning in the acquisition phase or on performance in the reversal phase, indicating that young people with TS learned the S-R associations in a typical manner and had no difficulty reversing and re-learning the associations. It is possible that learning the S-R associations in our task engaged primarily flexible, goal-directed reinforcement learning processes that are under cognitive control, an ability that appears to be spared in TS (Jackson et al., 2007; 2011; Roessner et al., 2008; Shephard et al., 2015), rather than more rigid and inflexible habit-learning mechanisms that are proposed to be hyper-active in TS and to underlie tics (Leckman & Riddle, 2000; Maia & Frank, 2011). It will be important for future work to further investigate reinforcement learning processes underlying tic formation and maintenance with a range of habit-based and goal-directed learning tasks in young people with the disorder.

The only difference we detected in TS was smaller P2 amplitudes during the reversal phase in the TS group compared with the TS+ADHD and control groups. We stress that this effect must be interpreted with caution because although the pairwise group contrasts were significant, they followed a trend-level group interaction. Our tentative interpretation of this

effect is that because young people with TS achieved the same level of behavioural performance as controls while simultaneously processing the feedback stimuli to a lesser extent (relying on the feedback less than controls), they may have been exhibiting better reversal learning ability than their typically developing peers. This pattern of effects is consistent with intact, and in some cases enhanced, cognitive control over motor behaviour young people with TS exhibit during experimental tasks (Baym et al., 2008; Greimel et al., 2011; Jackson, et al., 2007; 2011; Marsh et al., 2007; Ozonoff & Jensen, 1999; Ray Li et al., 2006; Roessner et al., 2008; Shephard et al., 2015), and might indicate that good cognitive control can also be exercised during learning contexts. Whether young people with TS can so easily control behaviours learned by habit-formation mechanisms will be a key question to address in future work. The absence of the P2 amplitude reduction in TS+ADHD may be explained by ADHD-related impairments in reversal learning, discussed in the following section. Further work is needed to attempt to replicate this finding in larger samples, particularly as the initial interaction did not quite reach significance. The medium effect size reported here suggests that this finding is worth investigating further.

4.2 ADHD-related effects on reinforcement learning

In contrast to our hypothesis of impaired learning in ADHD, but consistent with previous research (Groen et al., 2008; Luman et al., 2009; 2014; Umemoto et al., 2014), young people with ADHD learned the S-R associations at the same rate as young people without ADHD during the acquisition phase. The lower overall level of accuracy performance in ADHD-yes may be explained by more general difficulties concentrating on the task rather than a reinforcement learning impairment. However, the correlations between ADHD severity and FRN and P2 amplitude in the first learning block are suggestive of a subtle atypicality in reinforcement learning. Participants with TS+ADHD and ADHD with

the most severe symptoms exhibited the largest amplitudes of the P2 and FRN, which might reflect an over-reliance on external feedback to produce the correct responses in these young people as reported previously (Groen et al., 2008).

As predicted, participants with ADHD-yes were significantly impaired by the requirement to reverse and re-learn the S-R associations and were unable to regain the same level of accuracy they had achieved prior to reversal. Furthermore, FRN amplitude was largest in participants with the most severe ADHD during the first block following the reversal in reinforcement contingencies (task block 4), suggesting that young people with the most severe symptoms relied more on feedback to reverse the mappings. There was also a trend for smaller P3 amplitude during the reversal phase in participants with ADHD-yes. This effect should be interpreted with caution given that it did not quite reach statistical significance. We tentatively suggest that the amplitude reduction might reflect weaker consolidation of the S-R associations or less attention to the stimuli during the reversal phase in participants with ADHD. This finding was associated with a medium effect size but requires further replication in larger samples.

Importantly, the ADHD-related effects on learning and reversing the S-R associations were not qualified by interactions between the ADHD-present and TS-present group factors. This demonstrates that young people with TS+ADHD showed the same level of performance during the acquisition phase and the same impairment in reversing and re-learning the associations as young people with ADHD without tics. This indicates that co-occurring ADHD symptoms significantly impair the ability to modify learned behaviours in TS. This impairment may also be related to the involvement of other cognitive processes in reversal learning, such as motor inhibition. While motor inhibition is intact in young people with TS (Baym et al., 2008; Marsh et al., 2007; Ozonoff & Jensen, 1999; Ray Li et al., 2006; Roessner et al., 2008; Shephard et al., 2015), it has repeatedly been reported to be impaired in

ADHD (e.g. Holmes et al., 2010; Groom et al., 2010) and TS+ADHD (Greimel et al., 2011; Roessner et al., 2007; Shephard et al., 2015; Sukhodolsky et al., 2010). Such impairments may exacerbate difficulties controlling learned behaviours during reversal learning.

These findings have implications for the clinical treatment of tics in TS+ADHD: behavioural therapies that rely on the ability to modify tic behaviours, including HRT, may be less successful in young people with TS+ADHD because of underlying difficulties with the ability to alter behaviours, in addition to their difficulties with attention and impulsivity. Young people with TS+ADHD may also have difficulty with learning new behaviours by reinforcement, as indicated by the overall levels of lower accuracy in producing the correct S-R associations in the acquisition phase. This too may influence how well these young people can engage in behavioural therapies that require replacing tic behaviours with newly learned non-tic behaviours. The findings are also important from a theoretical perspective in terms of understanding the basis of TS+ADHD. An intriguing question is how opposing atypicalities in neurocognitive mechanisms, such as reinforcement learning, manifest in young people with both disorders. One possibility is that hyper-learning associated with TS and impaired learning associated with ADHD would cancel each other out, and therefore learning would be unaffected in individuals with TS+ADHD. However, the current findings do not support this and instead indicate that the expression of learning (and potentially other neurocognitive) atypicalities in these individuals is more complex.

4.3 Limitations and future directions

There were a number of limitations to the current study. Firstly, our sample sizes for the clinical groups, particularly the ADHD group, were modest and this should be considered when interpreting our findings. It should be noted however that we maximised the power to measure the effects of TS and ADHD by using a 2 x 2 factorial analysis, which ensured that

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these main effects were analysed in samples of no less than 26. The correlational analyses were also adequately powered and were crucial to measuring the impact of co-occurring ADHD on TS. Further, the participants were carefully recruited and characterised with phenotypic measures, resulting in well-defined clinical samples. This feature of the study ensured that our samples, although moderate in size, were representative of the clinical phenotype of TS, TS+ADHD and ADHD, thereby enhancing the reliability of our findings. Nevertheless, our findings require further investigation in larger samples appropriately powered to investigate interactions between TS and ADHD.

A second limitation is that we were unable to examine the influence of co-occurring OCD symptoms on reinforcement learning in the young people with TS and TS+ADHD because the number of these young people with co-occurring OCD was insufficient for analysis. OCD has been associated with impairments in reinforcement learning (e.g. Remijnse et al., 2006) and previous work has demonstrated that co-occurring OCD symptoms significantly impair reinforcement learning, as well as underlying neural activity, in adults with TS (Worbe et al., 2011). Since OCD frequently co-occurs with TS (Hirschtritt et al., 2015), it will be important for further research to investigate the effects of these symptoms on both habit-formation and goal-directed reinforcement learning processes in TS and TS+ADHD.

A final limitation is that although none of the participants were taking dopamine antagonists and methylphenidate was withdrawn prior to testing, a small number were taking other medications (e.g. aripiprazole) that could not be withdrawn and may have influenced the neurotransmitter systems underlying reinforcement learning. Future research with larger sample sizes will be needed to assess the effects of such medications on reinforcement learning in young people with TS and TS+ADHD. It would also be particularly interesting to examine whether administration of methylphenidate "normalises" the reversal learning

impairment in young people with TS+ADHD as this would have implications for the treatment of individuals with these co-occurring conditions, for example methylphenidate may help these young people with engaging in HRT for tics.

5. Conclusions

Co-occurring ADHD symptoms significantly impaired the reversal of learned stimulus-response associations in young people with TS+ADHD. Furthermore, young people with TS+ADHD and ADHD with the most severe ADHD symptoms showed greater processing of feedback information reflected in the P2 and FRN, suggesting a greater dependence on feedback when reversing learned associations. In contrast, young people with TS without co-occurring ADHD showed reduced neural processing of feedback during reversal learning with normal performance. These findings suggest that HRT and other behavioural tic therapies that require modification of established tic behaviours might be less successful in young people with co-occurring ADHD symptoms due to underlying impairments in reinforcement learning mechanisms.

Conflicts of interests

The authors have no conflicts of interests.

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Figure Captions

Figure 1 Behavioural performance in the learning and reversal task
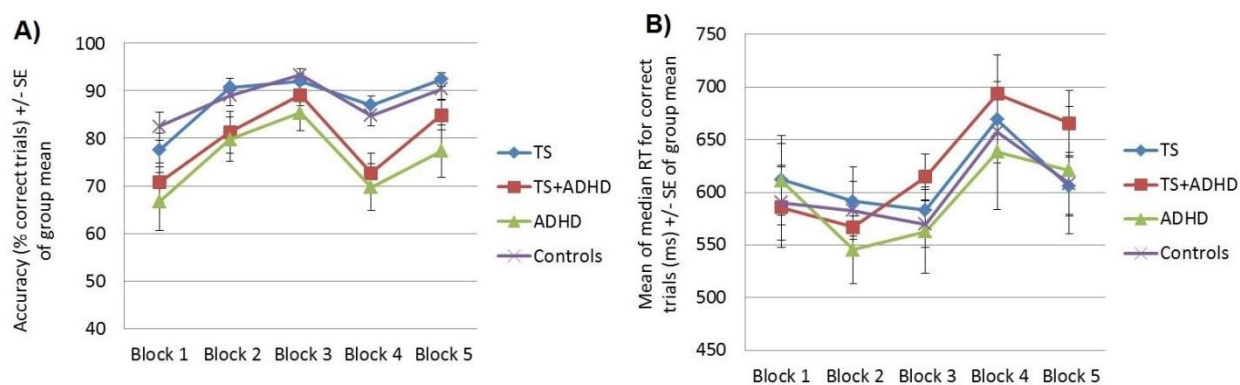
Group means for accuracy (A) and RT (B) are plotted by learning block and group

Figure 2 ERP amplitudes plotted by learning block

Group means for amplitudes of the P3 (A), feedback-locked P2 (B) and FRN (C) are plotted
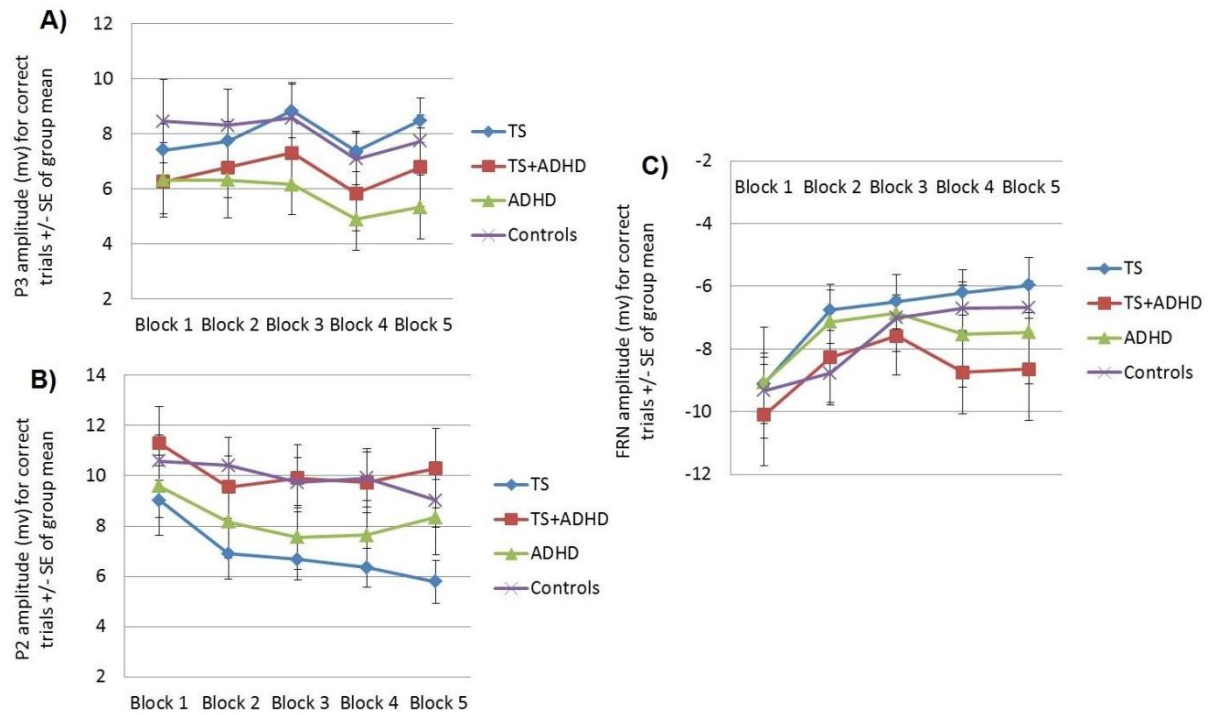
by learning block and group

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Figure 3 Stimulus-locked P3

Grand average stimulus-locked waveforms displaying the P3 at Pz for correct trials plotted by learning block for each group (TS: upper left, TS+ADHD: upper right, ADHD: lower left, Controls: lower right). The black line represents the waveform for block 1, red line for block 2, blue line for block 3, green line for the reversal block 4, and the pink line for block 5. The P3 was measured in the 300-600ms post-stimulus time-range (shaded area in the plots). The insets in each plot display an example of the P3 topography for each group; the topography of the component in block 4 is presented.
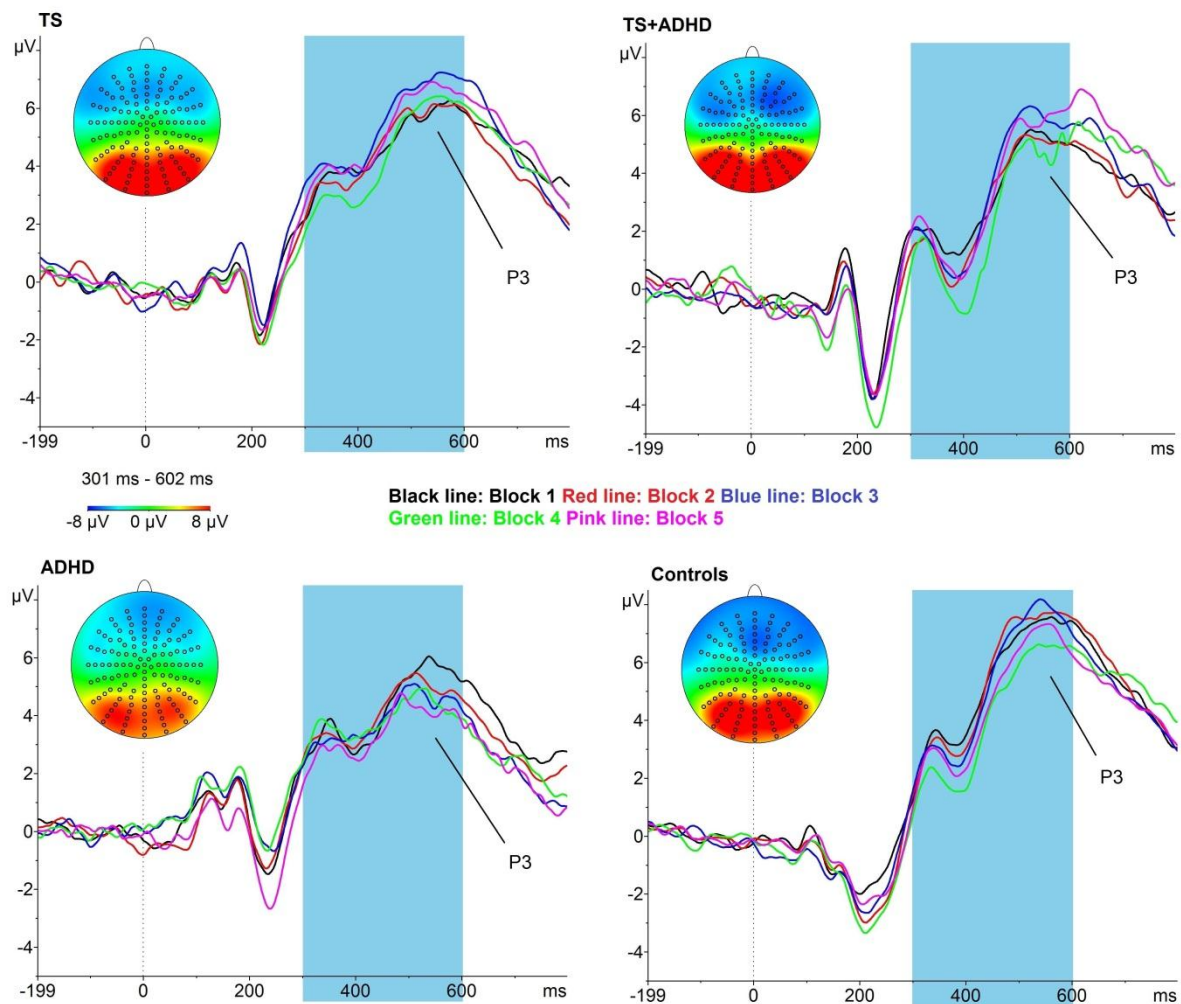
Figure 4 Feedback-locked P2

Grand average feedback-locked waveforms displaying the P2 at Fz for correct trials plotted by group (TS: upper left, TS+ADHD: upper right, ADHD: lower left, Controls: lower right). The black line represents the waveform for block 1, red line for block 2, blue line for block 3, green line for the reversal block 4, and the pink line for block 5. The P2 was measured in the 170-250ms post-feedback time-range (shaded area in plots) with reference to the preceding negative peak. The insets in each plot display an example of the P2 topography for each group; the topography of the component in block 4 is presented.
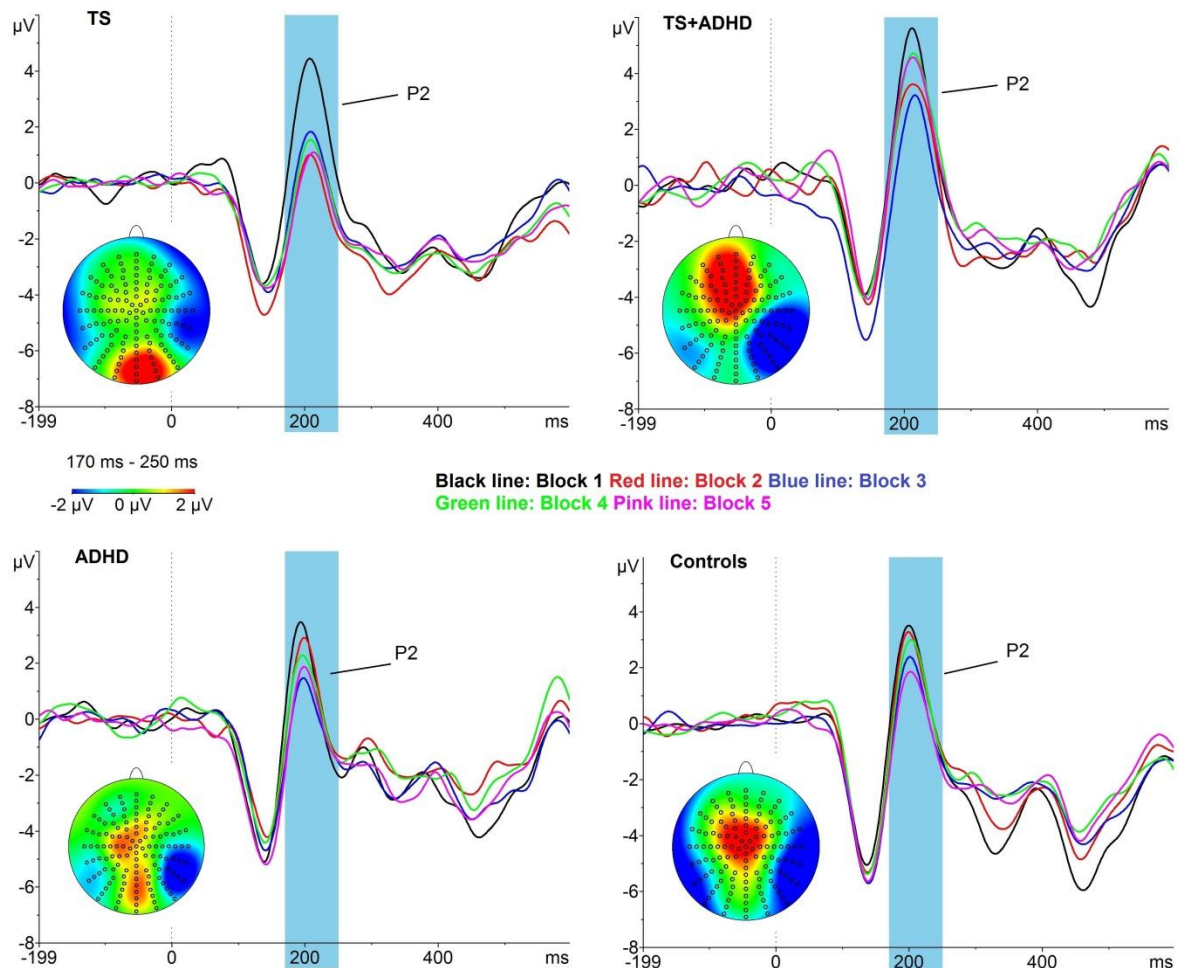
Figure 5 Feedback-Related Negativity (FRN)

Grand average feedback-locked waveforms displaying the FRN at FCz for correct trials plotted by group (TS: upper left, TS+ADHD: upper right, ADHD: lower left, Controls: lower right). The black line represents the waveform for block 1, red line for block 2, blue line for block 3, green line for the reversal block 4, and the pink line for block 5. The FRN was measured in the 200-400ms post-feedback time-range (shaded area in plots) with reference to the preceding positive peak. The insets in each plot display an example of the FRN topography for each group; the topography of the component in block 4 is presented.