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# **Working memory load affects repetitive behavior but not cognitive flexibility in adolescent autism spectrum disorder**

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## **Abstract**

**Objectives:** Autism Spectrum Disorder (ASD) is associated with repetitive and stereotyped behavior, suggesting that cognitive flexibility may be deficient in ASD. A central, yet not examined aspect to understand possible deficits in flexible behavior in ASD relates i) to the role of working memory and ii) to neurophysiological mechanisms underlying behavioral modulations.

**Methods:** We analyzed behavioral and neurophysiological (EEG) correlates of cognitive flexibility using a task switching paradigm with and without working memory load in adolescents with ASD and typically developing controls (TD).

**Results:** Adolescents with ASD vs TD show similar performance in task switching with no memory load, indicating that “pure” cognitive flexibility is not in deficit in adolescent ASD. However performance during task repetition decreases with increasing memory load. Neurophysiological data reflect the pattern of behavioral effects, showing modulations in P2 and P3 event-related potentials.

**Conclusions:** Working memory demands affect repetitive behavior while processes of cognitive flexibility are unaffected. Effects emerge due to deficits in preparatory attentional processes and deficits in task rule activation, organization and implementation of task-sets when repetitive behavior is concerned. It may be speculated that the habitual response mode in ASD (i.e. repetitive behavior) is particularly vulnerable to additional demands on executive control processes.

Words: 200

**Keywords:** autism spectrum disorder, working memory, cognitive flexibility, executive functions, EEG

## Introduction

Cognitive flexibility represents the ability to selectively switch and adapt behavior in response to changing environmental conditions (Miyake et al., 2000; Norman and Shallice, 1980). These processes have been investigated extensively (Allport et al., 1994; Rogers and Monsell, 1995) and it is well-known that switching between tasks usually requires more time and is performed less accurately than repetitions of tasks. These effects are referred to as “switch costs” (Rogers and Monsell, 1995). It is furthermore well-known that for these processes the prefrontal cortex (Dove et al., 2000), the basal ganglia and cortico-striatal networks (Beste et al., 2012; Hikosaka and Isoda, 2010; Yildiz and Beste, 2015; Zhang et al., 2016) as well as the anterior cingulate cortex (Johnstone et al., 2007; Liston et al., 2006; Luks et al., 2002) are of importance. These functional neuroanatomical structures are known to be altered in autism spectrum disorders (ASD) (for review: (Chmielewski and Beste, 2015; Geurts et al., 2009; Hill, 2004), giving rise to the assumption that task switching deficits play a central role in cognitive control deficits in ASD (Chmielewski and Beste, 2015). In light of the presence of restricted and repetitive behavior and a preference for behavioral and environmental consistency in ASD (D’Cruz et al., 2013), an in-depth understanding of dysfunctions in cognitive flexibility seem to be of scientific and clinical importance.

Despite of this, task switching processes in adolescent and adult ASD patients have not been examined intensively, existing studies reported mixed results and to the best of our knowledge only one study analyzed related cognitive subprocesses using neurophysiological (EEG) data (Yeung *et al.* 2016). While some studies found reduced performance, in terms of more total errors (representing the mean of switch *and* repeat trials) in ASD vs typically developing (TD) (Van Eylen et al., 2011; Yeung et al., 2016), others specified that performance deficits in ASD arise under specific conditions, i.e. when task switching is complicated through (i) increased memory load (Stoet and López, 2011), (ii) reduced task information (Shafritz et al., 2008) or (iii) auditory switching information (Mostert-Kerckhoffs et al., 2015). Studies

analyzing switching tasks with a moderate difficulty level (de Vries and Geurts, 2012; Yerys et al., 2009, stage 1-8 from 9) observed no differences in cognitive flexibility between ASD and TD. A critical factor determining performance during task switching in ASD may relate to the degree in how strongly switching is complicated through a) demands of working memory resources (Chmielewski and Beste, 2015; Stoet and López, 2011) and through b) deviations from learnt behaviors and preferences (Mostert-Kerckhoffs et al., 2015; Yerys et al., 2009).

The Goal of this study is to examine neurophysiological mechanisms and its modulations during working memory-based and non-working memory-based task switching in adolescent ASD and TD. To this end we use EEG methods (i.e., event-related potentials, ERPs). This enables us to examine which neural subprocesses in the information processing cascade underlie possible differential behavioral effects of cue- and memory-based task switching between adolescents with ASD and TD. We hypothesize that dysfunctions in cognitive flexibility in ASD only emerge when it is based on working memory processes. Therefore, processes relating to updating of working memory processes (indicated by the P3 ERP (Barceló, 2007; Polich, 2007; Polich and Kok, 1995)) and the allocation of processing resource (indicated by the P2 ERP (Capizzi et al., 2015; Finke et al., 2012)) may differ more between adolescents with ASD and TD than early perceptual and attentional processes (indicated by the P1 and N1 ERP; (Beste et al., 2010a; Herrmann and Knight, 2001). Response selection processes, indicated by the N2 (which index the resolution of task-set conflict and the selection of an appropriate response when a task has to be switched. e.g., (Gajewski et al., 2010a; Getzmann et al., 2013; Karayanidis et al., 2003) also represent important cognitive subprocesses during task switching (Beste et al., 2010b; Gajewski et al., 2010a, 2011). As the N2 is hence not directly modulated by working memory processes it is possible that processes reflected by the N2 are not differentially modulated between adolescents with ASD and TD during memory-based vs. non-memory-based task switching.

## Material and methods

*Participants (for details of demographical and clinical data refer to Table 1)*

A group of  $n = 20$  adolescents with ASD (ASD group) and a total of  $n = 20$  typically developing control adolescents (TD) took part in the experiment. Within the ASD group 11 patients were diagnosed with Asperger syndrome (F85.5), eight with infantile autism (F84.0) and one with atypical autism (F84.1) according to ICD10 (Döpfner et al., 2008). For the diagnosis of ASD i.e. established clinical assessment tools were applied, i.e. a standardized parental interview (ADI-R (Lord et al., 1994)), a standardized observation of the respective child (ADOS (Lord and Risi, 1998)) and a differential diagnostic examination (CBCL, (Achenbach, 1991a)). Within all domains (ADOS and ADI-R) patients exceeded cutoff values. We measured the intelligence quotient (IQ) using the HAWIK III (German version of Wechsler & Tewes, 1999). Inclusion criteria were that participants had to be right handers, had normal or corrected to normal vision, reported no psychiatric or neurological disorders except ASD, were free of medication and had an IQ  $>80$ . Patients were recruited out of a larger database of ASD patients of the outpatient clinic for autism. We recruited 23 patients who fulfilled the inclusion criteria and were prepared to participate on the study. After EEG artifact rejection 3 patients had to be excluded based on movement artifacts and/or increased noise during recording. Age matched TD were recruited, which also did not differ regarding intelligence quotient or gender from the ASD group (all  $p > .05$ , see Table 1). Before test protocol was conducted written informed consent was obtained from all participants. The institutional review board of the medical faculty of the TU Dresden approved the study, which was realized in accordance with the Declaration of Helsinki.

**Table 1****Demographical and clinical data of the ASD sample and TD.**

	ASD Group		Typically developing		Chi <sup>2</sup> – Test
	N = 20		N = 20		
<b>Gender</b>	Female	Male	Female	Male	
N	2	18	4	16	
%	10%	90%	20%	80%	$\chi^2 (1) = .784, p = .66$
					<u>t – test</u>
<b>Age (in years)</b>	14.20 ( $\pm 1.91$ )		13.55 ( $\pm 1.93$ )		$t(38) = .83, p = .41$
Age Range:	11 – 17 years		11 – 17 years		
<b>IQ</b>	114 ( $\pm 14$ )		112.88 ( $\pm 11.26$ )		$t(38) = .45, p = .65$
<b>ASD diagnosis at age (in years)</b>	10.8 ( $\pm 2.38$ )				
Age Range:	6 – 14 years				
<b>ADOS</b>					
Sum A: communication	3.87 ( $\pm 2.23$ )		/		
Sum B: mutual social interaction	7.93 ( $\pm 2.11$ )				
Total Score	11.81 ( $\pm 1.52$ )				
<b>ADI – R</b>					
Sum A: qualitative characteristics of reciprocal social interaction	14.64 ( $\pm 6.05$ )		/		
Sum B: qualitative characteristics of communication	11.56 ( $\pm 4.30$ )				
Sum C: restricted and repetitive, stereotyped behavior	3.32 ( $\pm 2.33$ )				

*Note:* Demographical and clinical data of the ASD sample and typically developing are depicted in table 1.

### *Task switching paradigm*

The procedure used to examine memory- and cue-based task switching was adapted (Gajewski et al., 2011; Wolff et al., 2016). Analog to both references, the paradigm was divided into a cue- and a memory-based block (refer Figure 1). In the cue-based block, a cue for one out of three rules ('NUM', 'GER' or 'SG') was displayed 1300ms prior to the onset of the digits (digits consisted from 1 – 9, excluding number 5). According to the respective displayed rule, participants had either to decide whether the digit was smaller or greater than 5 (when the rule was “NUM” short for “numerisch” = engl. "numeric"), even or uneven (when the rule was “GER” short for “gerade” = engl. "even") or presented in large or small size (when the rule was “SG” short for "Schriftgröße", meaning “font size”, font size was either 50 or 80). Finally, in the cue-based block, cues alternated randomly but with a balanced proportion of 33.3% each while the frequency of switching was set to 50%. In the memory-based block no cues were presented. Instead, participants saw 1300ms prior to the appearance of the digits a dummy cue („XXX“) and had to switch or repeat rules out of memory. Now a determined loop of rules had to be kept in mind. The sequence of rules had always the same order: NUM, NUM, NUM, GER, GER, GER, SG, SG, SG, NUM, NUM, NUM, GER,...). In case someone lost count and failed to apply the correct rule in 3 consecutive trials, the regular cues (i.e. NUM, GER, or SG) replaced the dummy cue in the following 3 trials. Just like for the cue-based block, there was a balanced proportion of each rule (33.33%), but the frequency of switching was reduced to 33.3% due to the fixed order of task rules in the memory block. During task execution, participants were seated in a separate room (to prevent any disturbances or distractions) in front of a monitor and a regular keypad. Hits and reaction times (RTs) were recorded using "Presentation" software (Neurobehavioral System, inc). Each session comprised an exercise block (18 trials per block, always completed before intoxication) and 12 experimental blocks (6 cue-based blocks [with 198 trials] and 6 memory-



based blocks [with 198 trials], resulting in a total of 396 trials). All blocks consisted of the same number of trials. Between the blocks, subjects were allowed to make optional pauses.

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*Insert Figure 1 about here*  
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### *EEG recording and analysis*

We recorded electroencephalography (EEG) with a sampling rate of 500 Hz and electrode impedances under 5 k $\Omega$  using a 60-channel system. Ag/AgCl-electrodes were mounted in an elastic cap and arranged in equidistant positions. Data processing was performed using the BrainVision Analyzer 2 software package (Fa. Brain Products). After recording, data were down-sampled to 256 Hz and filtered (band-pass filter from 0.5 to 20 Hz, with a slope of 48 dB/oct each). Raw data were inspected manually in order to reject non-ocular artifacts from the EEG. Afterwards, an independent component analysis (ICA; infomax algorithm) was conducted on the un-epoched data sets in order to remove recurring artifacts. ICA components revealing horizontal and vertical eye movements, blinks and pulse artifacts were manually rejected. Afterwards, the EEG data was segmented for switch and repeat trials, for cue- and memory-based blocks separately. Only trials with correct responses were taken into account. The segments started 200ms before target presentation of the respective trial and ended 1500ms after its onset. Subsequently, an automated artifact rejection procedure was conducted for all segments, with the following rejection criteria: activity below 0.5 $\mu$ V in a 100ms period and a maximal value difference of 200 $\mu$ V in a 200ms interval. To eliminate the reference potential from the data and to re-reference the data, we applied a current source density (CSD) transformation (Nunez and Pilgreen, 1991) which results in values for amplitudes in  $\mu$ V/m<sup>2</sup>. A baseline correction from -200ms to 0ms prior to target onset was applied; i. e., the baseline was set before the cue onset. For statistical analysis, ERP components were analyzed at the electrodes of their respective maximum amplitudes, relative

to pre stimulus baseline. Mean amplitudes were quantified for P1, N1 and P2 at electrodes P7 and P8 (time window P1: 100 – 130ms, time window N1: 150 – 170ms, time window P2: 300 – 400ms). Mean amplitudes were also quantified for N2 at fronto-central electrodes (FCz) in the time window from 300 – 310ms after target onset. Finally, mean P3 amplitudes were calculated at central electrodes (Pz) between 550 and 580 ms. This choice of electrodes was validated using statistical tests as described in (Muckschel et al., 2014). This validation procedure revealed the same electrode locations.

### *Statistics*

For behavioral data, we analyzed switch costs, switching RT, repetition RT, percentages of hits in switch trials and percentages of hits in repetition trials, for the cue- and memory-based blocks via a mixed-effects ANOVA, with the within-subject factors “condition” (switching, repetition) and “block” (cue-based, memory-based) and the between-subject factor “group” (ASD, TD). For the neurophysiological data, separate repeated-measures ANOVAs for each ERP component were performed. We calculated with the within-subject factors “electrode”, “condition” (switching, repetition) and “block” (cue-based, memory-based) and the between subject factor “group” (ASD, TD). Greenhouse–Geisser correction was applied wherever appropriate and all post-hoc tests were Bonferroni-corrected.

## **Results**

### *Behavioral Results*

#### *Accuracy*

A mixed effects ANOVA on accuracy (percentages of hits) yielded a significant main effect of “condition” ( $F[1,38] = 17.08$   $p < .001$ ,  $\eta^2 = .310$ ), indicating higher accuracy during task repetition ( $90.22\% \pm 1.27$ ) than during task switching ( $88.05\% \pm 1.44$ ) and importantly a significant interaction of “condition x block x group” ( $F[1,38] = 5.16$   $p = .029$ ,  $\eta^2 = .120$ ).

Post hoc tests analyzing i) both groups separately and ii) comparing differences in significant interactions by paired t-tests demonstrated a significant interaction of “condition x block” for the ASD group ( $F[1,19] = 7.84$   $p = .011$ ,  $\eta^2 = .292$ ). The ASD group revealed a higher accuracy in cue-based repetition ( $91.05\% \pm 1.51$ ) vs switching ( $87.40\% \pm 2.09$ ) ( $t[19] = 3.64$ ,  $p = .002$ ), while no corresponding effect was observed during memory-based repetition ( $88.53\% \pm 1.68$ ) vs switching ( $88.79\% \pm 1.83$ ) ( $p = .79$ ). Moreover, we observed significantly higher accuracy during cue-based repetition ( $91.05\% \pm 1.51$ ) vs memory-based repetition ( $88.53\% \pm 1.68$ ) ( $t[19] = 1.97$ ,  $p = .032$ ), while no corresponding effect was observed during cue-based switching ( $87.40\% \pm 2.09$ ) vs memory-based switching ( $88.79\% \pm 1.83$ ) ( $p = .27$ ). A corresponding analysis in TD revealed no significant interaction ( $F < 1$ ), indicating generally higher accuracy during repetition vs switching, in both, the cue- and the memory-based condition (see figure 2a).

#### *RTs and switch costs*

RTs were analyzed via mixed effects ANOVA using the within-subject factor “block (cue- vs. memory-based)”, “condition (repetition vs. switching)” and the between-subject factor “group (ASD group, TD)”. This analysis only revealed a main effect “condition” ( $F[1,38] = 135.66$ ,  $p < .001$ ,  $\eta^2 = .781$ ), indicating faster RTs during task repetition ( $824.5\text{ms} \pm 23.13$ ) versus task switching ( $912.8\text{ ms} \pm 24.23$ ) and “group” ( $F[1,38] = 5.39$   $p = .026$ ,  $\eta^2 = .124$ ), indicating generally decreased RTs in the ASD group ( $814.4\text{ms} \pm 33.07$ ) as compared to TD ( $922.94 \pm 33.07$ ). No other effect or interaction revealed significant results (all  $p > .059$ , see figure 2b). In addition to RTs we calculated the difference measure “switch costs” by subtracting RTs during task repetition from RTs during task switching. A mixed effects ANOVA on switch costs using the within-subject factor “block (cue- vs. memory-based)” and the between-subject factor “group (ASD group, TD)” revealed no significant effect (all  $p > .37$ ), indicating that neither TD, nor the ASD group showed a switch cost effect. In addition,

both groups showed comparable switch costs between the cue- (control group: 80.0ms  $\pm$  14, ASD group: 80.2ms  $\pm$  14) and the memory-based (TD: 96.7ms  $\pm$  19, ASD group: 96.4ms  $\pm$  19) block (see figure 2c).

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*Insert Figure 2 about here*  
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## *Neurophysiological Results*

### *Attentional ERPs*

Target-locked ERPs were analysed by calculating mixed-effects ANOVAs using the within-subject factors “electrode” (P7, P8), “condition” and “block”, as well as the between-subjects factor “group” (ASD group, TD). The P1, N1 and P2 ERPs are shown in Figure 3 and results are also summarized in Table 2.

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*Insert Figure 3 about here*  
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*P1:* The mixed effects ANOVA on the P1 amplitudes revealed a significant main effect of “block” ( $F[1,38] = 8.78$   $p = .005$ ,  $\eta^2 = .188$ ) with higher P1 amplitudes in memory- (24.99  $\mu\text{V}/\text{m}^2 \pm 3.61$ ) as compared to cue-based blocks (21.04  $\mu\text{V}/\text{m}^2 \pm 3.27$ ). No further effects or interaction were observed (all  $p > .05$ ). The mixed effects ANOVA on P1 latencies revealed also a significant main effect of “block” ( $F[1,38] = 19.65$   $p > .001$ ,  $\eta^2 = .341$ ) indicating earlier P1 latencies in the memory- (115.69 ms  $\pm$  1.78) as compared to the cue-based block (119.31 ms  $\pm$  1.58). In addition, a significant effect of “group” was observed ( $F[1,38] = 4.22$   $p = .047$ ,  $\eta^2 = .10$ ), indicating generally earlier P1 latencies in the control (114.15 ms  $\pm$  2.31) as compared to the ASD group (120.85 ms  $\pm$  2.31).

*N1:* The mixed-effects ANOVA on the N1 amplitudes revealed a significant effect of “block” ( $F[1,38] = 6.76$ ,  $p = .013$ ,  $\eta^2 = .151$ ) indicating higher N1 amplitudes ( $-15.47\mu\text{V}/\text{m}^2 \pm$

3.53) in memory- as compared to cue-based blocks ( $-12.67 \mu\text{V}/\text{m}^2 \pm 3.55$ ). The effect was further specified by the significant interaction of “block x condition” ( $F[1,38] = 4.62$   $p = .038$ ,  $\eta^2 = .108$ ), indicating increased N1 amplitudes during task repetition ( $-13.65 \mu\text{V}/\text{m}^2 \pm 3.52$ ) versus task switching ( $-11.66 \mu\text{V}/\text{m}^2 \pm 3.62$ ) in the memory-based block. In the cue-based block a reversed pattern was observed, namely increased N1 amplitudes during task switching ( $16.04 \mu\text{V}/\text{m}^2 \pm 3.55$ ) versus task repetition ( $14.90 \mu\text{V}/\text{m}^2 \pm 3.59$ ). No further significant effects or interaction were observed (all  $p > .05$ ). The mixed effects ANOVA on N1 latencies revealed no significant effects (all  $p > .18$ ).

P2: A mixed-effects ANOVA on P2 revealed a significant effect of block ( $F[1,38] = 14.16$   $p = .001$ ,  $\eta^2 = .272$ ) showing increased P2 amplitudes during cue- vs memory-based blocks. Moreover we observed a significant interaction of “electrode x block” ( $F[1,38] = 5.30$   $p = .027$ ,  $\eta^2 = .122$ ), which was further specified by the significant interactions “electrode x block x group” ( $F[1,38] = 4.92$   $p = .033$ ,  $\eta^2 = .115$ ) as well as “electrode x block x group x condition” ( $F[1,38] = 9.30$   $p = .004$ ,  $\eta^2 = .197$ ). Post hoc tests, analyzing i) the most complex interaction in both groups separately and ii) comparing differences in significant interactions by paired t-tests demonstrated in the ASD group a significant interaction of “electrode x condition x block” ( $F[1,19] = 7.23$ ,  $p = .015$ ,  $\eta^2 = .276$ ), showing significantly increased P2 amplitudes on the left hemisphere ( $t[19] = 2.38$ ,  $p = .028$ ) during cue-based repetition ( $31.10 \mu\text{V}/\text{m}^2 \pm 6.72$ ) vs switching ( $27.88 \mu\text{V}/\text{m}^2 \pm 6.43$ ), and no corresponding effect during memory-based repetition ( $25.36 \mu\text{V}/\text{m}^2 \pm 6.55$ ) vs switching ( $26.05 \mu\text{V}/\text{m}^2 \pm 6.68$ ) ( $t[19] = -.346$ ,  $p = .73$ ). Moreover we observed significantly increased amplitudes during cue-based repetition ( $31.10 \mu\text{V}/\text{m}^2 \pm 6.72$ ) vs memory-based repetition ( $25.36 \mu\text{V}/\text{m}^2 \pm 6.55$ ) ( $t[19] = 1.97$ ,  $p = .032$ ), while no corresponding effect was observed during cue-based switching ( $27.88 \mu\text{V}/\text{m}^2 \pm 6.43$ ) vs memory-based switching ( $26.05 \mu\text{V}/\text{m}^2 \pm 6.68$ ) ( $p = .46$ ). On the right hemisphere, however, no corresponding effect was observed (all  $p > .22$ ). In the control group, in contrast, no equivalent interaction was observed ( $F[1,19] = 2.60$ ,  $p = .12$ ,  $\eta^2 = .120$ ).

The mixed effects ANOVA on P2 latencies revealed also a significant interaction of “electrode x block x group” ( $F[1,38] = 4.92$   $p = .033$ ,  $\eta^2 = .115$ ). Post hoc tests analyzing both groups separately revealed a significant interaction “electrode x group” in the ASD group ( $F[1,19] = 4.77$   $p = .042$ ,  $\eta^2 = .201$ ) indicating significantly earlier P2 latencies in the cue-based block on the left ( $305.47$  ms  $\pm$  11.05) as compared to the right hemisphere ( $318.99$  ms  $\pm$  11.22), while P2 latencies during memory-based block do not differ significantly between the right ( $310.89$  ms  $\pm$  11.47) and the left ( $310.30$  ms  $\pm$  11.55) hemisphere. In contrast, in the control group, no equivalent interaction was observed ( $F[1,19] = .69$ ,  $p = .417$ ,  $\eta^2 = .035$ ).

### *Response-selection ERPs*

Target-locked ERPs reflecting response selection processes (i.e., N2 and P3) were analysed by calculating mixed-model ANOVAs with the within-subject factors “condition” and “block”, as well as the between-subjects factor “group”. The ERPs are shown in Figure 4 and are also summarized in Table 2.

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 Insert Figure 4 about here  
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N2: A mixed-effects ANOVA on the N2 revealed a significant main effect of “group” ( $F[1,37] = 6.17$   $p = .018$ ,  $\eta^2 = .143$ ), showing generally increased (i.e. more negative) N2 amplitudes in the ASD group ( $-6.90$   $\mu\text{V}/\text{m}^2 \pm 2.31$ ) as compared to TD ( $1.07$   $\mu\text{V}/\text{m}^2 \pm 2.25$ ). No further effect of interaction was significant (all  $p > .15$ ). The mixed effects ANOVA on N2 latencies revealed also no significant effects (all  $p > .086$ ).

P3: A mixed-effects ANOVA on the P3 revealed a significant main effect of “condition” ( $F[1,38] = 49.33$   $p < .001$ ,  $\eta^2 = .565$ ), showing increased P3 amplitudes during repetition ( $10.62$   $\mu\text{V}/\text{m}^2 \pm 1.30$ ) as compared to switching ( $5.32$   $\mu\text{V}/\text{m}^2 \pm 1.17$ ). This main effect was further specified by the significant interactions “condition x block” ( $F[1,38] = 4.47$

$p = .041$ ,  $\eta^2 = .105$ ) as well as “condition x block x group” ( $F[1,38] = 7.06$ ,  $p = .011$ ,  $\eta^2 = .157$ ). Post hoc tests, analyzing i) the most complex interaction in both groups separately and ii) comparing observed differences by paired t-tests, showed the ASD group to reveal a significant interaction of “condition x block” ( $F[1,19] = 7.20$ ,  $p = .015$ ,  $\eta^2 = .276$ ), indicating significantly ( $t[19] = 6.33$ ,  $p < .001$ ) increased P3 amplitudes during cue-based repetition ( $15.93\mu\text{V}/\text{m}^2 \pm 2.18$ ) vs switching ( $4.45\mu\text{V}/\text{m}^2 \pm 1.99$ ) and no corresponding effect ( $t[19] = .424$ ,  $p = .67$ ) during memory-based repetition ( $8.73\mu\text{V}/\text{m}^2 \pm 2.24$ ) vs switching ( $7.61\mu\text{V}/\text{m}^2 \pm 2.15$ ). Moreover we observed significantly increased amplitudes during cue-based repetition ( $15.93\mu\text{V}/\text{m}^2 \pm 2.18$ ) vs memory-based repetition ( $8.73\mu\text{V}/\text{m}^2 \pm 2.24$ ) ( $t[19] = 2.86$ ,  $p = .010$ ), while no corresponding effect was observed during cue-based switching ( $4.45\mu\text{V}/\text{m}^2 \pm 1.99$ ) vs memory based switching ( $7.61\mu\text{V}/\text{m}^2 \pm 2.15$ ) ( $p = .16$ ).

In the TD control group, in contrast, no corresponding effect was observed ( $F[1,19] = .350$ ,  $p = .561$ ,  $\eta^2 = .018$ ). The mixed effects ANOVA on P3 latencies revealed a significant effect of condition ( $F[1,38] = 7.04$ ,  $p = .012$ ,  $\eta^2 = .160$ ), indicating earlier P3 latencies during repetition ( $540.84 \text{ ms} \pm 6.46$ ) as compared to switching ( $556.92 \text{ ms} \pm 6.37$ ). In addition we observed a significant interaction of “condition x block x group” ( $F[1,38] = 4.59$ ,  $p = .039$ ,  $\eta^2 = .110$ ), indicating earlier P3 latencies during repetition vs switching in the cue-based block and earlier P3 latencies during switching vs repetition in the memory-based block in the ASD group. Post hoc tests, however, analyzing both groups separately revealed no significant interaction “condition x block”, neither in the ASD group ( $F[1,19] = 3.14$ ,  $p = .093$ ,  $\eta^2 = .149$ ) nor in TD ( $F[1,19] = 1.34$ ,  $p = .261$ ,  $\eta^2 = .066$ ).

**Table 2 Summary of the main neurophysiological results and their interpretation**

ERP	General Meaning	Main finding	Specific Interpretation	General Interpretation according to the behavioural results.
P1	- known to reflect perceptual or attentional processes (Luck et al. 1990; Wascher and Beste 2010)	<b>“block”</b> ( $F[1,38] = 8.78$ $p = .005$ , $\eta^2 = .188$ )	Early perceptual processes are generally increased during memory vs. cue-based blocks.	Results suggest that early perceptual and attentional processes do <u>not</u> explain the observed behavioral effects and thus the deficient performance in patients with ASD during task repetitions in terms with increased memory load.
N1	- known to reflect perceptual or attentional processes (Luck et al. 1990; Wascher and Beste 2010)	<b>“block”</b> ( $F[1,38] = 6.76$ , $p = .013$ , $\eta^2 = .151$ )	Attention is generally increased during memory vs. cue-based blocks.	
P2	- reflect processes of early task-set updating or task-goal activation (Oranje et al. 2004; Brown et al. 2007; De Baene and Brass 2014; Capizzi et al. 2015) possibly due to preparatory attentional control (Kieffaber and Hetrick 2005; Martin et al. 2011).	<b>“electrode x block x group x condition”</b> ( $F[1,38] = 9.30$ $p = .004$ , $\eta^2 = .197$ ).  <u>Post Hoc:</u>  ASD Group: <b>“electrode x condition x block”</b> ( $F[1,19] = 7.23$ , $p = .015$ , $\eta^2 = .276$ )  TD: <b>“electrode x condition x block”</b> ( $F[1,19] = 2.60$ , $p = .12$ , $\eta^2 = .120$ ).	Preparatory attentional processes and task rule activation seems to be altered in patients with ASD, while TD show no corresponding pattern. The effect in patients with ASD seems to emerge only in cases in which memory load is increased and when task sets need to be repeated.	Effects correspond with behavioral pattern, indicating that deficits in memory-based accuracy seem to be explained through i) deficits in preparatory attentional processes. Neural deficits occur only when repetitive behavior is concerned.
N2	- shown to reflect processes related to conflict resolution and response selection	<b>“group”</b> ( $F[1,37] = 6.17$ $p = .018$ , $\eta^2 = .143$ )	The level of cognitive conflict is generally higher in adolescent ASD vs TD.	Results suggest that processes of conflict monitoring do not explain the observed behavioral effects (refer to P1 and N1 general interpretation).
P3	- indicate mechanisms	<b>“condition x block x group”</b> ( $F[1,38] =$	Efficient activation and	Effects correspond with behavioral pattern, indicating



related to task rule activation, organization and implementation of task-sets (Barceló et al. 2000; Nicholson et al. 2005; Gajewski, Wild-Wall, et al. 2010; Beste et al. 2011)	7.06 $p = .011$ , $\eta^2 = .157$ . Post Hoc: ASD Group: “condition x block” ( $F[1,19] = 7.20$ , $p = .015$ , $\eta^2 = .276$ ) TD: “condition x block” ( $F[1,19] = .350$ , $p = .561$ , $\eta^2 = .018$ ).	implementation of processes of task rule activation seem to depend on the condition (repetitive vs switching) and the memory load (i.e. block = cue vs memory-based block) in patients with ASD, while TD show no corresponding pattern.	that deficits in memory-based accuracy seem to be further explained through deficits in task rule activation, organization and implementation of task-sets. Neural correlates suggest that deficits occur only when i) memory load is high and ii) when repetitive behavior is concerned.
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*Note:* Main ERP results and their interpretation are depicted in table 2.

## Discussion

We investigated how memory- and cue-based task switching processes are modulated in adolescent ASD compared to TD and the underlying neurophysiological mechanisms. Therefore the discussion focuses on group-related effects. Behavioral results show that adolescents with ASD, compared to TD, have no deficits in cognitive flexibility during cue-based blocks. This is well in line with studies, showing that cognitive flexibility in ASD is not affected when memory load is absent (Mostert-Kerckhoffs et al., 2015; de Vries and Geurts, 2012; Yerys et al., 2009). In addition, during cue-based blocks both groups show the usual pattern of lower accuracies during switching versus repetition trials, indicating that the retrieval of task-specific stimulus-response rules seems to be facilitated when rules can be repeated and when cues are presented explicitly without memory load in both groups (Koch, 2003).

However, while memory load has no influence on performance in adolescent TD, accuracy in the adolescent ASD group differs depending on both, the need of working memory and condition (switching vs. repetition). Yet, intriguingly, memory load has no effect on the accuracy during switching but decreases performance in repetition trials in adolescent ASD.

This is an unexpected finding, since it was assumed that with increased memory load processes of cognitive flexibility, i.e. switching, but not repetition processes are deficient in ASD (i.e. (Chmielewski and Beste, 2015)). This finding indicates that in adolescent ASD repetitive behavior is highly affected when it is triggered by working memory processes. Repetitive behavior normally seems to represent coping as well as homeostatic mechanisms in ASD, possibly helping to modulate levels of arousal (Leekam et al., 2011; Turner, 1999) and ASD patients feel distressed when being hampered executing repetitive behavior (Leekam et al., 2011). It is possible that the additional need of working memory interferes with the execution of repetitive behavior and therefore leads to performance decreases during repetition trials. It may be assumed that on switch trials the manipulation of working memory load may not have a differential effect to TD, because the “cognitive mode” (i.e. switching) per se deviates from the usually displayed repetitive behavior. It may be speculated the habitual response mode in ASD (i.e. repetitive in contrast to flexible behavior) is particularly vulnerable to additional demands on executive control processes (i.e. need of working memory). It may thus be assumed that the finding of reduced performance of repetitive behavior in ASD provides a link to an intervention that can be applied in clinical practice: adding working memory load in the treatment of repetitive and stereotype behavior in ASD may help to reduce this core symptom of ASD.

The neurophysiological data point to the mechanisms underlying the behavioral modulations. Neurophysiological parameters known to reflect perceptual or attentional processes (i.e. P1 and N1) (Luck et al., 1990; Wascher and Beste, 2010), as well as processes related to conflict resolution and response selection (N2) did not show interactions with condition, block and group. These results suggest that early perceptual processes as well as processes of conflict monitoring do not explain the observed behavioral effects. However, it needs to be noted that the level of cognitive conflict is generally higher in adolescent ASD, as indicated by the main

effect “group” observed in the N2 data (Botvinick, 2007; Botvinick et al., 2001; Chmielewski et al., 2016; Lamm et al., 2006; Nieuwenhuis et al., 2003; Rueda et al., 2004; Waxer and Morton, 2011; Yeung and Nieuwenhuis, 2009).

Interestingly, the P2 and the P3 data revealed similar differential effects dependent on group and experimental condition as found in the behavioral effects. The P2 has been suggested to reflect processes of early task-set updating or task-goal activation (Brown et al., 2007; Capizzi et al., 2015; De Baene and Brass, 2014; Oranje et al., 2004) possibly due to preparatory attentional control (Kieffaber and Hetrick, 2005; Martin et al., 2011). P2 is usually shown to be increased during switching versus repetition trials (Barcelo et al., 2006; and Capizzi et al., 2015; but see Finke et al., 2012; Jost et al., 2008; Logan and Bundesen, 2003) and is therefore suggested to represent a general “change detector” (Finke et al., 2012). Yet, in adolescent ASD we observed decreased P2 amplitudes in cue-based switching and memory-based repetition, as compared to cue-based repetition. Similar effects of switching versus repetition trials have been observed by Capizzi et al. (2015). It is possible that adolescents with ASD have an encoding benefit during cue-based repetition trials vs memory-based repetition trials, which vanishes in case of memory-based repetition trials (i.e. memory-based repetitive behavior) and leads to the observed behavioral effects. Deficits in memory-based repetition may therefore be attributable to a breakdown in task-set updating and/or preparatory attentional control processes. However, aside these processes also mechanisms related to task rule activation, organization and implementation of task-sets, as reflected by the P3 (Barceló et al., 2000; Beste et al., 2011; Gajewski et al., 2010b; Gohil et al., 2015; Nicholson et al., 2005; Stock et al., 2014), are of importance. In adolescent ASD there was no difference in the P3 between memory-based repetition and memory-based switching and the P3 was only modulated during repetition, but not during switching in adolescent ASD. This suggests that task set implementation and rule activation becomes demanding during repetitive behavior

when working memory information needs to be used to do so in ASD. This may, at least in part, be related to deficits related to the preparatory attentional control processes (refer discussion on the P2).

In summary the study shows that cognitive flexibility is not generally dysfunctional in adolescent ASD. When working memory demands are low adolescents with ASD perform at a similar level as TDs. Changes only occur when working memory demands are increased. However, there, it is repetitive behavior that is affected and not cognitive flexibility processes. These effects emerge due to deficits in preparatory attentional processes as well as deficits in task rule activation, organization and implementation of task-sets when repetitive behavior is concerned. It may be assumed that the common and habitual response mode in ASD (i.e. repetitive behavior) is particularly vulnerable to additional demands on executive control processes. These more detailed understanding might help to optimize the planning of existing as well as the development of new behavioral treatment programs for adolescent ASD.

### **Acknowledgements**

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### **Statement of Interest**

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## Figure Legends

### Figure 1

Task Switching Paradigm: The structure of the task switching paradigm is depicted. The cue-based block is shown in the upper part, the memory-based block in the lower part of the figure. In the memory-based block, the subjects had to remember when to switch a rule.

### Figure 2

Behavioral Performance: behavioral data shows (a) performance (% in hits) for all blocks (cue- and memory-based) and conditions (switching and repetition) comparing typically developing and the ASD group. Asterisks represent significant differences between conditions and blocks; (b) RTs for all blocks (cue- and memory-based) and conditions (switching and repetition) comparing typically developing and the ASD group and (c) switch costs, comparing typically developing and the ASD group. Error bars depict standard errors of the mean.

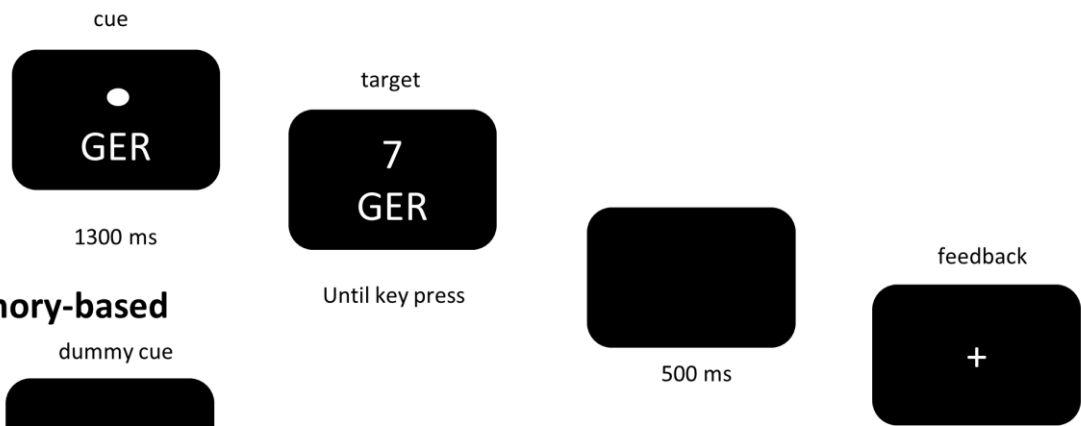
### Figure 3

Neurophysiological Performance of Attention: Event-related potentials (ERPs) show grand averages and voltage maps at occipito-temporal electrodes (P7, P8), depicting P1, N1 and P2 components for the two blocks (cue- and memory-based) and conditions (switching and repetition) in typically developing (left) and the ASD group (right).

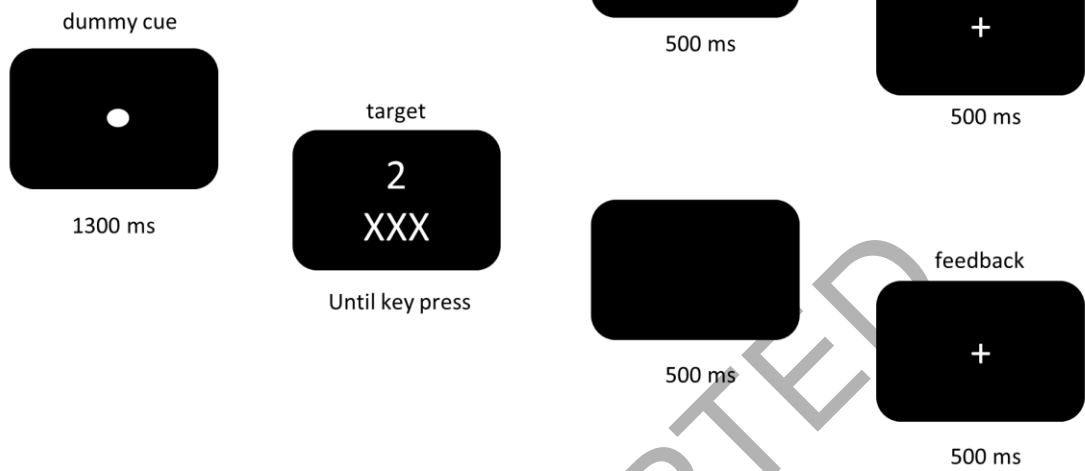
### Figure 4

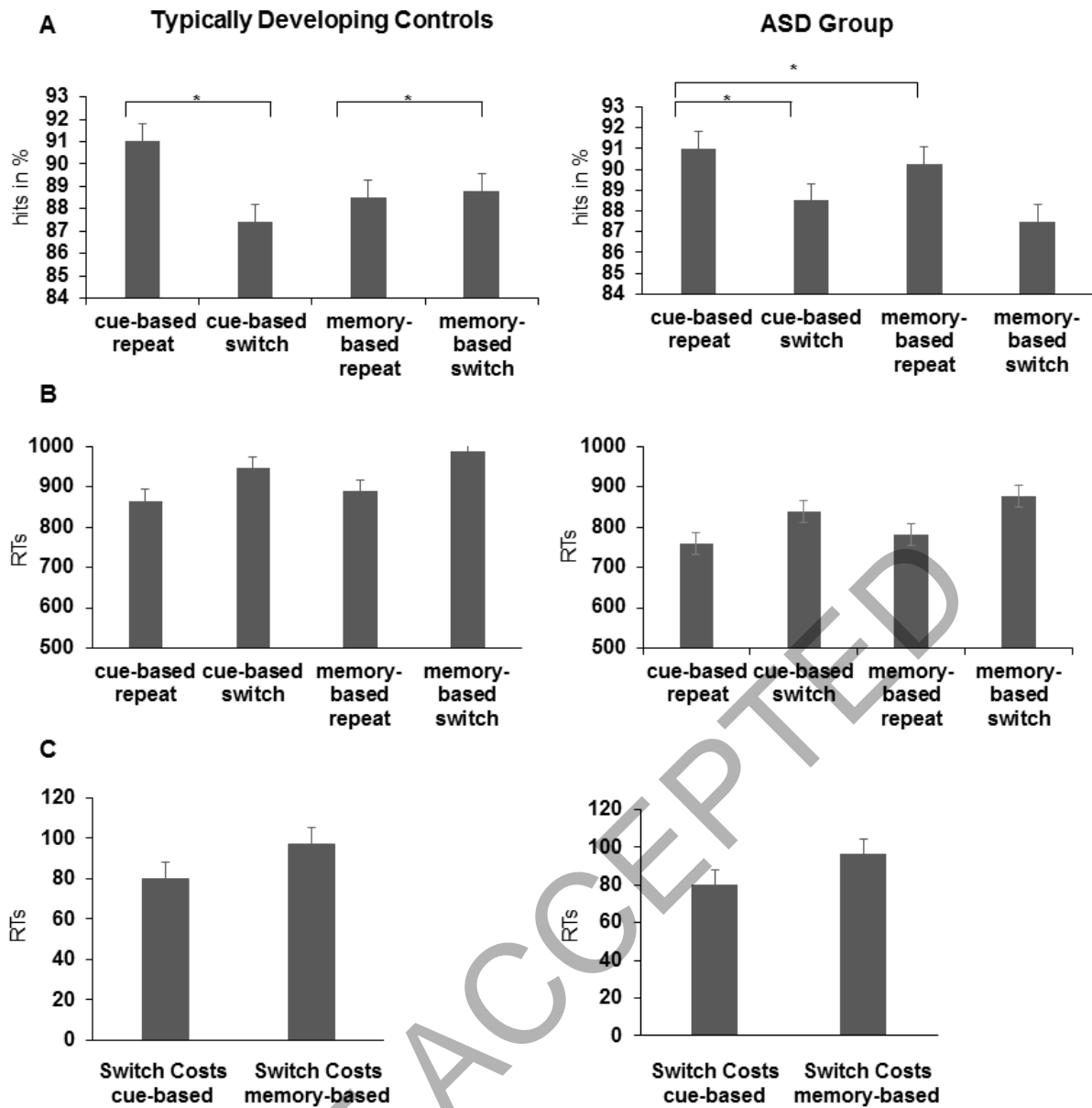
Neurophysiological Performance of Response Selection: Event-related potentials (ERPs) show grand averages and voltage maps at the central electrode (FCz) showing the N2 and at the parietal central electrode (Pz) showing the P3, for the two blocks (cue- and memory-based) and the two conditions (switching and repetition) in typically developing (left) and the ASD group (right).

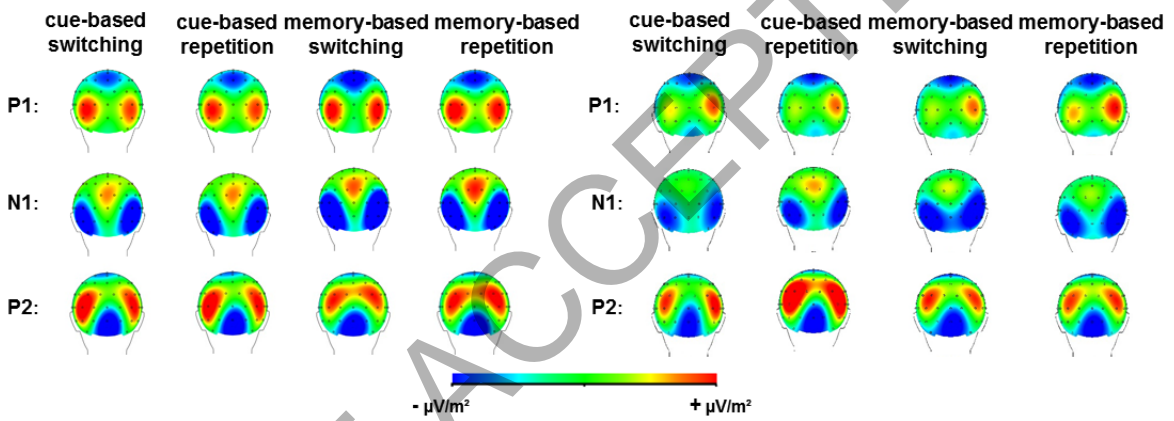
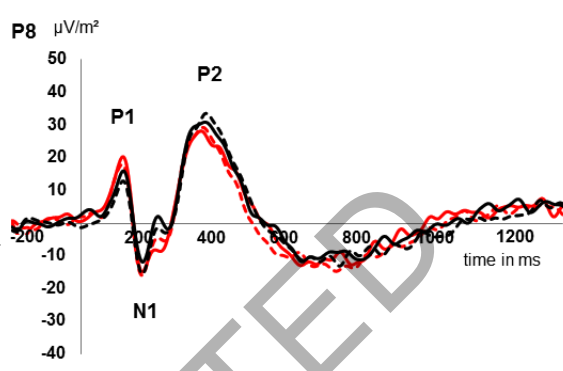
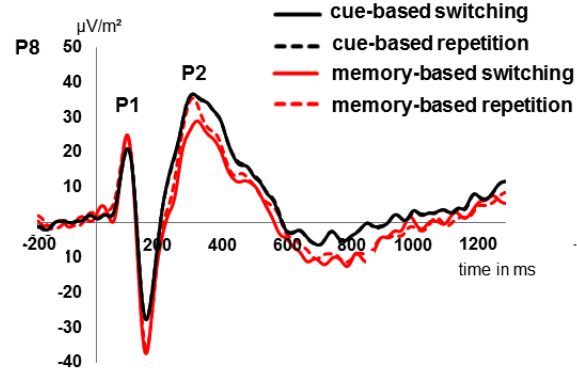
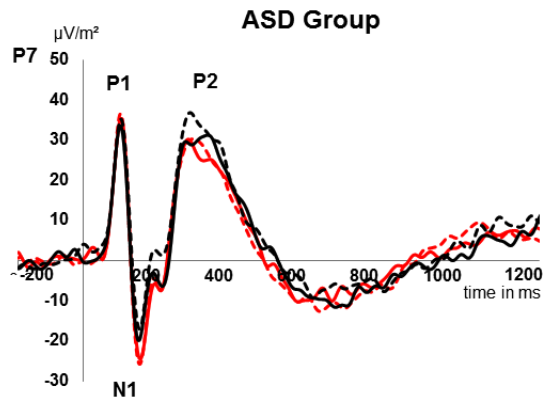
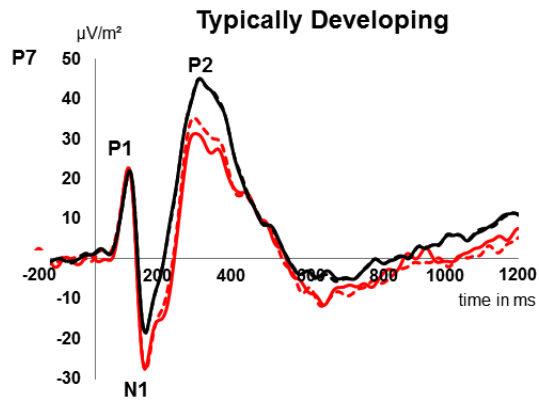
## cue-based



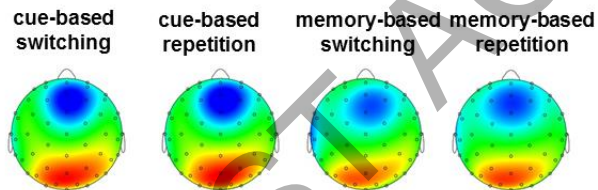
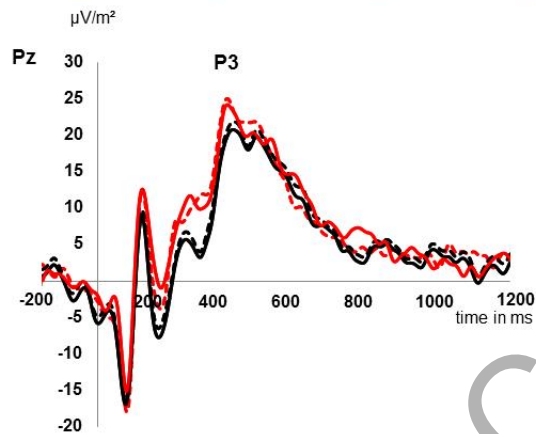
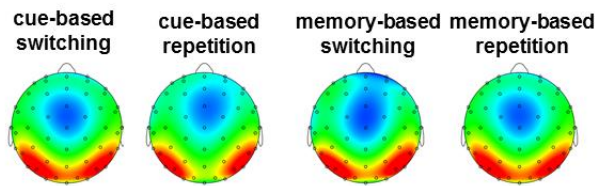
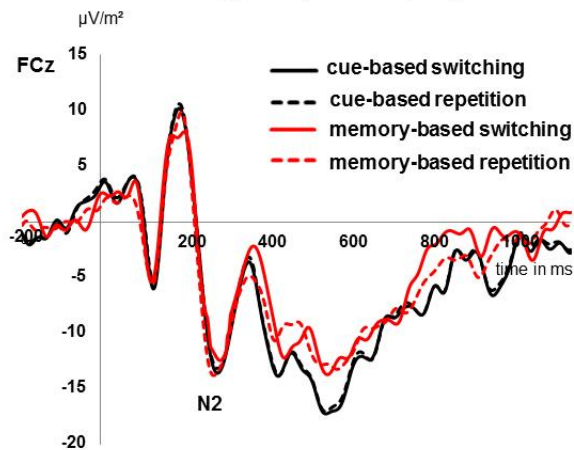
## memory-based



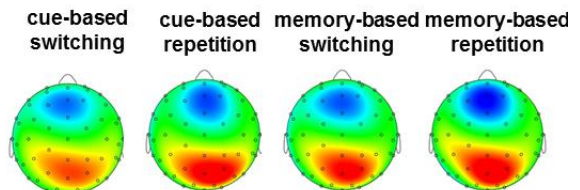
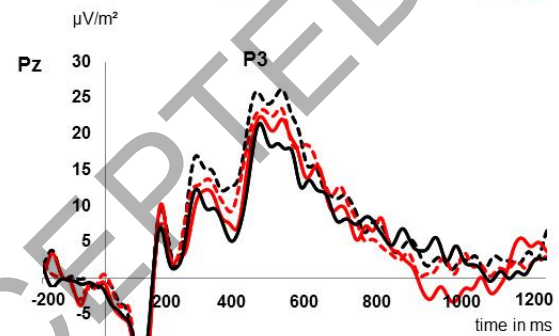
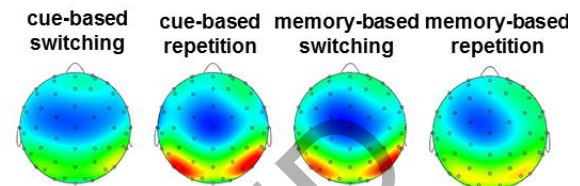
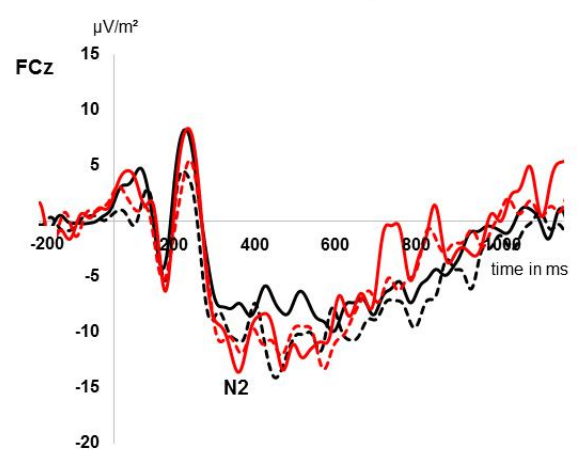




## Typically Developing



## ASD Group



-  $\mu\text{V}/\text{m}^2$  +  $\mu\text{V}/\text{m}^2$