Inflexibility in Autism Spectrum Disorders: need for certainty and atypical emotion processing share the blame.

Latinus Marianne¹, Cléry Helen¹, Andersson Frédéric¹, Bonnet-Brilhault Frédérique¹, Fonlupt Pierre², Gomot Marie¹

¹UMR1253, iBrain, Université de Tours, Inserm, Tours, France.

²INSERM U1028-CNRS UMR5292 'Brain Dynamics and Cognition', Centre de Neurosciences de Lyon, Lyon, France.

Running title: Emotion and Cognitive flexibility in ASD

Corresponding author:

Dr Marianne Latinus

UMR1253, iBrain, Université de Tours, Inserm

Centre de Pédiopsychiatrie

CHRU Bretonneau - 2 bd Tonnellé

37044 Tours Cedex 9 - France

E-mail: mlatinus@gmail.com

Tel: +33247478519

Fax: + 33247473846

Acknowledgements

The experimental part of this study was performed at CERMEP Imaging Facilities- Imagerie du vivant, Bron, F-69677, France. The authors would like to thank Catherine Fisher for the inclusion of both control and autistic participants. We are thankful to Alix Thillay for helpful comments on prior version of this manuscript. Development of the MacBrain Face Stimulus Set was overseen by Nim Tottenham and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development. Please contact Nim Tottenham at tott0006@tc.umn.edu for more information concerning the stimulus set. This research was supported by grants from the Agence Nationale de la Recherche (ANR-12-JSH2-0001), the “Fondation Orange” and by the Ministère des affaires sociales et de la santé, CHRU Bretonneau, Tours (PHRR05-FBB EPCA).

Lay Summary

The link between emotion and cognition in autism is rarely studied. Here, we showed that inflexible behaviors reflect the will to avoid social situations. This is related to an unusual brain response to change.

Abstract (200 words)

Although ASD (Autism Spectrum Disorder) diagnosis requires the co-occurrence of socio-emotional deficits and inflexible behaviors, the interaction between these two domains remains unexplored. We used an emotional Wisconsin Card Sorting Test adapted to fMRI to explore this question. ASD and control participants matched a central card (a face) with one of four surrounding cards according to one of three rules: frame color, facial identity or expression. Feedback informed participants on whether to change or maintain the current sorting rule. For each rule, we modeled feedback onsets to change, switch (confirming the newly found rule) and maintenance events. “Bias error”, which measures participants’ willingness to switch, was larger in ASD participants for the emotional sorting rule. Brain activity to change events showed no group differences. In response to switch events significantly larger activity was observed for ASD participants in bilateral Inferior Parietal Sulci. Inflexibility in ASD appears characterized by the unwillingness to switch toward processing socio-emotional information, rather than a major disruption in cognitive flexibility. However, a larger activity to switch events in ASD highlights the need for a higher level of certainty before setting into a stable processing stage, which may be particularly detrimental in the highly changeable socio-emotional environment.

Keywords: autism, cognitive flexibility, emotion, facial expression, fMRI, WCST, set-shifting, faces, inferior parietal sulcus.

Introduction

Patients with Autism Spectrum Disorder (ASD) display difficulties in changing strategy and adapting their perspective during daily activities, especially during social interactions. ASD is characterized by two main diagnostic criteria: persistent deficits in social communication and restricted, and repeated patterns of behavior, interests and activities (RRB). Although ASD diagnosis requires this dyad of symptoms to co-occur, research in the field is dissociated into two main domains (socio-emotional and cognitive), while their interactive effects remain largely unexplored. Research in ASD would benefit moving beyond the dual process approach towards more realistic models emphasizing their interactions (Ochsner & Phelps, 2007); here we investigate the interplay between emotion and cognition in ASD with an emotional Wisconsin Card Sorting Test (WCST; Henaff, Bayle, Krolak-Salmon, & Fonlupt, 2010) and functional Magnetic Resonance Imaging (fMRI).

Although the processes underlying RRB are not well understood, a potential explanation is cognitive inflexibility, e.g., a reduced ability to switch between mental processes in order to generate appropriate behavioral responses. Cognitive (in)flexibility is a component of executive functioning, that has been a particularly active topic of investigation in ASD (Elisabeth L. Hill, 2004; Ozonoff, Pennington, & Rogers, 1991; Rumsey, 1985; Russell, Jarrold, & Hood, 1999). Individuals with ASD generally experience difficulties in cognitive flexibility (Ozonoff & Jensen, 1999). Yet, laboratory studies of cognitive flexibility in ASD have provided conflicting results at odds with day-to-day behavior (Geurts, Corbett, & Solomon, 2009; Lopez, Lincoln, Ozonoff, & Lai, 2005; Van Eylen et al., 2011). Inconsistencies have repeatedly been described using a range of cognitive flexibility tasks with studies reporting either deficient (Lopez et al.,

2005; Pellicano, Maybery, Durkin, & Maley, 2006) or intact performance (E. L. Hill & Bird, 2006; Minshew, Goldstein, Muenz, & Payton, 1992) in ASD.

Cognitive flexibility requires monitoring the environment to realize that an ongoing rule is no longer valid, inhibiting previous responses, finding and shifting toward a new rule, and finally maintaining the new ongoing rule. The Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948) is the most widely used test to assess cognitive flexibility as it provides reliable behavioral indices of these successive processing steps. Briefly, participants have to find the correct sorting criterion that changes at random, by a trial-and-error approach with the help of feedback. Succeeding at the WCST rests on abilities in multiple cognitive domains: learning, memory, perception, attention and executive control. Different subcomponents of the WCST involve, in healthy participants, a distributed neural network including bilateral prefrontal cortex (PFC), both dorsolateral (dlPFC) and ventrolateral (vlPFC), posterior superior frontal sulcus (SFS), inferior parietal sulci (IPS), anterior cingulate cortex (ACC), temporo-parietal association cortex, and primary and secondary visual cortices as well as a range of subcortical structures such as basal ganglia, and cerebellum (e.g., Buchsbaum, Greer, Chang, & Berman, 2005 for review; Konishi et al., 1999; Monchi, Petrides, Petre, Worsley, & Dagher, 2001).

The behavioral performance of individuals with ASD on the WCST has generally been reported as impaired, with more perseverative errors and fewer categories completed than matched controls (CTRL) (Ozonoff & Jensen, 1999; Tsuchiya, Oki, Yahara, & Fujieda, 2005; Yasuda et al., 2014), although some studies report intact performance on some parameters (Kaland, Smith, & Mortensen, 2008; Liss et al., 2001; Minshew et al., 1992). These discrepancies have been attributed to participants characteristics and/or task explicitness (Van Eylen et al., 2011).

A recent meta-analysis including thirty-one WCST studies in children or adult participants with ASD confirmed poorer performance for four measures: number of categories completed, perseveration, failure-to-maintain-set and non-perseverative errors (Landry & Al-Taie, 2016).

115 The neural substrates of cognitive flexibility in ASD have rarely been studied (Schmitz et al.,
116 2006; Shafritz, Dichter, Baranek, & Belger, 2008; Yeung, Han, Sze, & Chan, 2016), and yielded
117 contradictory findings. Schmitz and collaborators (2006) reported increased activity in bilateral
118 IPS in participants with ASD when comparing switch to repeat trials, while Shafritz and
119 collaborators (2008) reported a larger activity for controls than participants with ASD in the
120 IPS, among other regions, for both target-maintain and target-shift trials.

121 Marked abnormalities in affective behaviors constitute a prominent feature of ASD, including
122 limited sharing of affect and difficulties in the perception and recognition of emotional
123 expressions (Hobson, 1991). Accordingly, brain functions involved in the processing of social
124 information have been found altered in ASD (Guillon et al., 2014; Kaiser & Pelphrey, 2012;
125 Nomi & Uddin, 2015; Sperdin & Schaer, 2016). Accurate processing of socio-emotional
126 stimuli, which are complex, multisensory and rapidly changing, requires fast tracking of salient
127 features and rapid adaption to subtle changes. They typically challenge the impaired skills of
128 individuals with ASD and questions remain as to whether socio-emotional impairments in ASD
129 are specific to emotional information processing or if they are rooted in a more general cognitive
130 dysfunction. Nevertheless, few studies have addressed the interactive effects of cognitive and
131 socio-emotional deficits in ASD (e.g., Dichter & Belger, 2007; Dichter, Felder, & Bodfish,
132 2009; DiCriscio et al., 2016; Gaigg, 2012; Shafritz, Bregman, Ikuta, & Szeszko, 2015). While
133 in typical individuals, attentional blink is partly overcome when the target stimuli are
134 emotionally charged this emotional modulation is reduced in ASD (e.g., Corden, Chilvers, &
135 Skuse, 2008; Gaigg & Bowler, 2009). In fMRI, social stimuli, but not non-social stimulation,
136 were shown to induce a decrease of activity in a network (including bilateral IPS, dlPFC, ACC
137 and right insula) mediating inhibition interference from irrelevant visual information in ASD
138 (Dichter & Belger, 2007). According to these findings, the influence of emotional processing
139 on cognitive functions could be reduced in ASD.

The aim of the current study was to explore the interplay between socio-emotional information processing and cognitive flexibility in autism. To this aim we used a computerized version of a modified WCST: the emotional WCST (Henaff et al., 2010), which is a highly sensitive indicator of mental flexibility and set maintenance applied to socio-emotional information. Although our work was mainly exploratory, under the hypothesis of a reduced influence of emotional processing on cognitive functions in ASD, at the behavioral level, we expected an interaction between sorting criteria and group on some measures of cognitive flexibility. In the fMRI analysis, we analyzed brain activity involved in different task-shifting steps as a function of sorting criteria; we expected an interaction between group, sorting criteria and task-shifting step.

Methods

Participants

Twelve participants with a diagnosis of Autism Spectrum Disorders partook in the experiment (1 female; mean age $\pm$ standard deviation (std) = 29.25 years $\pm$ 7.21; mean Intellectual Quotient=117.42 $\pm$ 22.59; ADOS score=10.08 $\pm$ (std)4.25; see supplementary material). Adults with ASD were matched with eleven healthy participants (1 female, 29.36 years $\pm$ 7.15), with no history of neurological and/or psychiatric disorders. All participants had normal or corrected-to-normal vision. The study was approved by the local ethics committee. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Stimuli

Face stimuli were chosen from the NimStim Face Stimulus Set (Tottenham et al., 2009; <http://www.macbrain.org/resources.htm>). Stimuli were surrounded by a colored frame (4 colors) and represented faces of four different individuals (2 males), displaying four different emotions (anger, happiness, fear, disgust). Stimuli were chosen to allow an easy identification

of emotions and identities. Basic emotions were presented to ensure that known emotion recognition difficulties in ASD would not influence the findings (de Vries & Geurts, 2012).

Experimental design and procedure

Participants, lying in a supine position in the scanner, viewed the stimuli, rear-projected on a screen at the back of the scanner, through a mirror attached to the antenna. A modified version of the emotional WCST was presented to participants using the Presentation Software.

Figure 1: Experimental design. A. Trial overview. A trial was designed as follows: the five cards were presented until participants responded; after their response, the chosen card was surrounded with a grey frame for 1000ms. Feedback was then provided: a green or red square was presented for 1000ms for correct or incorrect responses, respectively. Note that participants were trained on the correspondence of the feedback prior to the experiment. B. Sequence overview.

Participants were presented with 5 cards (Figure 1A): 1 central card and 4 surrounding cards. They were asked to match the central card with one of the four surrounding cards according to one of three criteria: frame color, facial identity or expression. The experiment lasted 20.8min;

participants performed as many trials as possible during the allocated time. Before the start of the experiment, participants were informed of the three sorting rules, and that they will change at random; they also knew that the first sorting rule was a frame color matching. The rule subsequently changed randomly, without warning, after 3-to-8 correct trials. At each trial (Figure 1), the current sorting criterion was only met by one card.

fMRI acquisition

Magnetic resonance data were acquired on a 1.5T Siemens Magnetom (Siemens AG, Erlangen, Germany) scanner at the CERMEP (Imagerie du Vivant, Bron, F-69677, France) imaging facilities. Structural image acquisition consisted in a 3D anatomical T1-weighted sequence (TR=1970ms; TE=3.9ms; inversion time=1100ms; FOV=256mm; matrix size: 256^2 voxel size: 1mm^3). Functional images were collected using a T2*-weighted gradient-echo planar imaging sequence (TR=2.5s; TE=50ms; flip angle=90°; FOV=220mm; Matrix=64x64; in-plane resolution=3.4x3.4mm²). The acquisition volume consisted of 29 interleaved axial slices with a 4mm slice thickness (no interslice gap); 500 volumes were acquired per participant.

Data analysis

Behavioural data: WCST scores

Classical indexes (e.g., perseverative errors, maintenance trials etc.) scored in a WCST were measured as percentage relative to the total number of trials (Jarvinen-Pasley & Heaton, 2007; see supplementary material). In addition, we propose a new score for evaluating the WCST, termed the “bias error”. The ‘bias error’ is the percentage of rule changes that required more than two trials (including the first negative feedback) to correctly identify the next rule. Indeed, while two incorrect responses following a rule change may be expected by chance, more than two errors may reflect a bias toward more automatic and comfortable responses.

Therefore, the bias error may reflect the willingness to avoid the realization of a specific criteria.

A mixed ANOVA with group as a between-subject factor and sorting criteria as within-subject factor was used to analyze bias error.

fMRI data: Image preprocessing and analysis

Image preprocessing and analysis were performed with SPM12b (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, <http://www.fil.ion.ucl.ac.uk/spm>), following classical guidelines (see supplementary material).

Functional data of the experimental block were analyzed in a two-level random-effects design.

At the first level, onsets were defined as the presentation of the feedback (Henaff et al., 2010).

To better understand brain activity related to several aspects of task-shifting and their interaction with sorting criteria, six types of feedback events were modelled (Figure 1B).

Change events, i.e., negative feedbacks indicating a need to change rule, were modelled according to the preceding rule (the rule that was correct in the previous trial): change-color,

change-identity, and change-emotion. They reflect the processes involved in error monitoring, and the need to shift to the new rule and inhibit the preceding rule. Switch events, i.e., the first

positive feedback following a change of rule, were modelled according to the current ongoing rule: switch-color, switch-identity, and switch-emotion. Switch events informed participants

that they have found the correct rule, and have to start maintaining the new rule. Maintenance events, which reflects processes involved in maintaining task-sets, regroup all other positive

feedbacks; they were also modelled according to the ongoing rule (maintenance-color, maintenance-identity, and maintenance-emotion). All other feedback events (e.g., failures)

were modelled in a ninth regressor of no interest. Therefore, the design matrix included 10 regressors (3 event types x 3 sorting criteria, plus one regressor of no interest), which contained

finite impulse responses representing the onset of feedback events convolved with a canonical hemodynamic response function. The design matrix also included realignment parameters as nuisance covariates to account for residual motion artefacts. Betas estimates were calculated for each of the 10 regressors. These betas images were then used to create three contrast images per sorting criteria in order to identify regions involved in different task-shifting steps per sorting criteria: 1) change vs. maintenance events; 2) change vs. switch events; 3) switch vs. maintenance events.

These contrast images were taken into a three-way mixed ANOVA (group x task-shifting step x sorting criteria), performed with GLMFlex (Version June 1st, 2014; http://mrtools.mgh.harvard.edu/index.php/GLM_Flex_Fast2;). Results are reported at an FWE-corrected cluster (FWE_c) threshold with a cluster-defining threshold of $p < 0.001$.

Results

Behavioural data: WCST scores

The percentage of rule changes occurring during the course of the experiment is indicative of overall success rate, with a higher number of changes reflecting a greater amount of category completed and thus overall better performance. Participants with ASD had a significantly smaller percentage of rule changes than control participants ($T(21) = -2.12$; $p = 0.046$). Percentages of PE (Figure 2A), non-perseverative errors and maintenance trials were not modulated by groups and showed no rule-by-group interaction. Other classical WCST scores are presented in supplementary material.

A 2-way mixed ANOVA (group x to-be-found sorting criteria) on “bias error” (Figure 2B) revealed a main effect of sorting criteria ($F(1.58, 33.14) = 8.56$; $p = 0.002$) and a significant interaction between group and sorting criteria ($F(1.58, 33.14) = 4.157$; $p = 0.033$). Student T-tests between groups ran on each sorting criteria revealed that participants with ASD committed

more errors than control participants when they had to find the emotion rule ($p=0.024$), while there was no significant group differences for the color or identity criteria. Notably there was no group difference for the number of maintenance errors during the emotion matching rule.

Figure 2: Behavioral results in the emotional WCST. A. Perseverative errors per sorting criteria. **B.** Bias error per group and sorting criteria. * $p = 0.024$.

fMRI data

At the chosen statistical threshold, there was neither a main effect of group, nor a sorting criteria by group interaction, and no three way interaction (e.g., task-shifting step by sorting criteria by group). As per our interest, below we report the main effects of task-shifting step and the task-shifting step by group interaction (other significant effects are presented in supplementary material).

(1) Main effect of Task-shifting step

A main effect of Task-shifting step was observed (cluster-defining threshold: $F(2,42)=8.18$, $p=0.001$; $FWEc=42$) in nine clusters. Overall task-shifting step modulated a large bilateral network overlapping both ventral and dorsal fronto-parietal networks (FPN), visual cortices and a range of subcortical structures (see Figure 3A; Table 1). More precisely, the first cluster overlapped bilateral insulae, putamen, posterior cingulate gyrus (pCG), bilateral superior and inferior parietal lobule (SPL, IPL), including IPS and extending to the supramarginal and angular gyri, middle frontal gyrus (MFG) of the right hemisphere and left hippocampus. A second cluster overlapped the cerebellum, extending to bilateral inferior occipital gyrus and left fusiform gyrus. Task-shifting step also modulated activity in posterior

and anterior medial superior frontal gyrus (SFG), the calcarine fissure extending to the lingual gyrus of both hemispheres, superior occipital gyrus, bilateral inferior frontal sulci (IFS), and left MFG.

Figure 3: Main effect of task-shifting step. **A.** Cluster-wise thresholded images of the main effect of Task-shifting step. **B.** Greater activity to change than switch (red) and maintenance events (blue); regions more activated to change than both switch and maintenance events are displayed in purple. Post-hocs tests were run only in voxels showing a significant modulation of activity by task-shifting step. **C.** Cluster displaying a greater activity to switch events than change (cyan) and maintenance (yellow) events.

To better interpret main effects of task-shifting step, statistical maps were evaluated for each task-shifting step independently, that is, we look at the modulation of activity in the above-mentioned clusters for the three contrasts of interest (Figure 3B, C): change vs. maintenance events, change vs. switch events, and switch vs. maintenance events.

Change vs. maintenance events

A larger activity to change events was observed in the medial SFG, bilateral anterior insulae, right MFG, bilateral IFS, middle-to-posterior Cingulate Gyrus (pCG), calcarine fissure extending to bilateral lingual gyri and precuneus, and around the IPS, extending to SPL and IPL(Figure 3B; blue).

A larger activity to maintenance than change events was observed in bilateral rolandic operculum, left hippocampus and in the medial anterior SFG.

Change vs. switch events

Change events yielded significantly different activity than switch events in medial SFG, and bilaterally in posterior IFS, anterior insulae, and in the medial occipital cortex overlapping the calcarine fissure and extending to the lingual gyrus and precuneus (Figure 3B; red).

A larger activity to switch than change events (Figure 3C; cyan) was observed in bilateral rolandic operculum, left hippocampus, medial anterior SFG; regions that were also more activated by maintenance than change events. In addition, a larger more activity to switch events was observed in bilateral putamen extending to posterior insulae, and bilateral SPL.

Switch vs. maintenance events

Among the regions showing a modulation of their activity by task-shifting step, none showed a larger activity to maintenance than switch events.

A larger activity to switch than maintenance events (Figure 3C; yellow) was observed in the cerebellum cluster, bilateral parietal cortex including IPS, SPL and IPL, right MFG, bilateral putamen and pCG.

(2) Group by task-shifting step interaction

Activity in the IPL of both hemispheres was further characterized by a group by task-shifting step interaction (cluster-defining threshold: $F(2,42)=8.18$, $p=0.001$; $FWEc = 35$; Figure 4A). In the IPS, there was no group difference for the change vs. maintenance contrast. However, in the ASD group, the IPS was strongly activated by switch events while it was mostly activated by change events in the control group.

Figure 4: Task-shifting step by group interaction. **A.** Cluster-wise thresholded (FWEc) images of the interaction. *Bar plots*: (red/dots: ASD; blue/stars: Control participants) represent the BOLD response in arbitrary unit in the right Inferior Parietal Lobule (IPL), left Inferior Temporal Gyrus (ITG) and right Superior Frontal Sulcus (SFS) for the (1) switch minus maintenance contrast; (2) Change minus maintenance events contrast; (3) change minus switch events contrast. Solid stars and circles represent individual data for CTRLs and ASD participants, respectively. Error bars represent standard error of mean. **B.** Overlap maps illustrate inter-subject variability in the Switch greater than maintenance events for ASD (top row) and CTRL (bottom row) participants. Bar graph represent the T values observed at the voxel of maximum consistency in each subject (i.e., each bar). Note that bilateral IPS and right SFS showed a high consistency of activation in our sample of ASD participants.

In addition, interaction between task-shifting step and group were found in the left inferior temporal gyrus, bilateral posterior superior frontal sulcus (SFS), right inferior frontal gyrus, and right anteriorMFG (Figure 4A; Table 2). In all clusters, this interaction was driven by an atypical response to switch events in the ASD group: switch events yielded larger activity than change and maintenance events, while in the CTRL group a larger activity was observed for change events. In summary, the interaction between group and task-shifting step mainly revealed that CTRL participants tended to process switch events as maintenance events, while ASD participants processed switch events similarly to change events.

Intersubject variability in each cluster is illustrated on Figure 4B using threshold-weighted overlap maps for each task-shifting step collapsed per sorting criteria (Seghier & Price, 2016). Overlap map revealed a consistent activation of bilateral IPS and right SFS for switch events relative to maintenance events in the ASD group; consistency reached a maximum value of 0.62 in the right IPS. All ASD participants, but one, presented a significantly ($p < .001$, uncorrected) larger activation for switch than maintenance events in the IPS, one participant presented a near threshold difference. Therefore, despite relatively small sample sizes, the group by task-shifting step observed in bilateral IPS, in particular, appears to reflect a genuine difference between ASD and control participants.

Discussion

We used an emotional Wisconsin Card Sorting Test (Henaff et al., 2010) in fMRI to explore the interplay between cognitive and emotional dimensions of ASD. Behavioral data highlighted a significant interaction between group and sorting criteria for “bias error”, a measure of the unwillingness to switch towards a specific sorting rule, but no group effect or interaction was observed on parameters measuring pure cognitive flexibility (e.g., perseverative errors). Accordingly, at the fMRI level, we found no group differences in the processing of change events relative to other events, providing further support to studies suggesting that brain

processes underlying cognitive flexibility are not impaired in ASD (e.g., Geurts et al., 2009). However, the processing of switch events yielded a larger activation in bilateral IPS in ASD participants suggesting an atypical processing of the confirming cue.

Behavioral results are only partially consistent with previous studies as we found no group difference for perseverative and non-perseverative errors (Landry & Al-Taie, 2016). This lack of difference could be attributed to task explicitness (Van Eylen et al., 2011): in our study task was relatively explicit as participants were aware of the general principle of the test and of the sorting rules. An interaction between group and sorting criteria was found on the “bias error” which reflects a bias away from the realization of a specific task. Participants with autism had a larger “bias error” than control participants but only when switching to the emotion sorting rule, which was equally maintained by both groups, highlighting no specific difficulties in performing socio-emotional matching. These exploratory findings indicate that inflexible behaviors in ASD are mostly characterized by the avoidance of switching toward processing of emotional information. This is of great importance for understanding the functional role of RRBs, as it suggests that patients with ASD may be displaying routines or repetitive behaviors not because of a ‘true’ lack of cognitive flexibility, but rather to avoid some specific (emotional) situations. This observation, if further confirmed, would suggest to tightly associate socio-emotional and cognitive rehabilitation programs.

At the fMRI level, we found modulations of brain activity by task-shifting step, and sorting criteria as well as an interaction between these two factors. Therefore, these data provide evidence that the processing of social information interact with cognitive task, as previously reported (e.g., Corden et al., 2008; Gaigg & Bowler, 2009). However, and contrarily to behavioral observations there was neither further interaction with group, nor any sorting criteria by group interaction. Despite a small sample size, strong interactions were observed between

task-shifting step and group, highlighting different cognitive strategies. In both groups, change events induced a larger activity than maintenance or switch events in a large bilateral neural network including both the dorsal and ventral FPN (Corbetta & Shulman, 2002), the medial SFG and visual cortices. On the contrary, ASD participants presented a larger activity to switch than maintenance events in bilateral posterior IPS, and right posterior SFS, consistent with Schmitz and collaborators (2006).

Change events are the only negative feedback events as such they act not only as an error feedback, but also as a start-cue indicating the need to find a new rule and start a new task-set. It makes sense to find activity related to processing a negative feedback in both ventral (here, involved in error monitoring) and dorsal (task-set instantiation) FPN (Corbetta & Shulman, 2002; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Dosenbach et al., 2007). Within the dorsal FPN, bilateral IPS and posterior SFS show cue-driven activity when participants prepare to shift their attention to a specific feature, suggesting that dorsal FPN also mediates non-spatial orienting of attention (Egner et al., 2008; Ptak, 2012). Task-set instantiation corresponds to the selection of new behaviorally-relevant information, and may occur through the updating of “priority maps” (Ptak, 2012). Priority maps are a topographically organized representations of the environment and encode feature-based expectancies, which confer a competitive processing advantage for the selection of task-related features (Egner et al., 2008). For control participants, the IPS was only activated in the reception of a negative feedback (e.g., change events), suggesting that change events are the only cues indicative of the need to start a new task-set and update priority maps. When switch events occurs, control participants have performed all tasks needed for the switch, and are set in a stable processing stage. However, IPS was consistently activated (across subjects) by switch events suggesting that they also act as start-cue in our sample of participants with ASD. Therefore, priority maps may be stabilized only after participants received a confirmatory positive feedback. A larger IPS and SFS

activation in people with ASD to switch events could reflect the need to adapt cognitive strategies until certainty regarding the task to-be-performed is achieved. Accordingly, it was shown that while control participants flexibly modulate cortical activity according to level of certainty, autistic participants cannot do so (Thillay et al., 2016). This observation suggests that people with ASD stabilized their priority maps only when reaching a high level of certainty. We did not find any interaction between group, sorting criteria and cognitive flexibility at the cerebral level. Note that the observed behavioral effects could not be tested as bias error corresponds to an insufficient number of trials for an fMRI analysis. Nonetheless, fMRI and behavioral data are consistent in that they show 1) no real deficit in cognitive flexibility *per se*, and 2) no interaction on traditional measures of cognitive flexibility and socio-emotional processing. fMRI data highlighted that a higher level of certainty was needed before switch-related brain activity decrease in ASD, while behavioral findings suggest that this high need for certainty might yield different behavioral outcomes depending on the task to-be-performed. Priority maps incorporate prior knowledge, acquired through experience, regarding the information relevant to the task to-be-performed (Fair et al., 2007; Zelinsky & Bisley, 2015). We hypothesize that the observed behavioral outcomes of the need for certainty is linked to prior knowledge of the task to-be-performed. For control participants, the existence of prior knowledge for the realization of the sorting tasks facilitates the selection of relevant information leading to smaller bias errors. A larger bias error in the emotion sorting task for the ASD group is expected to reflect the weakness of prior knowledge or of top-down influence for the realization of that particular task (Gomot & Wicker, 2012; Pellicano & Burr, 2012; Pellicano, Jeffery, Burr, & Rhodes, 2007). Moreover, this allows refining these theories by showing that these difficulties are particularly evident for socio-emotional information. The need for a high-level of certainty before setting in a stable task-set, combined with the weakness of prior knowledge in socio-emotional tasks may produce a greater avoidance of socio-emotional rules

leading to a larger bias error in the social sorting tasks. It remains to be determined whether the prior knowledge-related difficulties drives the need for certainty or whether the high need for certainty, which is rarely matched in socio-emotional contexts, prevents the generation of priors.

Conclusions

Using an emotional WCST with fMRI we showed that participants with ASD present a bias toward avoiding socio-emotional sorting tasks, and present an increased activity in IPS for switch events that may reflect a continuous updating of priority maps until a high level of certainty is reached. This need for certainty would be more detrimental for the realization of cognitive tasks, which rely on emotion-related prior knowledge.

An unusual processing of confirmatory events combined with atypical prior knowledge of socio-emotional information would thus constitute a hallmark of brain functioning in ASD. These findings provide new insights for the understanding of ASD and suggest that *these brain dysfunctions* tightly interact and should be considered conjointly in future research aiming at better understanding the interplay between the two clinical dimensions characteristic of ASD and their underlying mechanisms.

List of abbreviations

AC/PC : anterior/posterior Commissure ; ACC: Anterior Cingulate Cortex; ADOS-G: Autism Diagnostic Observation Schedule-Generic; AQ: Autism Spectrum Quotient; ASD: Autism Spectrum Disorders; BOLD: Blood Oxygen Level Dependent; CTRL: Control; dlPFC: dorsolateral PFC; FEF: Frontal Eye Field; FPN: Fronto-parietal Network; IFG/S: Inferior Frontal Gyrus/sulcus; IPS: intraparietal sulcus; IQ: Intellectual Quotient; LOC: Lateral Occipital Complex; MFG: Middle Frontal Gyrus; MNI: Montreal Neurological Institute; pCG: posterior cingulate cortex; PE : perseverative errors ; PFC: Prefrontal cortex; RH: Right Hemisphere; RRB: restricted, and repeated patterns of behavior; SFS/G: Superior Frontal

Sulcus/Gyrus; vlPFC: ventrolateral PFC; WAIS: Wechsler Adult Intelligence Scale; WCST: Wisconsin Card Sorting Test;

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the University Hospital of Tours; all participants provided written informed consent. Adults with autism included in the study were all legally adults, had no legal guardianship; they were thus allowed to approve research and/or medical programs that concern them.

Consent for publication

Stimuli displayed in Figure 1 were extracted from the NimStim database (<http://www.macbrain.org/resources.htm>) and correspond to models that provided consent for publications of their data.

Conflict of Interest

The authors declare no biomedical financial interests or potential conflicts of interest.

Authors' contributions

The study presented here results from teamwork. Study conception - MG. Study design: MG, PF. Data acquisition: ML, HC, FBB, PF, MG. Data analyses: ML, HC, FA, PF. Statistical analyses: ML, HC, FA, MG. Data interpretation: ML, FBB, MG. Draft the manuscript: ML, MG. Clinical evaluation of the patients: MG, FBB.

All authors provided approval for publication of the content.

478 **References**

- 479 Buchsbaum, B. R., Greer, S., Chang, W. L., & Berman, K. F. (2005). Meta-analysis of
480 neuroimaging studies of the Wisconsin card-sorting task and component processes. *Hum Brain*
481 *Mapp*, 25(1), 35-45.
- 482 Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention
483 in the brain. *Nat Rev Neurosci*, 3(3), 201-215.
- 484 Corden, B., Chilvers, R., & Skuse, D. (2008). Emotional modulation of perception in Asperger's
485 syndrome. *J Autism Dev Disord*, 38(6), 1072-1080.
- 486 de Vries, M., & Geurts, H. M. (2012). Cognitive flexibility in ASD; task switching with
487 emotional faces. *J Autism Dev Disord*, 42(12), 2558-2568.
- 488 Dichter, G. S., & Belger, A. (2007). Social stimuli interfere with cognitive control in autism.
489 *Neuroimage*, 35(3), 1219-1230.
- 490 Dichter, G. S., Felder, J. N., & Bodfish, J. W. (2009). Autism is characterized by dorsal anterior
491 cingulate hyperactivation during social target detection. *Soc Cogn Affect Neurosci*, 4(3), 215-
492 226.
- 493 DiCriscio, A. S., Miller, S. J., Hanna, E. K., Kovac, M., Turner-Brown, L., Sasson, N. J., et al.
494 (2016). Brief Report: Cognitive Control of Social and Nonsocial Visual Attention in Autism.
495 *Journal of autism and developmental disorders*, 46(8), 2797-2805.
- 496 Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-
497 networks architecture of top-down control. *Trends Cogn Sci*, 12(3), 99-105.
- 498 Dosenbach, N. U., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A.,
499 et al. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proc Natl*
500 *Acad Sci U S A*, 104(26), 11073-11078.
- 501 Egner, T., Monti, J. M., Tritschuh, E. H., Wieneke, C. A., Hirsch, J., & Mesulam, M. M. (2008).
502 Neural integration of top-down spatial and feature-based information in visual search. *J*
503 *Neurosci*, 28(24), 6141-6151.
- 504 Fair, D. A., Dosenbach, N. U., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., et
505 al. (2007). Development of distinct control networks through segregation and integration. *Proc*
506 *Natl Acad Sci U S A*, 104(33), 13507-13512.
- 507 Gaigg, S. B. (2012). The Interplay between Emotion and Cognition in Autism Spectrum
508 Disorder: Implications for Developmental Theory. *Front Integr Neurosci*, 6, 113.
- 509 Gaigg, S. B., & Bowler, D. M. (2009). Brief report: Attenuated emotional suppression of the
510 attentional blink in Autism Spectrum Disorder: another non-social abnormality? *J Autism Dev*
511 *Disord*, 39(8), 1211-1217.
- 512 Geurts, H. M., Corbett, B., & Solomon, M. (2009). The paradox of cognitive flexibility in
513 autism. *Trends Cogn Sci*, 13(2), 74-82.
- 514 Gomot, M., & Wicker, B. (2012). A challenging, unpredictable world for people with autism
515 spectrum disorder. *Int J Psychophysiol*, 83(2), 240-247.
- 516 Grant, D. A., & Berg, E. A. (1948). A behavioral analysis of degree of reinforcement and ease
517 of shifting to new responses in a Weigl-type card-sorting problem. *J Exp Psychol*, 38(4), 404-
518 411.
- 519 Guillon, Q., Hadjikhani, N., Baduel, S., Kruck, J., Arnaud, M., & Roge, B. (2014). Both dog
520 and human faces are explored abnormally by young children with autism spectrum disorders.
521 *Neuroreport*, 25(15), 1237-1241.
- 522 Henaff, M. A., Bayle, D., Krolak-Salmon, P., & Fonlupt, P. (2010). Cortical dynamics of a self
523 driven choice: a MEG study during a card sorting task. *Clin Neurophysiol*, 121(4), 508-515.
- 524 Hill, E. L. (2004). Executive dysfunction in autism☆. *Trends in Cognitive Sciences*, 8(1), 26-
525 32.

Hill, E. L., & Bird, C. M. (2006). Executive processes in Asperger syndrome: patterns of performance in a multiple case series. *Neuropsychologia*, 44(14), 2822-2835.
 Hobson, R. P. (1991). What is autism? *Psychiatr Clin North Am*, 14(1), 1-17.
 Jarvinen-Pasley, A., & Heaton, P. (2007). Evidence for reduced domain-specificity in auditory processing in autism. *Dev Sci*, 10(6), 786-793.
 Kaiser, M. D., & Pelphrey, K. A. (2012). Disrupted action perception in autism: behavioral evidence, neuroendophenotypes, and diagnostic utility. *Dev Cogn Neurosci*, 2(1), 25-35.
 Kaland, N., Smith, L., & Mortensen, E. L. (2008). Brief report: cognitive flexibility and focused attention in children and adolescents with Asperger syndrome or high-functioning autism as measured on the computerized version of the Wisconsin Card Sorting Test. *J Autism Dev Disord*, 38(6), 1161-1165.
 Konishi, S., Kawazu, M., Uchida, I., Kikyo, H., Asakura, I., & Miyashita, Y. (1999). Contribution of working memory to transient activation in human inferior prefrontal cortex during performance of the Wisconsin Card Sorting Test. *Cerebral Cortex*, 9(7), 745-753.
 Landry, O., & Al-Taie, S. (2016). A Meta-analysis of the Wisconsin Card Sort Task in Autism. *J Autism Dev Disord*, 46(4), 1220-1235.
 Liss, M., Fein, D., Allen, D., Dunn, M., Feinstein, C., Morris, R., et al. (2001). Executive functioning in high-functioning children with autism. *J Child Psychol Psychiatry*, 42(2), 261-270.
 Lopez, B. R., Lincoln, A. J., Ozonoff, S., & Lai, Z. (2005). Examining the relationship between executive functions and restricted, repetitive symptoms of Autistic Disorder. *J Autism Dev Disord*, 35(4), 445-460.
 Minshew, N. J., Goldstein, G., Muenz, L. R., & Payton, J. B. (1992). Neuropsychological functioning in nonmentally retarded autistic individuals. *J Clin Exp Neuropsychol*, 14(5), 749-761.
 Monchi, O., Petrides, M., Petre, V., Worsley, K., & Dagher, A. (2001). Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *Journal of Neuroscience*, 21(19), 7733-7741.
 Nomi, J. S., & Uddin, L. Q. (2015). Face processing in autism spectrum disorders: From brain regions to brain networks. *Neuropsychologia*, 71, 201-216.
 Ochsner, K. N., & Phelps, E. (2007). Emerging perspectives on emotion-cognition interactions. *Trends Cogn Sci*, 11(8), 317-318.
 Ozonoff, S., & Jensen, J. (1999). Brief report: specific executive function profiles in three neurodevelopmental disorders. *J Autism Dev Disord*, 29(2), 171-177.
 Ozonoff, S., Pennington, B. F., & Rogers, S. J. (1991). Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. *J Child Psychol Psychiatry*, 32(7), 1081-1105.
 Pellicano, E., & Burr, D. (2012). When the world becomes 'too real': a Bayesian explanation of autistic perception. *Trends Cogn Sci*, 16(10), 504-510.
 Pellicano, E., Jeffery, L., Burr, D., & Rhodes, G. (2007). Abnormal adaptive face-coding mechanisms in children with autism spectrum disorder. *Curr Biol*, 17(17), 1508-1512.
 Pellicano, E., Maybery, M., Durkin, K., & Maley, A. (2006). Multiple cognitive capabilities/deficits in children with an autism spectrum disorder: "weak" central coherence and its relationship to theory of mind and executive control. *Dev Psychopathol*, 18(1), 77-98.
 Ptak, R. (2012). The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. *Neuroscientist*, 18(5), 502-515.
 Rumsey, J. M. (1985). Conceptual problem-solving in highly verbal, nonretarded autistic men. *J Autism Dev Disord*, 15(1), 23-36.

Russell, J., Jarrold, C., & Hood, B. (1999). Two intact executive capacities in children with autism: implications for the core executive dysfunctions in the disorder. *J Autism Dev Disord*, 29(2), 103-112.

Schmitz, N., Rubia, K., Daly, E., Smith, A., Williams, S., & Murphy, D. G. (2006). Neural correlates of executive function in autistic spectrum disorders. *Biol Psychiatry*, 59(1), 7-16.

Seghier, M. L., & Price, C. J. (2016). Visualising inter-subject variability in fMRI using threshold-weighted overlap maps. *Sci Rep*, 6, 20170.

Shafritz, K. M., Bregman, J. D., Ikuta, T., & Szeszko, P. R. (2015). Neural systems mediating decision-making and response inhibition for social and nonsocial stimuli in autism. *Prog Neuropsychopharmacol Biol Psychiatry*, 60, 112-120.

Shafritz, K. M., Dichter, G. S., Baranek, G. T., & Belger, A. (2008). The neural circuitry mediating shifts in behavioral response and cognitive set in autism. *Biol Psychiatry*, 63(10), 974-980.

Sperdin, H. F., & Schaer, M. (2016). Aberrant Development of Speech Processing in Young Children with Autism: New Insights from Neuroimaging Biomarkers. *Front Neurosci*, 10, 393.

Thillay, A., Lemaire, M., Roux, S., Houy-Durand, E., Barthelemy, C., Knight, R. T., et al. (2016). Atypical Brain Mechanisms of Prediction According to Uncertainty in Autism. *Front Neurosci*, 10, 317.

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., et al. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res*, 168(3), 242-249.

Tsuchiya, E., Oki, J., Yahara, N., & Fujieda, K. (2005). Computerized version of the Wisconsin card sorting test in children with high-functioning autistic disorder or attention-deficit/hyperactivity disorder. *Brain Dev*, 27(3), 233-236.

Van Eylen, L., Boets, B., Steyaert, J., Evers, K., Wagemans, J., & Noens, I. (2011). Cognitive flexibility in autism spectrum disorder: Explaining the inconsistencies? *Research in Autism Spectrum Disorders*, 5(4), 1390-1401.

Yasuda, Y., Hashimoto, R., Ohi, K., Yamamori, H., Fujimoto, M., Umeda-Yano, S., et al. (2014). Cognitive inflexibility in Japanese adolescents and adults with autism spectrum disorders. *World J Psychiatry*, 4(2), 42-48.

Yeung, M. K., Han, Y. M., Sze, S. L., & Chan, A. S. (2016). Abnormal frontal theta oscillations underlie the cognitive flexibility deficits in children with high-functioning autism spectrum disorders. *Neuropsychology*, 30(3), 281-295.

Zelinsky, G. J., & Bisley, J. W. (2015). The what, where, and why of priority maps and their interactions with visual working memory. *Ann N Y Acad Sci*, 1339, 154-164.

Figure legends

Figure 1: Experimental design. A. Trial overview. A trial was designed as follows: the five cards were presented until participants responded; after their response, the chosen card was surrounded with a grey frame for 1000ms. Feedback was then provided: a green or red square was presented for 1000ms for correct or incorrect responses, respectively. Note that participants were trained on the correspondence of the feedback prior to the experiment. B. Sequence overview.

Figure 2: Behavioral results in the emotional WCST. A. Perseverative errors per sorting criteria. B. Bias error per group and sorting criteria. * $p = 0.024$.

Figure 3: Main effect of task-shifting step. A. Cluster-wise thresholded images of the main effect of Task-shifting step. B. Greater activity to change than switch (red) and maintenance events (blue); regions more activated to change than both switch and maintenance events are displayed in purple. Post-hocs tests were run only in voxels showing a significant modulation of activity by task-shifting step. C. Cluster displaying a greater activity to switch events than change (cyan) and maintenance (yellow) events.

Figure 4: Task-shifting step by group interaction. A. Cluster-wise thresholded (FWE_c) images of the interaction. *Bar plots*: (red/dots: ASD; blue/stars: Control participants) represent the BOLD response in arbitrary unit in the right Inferior Parietal Lobule (IPL), left Inferior Temporal Gyrus (ITG) and right Superior Frontal Sulcus (SFS) for the (1) switch minus maintenance contrast; (2) Change minus maintenance events contrast; (3) change minus switch events contrast. Solid stars and circles represent individual data for CTRLs and ASD participants, respectively. Error bars represent standard error of mean. B. Overlap maps illustrate inter-subject variability in the Switch greater than maintenance events for ASD (top row) and CTRL (bottom row) participants. Bar graph represent the T values observed at the

635 voxel of maximum consistency in each subject (i.e., each bar). Note that bilateral IPS and right
636 SFS showed a high consistency of activation in our sample of ASD participants.

637

638

Table 1: Main effects of task-shifting step. For the large cluster only one peak per brain regions is reported. SFG: superior frontal gyrus; SMA: supplementary motor area; Orientation: R: right hemisphere; L: left hemisphere; M: medial; P: posterior; A: anterior. F-values greater than 18.89 corresponds to a FWE-corrected voxel threshold.

Region	Orientation	Cluster size	F	Z	x	y	z
Insula	R	3972	84.05	7.84	33	20	6
	L	3972	52.25	6.84	-31	21	0
Inferior parietal sulcus	R	3972	17.88	4.57	-30	-55	46
	L	3972	8.91	3.24	45	-46	42
Superior Parietal Lobule	R	3972	43.56	6.45	-21	-46	74
	L	3972	27.99	5.50	30	-70	54
Rolandic operculum	R	3972	27.34	5.45	48	2	6
	L	3972	26.48	5.39	-45	2	10
Superior Frontal Gyrus	R	3972	24.62	5.23	30	62	2
Middle Frontal Gyrus	R	3972	39.67	6.25	51	44	2
	L	42	14.32	4.13	-33	50	18
Precuneus	R	3972	19.37	4.74	7	-52	72
	L	3972	16.66	4.43	-3	-46	74
SMA	R	3972	12.27	3.83	3	-10	66
Putamen	L	3972	26.28	5.37	-27	2	2

	R	3972	35	5.98	27	2	6
Pallidum	R	3972	41.84	6.36	27	-10	2
Hippocampus	L	3972	20.01	4.80	-25	-5	-20
Posterior Cingulate Cortex	R	3972	17.87	4.57	6	-52	34
	L	3972	11.14	3.65	-9	-10	42
Cerebellum – Crus VI	R	489	26.17	5.36	24	-82	-18
Cerebellum – Crus IV/V	R	489	20.78	4.88	9	-49	-18
Cerebellum – Vermis VI	M	489	36.53	6.07	0	-76	-18
Inferior Occipital Gyrus	L	489	23.07	5.1	-39	-82	-12
	R	489	19.5	4.75	51	-70	-14
Fusiform Gyrus	L	489	22.13	5.01	-21	-82	-18
	P	416	34.89	5.97	9	23	42
Superior frontal gyrus – Medial part	A	216	24.21	5.2	-6	65	18
	R	550	25.30	5.29	15	-49	2
Lingual Gyrus	L	550	15.37	4.27	-18	-55	-2
	R	550	16.79	4.45	18	-64	10
Calcarine	L	550	10.95	3.62	-18	-61	10
Inferior Frontal Gyrus	R	72	15.94	4.34	46	18	28
Ext. to precentral gyrus	L	118	13.98	4.09	-45	17	30
Superior Occipital Gyrus	L	46	21.99	5	-15	-100	18

643

644

645

Table 2: Group by task-shifting step interaction. Orientation: R: right hemisphere; L: left hemisphere; M: medial; P: posterior; A: anterior. F-values greater than 18.89 corresponds to a FWE-corrected voxel threshold.

Region	Orientation	Cluster size	T	Z	x	y	z
Inferior Parietal Sulcus	R	279	19.02	4.7	27	-67	50
	L	255	13.32	3.99	-24	-59	48
Superior Frontal sulcus	R	58	10.93	3.61	21	-4	58
	L	35	15.09	4.23	-21	11	66
Inferior Temporal Gyrus	L	58	21.8	4.98	-45	-49	-10
Middle Frontal sulcus	A, M	82	16.37	4.4	18	50	6
Inferior Frontal Gyrus	R	67	10.06	3.46	45	27	16

651
652

653