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

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Running title: Emotion and Cognitive flexibility in ASD

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39

40 **Lay Summary**

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

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46

47 **Abstract (200 words)**

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

64

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

67 **Introduction**

68

69 Patients with Autism Spectrum Disorder (ASD) display difficulties in changing strategy and
70 adapting their perspective during daily activities, especially during social interactions. ASD is
71 characterized by two main diagnostic criteria: persistent deficits in social communication and
72 restricted, and repeated patterns of behavior, interests and activities (RRB). Although ASD
73 diagnosis requires this dyad of symptoms to co-occur, research in the field is traditionally
74 dissociated into two main domains (socio-emotional and cognitive), while their interactive
75 effects, e.g. the cognitive control of social information, remain largely unexplored. This
76 schematic partition is possibly due to the prevalent view of the brain as organized into either
77 affective or cognitive components (see the meta-analysis of social and non-social processes in
78 ASD by Di Martino et al., 2009). However, based on the proposition that the neural basis of
79 emotion and cognition should be viewed as strongly non-modular (Pessoa, 2008), research in
80 ASD would benefit moving beyond the dual process approach towards more realistic models
81 emphasizing their interactions (Dichter, Felder, & Bodfish, 2009; Ochsner & Phelps, 2007).
82 Cognitive control refers to the ability to maintain a task, suppress inappropriate behavior and
83 flexibly adjust behavior according to changing environmental demands (Geurts, Corbett, &
84 Solomon, 2009). Here we investigate the interplay between emotion and cognition, by
85 studying the cognitive control of social and non-social information in ASD with an fMRI
86 (functional Magnetic Resonance Imaging) version of the emotional Wisconsin Card Sorting
87 Test (WCST; Henaff, Bayle, Krolak-Salmon, & Fonlupt, 2010).

88

89 Although the processes underlying RRB are not well understood, a potential explanation is
90 cognitive inflexibility, e.g., a reduced ability to switch between mental processes in order to
91 generate appropriate behavioral responses. Cognitive (in)flexibility is a component of

92 executive functioning, that has been a particularly active topic of investigation in ASD
93 (Elisabeth L. Hill, 2004; Ozonoff, Pennington, & Rogers, 1991; Rumsey, 1985; Russell,
94 Jarrold, & Hood, 1999) . Individuals with ASD generally experience difficulties in cognitive
95 flexibility (Ozonoff & Jensen, 1999). Yet, laboratory studies of cognitive flexibility in ASD
96 have provided conflicting results at odds with day-to-day behavior (Geurts et al., 2009;
97 Lopez, Lincoln, Ozonoff, & Lai, 2005; Van Eylen et al., 2011). Inconsistencies have
98 repeatedly been described using a range of cognitive flexibility tasks with studies reporting
99 either deficient (Lopez et al., 2005; Pellicano, Maybery, Durkin, & Maley, 2006) or intact
100 performance (E. L. Hill & Bird, 2006; Minshew, Goldstein, Muenz, & Payton, 1992) in ASD.
101 Cognitive flexibility refers to the ability to switch between different task demands, and
102 requires monitoring the environment to realize that an ongoing rule is no longer valid,
103 inhibiting previous responses, finding and shifting toward a new rule, and finally maintaining
104 the new ongoing rule. The Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948) is a
105 neuropsychological task-shifting test used test to assess cognitive flexibility; it provides
106 reliable behavioral indices of these successive processing steps. This task involves the
107 implementation of cognitive flexibility to unexpected changes, which typically challenges
108 ASD and causes significant daily difficulties (de Vries & Geurts, 2012; Yerys et al., 2009).
109 The WCST is the neuropsychological test of flexibility which presents the highest
110 discriminative power between controls and ASD (Geurts et al., 2009), although modified
111 version of the WCST making the change more explicit suppresses group differences (Van
112 Eylen et al., 2011). Briefly, participants have to switch attention between relevant dimensions
113 of a picture, by finding the correct sorting criterion that changes at random, by a trial-and-
114 error approach with the help of feedback. Succeeding at the WCST rests on abilities in
115 multiple cognitive domains: learning, memory, perception, attention and executive control.
116 Different subcomponents of the WCST involve, in healthy participants, a distributed neural

117 network including bilateral prefrontal cortex (PFC), both dorsolateral (dlPFC) and
118 ventrolateral (vlPFC), posterior superior frontal sulcus (SFS), inferior parietal sulci (IPS),
119 anterior cingulate cortex (ACC), temporo-parietal association cortex, and primary and
120 secondary visual cortices as well as a range of subcortical structures such as basal ganglia,
121 and cerebellum (e.g., Buchsbaum, Greer, Chang, & Berman, 2005 for review; Konishi et al.,
122 1999; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). The parietal cortex is involved in
123 the prioritization of behaviorally relevant attributes, both spatial and non-spatial, among
124 multi-attributes representations (Egner et al., 2008; Ptak, 2012; Wager, Jonides, & Reading,
125 2004), through the updating of “priority maps” (Ptak, 2012), that are topographically
126 organized representations of the environment which encode feature-based expectancies
127 (Egner et al., 2008). The PFC, and in particular the vlPFC (Wager, Jonides, Smith, & Nichols,
128 2005), has an important role in cognitive control; it is involved in representing the rule
129 underlying a task that allow guiding the selection of appropriate behavior (Miller & Cohen,
130 2001; Wager et al., 2004).

131 The behavioral performance of individuals with ASD on the WSCT has generally been
132 reported as impaired, with more perseverative errors and fewer categories completed than
133 matched controls (CTRL) (Ozonoff & Jensen, 1999; Tsuchiya, Oki, Yahara, & Fujieda, 2005;
134 Yasuda et al., 2014), although some studies report intact performance on some parameters
135 (Kaland, Smith, & Mortensen, 2008; Liss et al., 2001; Minshew et al., 1992). These
136 discrepancies have been attributed to participants characteristics and/or task explicitness (Van
137 Eylen et al., 2011). A recent meta-analysis including thirty-one WCST studies in children or
138 adult participants with ASD confirmed poorer performance for four measures: number of
139 categories completed, perseveration, failure-to-maintain-set and non-perseverative errors
140 (Landry & Al-Taie, 2016). The neural substrates of cognitive flexibility in ASD have rarely
141 been studied (Schmitz et al., 2006; Shafritz, Dichter, Baranek, & Belger, 2008; Yeung, Han,

142 Sze, & Chan, 2016), and yielded contradictory findings. Schmitz and collaborators (2006)
143 reported increased activity in bilateral IPS in participants with ASD when comparing switch
144 to repeat trials, while Shafritz and collaborators (2008) reported a larger activity for controls
145 than participants with ASD in the IPS, among other regions, for both target-maintain and
146 target-shift trials.

147

148 Marked abnormalities in affective behaviors constitute a prominent feature of ASD, including
149 limited sharing of affect and difficulties in the perception and recognition of emotional
150 expressions (Hobson, 1991). Accordingly, brain functions involved in the processing of social
151 information have been found altered in ASD (Batty, Meaux, Wittemeyer, Roge, & Taylor,
152 2011; Guillon et al., 2014; Kaiser & Pelphrey, 2012; Nomi & Uddin, 2015; Sperdin & Schaer,
153 2016). Accurate processing of socio-emotional stimuli, which are complex, multisensory and
154 rapidly changing, requires fast tracking of salient features and rapid adaption to subtle
155 changes. They typically challenge the impaired skills of individuals with ASD and questions
156 remain as to whether socio-emotional impairments in ASD are specific to emotional
157 information processing or if they are rooted in a more general cognitive dysfunction.
158 Nevertheless, few studies have addressed the interactive effects of cognitive and socio-
159 emotional deficits in ASD (e.g., Dichter & Belger, 2007; Dichter et al., 2009; DiCriscio et al.,
160 2016; Gaigg, 2012; Shafritz, Bregman, Ikuta, & Szeszko, 2015). Emotional stimuli tend to
161 have “priority processing” as they have been found to evoke earlier and stronger responses in
162 limbic areas, in visual recognition areas (Batty, Delaux, & Taylor, 2003; Vuilleumier &
163 Pourtois, 2007), as well as in subcortical structures associated with gating attention and eye
164 movements (Vuilleumier et al., 2002). While in typical individuals, attentional blink is partly
165 overcome when the target stimuli are emotionally charged, this emotional modulation is
166 reduced in ASD (e.g., Corden, Chilvers, & Skuse, 2008; Gaigg & Bowler, 2009). In the same

167 line, while typically developing children showed a higher precision in detecting faces than
168 butterflies in a social visual search task, this was not observed in ASD (Kovarski,
169 Siwiaszczyk, Malvy, Batty, & Latinus, 2019). In fMRI, social, but not non-social, stimulation
170 were shown to induce a decrease of activity in a network (including bilateral IPS, dlPFC,
171 ACC and right insula) mediating inhibition interference from irrelevant visual information in
172 ASD (Dichter & Belger, 2007). According to these findings, the influence of emotional
173 processing on cognitive functions could be reduced in ASD.

174
175 The aim of the current study was to explore the interplay between socio-emotional
176 information processing and cognitive flexibility in autism. To this aim we used a
177 computerized version of a modified WCST: the emotional WCST (Henaff et al., 2010), which
178 is a highly sensitive indicator of mental flexibility and set maintenance applied to socio-
179 emotional information. Although our work was mainly exploratory, under the hypothesis of a
180 reduced influence of emotional processing on cognitive functions in ASD, at the behavioral
181 level, we expected an interaction between sorting criteria and group on perseverative errors
182 and failure-to-maintain set. In the fMRI analysis, we analyzed brain activity involved in
183 different task-shifting steps as a function of sorting criteria; we expected an interaction
184 between group, sorting criteria and task-shifting step.

185 **Methods**

186 **Participants**

187 Twelve participants with a diagnosis of Autism Spectrum Disorders partook in the experiment
188 (1 female; mean age \pm standard deviation (std) = 29.25 years \pm 7.21; mean Intellectual
189 Quotient=117.42 \pm 22.59; ADOS score=10.08 \pm (std)4.25; see supplementary material). They
190 were recruited among patients attending units specialized in autism diagnosis and evaluation
191 (Centre de Ressource Autisme) or were referred by Psychiatrists all over France. Adults with

192 ASD were matched with eleven healthy participants (1 female, 29.36 years \pm 7.15; recruited
193 through an e-mail list and flyers at the University of Lyon), with no history of neurological
194 and/or psychiatric disorders. All participants had normal or corrected-to-normal vision. The
195 study was approved by the local ethics committee (CPP n°2006-20). All subjects gave
196 written informed consent in accordance with the Declaration of Helsinki.

197 **Stimuli**

198 Face stimuli were chosen from the NimStim Face Stimulus Set (Tottenham et al., 2009;
199 <http://www.macbrain.org/resources.htm>). Stimuli were surrounded by a colored frame (4
200 colors) and represented faces of four different individuals (2 males), displaying four different
201 emotions (anger, happiness, fear, disgust). Stimuli were chosen to allow an easy identification
202 of emotions and identities. Basic emotions were presented to ensure that known emotion
203 recognition difficulties in ASD would not influence the findings (de Vries & Geurts, 2012).

204

205 **Experimental design and procedure**

206 Participants, lying in a supine position in the scanner, viewed the stimuli, rear-projected on a
207 screen at the back of the scanner, through a mirror attached to the antenna. A modified
208 version of the emotional WCST was presented to participants using the Presentation Software.
209 Participants were presented with 5 cards (Figure 1A): 1 central card and 4 surrounding cards.
210 They were asked to match the central card with one of the four surrounding cards according to
211 one of three criteria: frame color, facial identity or expression. The experiment lasted
212 20.8min; participants performed as many trials as possible during the allocated time. Before
213 the start of the experiment, participants were informed of the three sorting rules, and that they
214 will change at random; they also knew that the first sorting rule was a frame color matching.
215 The rule subsequently changed randomly, without warning, after 3-to-8 correct trials. At each
216 trial (Figure 1), the current sorting criterion was only met by one card.

217

218 **fMRI acquisition**

219 Magnetic resonance data were acquired on a 1.5T Siemens Magnetom (Siemens AG,
220 Erlangen, Germany) scanner at the CERMEP (Imagerie du Vivant, Bron, F-69677, France)
221 imaging facilities. Structural image acquisition consisted in a 3D anatomical T1-weighted
222 sequence (TR=1970ms; TE=3.9ms; inversion time=1100ms; FOV=256mm; matrix size: 256²
223 voxel size: 1mm³). Functional images were collected using a T2*-weighted gradient-echo
224 planar imaging sequence (TR=2.5s; TE=50ms; flip angle=90°; FOV=220mm; Matrix=64x64;
225 in-plane resolution=3.4x3.4mm²). The acquisition volume consisted of 29 interleaved axial
226 slices with a 4mm slice thickness (no interslice gap); 500 volumes were acquired per
227 participant.

228

229 **Data analysis**

230 **Behavioural data: WCST scores**

231 Classical indexes (e.g., perseverative errors, maintenance trials etc.) scored in a WCST
232 were measured as percentage relative to the total number of trials (Jarvinen-Pasley & Heaton,
233 2007; see supplementary material). In addition, we propose a new score for evaluating the
234 WCST, termed the “bias error”. The ‘bias error’ is the percentage of rule changes that
235 required more than two trials (including the first negative feedback) to correctly identify the
236 next rule. Indeed, while two incorrect responses following a rule change may be expected by
237 chance, more than two errors may reflect a bias toward more automatic and comfortable
238 responses. Therefore, the bias error may reflect the willingness to avoid the realization of a
239 specific criteria.

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

242 **fMRI data: Image preprocessing and analysis**

243 Image preprocessing and analysis were performed with SPM12b (Statistical Parametric
244 Mapping, Wellcome Department of Cognitive Neurology, London,
245 <http://www.fil.ion.ucl.ac.uk/spm>), following classical guidelines (see supplementary
246 material). Functional data of the experimental block were analyzed in a two-level random-
247 effects design. At the first level, onsets were defined as the presentation of the feedback
248 (Henaff et al., 2010). To better understand brain activity related to several aspects of task-
249 shifting and their interaction with sorting criteria, six types of feedback events were modelled
250 (Figure 1B). Change events, i.e., negative feedbacks indicating a need to change rule, were
251 modelled according to the preceding rule (the rule that was correct in the previous trial):
252 change-color, change-identity, and change-emotion. They reflect the processes involved in
253 error monitoring, and the need to shift to the new rule and inhibit the preceding rule. Switch
254 events, i.e., the first positive feedback following a change of rule, were modelled according to
255 the current ongoing rule: switch-color, switch-identity, and switch-emotion. Switch events
256 informed participants that they have found the correct rule, and have to start maintaining the
257 new rule. Maintenance events, which reflects processes involved in maintaining task-sets,
258 regroup all other positive feedbacks; they were also modelled according to the ongoing rule
259 (maintenance-color, maintenance-identity, and maintenance-emotion). All other feedback
260 events (e.g., failures) were modelled in a ninth regressor of no interest. Therefore, the design
261 matrix included 10 regressors (3 event types x 3 sorting criteria, plus one regressor of no
262 interest), which contained finite impulse responses representing the onset of feedback events
263 convolved with a canonical hemodynamic response function. The design matrix also included
264 realignment parameters as nuisance covariates to account for residual motion artefacts. Betas
265 estimates were calculated for each of the 10 regressors. These betas images were then used to
266 create three contrast images per sorting criteria in order to identify regions involved in

267 different task-shifting steps per sorting criteria: 1) change vs. maintenance events; 2) change
268 vs. switch events; 3) switch vs. maintenance events.

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

273

274 **Results**

275 **Behavioural data: WCST scores**

276 The total number of trials performed by the participants varied between groups
277 ($T(21) = -3.05$; $p = 0.006$) with participants with ASD completing less trials ($312 \pm$ (standard
278 error of mean, s.e.m.) 10.34) than control participants (356.9 ± 9.99). However there was no
279 difference in the global percentage of errors between groups ($T(21) = 0.99$; $p = 0.33$).

280 The percentage of rule changes occurring during the course of the experiment is
281 indicative of overall success rate, with a higher number of changes reflecting a greater amount
282 of category completed and thus overall better performance. Participants with ASD had a
283 significantly smaller percentage of rule changes than control participants ($T(21) = -2.12$;
284 $p = 0.046$). Yet, participants with ASD were presented with the same proportion of changes in
285 each possible direction ($N = 6$: color-emotion, color-identity, identity-color, identity-emotion,
286 emotion-color, emotion-identity) than CTRL participants ($\text{abs}(T(21)) < 1.8$; all $p > 0.085$).
287 Percentages of PE (Figure 2A), non-perseverative errors and maintenance trials were not
288 modulated by groups and showed no rule-by-group interaction. A 2-way mixed ANOVA
289 (group x sorting criteria) on the percentage of failures-to-maintain-set (Figure 2C) revealed a
290 main effect of group ($F(1,21) = 5.76$; $p = 0.026$), showing that participants with ASD failed
291 more than control participants. A main effect of sorting criteria ($F(1,31,27.43) = 9.32$; $p = 0.003$)

292 revealed that participants failed more in the maintenance of the emotion rule than in the
293 identity ($p = 0.005$) and color ($p = 0.0004$) rules. Noteworthy there was no group by sorting
294 criteria interaction ($F(1.31,27.43)=2.68$; $p=0.1$).

295 A 2-way mixed ANOVA (group x to-be-found sorting criteria) on “bias error” (Figure
296 2B) revealed a main effect of sorting criteria ($F(1.58,33.14)=8.56$; $p=0.002$) and a significant
297 interaction between group and sorting criteria ($F(1.58,33.14)=4.157$; $p=0.033$). Student T-
298 tests between groups ran on each sorting criteria revealed that participants with ASD
299 committed more errors than control participants when they had to find the emotion rule
300 ($p=0.024$), while there was no significant group differences for the color or identity criteria.
301 Notably there was no group difference for the number of maintenance errors during the
302 emotion matching rule.

303

304 **fMRI data**

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

310 **(1) Main effect of Task-shifting step**

311 A main effect of Task-shifting step was observed (cluster-defining threshold:
312 $F(2,42)=8.18$, $p=0.001$; $FWEc=42$) in nine clusters. Overall task-shifting step modulated a
313 large bilateral network overlapping both ventral and dorsal fronto-parietal networks (FPN),
314 visual cortices and a range of subcortical structures (see Figure 3A; Table 1). More precisely,
315 the first cluster overlapped bilateral insulae, putamen, posterior cingulate gyrus (pCG),
316 bilateral superior and inferior parietal lobule (SPL, IPL), including IPS and extending to the

317 supramarginal and angular gyri, middle frontal gyrus (MFG) of the right hemisphere and left
318 hippocampus. A second cluster overlapped the cerebellum, extending to bilateral inferior
319 occipital gyrus and left fusiform gyrus. Task-shifting step also modulated activity in posterior
320 and anterior medial superior frontal gyrus (SFG), the calcarine fissure extending to the lingual
321 gyrus of both hemispheres, superior occipital gyrus, bilateral inferior frontal sulci (IFS), and
322 left MFG.

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

327 ***Change vs. maintenance events***

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

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

334 ***Change vs. switch events***

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

339 A larger activity to switch than change events (Figure 3C; cyan) was observed in
340 bilateral rolandic operculum, left hippocampus, medial anterior SFG; regions that were also

341 more activated by maintenance than change events. In addition, a larger activity to switch
342 events was observed in bilateral putamen extending to posterior insulae, and bilateral SPL.

343 *Switch vs. maintenance events*

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

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

349

350 **(2) Group by task-shifting step interaction**

351 Activity in the IPL of both hemispheres was further characterized by a group by task-shifting
352 step interaction (cluster-defining threshold: $F(2,42)=8.18$, $p=0.001$; $FWEc = 35$; Figure 4A).

353 In the IPS, there was no group difference for the change vs. maintenance contrast. However,
354 in the ASD group, the IPS was strongly activated by switch events while it was mostly
355 activated by change events in the control group.

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

364 Intersubject variability in each cluster is illustrated on Figure 4B using threshold-weighted
365 overlap maps for each task-shifting step collapsed per sorting criteria (Seghier & Price, 2016).

366 Overlap map revealed a consistent activation of bilateral IPS and right SFS for switch events
367 relative to maintenance events in the ASD group; consistency reached a maximum value of
368 0.62 in the right IPS. All ASD participants, but one, presented a significantly ($p < .001$,
369 uncorrected) larger activation for switch than maintenance events in the IPS, one participant
370 presented a near threshold difference. Therefore, despite relatively small sample sizes, the
371 group by task-shifting step observed in bilateral IPS, in particular, appears to reflect a genuine
372 difference between ASD and control participants.

373

374

375 **Discussion**

376 We used an emotional Wisconsin Card Sorting Test (Henaff et al., 2010) in fMRI to explore
377 the interplay between cognitive and emotional dimensions of ASD. Behavioral data
378 highlighted a significant interaction between group and sorting criteria for “bias error”, a
379 measure of the unwillingness to switch towards a specific sorting rule, but no group effect or
380 interaction was observed on parameters measuring pure cognitive flexibility (e.g.,
381 perseverative errors). Accordingly, at the fMRI level, we found no group differences in the
382 processing of change events relative to other events. However, the processing of switch events
383 yielded a larger activation in bilateral IPS in ASD participants suggesting an atypical
384 processing of the confirming cue.

385 Behavioral results are only partially consistent with previous studies as we found no group
386 difference for perseverative and non-perseverative errors (Landry & Al-Taie, 2016). This lack
387 of difference could be attributed to task explicitness (Van Eylen et al., 2011): in our study task
388 was relatively explicit as participants were aware of the general principle of the test and of the
389 sorting rules. An interaction between group and sorting criteria was found on the “bias error”
390 which reflects a bias away from the realization of a specific task. Participants with autism had

391 a larger “bias error” than control participants but only when switching to the emotion sorting
392 rule, which was equally maintained by both groups, highlighting no specific difficulties in
393 performing socio-emotional matching. These results differ from those of de Vries and Geurts
394 (2012), who reported a trend reflecting difficulty in disengaging from emotional faces during
395 task switching in ASD. Nonetheless, taken together these findings highlight difficulties in the
396 engagement/disengagement linked to socio-emotional stimulation. Our exploratory findings
397 indicate that inflexible behaviors in ASD are mostly characterized by the avoidance of
398 switching toward processing of emotional information. This is of great importance for
399 understanding the functional role of RRBs, as it suggests that patients with ASD may be
400 displaying routines or repetitive behaviors not because of a ‘true’ lack of cognitive flexibility,
401 but rather to avoid some specific (emotional) situations (Geurts et al., 2009). This observation,
402 if further confirmed, would suggest to tightly associate socio-emotional and cognitive
403 rehabilitation programs.

404 At the fMRI level, we found modulations of brain activity by task-shifting step, and sorting
405 criteria as well as an interaction between these two factors. Therefore, these data provide
406 evidence that the processing of social information interact with cognitive task, as previously
407 reported (e.g., Corden et al., 2008; Gaigg & Bowler, 2009). However, and contrarily to
408 behavioral observations there was neither further interaction with group, nor any sorting
409 criteria by group interaction. Despite a small sample size, strong interactions were observed
410 between task-shifting step and group, highlighting different cognitive strategies. In both
411 groups, change events induced a larger activity than maintenance or switch events in a large
412 bilateral neural network including both the dorsal and ventral FPN (Corbetta & Shulman,
413 2002), the medial SFG and visual cortices. On the contrary, ASD participants presented a
414 larger activity to switch than maintenance events in bilateral posterior IPS, and right posterior
415 SFS, consistent with Schmitz and collaborators (2006).

416 Change events are the only negative feedback events as such they act not only as an error
417 feedback, but also as a start-cue indicating the need to find a new rule and start a new task-set.
418 It makes sense to find activity related to processing a negative feedback in both ventral and
419 dorsal FPN (Corbetta & Shulman, 2002; Dosenbach, Fair, Cohen, Schlaggar, & Petersen,
420 2008; Dosenbach et al., 2007). Within the dorsal FPN, bilateral IPS and posterior SFS show
421 cue-driven activity when participants prepare to shift their attention to a specific feature or
422 attribute, suggesting that dorsal FPN also mediates non-spatial orienting of attention (Egner et
423 al., 2008; Ptak, 2012; Wager et al., 2004). Task-set instantiation corresponds to the
424 prioritization of new behaviorally-relevant attributes among multi-attributes representations
425 (Wager et al., 2004), and may occur through the updating of “priority maps” (Ptak, 2012).
426 Priority maps are topographically organized representations of the environment and encode
427 feature-based expectancies, which confer a competitive processing advantage for the selection
428 of task-related features (Egner et al., 2008).

429 For control participants, the IPS was only activated in the reception of a negative feedback
430 (e.g., change events), suggesting that change events are the only cues indicating the need to
431 start a new task-set, and to prioritize new attributes (e.g., update priority maps). When switch
432 events occurs, control participants have performed all tasks needed for the switch, and are set
433 in a stable processing stage. However, IPS was consistently activated (across ASD subjects)
434 by switch events suggesting that they also act as start-cue in our sample of participants with
435 ASD. Therefore, priority maps may be stabilized only after autistic participants received a
436 confirmatory positive feedback. A larger IPS and SFS activation in people with ASD to
437 switch events could reflect the need to adapt cognitive strategies until certainty regarding the
438 task to-be-performed is achieved. Accordingly, while control participants flexibly modulate
439 cortical activity according to level of certainty, autistic participants cannot do so (Thillay et

440 al., 2016). This observation suggests that people with ASD stabilized their priority maps only
441 when reaching a high level of certainty.

442 We did not find any interaction between group, sorting criteria and cognitive flexibility at the
443 cerebral level. Note that the observed behavioral effects could not be tested as bias error
444 corresponds to an insufficient number of trials for an fMRI analysis. Nonetheless, fMRI and
445 behavioral data are consistent in that they show 1) no real deficit in cognitive flexibility *per*
446 *se*, and 2) no interaction on traditional measures of cognitive flexibility and socio-emotional
447 processing. fMRI data highlighted that a higher level of certainty was needed before switch-
448 related brain activity decreases in ASD, while behavioral findings suggest that this high need
449 for certainty might yield different behavioral outcomes depending on the task to-be-
450 performed. Priority maps incorporate prior knowledge, acquired through experience,
451 regarding the information relevant to the task to-be-performed (Fair et al., 2007; Zelinsky &
452 Bisley, 2015). We hypothesize that the observed behavioral outcomes of the need for certainty
453 is linked to prior knowledge of the task to-be-performed. For control participants, the
454 existence of prior knowledge for the realization of the sorting tasks facilitates the selection of
455 relevant information leading to smaller bias errors. A larger bias error in the emotion sorting
456 task for the ASD group is expected to reflect the weakness of prior knowledge or of top-down
457 influence for the realization of that particular task (Gomot & Wicker, 2012; Pellicano & Burr,
458 2012; Pellicano, Jeffery, Burr, & Rhodes, 2007). Moreover, this allows refining these theories
459 by showing that these difficulties are particularly evident for socio-emotional information.

460 The need for a high-level of certainty before setting in a stable task-set, combined with the
461 weakness of prior knowledge in socio-emotional tasks may produce a greater avoidance of
462 socio-emotional rules leading to a larger bias error in the social sorting tasks. It remains to be
463 determined whether the prior knowledge-related difficulties drives the need for certainty or

464 whether the high need for certainty, which is rarely matched in socio-emotional contexts,
465 prevents the generation of priors.

466 **Conclusions**

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

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

478 **List of abbreviations**

479 AC/PC : anterior/posterior Commissure ; ACC: Anterior Cingulate Cortex; ADOS-G: Autism
480 Diagnostic Observation Schedule-Generic; AQ: Autism Spectrum Quotient; ASD: Autism
481 Spectrum Disorders; BOLD: Blood Oxygen Level Dependent; CTRL: Control; dlPFC:
482 dorsolateral PFC; FEF: Frontal Eye Field; FPN: Fronto-parietal Network; IFG/S: Inferior
483 Frontal Gyrus/sulcus; IPS: intraparietal sulcus; IQ: Intellectual Quotient; LOC: Lateral
484 Occipital Complex; MFG: Middle Frontal Gyrus; MNI: Montreal Neurological Institute;
485 pCG: posterior cingulate cortex; PE : perseverative errors ; PFC: Prefrontal cortex; RH: Right
486 Hemisphere; RRB: restricted, and repeated patterns of behavior; SFS/G: Superior Frontal
487 Sulcus/Gyrus; vlPFC: ventrolateral PFC; WAIS: Wechsler Adult Intelligence Scale; WCST:
488 Wisconsin Card Sorting Test;

489 **Ethics approval and consent to participate**

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

494 **Consent for publication**

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

498 **Conflict of Interest**

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

500 **Authors' contributions**

501 The study presented here results from teamwork. Study conception - MG. Study design: MG,
502 PF. Data acquisition: ML, HC, FBB, PF, MG. Data analyses: ML, HC, FA, PF. Statistical
503 analyses: ML, HC, FA, MG. Data interpretation: ML, FBB, MG. Draft the manuscript: ML,
504 MG. Clinical evaluation of the patients: MG, FBB.
505 All authors provided approval for publication of the content.

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673

674 **Figure legends**

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

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

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

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

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

700

701

702 Table 1: Main effects of task-shifting step. For the large cluster only one peak per brain regions is
703 reported. SFG: superior frontal gyrus; SMA: supplementary motor area; Orientation: R: right
704 hemisphere; L: left hemisphere; M: medial; P: posterior; A: anterior. F-values greater than 18.89
705 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

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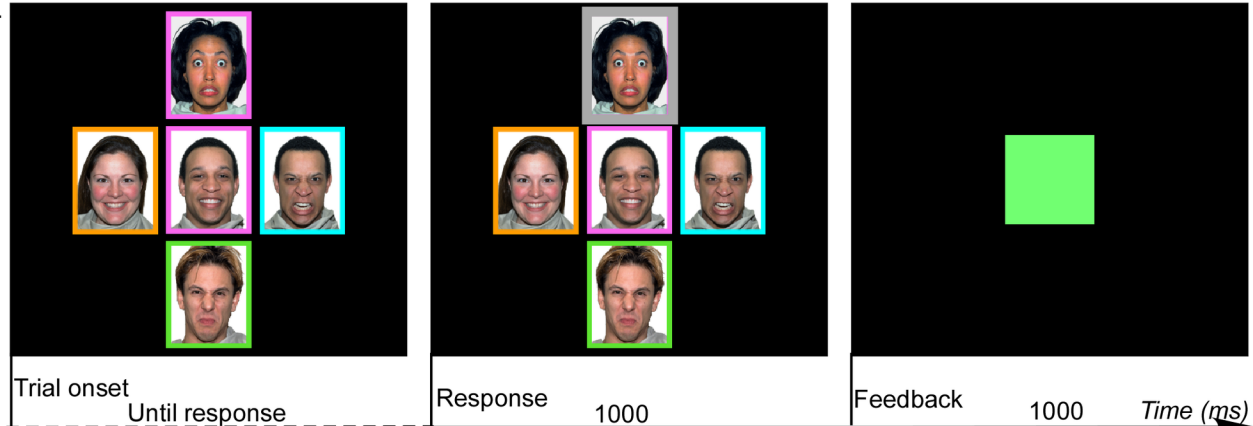
709 Table 2: Group by task-shifting step interaction. Orientation: R: right hemisphere; L: left hemisphere;
 710 M: medial; P: posterior; A: anterior. F-values greater than 18.89 corresponds to a FWE-corrected
 711 voxel threshold.

712

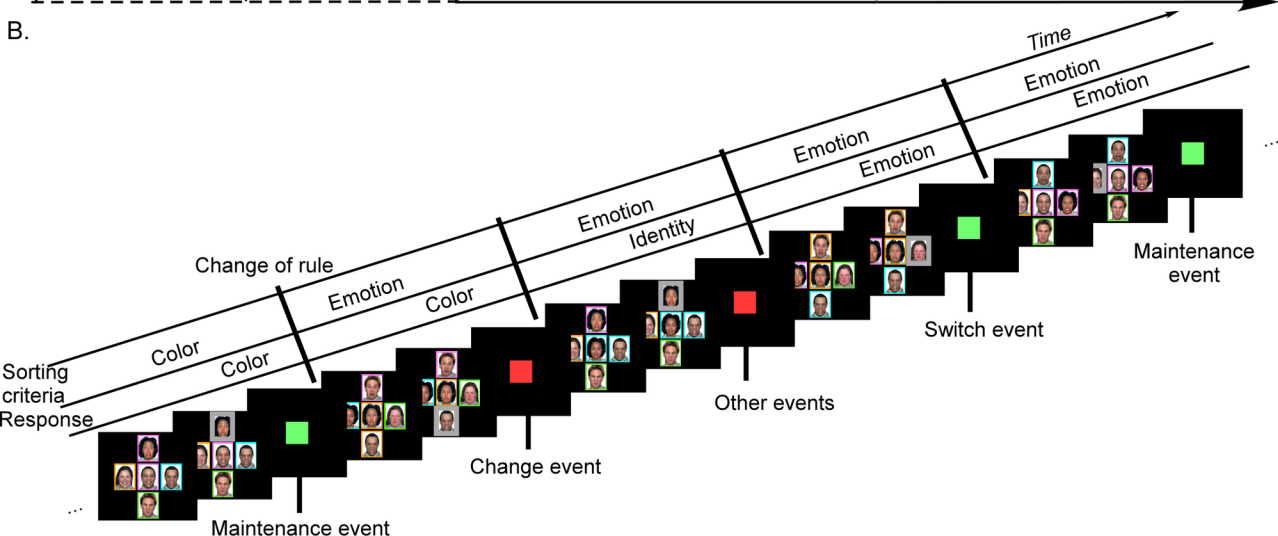
Region	Orientation	Cluster size	T	Z	x	y	z
Inferior Parietal Sulcus	R	279	19.02	4.7	27	-67	50
	L	255	13.32	3.99	-24	-59	48
Superior Frontal sulcus	R	58	10.93	3.61	21	-4	58
	L	35	15.09	4.23	-21	11	66
Inferior Temporal Gyrus	L	58	21.8	4.98	-45	-49	-10
Middle Frontal sulcus	A, M	82	16.37	4.4	18	50	6
Inferior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

713

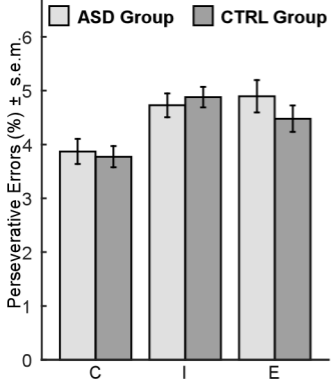
A.



B.



A. 7



B. 7

