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Autistic adolescents show atypical activation of the brain's mentalizing system even without a prior history of mentalizing problems

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ABSTRACT

Some autistic children pass classic Theory of Mind (ToM) tasks that others fail, but the significance of this finding is at present unclear. We identified two such groups of primary school age (labelled ToM+ and ToM−) and a matched comparison group of typically developing children (TD). Five years later we tested these participants again on a ToM test battery appropriate for adolescents and conducted an fMRI study with a story based ToM task. We also assessed autistic core symptoms at these two time points. At both times the ToM− group showed more severe social communication impairments than the ToM+ group, and while showing an improvement in mentalizing performance, they continued to show a significant impairment compared to the NT group. Two independent ROI analyses of the BOLD signal showed activation of the mentalizing network including medial prefrontal cortex, posterior cingulate and lateral temporal cortices. Strikingly, both ToM+ and ToM− groups showed very similar patterns of heightened activation in comparison with the NT group. No differences in other brain regions were apparent. Thus, autistic adolescents who do not have a history of mentalizing problems according to our ToM battery showed the same atypical neurophysiological response during mentalizing as children who did have such a history. This finding indicates that heterogeneity at the behavioural level may nevertheless map onto a similar phenotype at the neuro-cognitive level.

1. Introduction

One of the most enduring puzzles presented by autism is the huge difference that may be observed between individuals, while at the same time there is the compelling impression of similarity at some level. The impairments in social communication and interaction, recently reaffirmed as critical for a clinical diagnosis by DSMV, may also be critical to this intuitive impression. Although the precise nature of the social impairments remains elusive, the 'Theory of mind' or 'mentalizing' hypothesis (Baron-Cohen, 1995; Baron-Cohen, Leslie, & Frith, 1985; Frith, 2012) represents a systematic attempt to explain both mild and severe social impairments in autistic individuals. However, there is a problem for this hypothesis. It has long been known that some autistic individuals can solve Theory of Mind tasks and others do not (Happé, 1995; Moran et al., 2011). The question we address here is whether these are two distinct subgroups or whether both represent a similar neurocognitive phenotype, at the level of analysis provided by functional neuroimaging methods. We can answer the question on the basis of the presence or absence of atypical brain activation in those autistic children who have a history of being able to solve Theory of Mind tasks.

The existence of a mentalizing system in the brain is now well accepted (for reviews see Frith & Frith, 2012; Kennedy & Adolphs, 2012; Lieberman, 2007; Mitchell, 2009; Van Overwalle, 2009). There is also evidence for atypical brain activation in this system in autistic participants (Brüne & Brüne-Cohrs, 2006; Gilbert, Bird, Brindley, Frith, & Burgess, 2008; Gilbert, Meuwese, Towgood, Frith, & Burgess, 2009; Gotts et al., 2012; Kana, Libero, Hu, Deshpande, & Colburn, 2012; Lombardo et al., 2010; Marsh & Hamilton, 2011; Spengler, Bird, & Brass, 2010). However it is not known whether such atypical activation is present even in individuals who can solve Theory of Mind tasks. There may be an underlying impairment which is camouflaged at the behavioural level (Frith, 2004). Camouflage may happen when highly verbal individuals have learned to give accurate answers to Theory of Mind tests using effortful logical inferences. Thus good mentalizing performance does not necessarily imply intact intuitive mentalizing ability. Indeed problems in implicit mentalizing have been revealed in autistic adults who performed well on explicit mentalizing tasks (Begeer, Bernstein, van Wijhe, Scheeren, & Koot, 2012; Senju, Southgate, White, & Frith, 2009). On the other hand, it is possible

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that a subgroup of autistic individuals have no problems in understanding intentions and beliefs, or that they can fully overcome such problems. This should be evident not only at the behavioural but also the neural level. If so, this would suggest a distinct neurophysiologically defined phenotype.

To investigate this issue the present study took advantage of an existing population of autistic as well as neurotypical adolescents who had been extensively tested in childhood (White, Hill, Happé, & Frith, 2009). The sample of adolescents who participated in the present fMRI study were classified on the basis of their performance 5 years earlier on a large mentalizing test battery: Thus one subgroup consisted of those who had shown mentalizing performance as good as that of neurotypical (NT) children (ToM+), and another group consisted of those who had shown the more familiar pattern of mentalizing impairment (ToM−). We administered a second mentalizing test battery to find out to what extent performance changed over time. We also wanted to establish the validity of the mentalizing task performance. It would be pointless to classify subgroups on the performance of tests that were neither reliable over time nor valid in relation to their real world symptoms. Therefore we investigated whether ToM+ children had milder core symptoms on diagnostic tests, both in childhood and in adolescence.

Table 1
Behavioural data.

	NT	ToM−	ToM+
Background data			
N (M:F)	11 (10:1)	11 (9:2)	11 (10:1)
T2 age (years)	14.3 (1.6)	13.8 (1.1)	13.1 (1.9)
T1 WISC III Verbal IQ	118 (16)	110 (16)	111 (14)
T1 WISC III Performance IQ	103 (9)	103 (9)	95 (10)
T1 Clinical diagnosis	–	3 Autism/6 AS 2 ASD	8 AS 3 ASD
Assessment of core symptoms			
T1 3Di social [***,a]	3.4 (2.4)	14.2 (4.6)	10.3 (3.9)
Communication [***,b]	3.5 (2.0)	15.3 (4.3)	13.5 (3.3)
Repetitive behaviour [**,b]	2 (.4)	5.4 (2.8)	3.9 (2.9)
T2 ADOS social [*,c]	–	7.1 (4.2)	3.5 (2.8)
Communication	–	3.0 (1.7)	2.0 (.8)
Repetitive behaviour	–	3.0 (2.2)	1.8 (1.3)
Performance on mentalizing tasks			
T1 ToM battery (*z*-score)[***,d]	.0 (1.0)	−4.5 (1.4)	−.6 (0.8)
T2 ToM battery (*z*-score)[e]	.0 (1.0)	−1.3 (1.4)	−.7 (1.3)
T2 scanner ToM Stories (%)[**,c]	88 (10)	64 (22)	71 (17)
T2 scanner Non-ToM Stories (%)	85 (12)	75 (24)	77 (16)

Values are given as mean with standard deviation in brackets.
T1=time 1, T2=time 2.
ToM=theory of mind.
NT=neurotypical; ASD=autism spectrum disorder; AS=Asperger syndrome.
3Di=developmental, dimensional, and diagnostic interview.
ADOS=autism diagnostic observation schedule.

* $p<.05$.
** $p<.01$.
*** $p<.001$.
[a] ToM− ≠ ToM+ ≠ NT.
[b] ToM− = ToM+ ≠ NT.
[c] ToM− ≠ ToM+.
[d] ToM− ≠ TOM+ = NT.
[e] ToM− ≠ NT.

2. Methods

2.1. Participants

Ethical approval for the study was received from the UCL Research Ethics Committee and consent was obtained from the parents of all participants prior to inclusion in the study. The majority of individuals with ASD attended mainstream schools and all had IQs within the normal range (full scale IQ greater than 85).

The participants were aged 11–17 years. They were a self-selected subset of those who previously took part in a study by White et al. (2009) at time 1 (T1) when aged 7–12 years. The original sample included 45 children with autism spectrum disorder (ASD), diagnosed independently by a qualified clinician. Of these, 29 were willing to be involved in the study 5 years later at time 2 (T2), but 7 of these children were either unable to tolerate the scanning environment or their data were unusable due to movement in the scanner. The final sample of 22 adolescents with ASD was split into ToM− and ToM+ groups of 11 each. A further group of 11 typically developing adolescents was also recruited from the original sample. The three groups were comparable in age ($F(2,30)=1.56$, $p=.23$), gender ($\chi^2(2)=.57$, $p=.75$), verbal ($F(2,30)=.90$, $p=.42$) and performance IQ ($F(2,30)=2.44$, $p=.10$) (see Table 1).

For the assessment of core symptoms the developmental, dimensional and diagnostic interview (3Di: Skuse et al., 2004) was used at T1, and the autism diagnostic observation schedule (ADOS-G: Lord et al., 2000) at T2. The 3Di measure is similar to the autism diagnostic interview (ADI-R: Lord, Rutter, & Le Couteur, 1994) with which it correlates highly (r for each area of the triad of autistic features ranges from .53 to.64; Skuse et al., 2004).

2.2. T1 ToM battery

This battery included both the ToM Strange Stories and a false belief ToM battery. The original T1 cohort included 27 NT children (White et al., 2009) and, on the basis of this larger NT group′s performance, individual variance on both sets of stories was calculated, independent of age and IQ. This was done by entering raw data from these 27 NT children as the dependent variable in a regression, with T1 age, verbal, and performance IQ as predictors, and collecting the residuals. The same regression equation was then applied to the 22 children with ASD taking part in this study and all scores were converted to *z*-scores in relation to the larger NT group′s means and standard deviations. The average of the ToM Strange Stories and the false belief ToM battery *z*-scores was then calculated to provide an overall measure of T1 ToM test performance for each child. This method was necessary to provide an individual estimate of ToM ability independent of age and IQ on which the children with ASD could be divided, so as to avoid the ToM− group being populated with younger and lower-IQ individuals. All participants in the resulting ToM− group had T1 ToM *z*-scores lower than −2.5 in comparison to the T2 NT group.

2.3. T2 ToM battery

Of the 5 tests given at T2, two had been included in the T1 false belief battery and found then to be most discriminating between the groups, and three tasks were new to the participants. The two T1 tasks were 1st order false belief tasks: a test of real versus apparent emotion (Wellman & Liu, 2004), where a character wanted to create a false belief in others, and an interpretational false belief task (different picture to T1; Luckett, Powell, Messer, Thornton, & Schulz, 2002). The three new tasks were 2nd order false belief tasks: the coat story (Bowler, 1992), a homework story modelled on the icecream van story (Baron-Cohen, 1989), and a double bluff burglar story involving 2nd order deception (Happé, 1994). These were scored out of a total of 10. In all cases, the participant was asked to predict the knowledge of, behaviour of or emotion felt by another character on the basis of their mental state; this answer was marked as a pass or fail (1 or 0). The participant was also asked to justify why they had made that prediction; this was marked as a correct mental state justification (e.g., "because he doesn′t know that she knows that they′re out of stock"), a correct non-mental state justification (e.g., "because that′s where he had said he was going to go"), or an incorrect justification (e.g., "because he needed to get a new coat"; 1, 0.5, or 0, respectively). This additional scoring aimed to check for false positive responses when the participant was achieving the correct answer by guessing, and also was expected to increase the variation in responses with the aim of avoiding ceiling effects. Control questions were administered (memory and reality questions plus prompt questions during the longer stories), which all individuals were required to pass, to check for comprehension of the scenario.

2.4. T2 scanner task

Four different types of stories were administered: mental, human, animal and nature; for the present study only mental (ToM) and nature (non-ToM) were compared as the human and animal stories have previously been found to rely to a degree on mentalizing ability (White et al., 2009). The story text and proceeding question were identical to those given in White et al. (2009) but the participant was required to select an answer to this question from a choice of three possible responses. Participants listened to each story, question and response phase presented binaurally through headphones, as well as simultaneously following the text visually on a computer screen in order to aid comprehension (see Fig. 1).

The stories were presented during four blocks; each block involved 8 stories, 2 of each type, presented in a pseudorandom order, ensuring that two stories of the same type were not presented consecutively. Each story–question–response series lasted 58 s in total; the story phase was presented first (taking between 20 and