

Figure 1. Transverse MRI with FLAIR acquisition of TO's brain. Left sides of images correspond to right side of the brain.

number of studies remains limited and actual effects on social functions following damage to this area remain poorly understood (Gallagher & Frith, 2003). We present herein two cases with damage to the medial PFC and report on their performance on various kinds of theory of mind tests, whether personality changes were evident, and behavioral disturbances in daily activities.

METHODS

Profiles of cases with medial prefrontal damage

We tested two individuals, TO and HC, with damage to the medial PFC. The first case, TO, was a 31-year-old man. A full-time employee of a big electronics company in Japan, he had undergone neurosurgery for brain tumor. Magnetic resonance imaging (MRI) with FLAIR (fluid attenuated inversion recovery) acquisition revealed that damage extended through the left-dominant medial prefrontal and anterior cingulate cortices, reaching the left supplementary motor area (Figure 1). The right hand and leg were moderately paralyzed for a few months after surgery, but those symptoms later resolved.

The most striking aspect on TO was a reported change in personality. According to his self-report, he noticed that his sense of reality was attenuated after surgery, leading him to feel detached from the world despite being sure of

his location, and this feeling often occurred in a manner similar to a panic attack. These symptoms partly resembled the characteristics of depersonalization. He also mentioned that surgery had made him feel depressed, anxious and withdrawn from everything.

The second case, HC, was a 56-year-old man. An employer of a small private company in Japan, he had undergone surgery following rupture of a right pericallosal artery aneurysm. MRI with T1-weighted spin-echo acquisition revealed that the area of damage included the right-dominant medial prefrontal and anterior cingulate cortices, extending slightly into the right supplementary motor area (Figure 2).

According to self-reports, he noticed that his memory had deteriorated after surgery, with a feeling that most daily episodes could not be clearly remembered. He reported difficulty doing two things simultaneously, and became aware that everything needed a strong effort to be done. He also mentioned that his personality had changed after surgery, leading him to notice that feelings of sadness and anger had been dimmed and that he had become much more depressive, anxious and withdrawn compared to his previous personality.

Neuropsychological assessment

Three months after surgery, six of the more frequently used neuropsychological assessments

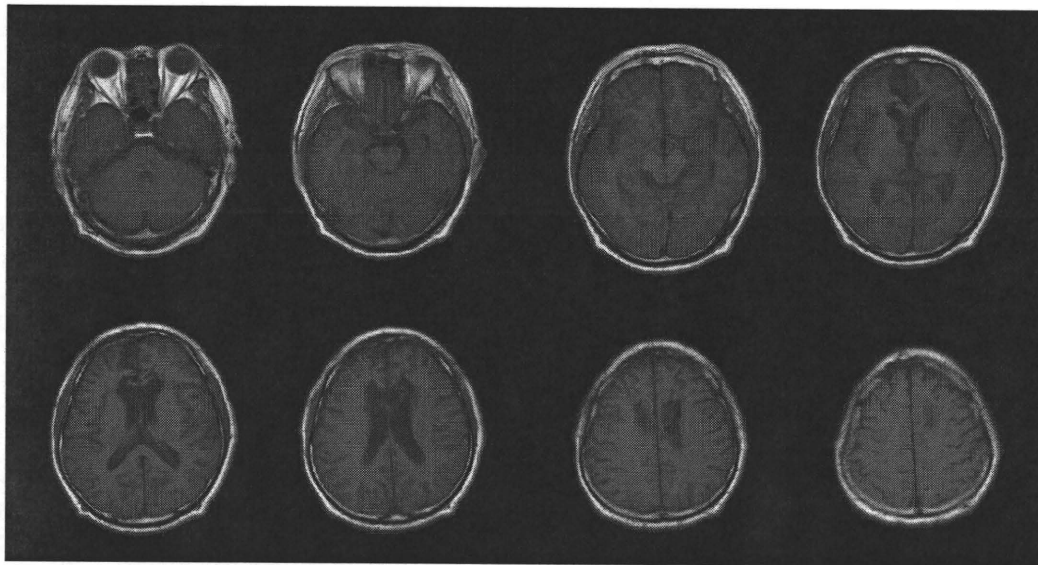


Figure 2. Transverse MRI with T1-weighted spin-echo acquisition of HC's brain. Left sides of images correspond to right side of the brain.

were conducted to examine higher-order cognitive functions in these cases. We selected: (1) Wechsler Adult Intelligence Scale-Revised (WAIS-R) for general intelligence, (2) Wechsler Memory Scale-Revised (WMS-R) for memory and attention, (3) Rey Auditory-Verbal Learning Test (RAVLT) for verbal recall ability, (4) Rey-Osterrieth Complex Figure Test (ROCFT) for visuoconstructive skills and visual memory, (5) Wisconsin Card Sorting Test (WCST) for abstract reasoning and ability to appropriately shift cognitive strategies, and (6) Stroop Test for selective attention and inhibition. The results of neuropsychological assessments in both cases are shown in Table 1.

TO's score on the intelligence test showed dissociation between verbal and performance intelligence quotient (IQ), with an inferior score on performance IQ. In the IQ test, he showed difficulty in performing subtests of block design, object assembly and digit symbols.

In terms of memory performance, TO showed lower scores on some measures for identifying delayed recall performance (e.g., delayed recall on WMS-R, RAVLT, and ROCFT) as compared to his relatively higher scores on other measures. The results of mild amnesia were consistent with his self-report regarding daily activities. For instance, he reported often becoming confused in remembering whether he has taken his medication.

TABLE 1
Neuropsychological assessments of TO and HC

<i>Test</i>	<i>TO</i>	<i>HC</i>
<i>Intelligence</i>		
Wechsler Adult Intelligence Scale-Revised (WAIS-R)		
Full scale IQ	88	91
Verbal IQ	101	92
Performance IQ	76	92
<i>Memory</i>		
Wechsler Memory Scale-Revised (WMS-R)		
Verbal memory	94	90
Visual memory	87	99
General memory	90	92
Attention and concentration	88	94
Delayed recall	65	100
Rey Auditory-Verbal Learning Test (RAVLT)		
Immediate recall, trials		
1-5	6-9-9-10-11/15	3-7-10-9-11/15
Delayed recall	5/15	7/15
Delayed recognition	11/15	14/15
Rey-Osterrieth Complex Figure Test (ROCFT)		
Immediate recall	35/36	36/36
Delayed recall	4/36	22/36
<i>Executive function</i>		
WCST (Wisconsin Card Sorting Test)		
Categories achieved	4	5
Total perseverative errors	1	0
Stroop Test		
24 non-interference colour naming (errors)	14s (0)	22s (0)
24 interference colour naming (errors)	26s (1)	29s (1)

TO's performances on tests for executive function were all within normal range. Performance on the standardized aphasic test did not show any difficulties in language activities.

The second case, HC, showed an intellectual performance within normal range. In terms of memory performance, he exhibited normal scores on WMS-R, although scores on RAVLT and ROCFT were somewhat lower. In fact, in terms of daily activities, he showed difficulty with temporal-order judgments for everyday episodes within a time range of a few days.

HC's performance on tests for executive function was also within normal range. Performance on the standardized aphasic test did not show any difficulties in language activities.

Experimental investigations

We tested the two cases using four types of story comprehension task to clarify theory of mind performance. These included: (1) first-order false belief test (Baron-Cohen, Leslie, & Frith, 1985; Frith & Frith, 1999), (2) second-order false belief test (Baron-Cohen, 1989), (3) strange stories test (Happé, 1994), (4) faux pas recognition test (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999). The first-order false belief test is one of the most famous tests for theory of mind reasoning. This test assesses the ability to recognize that others can have false beliefs about the world that can differ from reality, and that people's behaviors can be predicted by the representation of others' mental states. The more complex second-order false belief test requires participants to understand a second person's concerns about the world, based on social interactions of minds in which people are concerned about each other's mental states.

The last two tests were used to examine the more advanced theory of mind reasoning ability in the cases. The strange stories test assesses the ability to infer mental states in a story context for social understanding. We selected seven stories for each case: pretence; lie; white lie; figure of speech; double bluff; irony; and persuasion. A previous study reported that subjects with autism-spectrum disorders show impaired provision of context-appropriate mental state explanations for strange stories, compared to normal control subjects (Happé, 1994).

As well as the strange stories test, we used the faux pas recognition test to assess the ability to

recognize inappropriate statements in a story context (Baron-Cohen et al., 1999). We selected the original 10 faux pas stories and 10 control stories with no faux pas for TO and 7 faux pas stories and 7 control stories for HC, due to reported fatigue during testing. Subjects were presented with each story and asked whether a faux pas was contained. If a faux pas was detected, they were then asked for an explanation of it. We also requested that each subject answer two additional questions to test story comprehension in each story, to see whether a comprehensive understanding of each story was achieved. Baron-Cohen et al. (1999) reported that subjects with autism-spectrum disorders show impaired detection of faux pas on the faux pas recognition test compared to normal control subjects, despite intact story comprehension.

In addition, TO and HC were required to complete all 50 items in the Autism-Spectrum Quotient (AQ) questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). This questionnaire was developed as a self-administered method of screening for adults with normal intelligence and traits associated with autism-spectrum disorders. Score ranges from 0 to 50 in the questionnaire. Adults with Asperger syndrome or high-functioning autism show a mean score of 35.8, significantly higher than controls with a mean score of 16.4 (Baron-Cohen et al., 2001). Another recent study has shown that the threshold score for suspected Asperger syndrome or high-functioning autism is 26.0 (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005). The present study used the Japanese version of the questionnaire, for which significantly high reliability has been shown in test-retest and inter-rater measures (Wakabayashi, Tojo, Baron-Cohen, & Wheelwright, 2004). In this version, adults with Asperger syndrome or high-functioning autism show a mean score of 37.9, significantly higher than controls with a mean score of 18.5 (Wakabayashi et al., 2004).

RESULTS

Theory of mind tests

Both cases passed the first- and second-order false belief tests, providing expected answers suggesting a proper understanding of each story. In terms of advanced theory of mind tests, both

cases showed good performance on the strange stories test. Overall percentage of providing appropriate explanations for given stories was 85.7% (just one error out of seven) in TO and 100% in HC on the strange stories test. On the faux pas recognition test, the percentage of detecting faux pas and having appropriate explanations was 60.0% in TO and 100% in HC for the provided faux pas stories. In contrast, the percentage of detecting “no” faux pas was 70.0% in TO and 57.1% in HC for the provided control stories. Both cases thus reported faux pas even in control stories without any faux pas. In addition, both cases showed higher scores on the two questions for story comprehension (92.5% for TO and 89.3% for HC).

Autism-spectrum quotient

AQ scores were 31 for TO and 29 for HC, above the threshold score for Asperger syndrome or high-functioning autism of 26 as defined by Woodbury-Smith et al. (2005). Interestingly, both cases spontaneously reported just after completing the questionnaire that they were sure that some of the personality traits focused on in the questionnaire identified the actual personality changes they felt. We then asked them to complete the AQ again for what they supposed their original personality was before surgery. AQ scores for purported pre-surgical state of the two cases were 13 for TO and 23 for HC, much lower than the initial scores and below the threshold score for Asperger syndrome or high-functioning autism. Both cases thus appear to have developed some autistic personality traits following surgical operations. All items representing autistic personality traits developed after surgical operations in both cases are listed in Table 2.

A general finding was that the two cases had developed some characteristics of autism after surgical operations. To specify these characteristics in greater detail, we compared those items to items identified in a two-factor structure model (Hoekstra, Bartels, Cath, & Boomsma, 2008). Two factors were identified among all 50 items in the AQ, namely “social interaction” factor and “attention to detail” factor. In TO, all 18 items fell into the “social interaction” factor, while in HC, 6 of 7 items fell into the “social interaction” factor (Table 2). The only item falling into the “attention to detail” factor in HC was item 9,

TABLE 2

All items representing development of autistic personality traits after surgical operations in both cases

<i>TO</i>	
Items changing from <i>definitely disagree</i> or <i>slightly disagree</i> to <i>definitely agree</i> or <i>slightly agree</i>	
(4)	I frequently get so strongly absorbed in one thing that I lose sight of other things.
(13)	I would rather go to library than a party.
(16)	I tend to have very strong interests, which I get upset about if I can't pursue.
(20)	When I'm reading a story, I find it difficult to work out the characters' intentions.
(21)	I don't particularly enjoy reading fiction.
(22)	I find it hard to make new friends.
(35)	I am often the last to understand the point of a joke.
(45)	I find it difficult to work out people's intentions.
(46)	New situations make me anxious.
Items changing from <i>definitely agree</i> or <i>slightly agree</i> to <i>definitely disagree</i> or <i>slightly disagree</i>	
(8)	When I'm reading a story, I can easily imagine what the characters might look like.
(10)	In a social group, I can easily keep track of several different people's conversations.
(14)	I find making up stories easy.
(17)	I enjoy social chit-chat.
(25)	It does not upset me if my daily routine is disturbed.
(38)	I am good at social chit-chat.
(44)	I enjoy social occasions.
(47)	I enjoy meeting new people.
(48)	I am a good diplomat.
<i>HC</i>	
Items changing from <i>definitely disagree</i> or <i>slightly disagree</i> to <i>definitely agree</i> or <i>slightly agree</i>	
(9)	I am fascinated by dates.
(42)	I find it difficult to imagine what it would be like to be someone else.
(45)	I find it difficult to work out people's intentions.
Items changing from <i>definitely agree</i> or <i>slightly agree</i> to <i>definitely disagree</i> or <i>slightly disagree</i>	
(8)	When I'm reading a story, I can easily imagine what the characters might look like.
(10)	In a social group, I can easily keep track of several different people's conversations.
(11)	I find social situations easy.
(25)	It does not upset me if my daily routine is disturbed.

Notes: The number in the top of each item indicates the item number in the AQ questionnaire (Baron-Cohen et al., 2001).

which showed that he had become fascinated by dates.

In another opportunity separate from the present study, we asked 11 cases with damage to other parts of the brain (orbitofrontal lesion, $n=3$; basal forebrain lesion, $n=3$; dorsolateral prefrontal lesion, $n=2$; medial temporal lesion, $n=1$; amygdala lesion, $n=1$; and traumatic brain injury, $n=1$) to complete the AQ, to compare

scores and possible personality changes detected by the AQ. Mean score for the 11 cases was 17.0 (range 9–25), and median score was 17.0. All cases declared that personality traits identified on the AQ were unchanged after surgical operations or closed-head injuries.

DISCUSSION

In this study, we presented two cases with damage to the medial PFC and reported performance on various theory of mind tests, personality changes, and behavioral disturbances in daily activities. The two cases displayed damage basically limited to the medial PFC and showed mild difficulties in memory performance in daily activities, but no serious problems in language activities and executive functions. These patterns of results are basically consistent with previous case studies regarding damage to the same area of the brain (Baird et al., 2006; Bird et al., 2004). Concerning theory of mind tests, performance in the first- and second-order false belief test was perfect in both cases. Performance in the advanced theory of mind tests in TO was slightly impaired regarding the provision of appropriate explanations in the strange stories test and was considerably impaired in the identification of inappropriate verbal expressions for given contexts in the faux pas detection test. In contrast, performance in advanced theory of mind tests in HC was not impaired at all in either test. An interesting finding in both cases was that a faux pas was often reported even in control stories without any obvious faux pas.

The notable finding was that both cases showed some difficulties on the faux pas recognition test. The percentage of detecting faux pas and providing appropriate explanations in HC was 100%, compared to 60.0% in TO. Lower performance by TO may have been caused by deficits in delayed recall performance as found in WMS-R and ROCFT (Table 1). Although TO showed higher scores on the two questions for story comprehension (92.5%), he experienced difficulty in recalling the exact story contents. In fact, TO reported the presence of faux pas for all 10 faux pas stories, but could not recall what the exact contents were in each story. Taking these facts into account, his basic performance for detecting faux pas may not have been greatly reduced.

In contrast, both subjects sometimes incorrectly reported faux pas even in stories containing no faux pas, although they could correctly recognize faux pas in stories containing faux pas. Various factors could explain this pattern of results. First, this pattern could result from perseveration of response in both cases. The response for detecting faux pas could be a prevailing response, as half of the questions in the faux pas test did contain faux pas. However, no strong evidence of perseveration was found in either case, since we found very few total perseveration errors on WCST. Second, the pattern could result from general difficulty in understanding global contexts in complex situations. If this were the case, the subjects would show some problems in detecting faux pas in stories containing faux pas. However, the results were in direct opposition to this prediction. A final possibility is overcompensation. In a psychiatric sense, this is often defined as an attempt to overcome an actual defect or unwanted trait by exaggerating in the opposite direction. Self-reports from the two cases indicated that personality change extended to abnormal feelings in some emotional dimensions. Unfortunately, we did not perform any questionnaires examining anxiety traits, even though both subjects reported anxiety after surgery. These changes may have resulted in subjects being more sensitive to verbal expressions compared to before surgery. The explanation of overcompensation is considered the most plausible for understanding the over-detection of faux pas.

The most interesting finding in the present study was that the two cases showed personality changes after surgery, resulting in some characteristics of autism. These tendencies were mainly clarified by findings from the AQ questionnaire. According to the self-reports shown in Table 2, both cases showed a lack of theory of mind ability in everyday life, reduced spontaneous seeking to communicate with others after surgery, and obsessive focus on a single subject. To elucidate greater detail of those characteristics, we compared those items to the items identified in a two-factor structure model (Hoekstra et al., 2008). As a result, 25 items among the total 26 items for the development of autistic personality traits after surgical operations in both cases fell into the “social interaction” factor. This basically identified acquired functional deficits following damage to the medial PFC as a lack of social interaction. Surprisingly, HC even reported

becoming fascinated by dates, which is considered a strong characteristic of autism. Our results for the number of cases with damage to other areas besides the medial PFC revealed that these personality changes resulted from damage to the medial PFC alone.

However, there are limitations to the interpretation of the present results. We asked the cases to fill out the same questionnaire (AQ) twice, and requested on the second trial that they answer from the perspective of their previous personality before surgery. This obviously represents a “retrospective report” in the post-operative period, and the data are clearly of questionable validity. However, the second AQ trial based on self-reports revealed that some personality traits identified by the questionnaire matched well with actual personality changes reported after surgery. This suggests that results of the second trials were substantially valid. The results were consistent with previous imaging studies for Asperger syndrome, showing that the medial PFC is highly involved in understanding theory of mind stories compared to understanding control stories in normal control and Asperger syndrome groups, although level of peak activation was lower in the Asperger group (Happé et al., 1996). Another interpretation of the AQ rise in both cases is the effect of increased depression and/or anxiety. TO and HC both mentioned feeling depressive and anxious in everyday life. Depression and/or anxiety alone might increase the AQ score. However, most of our control cases with damage to other areas beside the medial PFC reported feeling more or less depressed and anxious, but did not show any increase in AQ score after the damage. This evidence suggests that depression or anxiety alone may not greatly affect AQ score.

In terms of laterality of damage in the medial PFC, clarifying differences in the extent to which cases show damage in each hemisphere is generally difficult (Gilbert, Williamson, Dumontheil, Simons, Frith, & Burgess, 2007). As mentioned above, some previous results support the notion that right hemisphere damage shows as impaired understanding of materials requiring attribution of mental state (Happé et al., 1999). More precise examinations of the present results in the two cases suggest that left-sided damage (TO) resulted in greater acquisition of autism traits than right-sided damage (HC). In contrast, oversensitivity in faux pas tests was relatively more associated with right-sided damage (HC) than left-sided damage (TO). Whether these dissocia-

tive patterns of results with laterality in the medial PFC are essential remains unclear. This inference is consistent with a previous study that reviewed the effect of laterality on theory of mind deficits and found no clear distinction in terms of the laterality of damage (Bird et al., 2004). Further studies are required to clarify this issue.

We were also able to determine the exact location of damage in the medial PFC. Amodio & Frith (2006) reported that the more posterior region of the rostral medial PFC is activated by cognitive tasks (e.g., action monitoring and attention), whereas the more anterior region of the rostral medial PFC is activated by emotional tasks (e.g., rating emotional responses to pictures of varying valence) according to a meta-analysis of task-related neural activations observed in the medial PFC. From these perspectives, TO displayed major damage in the more posterior region of the medial PFC, whereas HC showed major damage to the more anterior region of the medial PFC. Although TO's scores on neuropsychological tests showed no declines in executive functions, scores for attention and concentration and for delayed memory in WMS-R were mildly declined. This suggests that TO experienced some minor deficits in attention functions, consistent with the notion expressed by Amodio & Frith (2006), and also suggests that his amnesic syndrome resulted in lower scores in advanced theory of mind tests. Moreover, the result that TO showed greater acquisition of autism traits than HC seems to be explained by greater declines in social interaction, caused by reduced higher cognitive functions and the following reduced motivation to social communications. This explanation is consistent with some previous studies suggesting that dorsal areas within the PFC are highly involved in social behavior, along with the orbitofrontal cortex (Hornak et al., 2003; Mah, Miriam, & Grafman, 2004; Rudebeck, Bannerman, & Rushworth, 2008).

However, performance in theory of mind tests was less impaired for HC, who displayed major damage to the more anterior region of the medial PFC, than for TO. This is consistent with the previous study (Bird et al., 2004) and is inconsistent with the concepts of Amodio and Frith (2006). The anterior medial PFC is presumably required for efficient realization in theory of mind reasoning, but such reasoning may receive support from other brain areas besides the medial PFC in adults. If the anterior medial PFC plays an important role in theory of mind reasoning

through development, we then need to examine whether adults with early-onset damage to the anterior medial PFC show any deficit in theory of mind performance.

Previous studies have reported functional abnormality in the medial PFC in autism-spectrum disorders during social task performance like theory of mind reasoning (Di Martino et al., 2009). Based on the model by Hoekstra et al. (2008), autism personality traits detected in AQ were divided into “social interaction” and “attention to detail” factors. Considering our result that nearly all items for the development of autistic personality traits in both cases fell into the “social interaction” factor, the medial prefrontal area does not seem to be involved in the personality trait for “attention to detail”. Functional abnormality in the medial PFC in autism-spectrum disorders is likely to be associated with a lack of social interaction.

The present study remains preliminary, but some essential implications help in understanding the possible roles of the medial PFC. More research is evidently required to confirm the hypotheses discussed in this study. Besides theory of mind functioning, several recent neuroimaging studies have shown that the medial PFC is involved in moral judgment (Greene, Sommerville, Nyström, Darley, & Cohen, 2001), self-referential processing (Kelley et al., 2002; Schaefer, Berens, Heinze, & Rotte, 2006), memory for self (Macrae, Moran, Heatherton, Banfield, & Kelley, 2004), and detecting the communicative intentions of others (Kampe, Frith, & Frith, 2003). If we expand our discussion by extending the region of interest from the medial PFC to the adjacent anterior cingulate cortex, arguments can be made from the perspectives of cognitive control (MacDonald, Cohen, Stenger, & Carter, 2000), error detection or online monitoring (Carter et al., 2000). Furthermore, the influence of damage to other “social brain” areas needs to be examined. As a recent meta-analysis indicated, the right anterior insula was found to be hypoactive in autism-spectrum disorders compared to the neurotypical control (Di Martino et al., 2009). This area is known to be involved in empathy processing (Singer et al., 2004, 2006). As well as the superior temporal sulcus, amygdala, and posterior cingulate, further examination of the influence of selective damage to these areas on theory of mind performance is required.

Finally, from a comparative neurocognitive perspective, the medial PFC is sure to be an essential area in reaching a full understanding of

the development or evolution of social communications (Rushworth, Walton, Kennerley, & Bannerman, 2004). A morphological study indicated large spindle-shaped cells in layer Vb of the anterior cingulate cortex in pongids and hominids, but not in any other primate species or mammalian taxa (Nimchinsky et al., 1999). Although the ways in which spindle cells contribute to social functions of the anterior cingulate cortex remain unclear, this observation is obviously of great interest in attempts to clarify the mechanisms of possible evolutionary changes to adapt to social worlds.

In sum, we have reported two neurological cases with damage to the medial PFC, focusing on theory of mind performance and personality change. Following damage to this area, both cases showed no impairment on standard theory of mind tests and mild impairments on advanced theory of mind tests. Interestingly, personality changes were found in both cases after surgical operations, leading to characteristics of autism mainly presenting as a lack of social interaction. Recent studies have shown that the medial PFC is involved in various kinds of theory of mind tests. The medial PFC is presumably required for efficient realization in theory of mind reasoning, but such reasoning may receive support from other brain areas in adults. If the medial PFC plays an important role in theory of mind reasoning through development, the critical question in understanding its functions would be whether adults with early-onset damage to the medial PFC show any deficit in theory of mind performance.

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