

Self Responses along Cingulate Cortex Reveal Quantitative Neural Phenotype for High-Functioning Autism

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DOI 10.1016/j.neuron.2007.12.020

SUMMARY

Attributing behavioral outcomes correctly to oneself or to other agents is essential for all productive social exchange. We approach this issue in high-functioning males with autism spectrum disorder (ASD) using two separate fMRI paradigms. First, using a visual imagery task, we extract a basis set for responses along the cingulate cortex of control subjects that reveals an agent-specific eigenvector (self eigenmode) associated with imagining oneself executing a specific motor act. Second, we show that the same self eigenmode arises during one's own decision (the self phase) in an interpersonal exchange game (iterated trust game). Third, using this exchange game, we show that ASD males exhibit a severely diminished cingulate self response when playing the game with a human partner. This diminishment covaries parametrically with their behaviorally assessed symptom severity, suggesting its value as an objective endophenotype. These findings may provide a quantitative assessment tool for high-functioning ASD.

INTRODUCTION

Reciprocal social interaction requires creatures to detect other agents, sense the social signals they emit, and extract relevant information carried by this important signal class. Social signals are a broad and difficult cognitive domain to quantify in humans due in part to the vast empirical and nonempirical literature built around the idea of a social agent acting in the context of others and the myriad of concepts surrounding the idea of the "self" (Decety and Sommerville, 2003; Dennett, 2001; Lieberman, 2007; Mitchell et al., 2006; Northoff et al., 2006; Ochsner et al., 2005; Saxe et al., 2004; Uddin et al., 2007; Vogeley and Fink, 2003). Nonetheless, some of the most important patholo-

gies of mental life revolve around perturbed function in the social domain. One notable example is autism spectrum disorder (ASD). Many symptoms characterize humans diagnosed on this spectrum; however, one prominent feature is the perturbed reaction to social signals emitted by other individuals (American Psychiatric Association, 2000; Baron-Cohen, 2001; Frith, 2001, 2003; Klin et al., 2002; Lord et al., 2000a; Oberman and Ramachandran, 2007).

In recent years, mathematically portrayed economic exchange games have added a new approach to assessing a subject's model of their partner and themselves during an active interpersonal exchange (Delgado et al., 2005; King-Casas et al., 2005; Rilling et al., 2002, 2004; Sanfey et al., 2003; Singer et al., 2006). Fairness games dominate these recent efforts because they assess a subject's internal norm for what is fair in an exchange, and they require that each subject models some aspect of their partner's mental state during the game (Camerer, 2003; Camerer and Fehr, 2006; Kagel and Roth, 1997; Montague and Lohrenz, 2007). Such simplified settings provide an excellent starting point for quantitative descriptions of social signaling and its pathologies because the parameter space is manageable, and reasonable normative solutions to these games exist (Camerer, 2003; but see Greenwald and Jafari, 2003 for complications in solution concepts).

Recent work using the multiround trust game (Figure 1A; King-Casas et al., 2005; Tomlin et al., 2006; also see Results and Experimental Procedures) has identified activations along human cingulate cortex consistent with agent-specific response patterns generated during interpersonal exchange with another human. These patterns differentiate outcomes following revelation of the partner's decision ("not self" or "other" response) from those following submission of one's own decision ("self" response). Remarkably, the patterns are spatially complementary (Figure 1B, adapted from Tomlin et al., 2006), and almost no manipulation perturbs them except one: the removal of the interactive partner (Tomlin et al., 2006). Removal of the social partner causes the cingulate response patterns to disappear even though the sensory, motor, and reward elements of the task

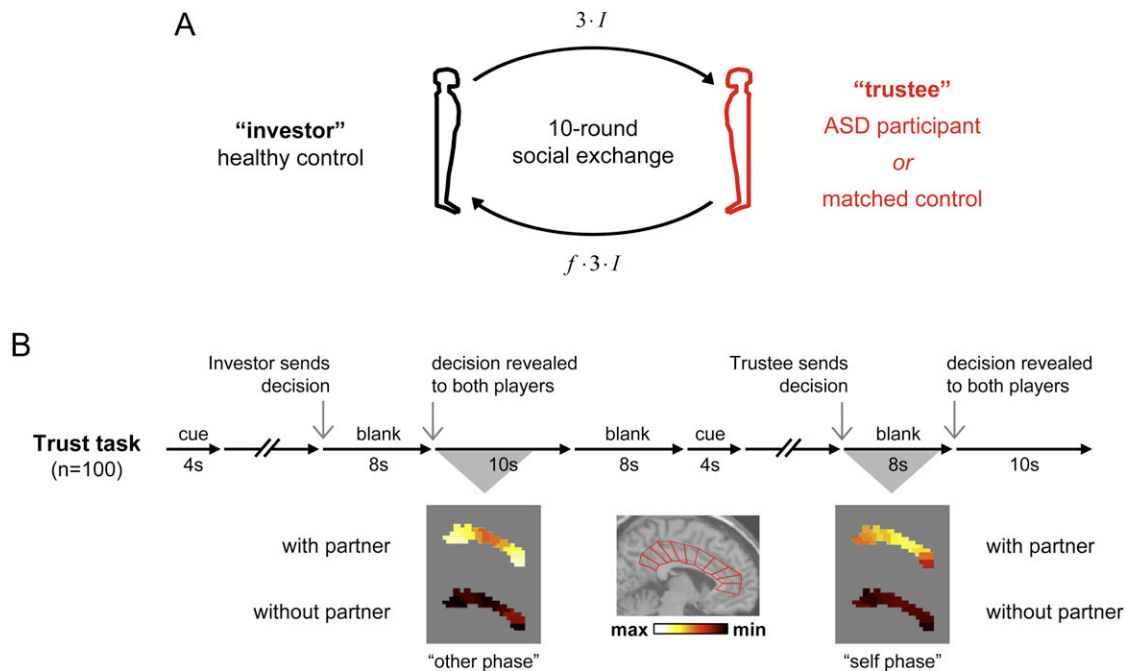


Figure 1. Schematic Representation of the Multiround Trust Game and Agent-Specific BOLD Responses along Cingulate Cortex

(A) Schematic representation of the multiround trust game. In each round, player 1, the “Investor,” is endowed with 20 monetary units. The Investor chooses to send some portion I of this amount to player 2, the “Trustee.” This amount is tripled to $3I$ and sent to the Trustee, who returns some fraction f of the tripled amount. The interaction continues for ten rounds, and the players maintain their respective roles throughout the game. For events labeled “ASD,” the Investor is a non-psychiatric control participant, and the Trustee is a male with autism spectrum disorder or an age- and IQ-matched male control.

(B) Trust task events from which cingulate responses are taken. The base of the gray triangles identify the two 8 s epochs where the “other” and “self” responses are defined, in both cases for the Trustee’s brain. The “other” response is taken as the peak BOLD response in the 8 s following the revelation of the Investor’s decision averaged with its two flanking points, and the “self” response is taken as the peak response in the 8 s following submission of the Trustee decision averaged with its two flanking points. The middle panel depicts the 11 regions of interest (ROIs) along the medial bank of cingulate cortex. The left panel shows the average cingulate “other” response for each of the 11 domains from a database of 100 Trustees in this game. The right panel shows the cingulate “self” response from the same database. The lower panels show that these agent-specific response patterns disappear outside the context of social exchange when the interactive partner is removed yet motor, monetary earnings, and visual aspects of the game remain constant (adapted from Tomlin et al., 2006); $n = 17$ and 15 for sensory and motor controls, respectively. Maximum and minimum activations in the “other” response are 0.25% and -0.10% change in MR signal, and 0.30% and -0.20% in the cingulate “self” response.

remain intact (Figure 1B, adapted from Tomlin et al., 2006). These results from the trust game are consistent with agent-specific cingulate responses observed in a range of other experiments. Anterior and posterior cingulate activation occurs in response to the revelation of decisions of others in two-person games like the Ultimatum and Prisoner’s Dilemma games (Rilling et al., 2004). Furthermore, increased middle cingulate activation is commonly observed in response to one’s own social decisions or emotions (Jackson et al., 2006; Lamm et al., 2007; Singer et al., 2004; Tomlin et al., 2006).

The consistency of these agent-specific cingulate response patterns and their capacity to be estimated from single subjects (see Supplementary Online Materials of Tomlin et al., 2006) suggest their utility for understanding pathologies characterized by impairments in the social domain. In this paper, we pursued two goals. First, we sought to develop a standard basis set for the cingulate response against which expressions of agency might be compared quantitatively across groups. Second, we sought to use this neural basis set to assess agent-specific responses in a group specifically impaired in the social domain: individuals with autism spectrum disorder.

RESULTS

The results fall into three domains, which we sketch here. First, we report data from a visual imagery task used to validate our designation of the “self” and “other” response patterns along cingulate cortex (Rilling et al., 2004; Tomlin et al., 2006). The imagery task has two important epochs: one where subjects watch others performing specialized actions and another where subjects imagine themselves performing the action. The imagery experiment removes the complicating features present in the trust game: playing another human, motor acts to report decisions, gaining and losing money, and rounds preceding and following each choice. Second, we use principal component analysis of the cingulate responses during the “imagining self” epoch to produce a neural basis set. This approach identifies a “self eigenmode” which differentiates “imagining self” from “watching others” and which also appears during the “self” phase of the trust game. Finally, we use the self eigenmode to quantify cingulate responses of high-functioning males with autism playing the multiround trust game with a human partner.

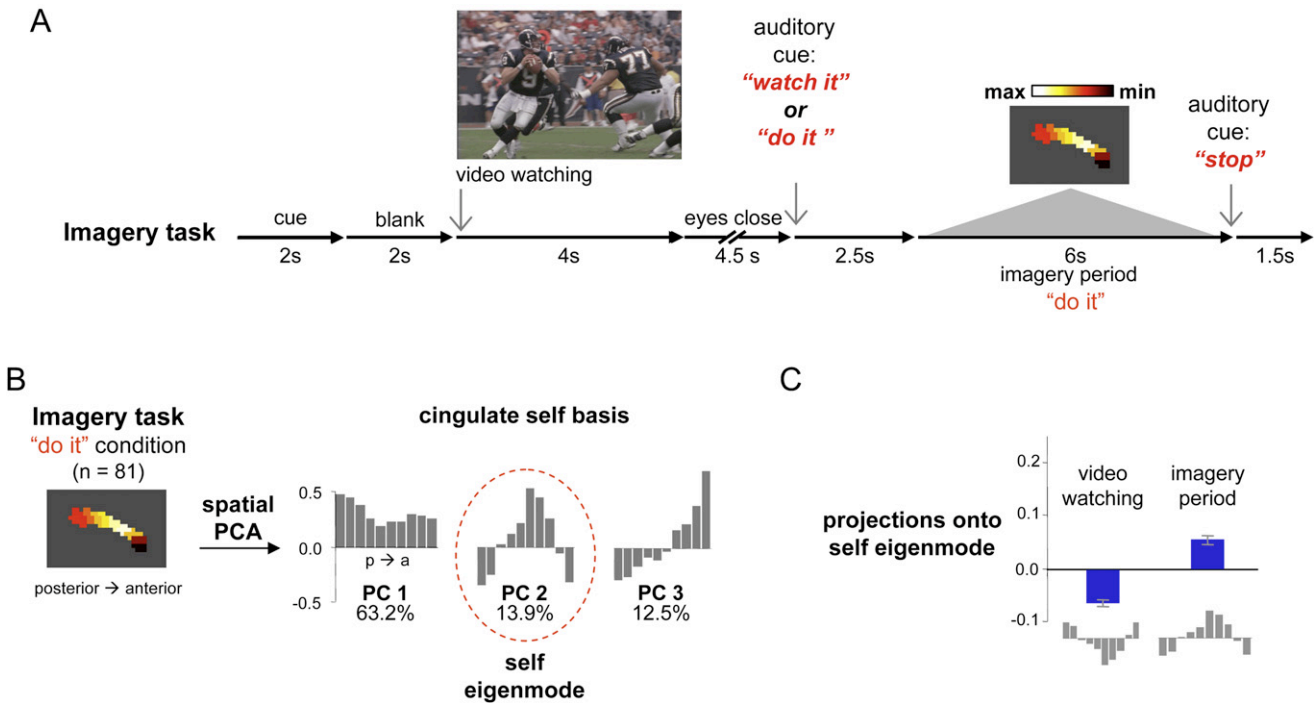


Figure 2. Cingulate Self Response and Self Eigenmode Identified in Visual Imagery Task

(A) Schematic representation of the visual imagery task. In each trial, subjects were presented with a visual cue (2 s) indicating a target person to be presented in an upcoming video. The subsequent video clip (4 s) depicted a specialized athletic act (e.g., kicking, throwing, dancing). Subjects were instructed to close their eyes upon video offset, then presented with an auditory cue to either “watch it” or “do it.” “Watch it” indicated that subjects were to imagine watching the actions in the video again, keeping the perspective of a spectator (third-person perspective). The “do it” cue indicated that subjects were to imagine the actions in the video from the perspective of the target athlete (first-person perspective). A final auditory cue (“stop”) indicated the end of the trial, upon which subjects were to open their eyes in preparation for the next trial. Maximum and minimum values in the mean cingulate “do it” BOLD response are 0.03% and -0.12% change in MR signal.

(B) Imagery task identifies cingulate self basis. Spatial principal components analysis was performed on cingulate responses comprising participants’ peak % MR signal change extracted from ten equally sized spatial domains along the anterior-posterior axis of the medial cingulate cortex. The most posterior cingulate domain is marked with a “p,” and the most anterior domain is denoted “a.” Note that the spatial pattern of principal component 2 (dotted red circle) resembles that of the “self” response seen directly in the time series of the “self” phase of both the visual imagery task and the multiround trust game (Figures 1B and 2A).

(C) Cingulate “self eigenmode” identified in visual imagery task. BOLD responses from the video-watching (“other”) and first-person (“self”) imagery phases of the visual imagery task are projected respectively onto the cingulate self-basis. The projection coefficients, plotted with SEM bars, of the BOLD responses on principal component 2 (Figure 2B, dotted red circle) significantly differentiates the two experimental conditions ($p = 1.87 \times 10^{-15}$) and warrants the term “self eigenmode” to describe this discriminating eigenvector.

Visual Imagery Task

Subjects watched short film clips depicting athletic actions (e.g., kicking a ball, dancing), then closed their eyes and imagined themselves performing that act from a first-person “self” perspective (see Figure 2A and Experimental Procedures). The task contains an epoch of watching others perform an action and an epoch where the subjects imagine themselves performing the action. These distinct task demands respectively define the “other” and “self” conditions in the visual imagery task.

Multiround Trust Game

The multiround trust game is an economic exchange game between two interacting players (Delgado et al., 2005; King-Casas et al., 2005; McCabe et al., 2001; Tomlin et al., 2006). It is a simple game to play and evokes parameterized social signals characteristic of many reciprocal interactions. During each round, one player (“Investor”) is endowed with a resource (here 20 monetary units) and chooses to send some portion of the endowment to

their partner, the “Trustee.” This chosen amount is tripled on its way to the Trustee, and the Trustee decides what fraction of the tripled amount to repay to the Investor (Figure 1A). This pay-repay cycle and the two decisions within it (*invest*, *repay*) constitute a round of play. The basic exchange is repeated within the interacting partners for ten rounds. Players maintain their respective roles for all ten rounds. The game engages basic social exchange mechanisms since players must repeatedly produce self-initiated actions and recognize their partner as a separate receiving agent during the social interaction. The revelation of a partner’s decision and the submission of a player’s decision respectively define the “other” and “self” phases of the trust game.

Agent-Specific Basis Sets in Cingulate Cortex

As outlined above, neural responses elicited in unselected control populations playing the multiround trust game are well characterized (Delgado et al., 2005; King-Casas et al., 2005; McCabe

et al., 2001; Tomlin et al., 2006; Figure 1B). While the robust cingulate activation patterns following the submission of one’s “own” decision and the observation of an “other’s” decision are highly suggestive of distinct agent-specific hemodynamic responses, the observed “self” and “other” response patterns may be influenced by motor actions, responses to monetary rewards, or reactions to one’s partner in the game. To reduce the functional heterogeneity of responses elicited in the cingulate cortex (Botvinick et al., 2001; Rushworth et al., 2007), we implemented a visual imagery task that required participants merely to imagine performing an act from the first-person (“self”) perspective (cf. K.T.K. et al., unpublished data). The peak hemodynamic response during the self-imagery phase was extracted from each of ten equally sized spatial domains along the anterior-posterior axis of the cingulate cortex. As illustrated in Figure 2A, the self phase of the visual imagery task elicits a hemodynamic activation pattern along the anterior-posterior axis of the cingulate cortex identical to that seen in the self phase of the multi-round trust game. Specifically, when simply imagining performing a motor act from the first-person perspective, subjects ($n = 81$ controls) exhibit greater middle cingulate activation relative to anterior and posterior cingulate (Figure 2A; cf. K.T.K. et al., unpublished data).

A neural basis set upon which the cingulate “self” response could be further quantified was then defined using spatial principal components analyses (sPCA) of the peak BOLD responses across the ten domains of cingulate tissue space extracted from 81 subjects during the “self” phase of the visual imagery task (see [Experimental Procedures](#) and K.T.K. et al., unpublished data). The first three principal components resulting from this sPCA account for 89.6% of the variance in the hemodynamic response in the self phase of the imagery task (Figure 2B). These eigenvectors thus comprise a neural “self basis” upon which subjects’ hemodynamic responses in cingulate cortex was further characterized.

Visual Imagery Task Identifies Self Eigenmode

Projections of the self-phase cingulate BOLD response patterns upon each principal component of the self basis further revealed that only one eigenvector differentiated the video-watching (“other”) and self-imagery (“self”) phases of the visual imagery task (Figure 2C; see also [Experimental Procedures](#) and K.T.K. et al., unpublished data). This eigenvector, principal component 2 in Figure 2B, is subsequently designated the “self eigenmode.” We note that the shape of the self-eigenmode parallels that seen in the hemodynamic “self” activation pattern across the cingulate cortex in *both* the multi-round trust game and visual imagery task: relatively greater activation in middle cingulate domains and less activation in the anterior and posterior ends of the cingulate cortex (compare the spatial distribution of PC2 in Figure 2B to the cingulate BOLD response in Figure 2A).

Self Eigenmode Arises in Multi-round Trust Game

Parallel analyses of hemodynamic responses in the “other” and “self” phases of the multi-round trust game reveal patterns remarkably similar to those seen in the visual imagery task along the anterior-posterior axis of the cingulate cortex. That is, sPCA of peak BOLD activations in the “self” phase of the trust game yielded a neural basis whose first three components account for 92.6% of the variance in cingulate hemodynamic response.

Moreover, the trust task self basis contains an eigenvector (PC3 in Figure 3B) whose shape closely resembles both the self eigenmode identified in the visual imagery task (PC2 in Figure 2B) and the BOLD response pattern in the self phase of the trust game: greater amplitude in middle cingulate domains and smaller response in the anterior and posterior ends of the cingulate cortex (compare PC3 in Figure 3B to the cingulate BOLD response depicted directly above and to the self eigenmode in Figure 2B). In contrast, sPCA of peak BOLD activations in the “other” phase of the trust game reveals a neural basis identical to that seen in the “self” phase, *except* in one eigenvector (PC3, red dotted circle, Figure 3A) that is exactly the shape of an inverted self eigenmode. Expression of the self eigenmode is near zero or negative “other” phase of the multi-round trust game (Figure 4A) and reaches maximal positive amplitude subsequent to a players’ decision during the “self” phase (Figure 4B) of the game.

Diminished “Self” Response in Autism Spectrum Disorder

The presence of the self eigenmode in the trust game suggests the utility of using this measure to characterize individuals with specific impairments in the social domain that may be conferred by deficits in agent-specific inferences. To this end, we detailed the response pattern along the medial bank of cingulate cortex in individuals with ASD while they played the multi-round trust game (see [Experimental Procedures](#) for complete participant characteristics).

Behavioral Play of the ASD Group Does Not Differ on the Multi-round Trust Game

To first confirm basic cognitive understanding of the trust task demands, we examined the behavioral strategies in the ASD group as compared with both our large neurobehavioral database in the trust game and also a group of age- and IQ-matched controls. In addition, the 15 database pairs closest to the ASD average behavioral vector comprised a “behavioral control group” that was later used to test the possibility that play with an individual with ASD somehow accounted for any observed neural differences. As depicted in Figures 5A–5C, the behavioral trajectories and game outcomes of the ASD group did not differ from any of the three control groups, providing strong evidence that in both the ASD group and adolescent controls, cognitive understanding of the task was intact.

Diminished “Self” Response in BOLD Analysis of Cingulate Cortex in ASD

Despite the intact behavioral play, a stark difference between the cingulate response patterns of the ASD and the two unique control groups emerged from time series analyses of the “self” and “other” phases of the trust game. The age- and IQ-matched control group showed strong middle cingulate activation subsequent to their own decisions that exactly resembled the cingulate “self” response patterns reported previously in both the trust game and perspective-taking tasks (Figures 1B and 2B; Jackson et al., 2006; Lamm et al., 2007; Singer et al., 2004; Tomlin et al., 2006; K.T.K. et al., unpublished data). In striking contrast, the self response pattern was absent in the ASD group (Figure 6A; third row, white asterisk) and resembles that observed when controls play the game in the absence of a social partner (Figure 1B and

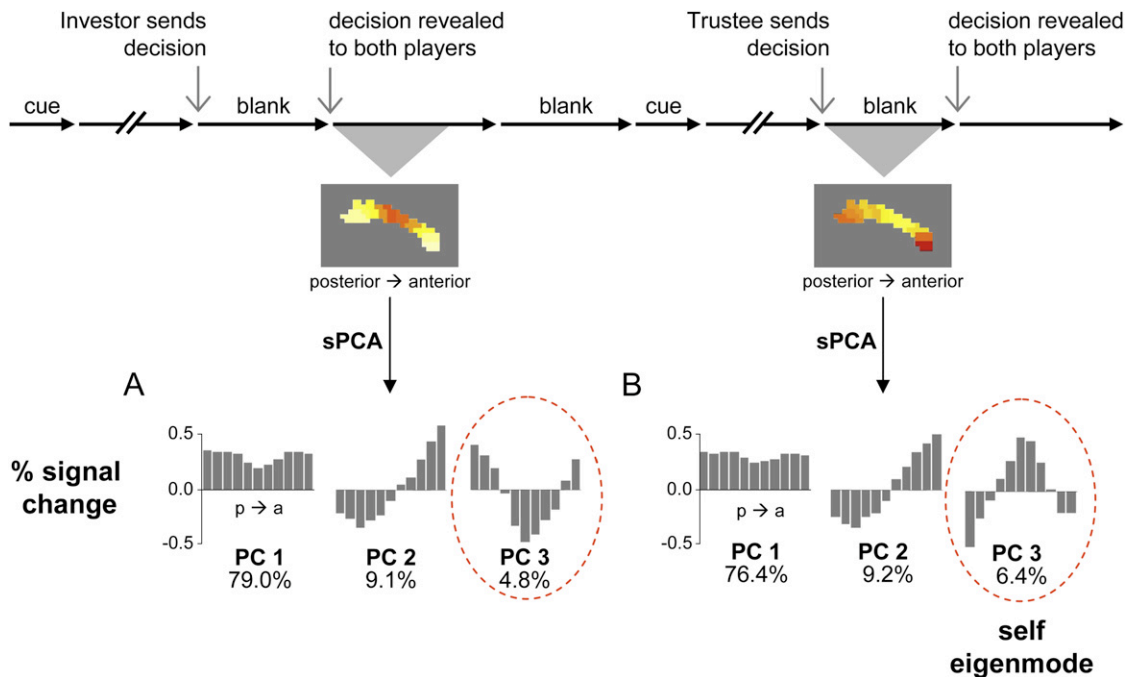


Figure 3. Trust Task Reveals Complementary Agent-Specific Cingulate Basis Sets and Self Eigenmode

Spatial principal components analysis (sPCA) was performed on our database of normative cingulate “other” responses consisting of 100 adult Trustees’ average peak % MR signal changes extracted from 11 distinct and equally sized spatial domains along the anterior-posterior axis of medial cingulate cortex; mean cingulate BOLD responses reproduced from Figure 1B and Tomlin et al. (2006). The results of the sPCA on cingulate responses in the “other” and “self” phases of the trust game are depicted here. Segment “p” refers to the most posterior cingulate domain; segment “a” refers to the most anterior cingulate domain.

(A) The “other” phase of the trust game is depicted here and references the time points surrounding the revelation of the Investor’s decision to the Trustee’s brain. The spatial patterns of the first three principal components, accounting for 92.9% of the variance in cingulate activation, are illustrated here. Note that the spatial pattern of principal component 3 (dotted red circle) resembles the normative “other” response observed in the time series data and is an inverted complement of the self eigenmode.

(B) The “self” phase of the trust game is depicted here and references the time points surrounding the submission of the Trustee’s own decision in the game. The spatial patterns of the first three principal components, accounting for 92.0% of the variance in cingulate “self” activation, are illustrated here. The spatial pattern of principal component 3 (dotted red circle) closely resembles that of the self eigenmode and the normative “self” response reported directly from the time series in the visual imagery task and multiround trust game (see Figure 1A and Tomlin et al., 2006).

Tomlin et al., 2006). Equally important, the reduction in the cingulate response was not all-or-none but correlated with symptom severity in the ASD group (Figure 6B; as assessed with the Autism Diagnostic Interview-Revised; Lord et al., 1994). Despite the diminished “self” response, ASD participants had a normal “other” response pattern that was indistinguishable from the age- and IQ- matched controls and exactly resembled the “other” response reported previously to the revelation of the social decisions of others (Figures 6A, 1B, and see Figure S1 available online; Rilling et al., 2004; Tomlin et al., 2006).

Self Eigenmode Reduces Diminished ASD Self Response to Single Projection Coefficient

Finally, we used the neural agent-specific basis sets identified in the trust game and visual imagery tasks as normative standards against which the ASD cingulate “self” deficit could be quantified. Specifically, we projected the cingulate responses of the ASD group and the age- and IQ-matched controls onto both the neural “self” and “other” bases of the trust task and compared the projection coefficients across groups on each principal component. The projections were not different except in one principal component and one condition—the third princi-

pal component of the cingulate “self” basis, or the self eigenmode. In this projection, the ASD group-averaged coefficient differed significantly from both the age- and IQ- controls and behavior-matched controls (Figure 6C). Moreover, the ASD projection coefficient onto the self eigenmode (PC3) was not different from zero ($p = 0.19$) while the coefficients of the adolescent and behavior-matched controls were both significantly different from zero ($p = 0.000013$ and $p = 0.0000054$, respectively; Figure 6C). As further detailed in the Supplemental Data (Figure S1), the ASD and control groups did not differ on any projection coefficient onto any eigenmode identified in the “other” basis.

DISCUSSION

In two distinct large data sets and experimental tasks, we report robust agent-specific hemodynamic response patterns along the anterior-posterior axis of the cingulate cortex. Linear space analyses of these response patterns defined agent-specific cingulate basis sets containing a single eigenmode that differentiates “self” from “other” task phases. Equally important, the reduction of agent-specific responses to a single discriminating

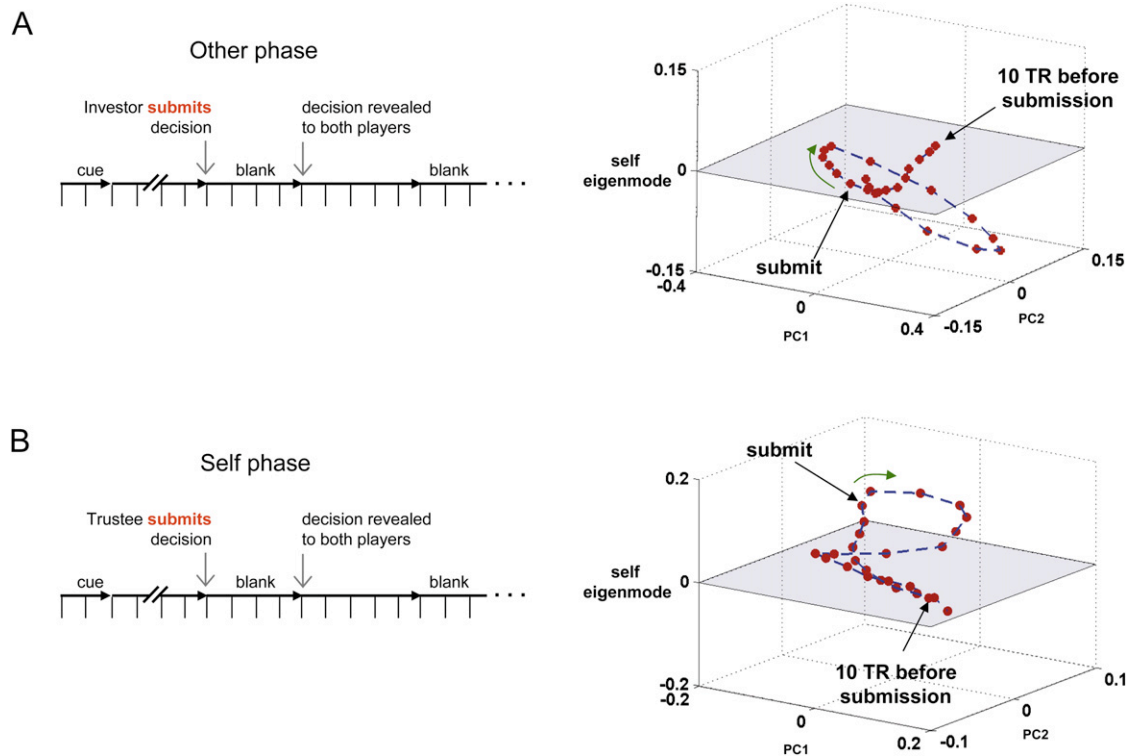


Figure 4. Expression of the Self Eigenmode during the Multiround Trust Game

Trustees' cingulate hemodynamic response patterns at each TR (2 s) in the “other” and “self” phases of the trust game were projected into the three-dimensional space whose axes comprise the first three eigenvectors of the neural self basis (projection coefficients at each TR indicated by red circles). In doing so, we tracked the expression of the self eigenmode (PC3 in Figure 3B) across the course of the trust game. The coefficient of the self eigenmode is (A) near zero or negative during the entire “other” phase of the trust game and (B) reaches maximal positive amplitude after the submission of players' decisions.

vector, the self eigenmode, allowed the detailed examination of these patterns in individuals with ASD.

During the multiround trust game, high-functioning males with ASD lack a neural activation pattern in cingulate regions previously shown to encode robust self-specific responses. In stark contrast with the missing self response, the ASD cingulate cortex responded normally when shown a social partner's decision. The normal response of the ASD cingulate cortex to the decision of others highlights that the diminished self response is not a global anomaly of the cingulate in ASD but rather a deficit specific to the self phase of the trust game. The absent self response closely resembles the lack of cingulate activation when healthy controls perform the iterated trust game outside the context of a social exchange and instead submit computer-guided responses in the absence of a responsive social partner (Tomlin et al., 2006).

The reduced cingulate self response pattern (i.e., reduced self eigenmode) and intact other response suggests that in the context of the iterated trust game, individuals with ASD may be impaired in the capacity to represent the social intent of their own behaviors, yet remain able to represent the actions of others. That is, the capacity to represent simple social actions of others may exist despite impoverished models of one's own intentions. In this case, the “other” response pattern may reflect cingulate functions related less to intuiting others' social intent than obser-

vations of others' acts (e.g., Amodio and Frith, 2006; cf. K.T.K. et al., unpublished data). In comparison, the reduced cingulate self response pattern may reflect a diminished capacity to model one's own social intent that subsequently contributes to the poor performance commonly seen in individuals with ASD on theory-of-mind tasks. These tasks typically require a subject to put himself “in another agent's shoes” to infer the intentions of that agent (Frith and Frith, 2006) and, by extension, individuals lacking a capacity to delineate their own intentions are likely unable to attribute the social goals or intentions of others. Although our data cannot distinguish among these hypotheses, the diminished self response in ASD supports a recent shift toward understanding autism in the context of dysfunctions in introspection or self-referential processing (Baron-Cohen, 2001; Frith, 2001, 2003; Hill, and Frith, 2003; Iacoboni, 2006; Kennedy et al., 2006).

It should be emphasized that the precise cognitive processes elicited by the submission of a player's decision and revelation of a partner's decision in the iterated trust game are complex; consequently, we use the terms “self” and “other” in the trust game primarily to label the observed spatial patterns of response that appear across the medial bank of the cingulate in the two distinct phases of the task: subsequent to a player's own decision (“self”) and subsequent to the revelation of the partner's decision (“other”). Both phases of the trust task are very likely

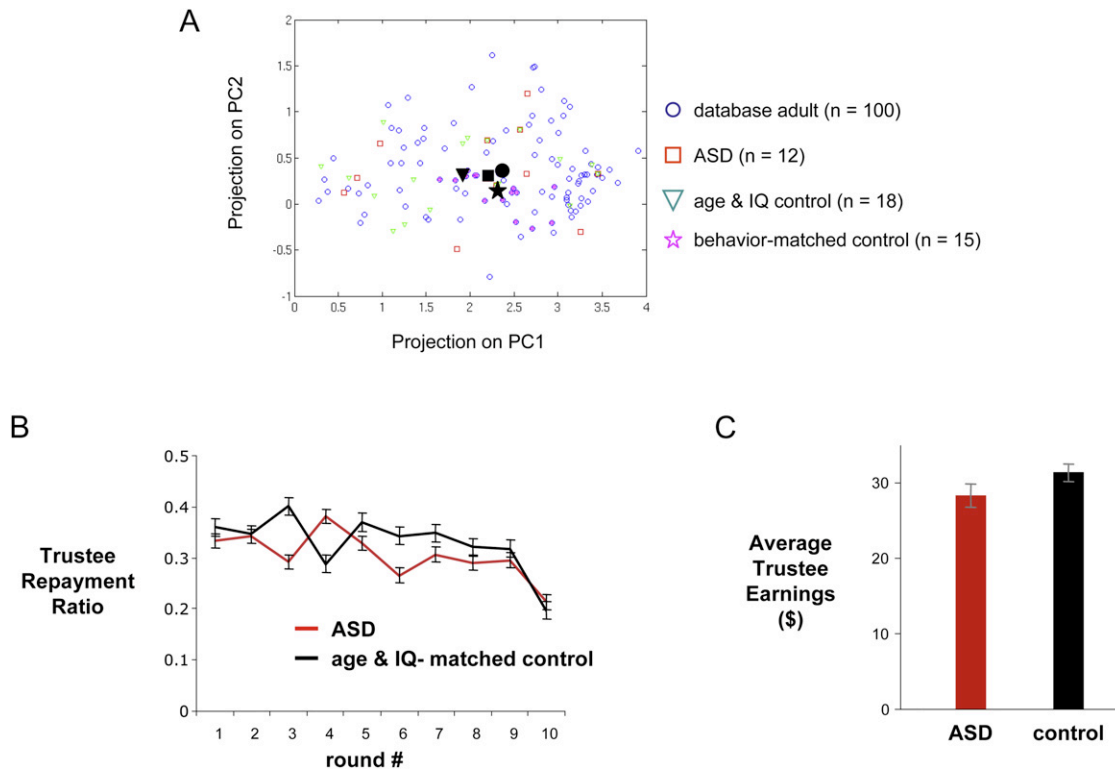


Figure 5. Behavioral Characterization of ASD, Age- and IQ-Matched Control, and Behavior-Matched Control Pairs on the Iterated Trust Game

(A) Dyadic behavioral trajectories do not differ among ASD, normative, and age- and IQ-matched controls. To characterize the behavioral exchange of each experimental pair, we formed vectors composed of the series of investment ratios ($I = \text{Investment}/20$) and fractions of Trustee repayments ($R = \text{repayment}/3 \cdot I$) over the ten rounds of a dyad's exchange. The behavioral vector for each pair p is denoted $U^p = (I_1, R_1, I_2, R_2, \dots, I_9, R_9, I_{10}, R_{10})$, where I_n represents the fraction invested in round n and R_n represents the fraction repaid in round n . All Investors were adult controls; the indicated experimental groups are identified by the participants in the Trustee role. The behavioral vectors for each pair of each experimental group (ASD, age and IQ control, database adult control) are projected onto the plane defined by the first two principal components of the behavioral data from 100 iterated trust exchanges in our database of adult controls. The projections of the 20-dimensional behavioral vectors onto this plane are identified as follows: blue circles = database adults, red squares = ASD, green triangles = age and IQ-matched controls, blue circles with overlaid purple stars = behavioral controls. Open shapes represent the projections of the behavioral vectors of each pair; solid black shapes represent the projections of the average behavioral vector of the indicated group. Behavioral controls are those 15 pairs from our normative database whose pattern of play most closely resembled that of the ASD pairs (see [Experimental Procedures](#) for detailed description of control selection).

(B) Round-by-round trustee repayment ratio and SEM for ASD and age- and IQ-matched control groups. Average trustee repayment ratio across the ten rounds of the trust game do not differ between ASD and controls, supporting intact cognitive understanding of the basic elements of the task.

(C) Average Trustee earnings and SEM for ASD and age- and IQ-matched controls. Average total earnings on the multiround trust game do not differ between the ASD and control group.

accompanied by a myriad of complex cognitive phenomena. For example, in the “self” phase of the game, inferring the social goals and intentions of others is expected for healthy individuals—making a gesture in a social interaction should elicit computations of how one's actions influence the behavior of one's partner (Frith and Frith, 2006; King-Casas et al., 2005). Although the current data cannot be definitive with regard to the function of the cingulate cortex, the data from the visual imagery task supports the designation of the “self” pattern in both tasks. Moreover, while deficiencies in the social domain are specifically implicated in autism (American Psychiatric Association, 2000; Baron-Cohen, 2001; Frith, 2001, 2003; Klin et al., 2002; Lord et al., 2000a; Oberman and Ramachandran, 2007), the degree to which our data fit with existing theories about ASD remains an intriguing avenue of future research.

The self eigenmode provides a useful quantitative measure for differentiating the “other” condition from the “self” condition on both the trust game and the imagery task. In the imagery task, the “watching others” epoch showed a negative projection coefficient onto the self eigenmode as estimated from a large number of subjects ($n = 81$; $p = 1.87 \times 10^{-15}$; Figure 2). The negative projection coefficient means that the “watching others” condition elicits a spatial pattern of response complementary to the self eigenmode (Figure 2C) and exactly analogous to the response when a partner's decision is revealed in the trust game (Figure 3). To reiterate, the peak response domain in the self eigenmode (middle portions of the cingulate) lies precisely in the same regions identified when subjects imagine emotions or actions from a first-person perspective (Jackson et al., 2006; Lamm et al., 2007; Singer et al., 2004).

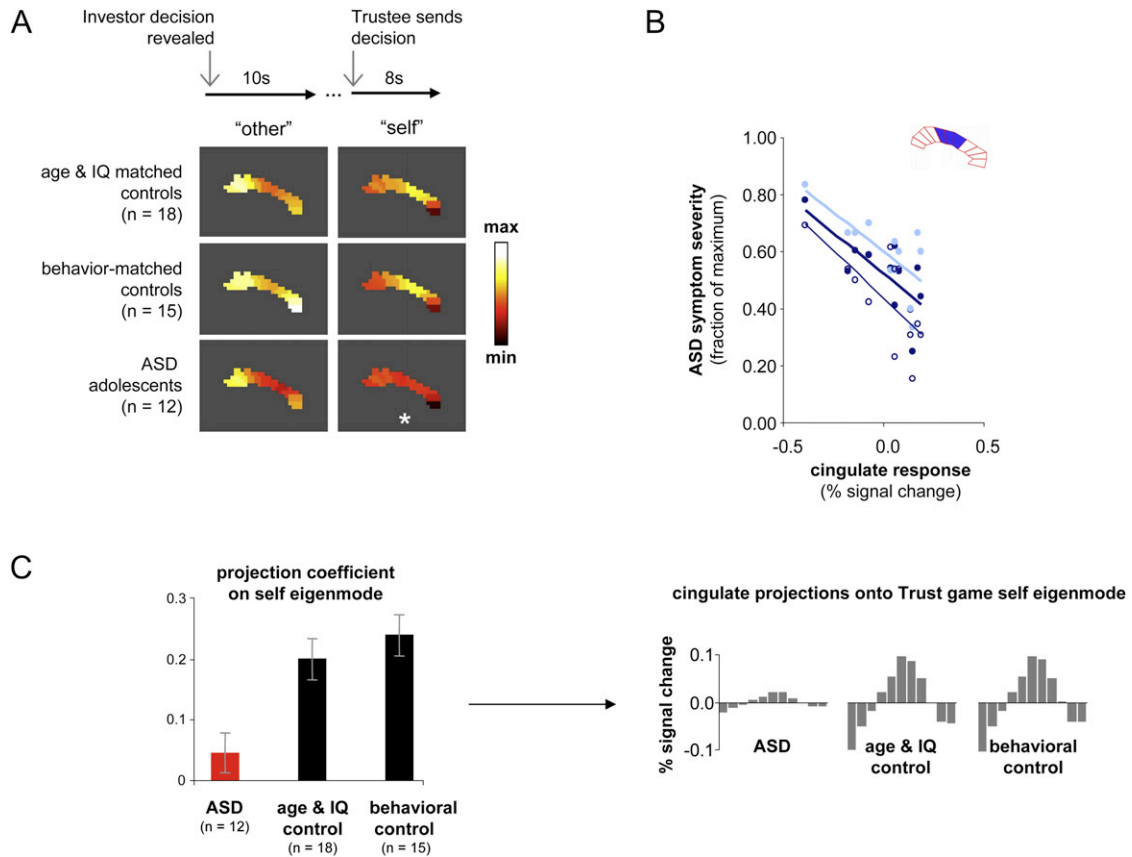


Figure 6. Diminished Cingulate “Self” Response in Autism Spectrum Disorder

(A) Participants with ASD lack cingulate “self” response pattern. Cingulate responses to the revelation of a partner’s decision (“other” response pattern) and following the submission of one’s own decision (“self” response pattern) are shown for the ASD group (n = 12), age- and IQ-matched controls (n = 18), and controls whose pattern of play was behavior-matched to the ASD dyads (n = 15; see [Experimental Procedures](#) for details of group selection). The revelation of a social partner’s decision elicits an unperturbed cingulate response pattern in the ASD and control groups (left column). In stark contrast, the activation following one’s own decision is missing in the ASD group (white asterisk; $p = 0.001$ two-tailed for ASD versus age- and IQ-matched controls; $p = 0.0004$ for ASD versus behavior-matched controls). Maximum and minimum activations in the “other” response are 0.25% and -0.10% change in MR signal, and 0.30% and -0.20% in the cingulate “self” response.

(B) Lack of cingulate “self” response pattern relates parametrically to ASD symptom severity. The reduction in the “self” response pattern in ASD participants correlates with symptom severity on the Autism Diagnostic Interview-Revised. The ASD participants’ average cingulate response across the three middle segments and the fraction of maximum ADI subscale score are depicted: ADI total score (dark circles; $r = -0.73$, $p = 0.007$), ADI social subscale (light circles; $r = -0.70$, $p = 0.011$), and ADI communication subscale (open circles; $r = -0.69$, $p = 0.012$). No significant correlation was observed between the ADI repetitive behavior subscale and cingulate “self” response ($r = -0.34$, $p = 0.28$). Moreover, *no significant correlations* were observed between scores on any ADI symptom domain and any cingulate region’s “other” response.

(C) Cingulate response basis set reduces diminished ASD “self” response to a single projection coefficient. To test for between-group differences in the “self” cingulate response pattern, two-tailed t tests were performed on the ASD and the two control groups’ expansion coefficients onto each principal component (PC) of the neural “self” basis set. This analysis identified an attenuated response in the ASD group specifically along the self-eigenmode (PC3 in [Figure 3B](#)) compared with both the age- and IQ-matched controls ($p = 0.0036$) and the behavior-matched controls ($p = 0.00043$; SEM is indicated; see [Experimental Procedures](#) for control selection procedures). For all other comparisons between the ASD and control groups on the remaining PCs, $p > 0.1$. The diminished contribution of the self eigenmode to the cingulate BOLD response in ASD is illustrated in the right panel.

Future parametric experiments are required to make functional distinctions of cingulate cortex with precision. Ultimately, the quantification of neural phenotypes using neural response basis sets elicited in the context of social exchange may serve as a diagnostic tool, identify subtypes of autism, or be used to seek covariates in genetic databases. More generally, the use of neural response basis sets derived from large normal data sets facilitates the reduction of complex phenotypes to single coefficients relative to normative

standards. In ASD, the present data suggest that a quantitative analysis of neural responses on tasks as simple as video-watching may be of diagnostic and therapeutic utility. Indeed, the further question emerges whether the cingulate “self” response and related capacity in ASD may be evoked with real-time feedback about the self eigenmode combined with targeted task instructions or behavioral therapies dedicated to increasing individuals’ representations of the self role in goal-directed social interactions.

Table 1. Demographic and Diagnostic Measures

Variable	Control Group (n = 18)	ASD Group (n = 12)
	Mean ± SD	Mean ± SD
Age	14.9 ± 2.2	16.5 ± 3.3
IQ ^a		
Composite	108 ± 13	103 ± 18
Verbal	108 ± 13	101 ± 18
Nonverbal	106 ± 15	105 ± 15
ADI-R ^b		
Social interaction	—	17.9 ± 4.0
Communication	—	11.1 ± 4.3
Stereotyped behavior	—	6.2 ± 2.6

All between-group comparisons, $p > 0.1$.

Social interaction: qualitative abnormalities in reciprocal social interaction.

Communication: qualitative abnormalities in communication.

Stereotyped behavior: restricted, repetitive, stereotyped patterns of behavior.

^a Assessed with the Kaufman Brief Intelligence Test, Second Edition.

^b Autism Diagnostic Interview-Revised.

EXPERIMENTAL PROCEDURES

Participants

Multiround Trust Game with ASD

Participants comprised 16 high-functioning adolescent and young adults with autism spectrum disorder (ASD) and 20 typically developing control adolescents. All participants were male. Due to excessive motion during the experiment, four ASD and two control individuals were excluded from analysis. This brought the ASD group to 12 and the control group to 18 participants who underwent analysis of BOLD responses. The ASD group was recruited from the University of Alabama Autism Spectrum Disorders Research Clinic (L. Klinger, Director). Age-, gender-, and IQ-matched control individuals with no known psychiatric disorders were recruited from the Houston metropolitan area by word of mouth and internet and poster advertisements. Following an initial screening in which basic fMRI contraindications were assessed, qualifying individuals were invited to the laboratory for diagnostic assessment and scanning. In accordance with the Institutional Review Boards of Baylor College of Medicine and the University of Alabama, Tuscaloosa, written informed consent, or parental assent for participants under 18, was obtained at the first laboratory visit.

Inclusion and exclusion criteria for the ASD group were assessed using the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000b), administered by a PhD-level clinical psychologist or trained advanced doctoral students. Diagnoses of ASD were subsequently made according to DSM-IV criteria for autistic disorder, Asperger's disorder, or PDD NOS. For all adolescents, IQ was assessed with the Kaufman Brief Intelligence Test, Second Edition (K-BIT-2; Kaufman and Kaufman, 2004). The following exclusion criteria were additionally applied to all potential participants during recruitment: left-handedness, history of seizures, head injuries resulting in more than 10 min of unconsciousness or with neurological sequelae. History of taking psychotropic medication was a further exclusion criterion for the control group. The current psychotropic medication use among participants with ASD was: sertraline ($n = 1$), atomoxetine ($n = 1$), sertraline and methylphenidate ($n = 1$).

The ASD and control groups did not differ on gender, age, or IQ measures. Means and standard deviations of these measures are presented in Table 1.

Visual Imagery Task with Controls

A total of 81 subjects performed the visual imagery task. Individuals were trained athletes recruited from local professional athletic teams and collegiate institutions' athletic departments (cf. K.T.K. et al., unpublished data). All

subjects provided written informed consent in accordance with Institutional Review Board guidelines at Baylor College of Medicine.

Task Procedures

Multiround Trust Game

The multiround trust game is an iterated economic exchange between two players (King-Casas et al., 2005; Tomlin et al., 2006; Figure 1A). During each round, one player (“Investor”) is endowed with a resource (here 20 monetary units) and chooses to send some portion I to their partner the “Trustee.” This chosen amount is tripled to $3I$, and the Trustee decides what fraction f of the tripled amount to repay to the Investor (Figure 1A). This pay-repay cycle constitutes a round of play, and the basic exchange is repeated within the interacting partners for ten rounds. In the present version of the trust game, players maintained their respective roles for all ten rounds and did not meet before, during, or after the game. Players were not given any cues or suggestions about strategy. The timeline of events is presented in Figure 1B; rounds were separated by a variable 12 to 42 s intertrial interval.

Visual Imagery Task

Subjects were instructed that they would be viewing videos of individuals performing specialized athletic acts and asked to imagine these performances from two different perspectives (Figure 2A). Each video clip in the imagery task depicts athletes performing in the presence of other players. These athletes include quarterbacks throwing to other football players, soccer players kicking the ball to teammates, and ballerinas dancing amidst a troupe. At the beginning of each trial, subjects were cued to a target person. The video was then presented (4 s) and on completion of the video, subjects were presented with a brief auditory cue to “watch it” or “do it.” Subjects were instructed to close their eyes subsequent to completion of the video, and prior to the auditory cue (4.5 s window). On “watch it” trials, subjects were asked to imagine watching the actions in the video again, from the spectator (third-person) perspective. On “do it” trials, subjects were instructed to imagine performing the actions from the perspective of target person in the video (first-person). Subjects were given 6 s to visualize in the indicated perspective prior to an auditory cue to “stop,” at which time the subjects were to open their eyes and await the beginning of the next trial (intertrial interval = 8 s). The timeline of events is presented in Figure 2A.

All subjects saw the same video clips twice during a session. A total of 24 clips (six from each of four sports) were shown twice to each subject, such that each clip was imagined in both the first- and third-person perspective. The order of presentation of the clips and the perspective instructions were random.

fMRI Data Acquisition and Reduction

All scans were performed on a Siemens 3.0 Tesla Allegra scanner. Initial high-resolution T1-weighted scans were acquired using an MP-RAGE sequence (Siemens). Continuous whole-brain imaging was performed as participants engaged in the interpersonal exchange task. Functional run details were as follows: echo-planar imaging, gradient recalled echo; repetition time (TR) = 2000 ms; echo time (TE) = 40 ms; flip angle = 90°; 64 × 64 matrix, 26 4 mm axial slices acquired parallel to the anteroposterior commissural line for measurement of the BOLD effect (Kwong et al., 1992; Ogawa et al., 1990a, 1990b). Scanning yielded functional 3.3 mm × 3.3 mm × 4.0 mm voxels.

Data reduction was performed using SPM2 (<http://fil.ion.ucl.ac.uk/spm>; Friston et al., 1995). Motion correction to the first functional scan was performed using a six-parameter rigid-body transformation within subjects (Friston et al., 1996). The average of the motion-corrected images was coregistered to each individual's structural MRI using a 12 parameter affine transformation. Slice timing artifact was corrected, and images were subsequently spatially normalized to the MNI template by applying a 12 parameter affine transformation, followed by a nonlinear warping using basis functions as recommended by Ashburner and Friston (1999). Images were resampled to 4 mm × 4 mm × 4 mm voxels during normalization. Finally, images were smoothed with an 8 mm isotropic Gaussian kernel and high-pass filtered in the temporal domain.

Cingulate Analysis

The cingulate cortex was examined using a detailed region-of-interest (ROI) analysis identical to that described in Tomlin et al. (2006). First, the cingulate

gyrus was outlined by hand using the canonical T1 image included with SPM 2 (resolution 1.6 mm × 1.6 mm × 1.5 mm). After selection, structural voxels were converted into the analogous voxels for a functional image; any functional voxel overlapping a designated structural voxel caused the functional voxel to be included. The resulting mask comprised 398 voxels for the entire cingulate gyrus.

In order to examine separate functional domains within the cingulate, the mask was further divided into 11 nonoverlapping regions along the anterior-posterior axis. Specifically, voxels were grouped according to their angle relative to a point equidistant from the anterior and posterior extremes of the cingulate mask ($x = 0, y = -3.5, z = 13$) whose location along the dorsal-ventral axis was aligned to the ventral edge of the posterior cingulate. The angular boundaries for the zones were designated such that each area contained approximately the same number of voxels, and voxels across left- and right- cingulate cortex were pooled for each area. Each domain thus included 36.2 ± 2.1 voxels and extended 4 voxels bilaterally from the midline. Each domain was then used as a separate mask for ROI analysis for which the raw MR response was compiled.

To compute the magnitude of cingulate self responses, MR values were averaged across the point of maximal activation and two adjacent flanking points within 8 s following the submissions of one's own decision (averaged across the ten rounds of the multiround trust game) or subsequent to the auditory cue “do it” (visual imagery task). For responses to partner reveal screens (“other” response), MR values corresponding to the peak activity within 8 s after screen onset activations were identified, averaged across rounds, and compiled across the point of maximal activation and the two adjacent flanking points. These analyses were performed for each cingulate domain and represent the responsiveness of each segment to the submission of one's “own” decision and the revelation of a partner's decision (“other”), respectively.

Principal Component Analyses

To examine differential spatial activation patterns in cingulate responses, spatial principal component analysis (sPCA) was performed on (1) the cingulate responses of the 81 subjects in the visual imagery task and on (2) our trust task database containing the cingulate responses of 100 unselected control adults who played the Trustee role in the same multiround trust game played here by ASD subjects (King-Casas et al., 2005; Tomlin et al., 2006). In the multiround trust game, the PCA of the cingulate “self” and “other” responses was thus performed on the dataset consisting of 100 11-dimensional vectors representing each Trustee's cingulate response following the submission of her decision on the game (“self” phase) or following the revelation of her partners' decision (“other” phase). The principal components were calculated as the eigenvectors of the covariance matrix of the 11-dimensional dataset. Keeping all the variance of the data, basis sets for the 11-dimensional cingulate space in the “self” and “other” phases of the task were obtained.

The cingulate hemodynamic response data of the age- and IQ-control and ASD groups were then projected onto this basis, yielding a projection matrix upon which two sample t tests were performed to calculate the degree of statistical differences between the ASD and control groups along each principal component. This analysis yielded a p value for each component as indicated in Figures 6C and S1.

The spatial contribution of each of these components to the cingulate “self” response was obtained by keeping the projections along that component unchanged while setting all other projections to zero and multiplying the resulting projection matrix by the conjugate basis set, the transpose of the normative cingulate basis. As illustrated in Figure 6C and Supplemental Data, ASD and control populations differed only on one component in one phase of the task, PC3 in the self phase whose shape resembles the normative “self” response seen directly in the time-series data.

Selection of Behavioral Control Pairs

It was possible that a perturbed pattern of monetary exchange with an ASD trustee induced behavioral anomalies in the partner, thus inducing any observed neural differences. To test this possibility, we compared the ASD neural response patterns with a group of individuals from our normative database whose pattern of play matched that of the ASD group. The “behavioral-match” selection was as follows: We first formed behavioral vectors for each dyad to

characterize their behavioral exchange. Each vector was composed of the series of investment ratios ($I = \text{Investment}/20$) and fractions of Trustee repayments ($R = \text{repayment}/3 \cdot I$) over the ten rounds of a dyad's exchange. These vectors thus represent the monetary exchange pattern within a pair, and we calculated the average such vector for pairs with an ASD trustee. From our normative database, we then identified monetary exchange patterns that matched the average ASD pattern of play. Specifically, the behavioral vector for each pair p was denoted $U^p = (I_1, R_1, I_2, R_2, \dots, I_9, R_9, I_{10}, R_{10})$, and the average vector for the 12 pairs with an ASD Trustee was denoted \bar{U}^A . The collection of control dyads “close” to this average was identified as those 15 normative subject pairs whose pattern of exchange resembled the patterns for the ASD subjects. The distance function that defined these pairs in 20-dimensional behavioral space was as follows: $d(p, \bar{U}^A) = \sum_{j=1}^{20} |U_j^p - \bar{U}_j^A|$. A threshold of 3.65 yielded 15 normative subject pairs. The points in Figure 5A represent the projections of these 20-dimensional behavioral vectors onto the plane defined by the first two principal components of the normative behavioral data. The behavioral controls are indicated by stars overlaid on the blue circles which denote behavior of controls in our normative database. The projection of the average vector of the 12 ASD pairs, \bar{U}^A , is shown as a solid square and lies well-within the space defined by normative monetary exchange.

Supplemental Data

The Supplemental Data for this article can be found online at <http://www.neuron.org/cgi/content/full/57/3/463/DC1/>.

ACKNOWLEDGMENTS

This work was supported by The Kane Family Foundation (P.R.M.), The Dana Foundation and Autism Speaks (P.R.M.), National Institute on Drug Abuse (R01 DA11723 to P.R.M.), National Institute of Neurological Disorders and Stroke (R01 NS045790 to P.R.M.), The Angel Williamson Imaging Center, and the American Psychological Association (T32 MH18882 to P.H.C.). We thank M. Friedlander for establishing the collaboration between the BCM Computational Psychiatry Unit and the UA Autism Spectrum Disorders Research Clinic; B. King-Casas (supported by the National Institute of Mental Health F32 MH078485) and T. Lohrenz for scientific discussion; the Hyperscan Development Team at BCM for Network Experiment Management Object (NEMO) software implementation (www.hnl.bcm.tmc.edu/nemo/); X. Cui and J. Li for xjView image viewing software (<http://people.hnl.bcm.tmc.edu/cuixu/xjView/>); and P. Baldwin, C. Bracero, A. Harvey, C. Klein, J. McGee, S. Moore, K. Pfeiffer, R. Pohl, and J. Schwind for discussion and technical assistance.

Received: October 6, 2007

Revised: December 5, 2007

Accepted: December 11, 2007

Published: February 6, 2008

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