

# Intact emotion facilitation for nonsocial stimuli in autism: Is amygdala impairment in autism specific for social information?

MIKLE SOUTH,<sup>1,2</sup> SALLY OZONOFF,<sup>3</sup> YANA SUCHY,<sup>1,4</sup> RAYMOND P. KESNER,<sup>1,4</sup>  
WILLIAM M. McMAHON,<sup>2,4</sup> AND JANET E. LAINHART<sup>2,4</sup>

<sup>1</sup>Department of Psychology, University of Utah, Salt Lake City, Utah

<sup>2</sup>Department of Psychiatry, University of Utah School of Medicine and Utah Autism Research Project, Salt Lake City, Utah

<sup>3</sup>M.I.N.D. Institute, Department of Psychiatry and Behavioral Sciences, University of California–Davis, Sacramento, California

<sup>4</sup>The Brain Institute at the University of Utah, Salt Lake City, Utah

(RECEIVED April 25, 2007; FINAL REVISION July 11, 2007; ACCEPTED July 18, 2007)

## Abstract

Atypical amygdala development may play a key role in the emergence of social disability and other symptoms of autism (Baron-Cohen et al., 2000; Schultz, 2005). The mechanisms by which this may occur have received little attention, however, and most support from behavioral and imaging studies has been concerned with socially relevant stimuli such as faces. Given the complexity of amygdala function and its known role in many other emotional tasks, we examined whether individuals with autism would demonstrate impaired performance on several tasks that have been shown to require activation of the amygdala but that do not have any explicit social meaning. Relative to a typical comparison group matched for age and IQ, our sample of 37 adolescents and adults with autism (mean age = 19.7 years) demonstrated equivalent facilitation for perception and learning of emotionally relevant stimuli. On each of four tasks, there were significant main effects of emotion condition on performance for both groups. Future research regarding atypical amygdala function and emotion processing in autism should consider whether the response to nonsocial emotion factors (including negative valence or high arousal) may be intact, despite difficulties in responding to socially relevant stimuli. (*JINS*, 2008, *14*, 42–54.)

**Keywords:** Autistic disorder, Limbic system, Motivation, Emotion, Learning, Prefrontal cortex

## INTRODUCTION

Autism is a complex developmental disorder marked by impairments in reciprocal social interaction and communication, and the presence of restricted, repetitive behaviors and interests. Behavioral, psychophysiological, and neuroimaging studies in autism consistently demonstrate deficits in the building blocks for social interaction, such as impaired recognition and memory for facial and vocal expressions (Golan et al., 2006; Humphreys et al., 2007; Paul et al., 2005); reduced use and recognition of emotionally salient aspects of imitation and gesture (Colgan et al., 2006; Hobson & Meyer, 2005); and limited consideration of others'

mental states in joint attention or theory of mind tasks (Baron-Cohen et al., 1999; Rutherford et al., 2006).

Research regarding the neurobiological origins of autism has focused on identification of brain mechanisms that are essential for the perception and integration of information that is rich in social meaning (Schultz, 2005). Findings from anatomical, behavioral, and functional neuroimaging studies in autism have suggested abnormal structure and function of the amygdala (Baron-Cohen et al., 2000; Munson et al., 2006), although there remain many inconsistencies in results and in interpretation. Bauman and Kemper (1985, 1988) published seminal findings of normal volume but smaller neuron size and increased cell density in the amygdala as well as several other brain regions of autopsied brains of people with autism. Recent neuroimaging studies of amygdala volume in autism have been mixed, with some reporting increased volume relative to controls (Howard

Correspondence and reprint requests to: Mikle South, Brigham Young University, Department of Psychology, 1001 Kimball Tower, P.O. Box 25543, Provo, UT 84602-5543. E-mail: mikle\_south@byu.edu

et al., 2000; Sparks et al., 2002), others showing reduced volume (Abell et al., 1999; Pierce et al., 2001), and others finding no difference (Bigler et al., 2003; Haznedar et al., 2000). A cross-sectional study of age effects by Schumann et al. (2004) reported that amygdala volume in an autism sample 7.5 to 12.5 years of age was larger than the comparison group, but there was no difference in the adolescent groups. Bigler et al. (2003) have pointed out numerous methodological limitations in previous reports of volumetric measurements and further conclude that brain abnormalities in autism are likely more related to functional organization than to gross volumetric differences.

At least five research groups have reported *hypoactivation* of the amygdala during social perception tasks (Ashwin et al., 2006; Baron-Cohen et al., 1999; Grelotti et al., 2005; Schultz et al., 2005; Wang et al., 2004). Munson et al. (2006) found that larger right amygdala volume is positively correlated with atypical social development in young children with autism. However, other neuroimaging studies of social perception in autism have suggested that such findings may be related to task-specific characteristics such as the familiarity of the face stimuli (Pierce et al., 2004; see also Hadjikhani et al., 2004). Eye gaze appears to rely in part on amygdala function (Adolphs et al., 2005). Studies of eye gaze in autism have reported discrepancies for dynamic social stimuli (Klin et al., 2002; Speer et al., 2007), although eye gaze for static photos is more intact (Pelphrey et al., 2002; van der Geest et al., 2002).

The amygdala is a complex set of separate, but closely connected nuclei at the base of the temporal lobes that are critically involved in early emotion perception and response (Davis & Whalen, 2001). It is critically involved in the detection of, and learning about, emotionally relevant stimuli, including events that have high *social* salience such as recognizing the meaning of facial expressions (Pasley et al., 2004; Vuilleumier & Pourtois, 2007). The “amygdala theory” of autism (Baron-Cohen et al., 2000; see also Bachevalier, 1996; Howard et al., 2000; Schultz et al., 2003) proposes that atypical social development in autism may arise from primary dysfunction in the amygdala and related “social brain” structures (Brothers, 1996; Skuse et al., 2003).

### Social Information Processing in Autism

Waterhouse et al. (1996) and Schultz (2005) have proposed that there may be a general amygdala deficit in autism that disrupts the assignment or association of reinforcement value to incoming stimuli. Schultz (2005) speculated how such a deficit may specifically impair social development in autism: during face perception, autistic infants experience reduced reinforcement from the amygdala to enhance innate preference for faces (Kelly et al., 2005; Turati et al., 2002). This leads to a reduction in attention for faces (Adolphs et al., 2005) and a subsequent failure to develop face-specific skills in related brain areas such as face regions of the fusiform gyrus, as has been frequently shown among individuals with autism (e.g., Schultz et al., 2000; Wang et al., 2004). Such

failure could markedly reduce the development of social scaffolding (i.e., an impaired “language of faces”), leading to further deficits in social and communicative functioning and to the emergence of repetitive behaviors due to social isolation (Suomi & Harlow, 1971).

Whereas Schultz’s model highlights the amygdala’s role in social *perception* deficits in autism, Bachevalier and Loveland (2006) focus on developmental abnormalities in the amygdala in relation to the *regulation* of social behavior, that is, “the ability to select and initiate complex behaviors in response to the specific conditions of the social environment” (Bachevalier & Loveland, p. 98). This skill requires a cooperative effort between the amygdala, which detects emotional significance, and the orbitofrontal cortex, which evaluates the functional significance of inputs from the amygdala in the context of a constantly changing social world (Loveland, 2001; see also Sabbagh, 2004; Vollm et al., 2006). In general, orbital frontal cortex and related areas of the ventromedial prefrontal cortex (vmPFC) are critical for comparing past and present emotional salience, and for modulating amygdala activation in response to environmental changes (Rauch et al., 2006; Sotres-Bayon et al., 2004). Disruption at any point in this ongoing cycle of perception and action would adversely affect both processes and impair the ability to track and respond to rapid changes in social situations (including gestures, face and voice expressions, and variations in verbal meaning).

### Nonsocial Emotion Processing in Autism

In contrast to research on social cognition in autism, there is little research regarding perception and learning for nonsocial emotions, despite the critical role of the amygdala in many processes that involve emotion more generally (reviewed by Davis and Whalen, 2001). For instance, the amygdala plays a critical role in the detection of naturally occurring threats (Merckelbach et al., 1995; Ohman, 2005; see also Larson et al., 2006); classic conditioning to aversive stimuli (Cheng et al., 2006; Phelps & LeDoux, 2005); and the anticipation of nonsocial reward (Balleine & Killcross, 2006; Bechara et al., 1995).

Although an early influential review by Baron-Cohen et al. (1999) recommended that future studies examine both fear recognition and fear conditioning in autism, only a few studies published since then have specifically examined fear outside of the social context. Bernier et al. (2005) found no differences in latency or amplitude of the potentiated startle reflex between autism spectrum and comparison groups, suggesting that the amygdala mechanisms involved in fear conditioning and subsequent potentiation of the startle pathway may *not* be affected in autism. Johnson et al. (2006) found mixed evidence for abnormality in Asperger’s syndrome on the Iowa Gambling task, which has been shown to depend on the critical emotion monitoring loop between the amygdala and medial prefrontal cortex described above.

Taken together, functional and structural imaging research suggest amygdala abnormalities in autism, at least for face

**Table 1.** Algorithm of factor definitions used for each IQ test

	<i>n</i> =	Verbal IQ composite	Nonverbal IQ composite	Full-scale IQ composite
WISC-III	2	Verbal IQ	Performance IQ	Full-scale IQ
WAIS-III	44	Verbal Comprehension Index	Perceptual Organization Index	Full-scale IQ
WASI	11	Verbal IQ	Performance IQ	Full-scale IQ
DAS	18	Verbal ability	Average of nonverbal reasoning ability and spatial ability	General conceptual ability

*Note.* WISC-III = Wechsler Intelligence Scale for Children–Third Edition; WAIS-III = Wechsler Adult Intelligence Scale–Third Edition; WASI = Wechsler Abbreviated Scales of Intelligence; DAS = Differential Abilities Scale. All Verbal scales include a vocabulary definition subtest and a word similarities subtest. All Non-verbal scales include a block patterns subtest and a matrices subtest, except for the WISC-III, which has no matrices subtest.

processing, while the few existing studies that use fear conditioning without a social element have found intact performance in autism. Thus, it is unclear whether there is global amygdala abnormality in autism, or whether impaired function is specific to socially relevant emotion stimuli. The purpose of the present study was to determine whether individuals with autism exhibit abnormal processing of emotion stimuli or situations that are *not* socially relevant but that are nevertheless known to depend on the integrity of the amygdala.

To that end, we used four behavioral tasks that are known to engage amygdala activity for the evaluation of emotional significance (see Baxter & Murray, 2002; Phelps & LeDoux, 2005). Consistent with the amygdala theory of autism, we expected that our sample of 37 adolescents and adults with autism would demonstrate reduced facilitation of emotional cues, relative to an age- and IQ-matched comparison group, even in the absence of socially salient information.

## METHODS

### Participants

A total of 37 (36 males) participants with autism (the AUT group) and 38 (36 males) typically developing comparison participants (the TC group) completed the study. IQ testing was completed at the same time as other study measures, with three exceptions for participants who had been part of previous research projects: one 29-year-old AUT group participant whose IQ data were 4 years old, and 2 TC group

participants whose IQ data were 3 years old. This study was conducted as part of a larger research project that used a standard algorithm for comparing scores from the different IQ tests given as appropriate to age and developmental status. The algorithm and the number of participants tested with each measure are shown in Table 1. Groups were comparable for age and IQ (see Table 2).

All AUT group participants were diagnosed with Autistic Disorder by one or more authors (J.E.L., W.M.M., S.O., M.S.) experienced in the diagnosis of autism. Diagnostic decisions were based on individual observation, parent interview, and data from structured research assessments (summarized in Table 3) including the Autism Diagnostic Interview–Revised (ADI-R; Lord et al., 1994), which measured lifetime severity; and from the Autism Diagnostic Observation Schedule–Generic (ADOS-G; Lord et al., 2000), a measure of current symptom severity. Final diagnosis was according to DSM-IV criteria regardless of whether strict cutoffs were met for the research diagnostic measures.

All consent and research procedures were approved by the University of Utah Internal Review Board. Both AUT and TC participants were recruited as part of ongoing research at the Utah Autism Research Project, either from existing research databases, from flyers sent to autism service agencies or posted on the University of Utah campus, or by word of mouth in the community. Experimental tasks were administered *via* computer using the DirectRT software package (Empirisoft Inc., 2003), except for the Gambling task, which used a stand-alone program. Participants were instructed to use only their dominant hand to respond

**Table 2.** Group comparisons of age and IQ scores

Measure	<i>M</i>		<i>SD</i>		Range		<i>t</i>	<i>d</i>
	AUT	TC	AUT	TC	AUT	TC		
Age (years)	19.7	19.2	5.3	6.0	11–33	11–38	0.40	.08
Verbal composite IQ	115.1	112.2	17.2	13.5	89–150	87–142	0.83	.19
Nonverbal composite IQ	108.0	112.2	16.0	14.9	76–138	86–145	1.19	.27
Full-scale composite IQ	107.7	112.7	15.1	14.1	88–140	85–143	1.49	.34

*Note.* No significant between-group differences. AUT *n* = 37; TC *n* = 38. AUT = autism group; TC = typical comparison group.

**Table 3.** Summary of diagnostic measures for 35 AUT participants

Measure	Scale	<i>M</i>	<i>SD</i>	Range	Research diagnostic cutoff
ADOS	Social interaction	8.20	2.17	5–14	6
	Communication	4.69	1.23	2–7	3
	Algorithm total	12.89	2.97	8–21	10
ADI-R	Social interaction	20.59	5.51	11–30	10
	Communication	15.10	4.18	6–22	8
	Repetitive behavior	6.28	1.81	3–10	3

Note. ADOS = Autism Diagnostic Observation Schedule, *n* = 35; ADI-R = Autism Diagnostic Interview-Revised, *n* = 29; AUT = autism group.

using a custom-built box with six arcade-style buttons. Most participants (85%) were tested in research offices using a desktop PC (15-inch display); the rest (10 AUT, 1 TC participants) were tested in a quiet place in their home using a notebook personal computer (14-inch display). For all tasks, response latencies and accuracy were recorded and used as dependent variables in statistical analyses.

## MEASURES

Brief summaries of the measures, along with evidence for amygdala involvement in task performance and possible functional pathways, are presented in Table 4.

### Snake in the Grass Task (Flykt, 2005; Ohman et al., 2001)

LeDoux (1994) proposed a dual-route model through which the amygdala receives input on emotional salience: a coarse but rapid subcortical input directly from the thalamus, and slower routes from cortical sensory areas. Beyond extensive findings from the animal literature, support for the rapid subcortical pathway in humans comes from numerous neuroimaging studies using facial expressions (Morris et al., 1999; Pasley et al., 2004; Reinders et al., 2006). Ohman et al. (2001) reported decreased response time to fear-relevant stimuli (snakes and spiders) *versus* fear-irrelevant stimuli (flowers and mushrooms) in a visual search task administered to healthy college students. They suggest that this “snake in the grass” effect arises from an evolutionary bias toward immediate detection of threat, mediated

**Table 4.** Amygdala contributions to performance on experimental tasks

Task name	Task description	Evidence for amygdala involvement	Possible functional pathways
Snake in the Grass	Visual search for threat-relevant stimuli	In typical populations, faster response to fear than nonfear stimuli (Ohman et al., 2001). In a study of snake-phobic individuals, there is faster, briefer fMRI amygdala activation in response to pictures of snakes (Larson et al., 2006).	Rapid, incomplete processing of coarse sensory information <i>via</i> thalamus to lateral amygdala (LeDoux, 1994, 2000; Ohman & Mineka, 2001); vigilance mechanisms in amygdala central nucleus (Davis & Whalen, 2001)
Mere Exposure	Brief exposure to novel abstract stimuli enhances preference	Patients with selective amygdala damage, but not patients with hippocampus damage, are impaired for novel words and drawings (Chiba et al., in preparation)	Classic conditioning pathway (involving connections between lateral nucleus of the amygdala and medial prefrontal cortex) (Zajonc, 2001)
Affective Word Memory	Short-term recognition memory for emotional and neutral words	Positive correlation between fMRI amygdala activation and arousal ratings of affective words (Lewis et al., 2007)	Encoding of affective information in basolateral complex (Adolphs et al., 1999); feedback loop to semantic processing regions of temporal cortex (Nakic et al., 2006)
Hungry Donkey Test (modified Iowa Gambling Task)	Decision-making task between high-risk, high-yield choices and low-risk, low-yield choices	Impaired performance on gambling task for patients with selective amygdala damage, but not patients with hippocampus damage; skin conductance responses reduced beyond that seen in patients with orbitofrontal damage alone (Bechara et al., 1999; Brand et al., 2007)	Feedback loop involving medial prefrontal cortex, comparing current (lateral nucleus of the amygdala) and past (hippocampus) affective valence (Brand et al., 2007; Sotres-Bayon et al., 2004)

through thalamo-amygdala pathways. Recently, Larson et al. (2006) reported brief but strong amygdala responses to pictures of spiders in a functional magnetic resonance imaging (fMRI) study of spider phobic participants, in contrast to weaker but more sustained amygdala activation in healthy comparison participants. Support for this pathway also comes from potentiated startle studies (Merckelbach et al., 1995).

This study used the Snake in the Grass task, which displays a series of  $3 \times 3$  photographic arrays of threat-relevant (spiders or snakes) and threat-irrelevant (flowers or mushrooms) stimuli imposed on a grid background. Participants were instructed to quickly search each array and indicate whether all nine pictures were from the same object category (e.g., all snakes or all mushrooms), or whether there was a discrepant stimulus in the picture (e.g., one spider in the midst of eight flowers). There were 144 stimulus arrays evenly distributed with regard to category (each category appeared the same number of times in both discrepant and nondiscrepant conditions) and grid position. Response time and task accuracy were measured. We expected that reduced emotional facilitation would result in less of a difference in reaction time for the fear *versus* the nonfear condition.

### Mere Exposure Task

In the mere exposure paradigm (Zajonc, 1968), preference for a particular stimulus object is enhanced by repeated exposures to that object, even when the exposure is brief or masked and cannot be recalled in explicit memory. The amygdala is important for implicit (nonconscious) processing of affective stimuli (Hannula et al., 2005; Phelps & LeDoux, 2005) and also plays a key role in the formation of reward-based preference in humans and animals (Adolphs & Tranel, 1999; Gilbert et al., 2003). Although the neural substrates of the mere exposure effect have not been systematically defined, Zajonc (2001) has postulated that it may involve a classic conditioning mechanism involving the amygdala (but see Willems et al., 2002, for alternative explanations). Chiba et al. (in preparation) demonstrated the mere exposure preference effect for participants with either left or right temporal lobe resections that were limited to temporal neocortex and/or the hippocampus, as well as for participants with either left or right partial complex temporal lobe epilepsy. However, participants with left or right temporal lobe resections that included the amygdala in addition to the hippocampus *did not* display the exposure preference effect.

This study presented an adaptation of the Chiba et al. task. During the first *study* phase, participants were shown a series of eight real but unfamiliar English words (i.e., *higgle*, *milter*), and eight novel abstract grayscale brush-stroke drawings created using computer paint software. Each stimulus was shown for 800 ms, followed by a 500-ms interstimulus interval. During the second *liking* phase, participants were shown each of the original target stimuli side-

by-side with a novel distracter stimulus. Participants were instructed to respond as quickly as possible to the question “which one do you like better?” Stimuli remained on the screen until a response was chosen. Stimulus order within a block was different during each phase of the task and was the same for all participants; the presentation of words always preceded the presentation of drawings. We hypothesized that reduced emotional facilitation would be demonstrated by a decreased preference for the target vis-à-vis the distracter stimuli and decreased benefit in reaction time for target *versus* distracter stimuli.

### Affective Word Memory Task

The critical role of the human amygdala for processing affectively charged stimuli has been demonstrated across many modalities, including affective pictures (Sabatinelli et al., 2005); sounds (Sander et al., 2003); odors (Winston et al., 2005); and words (Lewis et al., 2007). Research regarding human responses to affectively charged stimuli has traditionally focused on two dissociated attributes of *valence* (i.e., whether the affect is positive or negative), and *arousal* (i.e., how intense is the reaction elicited by the stimulus). A recent fMRI study of viewing affective words (Lewis et al., 2007) found that amygdala activation is more strongly correlated with *arousal*, whereas vmPFC activation is more strongly associated with *valence*.

For the present study, participants were initially presented with a list of 40 words appearing sequentially for 1250 ms each (100-ms intertrial interval). There were 12 unpleasant (negative) words (6 low-arousal, e.g., “waste,” and 6 high-arousal, e.g. “crash”); 12 pleasant (positive) words (6 low-arousal, e.g., “relaxed,” and 6 high-arousal, e.g. “riches”); and 16 emotionally neutral words (“paper,” “cork”). All words were short and easy to read, taken from the Affective Norms for English Words (Bradley & Lang, 1999). Participants were next shown a mix of the same 40 target stimuli and 40 new distracter stimuli, also presented sequentially. Instructions were to choose as quickly as possible whether each word had been seen previously; stimuli remained on the screen until the participant responded, up to 8000 ms. Stimulus lists were ordered pseudorandomly so that no valence/arousal combination appeared three times consecutively, and were identical for all participants. Data were collected for response time and accuracy (recall of previously seen words). For this task, evidence of reduced emotional facilitation would consist of less marked benefit in recognition and reaction time for high arousal *versus* neutral or low arousal words.

### Gambling Task

The amygdala response to emotion is modulated by close connections to monitoring regions in the vmPFC, which in humans is essentially involved in rapid integration of sen-

sory information and subsequent decision making (Brothers, 1996). The Iowa Gambling Task (IGT; Bechara et al., 1994) was developed as a laboratory analog of real-life decision making. Participants choose cards from four decks, which indicate varying amounts of reward or punishment. Successful completion requires inhibition of the impulse to take from the decks that provide large reward but also large punishments and eventually result in a net loss. Patients with vmPFC damage perseverate in choosing from the disadvantageous decks, despite showing skin conductance responses in anticipation of making a bad choice (Bechara et al., 1994). In a subsequent study, Bechara and colleagues (1999) found that patients with amygdala damage did *not* show conditioned response acquisition (i.e., no skin conductance either in anticipation of a bad choice or response to the punishment), despite intact explicit memory of both the conditioned and unconditioned stimulus properties. Patients with damage to the hippocampus but intact amygdala showed appropriate conditioning. Brand et al. (2007) likewise report that three patients with Urbach–Wiethe disease, which selectively damages amygdala bilaterally, demonstrate impaired performance and reduced skin conductance response for the IGT.

We used a variation of the IGT intended to be appropriate for younger or developmentally atypical participants, the Hungry Donkey Test (HDT; Crone & van der Molen, 2004). Instead of choosing cards from decks and using money as the currency, the HDT requires participants to choose from four doors to reveal several apples to feed a “hungry donkey” pictured at the bottom of the screen. Participants are informed that “mean donkeys” behind each door might also take apples away (in which case the pictured apples are crossed out), and that the number of apples behind each door may change from one trial to the next. Two of the doors provided larger rewards on most trials but also unpredictable large losses in either frequent small doses or infrequent large doses; the second set of doors provided for a smaller net gain, but also smaller losses, delivered in identical dose proportions as the first set. Choosing the *disadvantageous* doors will always result in long-term loss, while the *advantageous* doors bring small-scale long-term gain. The reinforcement schedule was proportionally the same as for the original Iowa Gambling Task, but the amount was reduced by a factor of 25. There were 200 trials and a graphical representation of net apples gained was displayed throughout the task. The primary variable was the net difference in results (i.e., number of apples earned) resulting from the mean number of advantageous and disadvantageous choices, calculated across 10 blocks of 20 trials each. Choice strategy was analyzed by examining the number of choices made for the two *advantageous* doors (e.g., small reward but small punishment) *versus* number of choices made for the two *disadvantageous* doors. We hypothesized that reduced emotional facilitation would result in a reduced difference in choosing the advantageous doors, that is, a flatter learning curve, as well as a flatter curve for reaction time data.

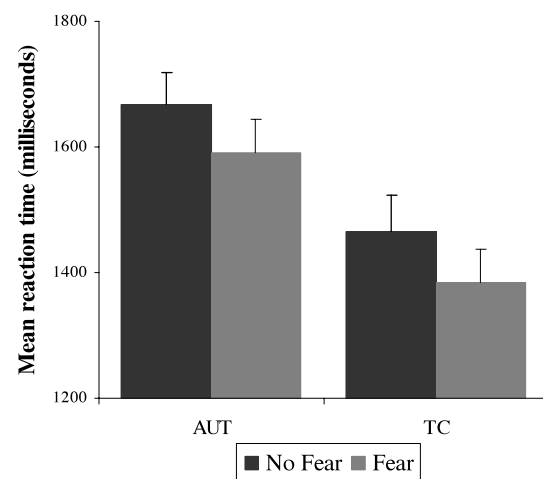
## RESULTS

Due to technical problems or participant refusal, data were missing for 1 TC participant on the Exposure task, 4 participants (3 AUT) for the Snakes task, and 2 participants (1 AUT) for the Words task response time variable. Difficulties with the user interface on the separate Gambling task resulted in lost data for 13 participants (5 AUT, 8 TC). There were no significant differences for age or IQ between diagnostic groups within this smaller sample ( $n = 62$ ) for the Gambling Task.

Contrary to expectation, both the TC and AUT groups demonstrated clear evidence of emotional facilitation, as shown in Figures 1–4. For every task, repeated-measures analysis of variance (ANOVA) analyses on the primary dependent variable demonstrated significant effects of emotion condition and no interaction of diagnostic group  $\times$  emotion condition. Specific tasks results are detailed below.

### Snakes Task

As shown in Figure 1, there was a significant main effect of emotion condition [fear < no-fear,  $F(1,69) = 39.01$ ;  $p < .001$ ] and also a main effect for group [AUT > TC,  $F(1,69) = 7.12$ ;  $p < .01$ ], but there was no significant group  $\times$  emotion interaction [ $F(1,69) = .02$ ;  $p = .90$ ], indicating the facilitation of the threat stimuli was comparable for both groups. Planned *post hoc* analyses indicated that the effect of emotion was significant for each group separately, with both groups performing faster during the fear than the no-fear condition (AUT  $t = 4.0$ ; TC  $t = 4.89$ ;  $p$ 's < .001). Both groups correctly identified >95% of the target stimuli, and there were no effects of emotion or group for the accuracy variable.



**Fig. 1.** Response time for the Snakes task: main effect of emotion condition (fear condition is faster than no-fear condition) for both groups. There is a main effect (TC faster than AUT) but no group  $\times$  condition interaction. Error bars represent 1 standard error of the mean. AUT = autism group; TC = typical comparison group.

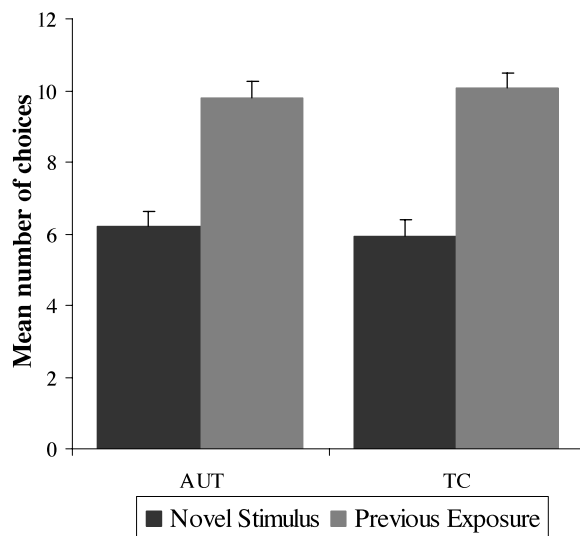
## Mere Exposure Task

As shown in Figure 2, both groups demonstrated a comparably strong “mere exposure” effect, an accuracy measure that indicates a statistically significant preference for previously displayed target stimuli over novel contrast stimuli [ $F(1,72) = 10.15$ ;  $p < .001$ ]. Planned *post hoc* analyses indicated that the effect of exposure was significant for each group separately (AUT  $t = 4.18$ ; TC  $t = 4.56$ ;  $p$ 's  $< .001$ ). Reaction time analyses showed that the previously seen stimuli were identified faster than distracters for both groups [ $F(1,72) = 29.37$ ;  $p < .001$ ]. There was no significant main effect for diagnostic group [ $F(1,72) = .45$ ;  $p = .51$ ] or group  $\times$  exposure condition interaction [ $F(1,72) = .34$ ;  $p = .56$ ].

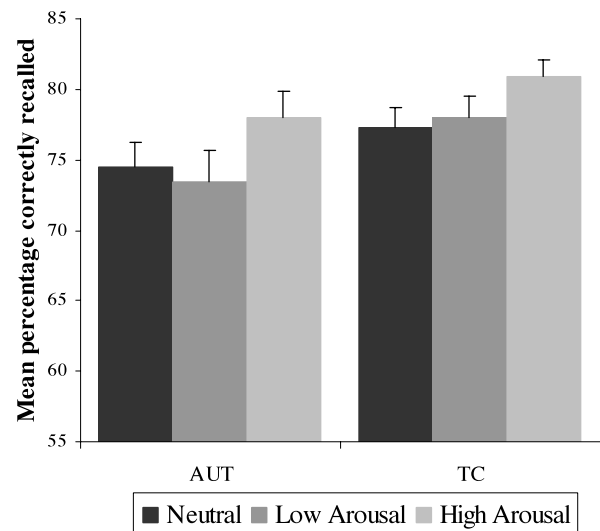
## Affective Words Memory task

The accuracy variable was measured as the percentage of target words that were correctly remembered. As shown in Figure 3, there were significant main effects of emotion condition for separate analyses of *valence* condition [negative  $>$  neutral  $>$  positive,  $F(2,70) = 22.62$ ;  $p < .001$ ]; and *arousal* condition [high  $>$  neutral  $>$  low,  $F(2,70) = 5.82$ ;  $p < .001$ ]. There were no significant effects of group or group  $\times$  condition interaction for either analysis: *valence* group,  $F(2,70) = 3.02$ ;  $p = .09$ ; interaction,  $F(2,70) = .14$ ;  $p = .87$ ; *arousal* group,  $F(2,70) = 3.02$ ;  $p = .09$ ; interaction,  $F(2,70) = .33$ ;  $p = .72$ .

Mean reaction times for *valence* indicated that the negative emotion condition was fastest for both groups: AUT negative  $M = 1024.1$  ms ( $SD = 245.9$ ), positive  $M = 1065.78$  ms (264.4), neutral  $M = 1054.1$  ms (211.8); TC



**Fig. 2.** Accuracy for the Mere Exposure task: main effect of condition (previously exposed condition is preferred over the novel condition) for both groups; no main effect for group or group  $\times$  condition interaction. Error bars represent 1 standard error of the mean. AUT = autism group; TC = typical comparison group.



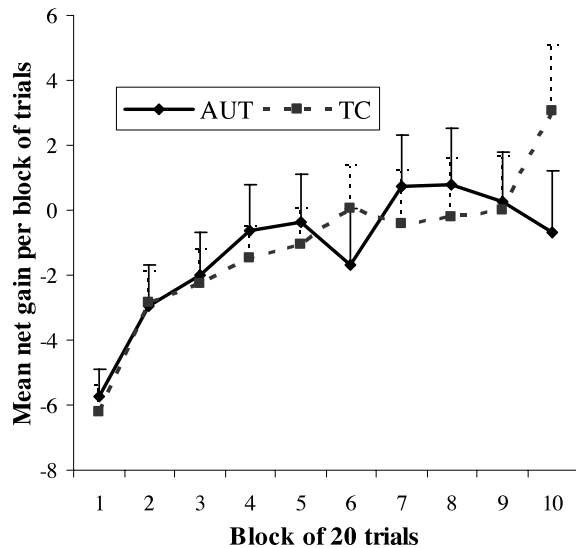
**Fig. 3.** Accuracy for the Emotion Word Recognition task: main effect of arousal condition (high arousal is recalled more accurately than low arousal and neutral conditions) for both groups; no main effect for group or group  $\times$  condition interaction. Error bars represent 1 standard error of the mean. AUT = autism group; TC = typical comparison group.

negative  $M = 916.77$  ms (134.8), positive  $M = 955.2$  ms (155.1), neutral  $M = 654.68$  ms (157.7). The main effect of emotion condition was statistically significant [ $F(2,70) = 4.20$ ;  $p < .05$ ], as was the main effect for group [AUT  $>$  TC;  $F(1,71) = 5.77$ ;  $p < .05$ ]; there was no significant condition  $\times$  group interaction [ $F(2,70) = .11$ ;  $p = .90$ ]. Mean reaction times for *arousal* indicated that the emotion arousal conditions were faster than neutral for both groups: AUT high arousal  $M = 1050.15$  (257.5), low arousal  $M = 1039.73$  (248.9), neutral  $M = 1054.1$  (211.8); TC high  $M = 948.6$  (156.0), low  $M = 923.37$  (136.4), neutral  $M = 954.68$  (157.7). There was a significant main effect for diagnostic group [AUT  $>$  TC;  $F(1,71) = 5.77$ ;  $p < .05$ ] but not for emotion condition [ $F(2,70) = 1.56$ ;  $p = .21$ ] or a condition  $\times$  group interaction [ $F(2,70) = .23$ ;  $p = .80$ ].

## Gambling Task

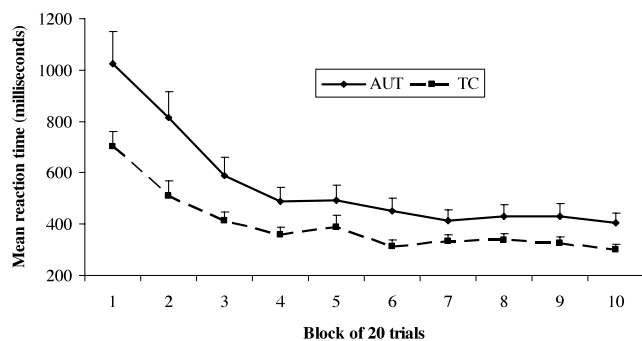
As seen in Figure 4, both groups demonstrated a change over time in favor of more advantageous responses. Repeated-measures ANOVA analysis using choice condition as the dependent variable, trial block as the within-subjects factor, and diagnostic group as the between-subjects factor showed a significant main effect of time intervals across the 10 blocks, indicative of improved performance over the course of the experiment:  $F(9,52) = 4.07$ ,  $p < .001$ . There were no significant effects of group [ $F(1,60) = .01$ ,  $p = .94$ ] or group  $\times$  time interval interaction [ $F(9,52) = 1.09$ ,  $p = .39$ ].

Reaction time data (seen in Figure 5) indicated that both groups showed faster performance as the task progressed, with both groups appearing to stabilize their response times



**Fig. 4.** Net gain across trial blocks for the Gambling Task: main effect for trial block (net gain per block increases over time) for both groups; no main effect for group or group  $\times$  trial block interaction. Error bars represent 1 standard error of the mean. AUT = autism group; TC = typical comparison group.

by approximately the fourth block of trials (see Figure 5). Change in response time across the 10 blocks was statistically significant [ $F(9, 52) = 7.64, p < .001$ ], and there was a significant effect of group [AUT > TC;  $F(1, 60) = 5.75, p < .05$ ]. There was again no group  $\times$  block interaction [ $F(9, 52) = 1.21, p = .31$ ]. Analysis of choice strategy demonstrated that both groups favored the same strategy of reduced frequency of punishment and a small but steady advantage in reward value, as opposed to the doors containing large but infrequent losses and gains [ $F(9, 52) = 5.47, p < .001$ ]; there were no significant group or group  $\times$  choice type interactions. Although this version of the Gambling task was modified to be appropriate for younger or more impaired samples, neither the AUT nor TC group demonstrated ceiling effects for this study.



**Fig. 5.** Decrease in mean reaction time for the Gambling Task across trial blocks. Significant main effects for trial block and for group; no group  $\times$  trial block interaction. Error bars represent 1 standard error of the mean. AUT = autism group; TC = typical comparison group.

## Effects of Age

Due to concerns about the heterogeneity of age in our sample, we reanalyzed our data after dividing the sample into older (19 and older) and younger groups. There were no meaningful changes in results or interpretations. Effects were identical to the combined analyses already reported, with two exceptions: the Gambling task net choices variable did not show a significant main effect across trial blocks for the younger group [ $F(9, 16) = 1.67, p = 1.18$ ]; and the main effect of emotion condition for Words response time was not significant in the older group [ $F(2, 37) = 1.35, p = .27$ ].

## DISCUSSION

This study found what appears to be intact performance on four separate tasks that are known to depend in part on amygdala function, in a sample of 37 participants diagnosed with high-functioning autism relative to age- and IQ-matched typically developing controls. Our results suggest that there may be aspects of emotion processing, known to involve amygdala function, that remain intact in higher functioning individuals with autism. In contrast to the majority of previous studies of amygdala function in autism, these tasks had little overt social relevance, suggesting that amygdala dysfunction in autism may be specific to social information. In light of these and other recent, related findings (e.g., Bernier et al., 2005; Johnson et al., 2006), it is clear that future research will need to explicate specific processes and pathways of amygdala development in autism to understand the contribution of amygdala-based mechanisms to the primary social dysfunction that is the hallmark of autism.

The present study had several limitations. We did not use a task that was explicitly and exclusively based on social perception; findings of a crossover interaction between social and nonsocial tasks in future studies would greatly strengthen our conclusions. Although our analyses did not find significant effects due to age, the wide age range in our autism sample (11–33 years of age) remains a concern: it is possible that some participants with autism in our study, especially given their relatively high cognitive functioning, had developed compensatory strategies to overcome earlier amygdala dysfunction. Research with autism samples from a lower range of cognitive functioning would help clarify whether aspects of amygdala function are intact in all individuals on the spectrum or only those who are higher functioning. Although the AUT sample in this study generally showed substantial symptom severity, there was considerable variability and some individuals demonstrated mild autism symptoms (see Table 2). All IQ scores were above the mental retardation range, which significantly narrows generalizability across the autism spectrum.

## Specificity of Amygdala Pathways

The amygdala is a complex structure of 13+ nuclei that share many similarities in structure and function, but also



are involved in numerous distinct pathways throughout the brain. LeDoux and colleagues (e.g., Sotres-Bayon et al., 2004) have described a circuit for classic fear conditioning that depends on the association of incoming sensory stimuli that arrive in close temporal proximity in the lateral nucleus of the amygdala, and sequential activation of the fear response through the central nucleus. Sotres-Bayon et al. demonstrated that this pathway does *not involve the basal nucleus*, which lies adjacent to the lateral and central nuclei. However, amygdala pathways involved in rapid detection and interpretation of *facial expressions*, which also depend on sensory inputs to the lateral nucleus, provide very rapid feedback to ventral visual pathways in the temporal lobe that leave the amygdala *through the basal nucleus* (Vuilleumier & Pourtois, 2007; see also Amaral, 2002). This finding opens the possibility, although more exact mechanisms have yet to be defined, that the basal nucleus is particularly important in social information processing. Balentine and Killcross (2006) posit that the lateral and central nuclei work in parallel in the case of appetitive conditioning, each encoding separate aspects of sensory reward and motivation. This explanation could likewise account for impairment in some but not all aspects of associative learning, rather than a more comprehensive deficit that has been previously proposed for autism (Schultz, 2005; Waterhouse et al., 1996). Alternatively, Amaral and colleagues (Amaral & Corbett, 2003) propose that symptoms of abnormal fears and increased anxiety are independent of social impairment in autism, and that clinical manifestations of atypical amygdala function in autism are limited to comorbid (but not causally related) anxiety.

In light of current technical limitations on the ability to effectively image specific nuclei of the amygdala in humans, behavioral experiments using both humans and animals may be the best available method of differentiating specific amygdala circuits and their functionality in people with autism. For example, Adolphs et al. (2005) have proposed that the amygdala specifically contributes to the recognition of fearful facial expressions by directing attention to the eye region. Davidson and colleagues (Dalton et al., 2005) report that gaze fixation on the eye regions while viewing faces is positively correlated with fMRI activation of the amygdala and fusiform gyrus in one autism sample. Dalton et al. further suggest that eye gaze in some individuals with autism leads to heightened amygdala activation, perhaps indicating increased fear or anxiety in social situations. Such interactions between behavioral and neuroimaging studies of basic amygdala functions (for instance, classic fear conditioning) are sorely needed in the field.

There is a similar need to increase the specificity of “amygdala phenotypes” across different forms of psychopathology. Similar circuits are implicated in other disorders of affective regulation, including deficits in memory for fearful faces in children and adolescents with major depressive disorder; as well as associations between response to threat and amygdala activation in fMRI, which may be linked to anxiety disorders (reviewed in Pine et al., 2004). Associa-

tions between amygdala function and/or activation have been documented for psychopathy, bipolar disorder, substance abuse, schizophrenia, and posttraumatic stress disorder. Contrasting the nature of different amygdala phenotypes at both the biological and behavioral level will necessarily involve multiple methods using both human and animal models (Nelson et al., 2002). Increased specificity of behavioral and neuroimaging markers may in turn lead to the identification of genetic markers that correspond directly to subnuclei of the amygdala (Zirlinger & Anderson, 2003).

It is also important to consider whether amygdala capacity or function may initially be intact, then becomes compromised as a secondary effect of dysfunction elsewhere in the social perceptual system. For instance, if an abnormality in the white matter pathways between the fusiform face area and the limbic system prevented vital social perceptual information from reaching the amygdala, the amygdala would not be able to provide salient feedback to other ventromedial/orbitofrontal systems that are essential to the evaluation and response to social information.

### Developmental Factors

There is a great need to better understand developmental influences on emotion processing in typical and developmentally abnormal populations. The amygdala grows significantly in structure and function through childhood and adolescence (Giedd et al., 1996; Killgore & Yurgelun-Todd, 2004). The lower age range for this study was limited by the nature of the tasks, and future research in this area would benefit from designs and samples that allow for more precise attention to age-based characteristics and, in particular, to younger children. Future studies would also benefit from reaction time control tasks that parse the effects of cognitive processing speed and motor speed.

### Perception and Motivation

It is often difficult to ascertain whether atypical levels of motivation in autism are a primary feature of the condition or are secondary to the repeated failures that arise from the cognitive, language, and social deficits of the syndrome. Our current autism sample did not demonstrate insensitivity to reward: it appears they were able to appreciate immediate feedback for a choice and use that feedback to influence upcoming decisions. Future studies may rely on more sophisticated manipulations of reward and punishment contingencies to elucidate motivational pathways in autism. Future designs may also incorporate different categories of nonsocial emotions, including variations in type (e.g., fear, disgust, and pleasure) as well as gradations in valence and arousal.

All of the tasks used in this study are adaptable for both psychophysiological and neuroimaging studies that would provide more direct measures of amygdala and other regional activation. Such measures would be especially useful at separating differences in emotional response from possible

global impairments in motor speed or generalized processing problems.

Although the AUT group was significantly slower on several tasks, there were no interactions between group and emotion condition on response time variables, and we do not believe that the between-groups differences are a function of differences in emotion processing. Nonetheless, measures such as skin conductance response or fMRI activation to fearful targets would provide more evidence regarding amygdala involvement in these tasks.

## Conclusion

This report highlights the challenge of modeling neural mechanisms through which selective impairments may arise, despite intact functioning elsewhere in the same systems. Developmental influences on emotion and learning is an essential area of study in research on autism. As research regarding emotion processing in autism progresses, it will become increasingly important to improve the specificity of models regarding the similarities and differences in amygdala development and function across syndromes and subtypes of developmental psychopathology.

## ACKNOWLEDGMENTS

This work was supported by an NIMH National Research Service Award (F-31 MH 12566) and a University of Utah Marriner S. Eccles Graduate Fellowship in Political Economy to Mickle South; and by an NICHD program project grant (PO1 HD 35476) to William M. McMahon and Janet E. Lainhart, as part of the NICHD/NIDCD Collaborative Network on the Neurobiology and Genetics of Autism. We thank Nicanor Garcia for assistance with data collection; Hilary Coon, PhD, for statistical consultation; and Sherri Provencal, PhD, and Judith Miller, PhD, for assistance with assessment and project design. We especially thank the participants and their families for their continued dedication to research on autism.

## REFERENCES

Abell, F., Krams, M., Ashburner, J., Passingham, R., Friston, K., Frackowiak, R., Happe, F., Frith, C., & Frith, U. (1999). The neuroanatomy of autism: A voxel-based whole brain analysis of structural scans. *Neuroreport*, *10*, 1647–1651.

Adolphs, R., Gosselin, F., Buchanan, T.W., Tranel, D., Schyns, P., & Damasio, A.R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature*, *433*, 68–72.

Adolphs, R. & Tranel, D. (1999). Preferences for visual stimuli following amygdala damage. *Journal of Cognitive Neuroscience*, *11*, 610–616.

Adolphs, R., Tranel, D., Hamann, S., Young, A.W., Calder, A.J., Phelps, E.A., Anderson, A., Lee, G.P., & Damasio, A.R. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, *37*, 1111–1117.

Amaral, D.G. (2002). The primate amygdala and the neurobiology of social behavior: Implications for understanding social anxiety. *Biological Psychiatry*, *51*, 7–11.

Amaral, D.G. & Corbett, B.A. (2003). The amygdala, autism, and anxiety. *Novartis Foundation Symposium*, *251*, 177–187.

Ashwin, S., Wheelwright, S., & Baron-Cohen, S. (2006). Finding a face in the crowd: Testing the anger superiority effect in Asperger Syndrome. *Brain and Cognition*, *61*, 78–95.

Bachevalier, J. (1996). Brief report: Medial temporal lobe and autism: A putative animal model in primates. *Journal of Autism and Developmental Disorders*, *26*, 217–220.

Bachevalier, J. & Loveland, K.A. (2006). Orbitofrontal-amygdala circuit and self-regulation of social-emotional behavior in autism. *Neuroscience and Biobehavioral Reviews*, *30*, 97–117.

Balleine, B.W. & Killcross, S. (2006). Parallel incentive processing: An integrated view of amygdala function. *Trends in Neuroscience*, *29*, 272–279.

Bauman, M.L. & Kemper, T.L. (1985). Histoanatomic observations of the brain in early infantile autism. *Neurology*, *35*, 866–874.

Bauman, M.L. & Kemper, T.L. (1988). Limbic and cerebellar abnormalities: Consistent findings in infantile autism. *Journal of Neuropathology and Experimental Neurology*, *47*, 369.

Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C., & Williams, S.C.R. (2000). The amygdala theory of autism. *Neuroscience & Biobehavioral Reviews*, *24*, 355–364.

Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., & Williams, S.C. (1999). Social intelligence in the normal and autistic brain: An fMRI study. *European Journal of Neuroscience*, *11*, 1891–1898.

Baxter, M.G. & Murray, E.A. (2002). The amygdala and reward. *Nature Reviews Neuroscience*, *3*, 563–573.

Bechara, A., Damasio, A.R., Damasio, H., & Anderson, S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, *50*, 7–15.

Bechara, A., Damasio, H., Damasio, A.R., & Lee, G.P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision making. *Journal of Neuroscience*, *19*, 5473–5481.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., & Damasio, A.R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, *269*, 1115–1118.

Bernier, R., Dawson, G., Panagiotides, H., & Webb, S. (2005). Individuals with autism spectrum disorders show normal responses to a fear potential startle paradigm. *Journal of Autism and Developmental Disorders*, *35*, 575–583.

Bigler, E.D., Tate, D.F., Neely, E.S., Wolfson, L.J., Miller, M.J., Rice, S.A., Cleavinger, H., Anderson, C., Coon, H., Ozonoff, S., Johnson, M., Dinh, E., Lu, J., McMahon, W.M., & Lainhart, J.E. (2003). Temporal lobe, autism, and macrocephaly. *American Journal of Neuroradiology*, *24*, 2066–2076.

Bradley, M.M. & Lang, P.J. (1999). *Affective norms for English words (ANEW): Instruction manual and affective ratings (technical report C-1)*. Gainesville, FL: NIMH Center for the Study of Emotion and Attention.

Brand, M., Grabenhorst, F., Starcke, K., Vanderkerckhove, M.M., & Markowitsch, H.J. (2007). Role of the amygdala in decisions under ambiguity and decisions under risk: Evidence from patients with Urbach-Wiethe disease. *Neuropsychologia*, *45*, 1305–1317.

Brothers, L. (1996). Brain mechanisms of social cognition. *Journal of Psychopharmacology*, *10*, 2–8.

Cheng, D.T., Knight, D.C., Smith, C.N., & Helmstetter, F.J. (2006). Human amygdala activity during the expression of fear responses. *Behavioral Neuroscience*, *120*, 1187–1195.

Chiba, A.A., Kesner, R.P., Matsuo, F., Heilbrun, M.P., & Madden,

- K.L. A dissociation between affect and recognition following unilateral temporal lobectomy including the amygdala. (in preparation).
- Colgan, S.E., Lanter, E., McComish, C., Watson, L.R., Crais, E.R., & Baranek, G.T. (2006). Analysis of social interaction gestures in infants with autism. *Child Neuropsychology*, *12*, 307–319.
- Crone, E.A. & van der Molen, M.W. (2004). Developmental changes in real life decision making: Performance on a gambling task previously shown to depend on the ventromedial prefrontal cortex. *Developmental Neuropsychology*, *25*, 251–279.
- Dalton, K.M., Nacewicz, B.M., Johnstone, T., Schaefer, H.S., Gernsbacher, M.A., Goldsmith, H.H., Alexander, A.L., & Davidson, R.J. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience*, *8*, 519–526.
- Davis, M. & Whalen, P.J. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry*, *6*, 13–24.
- Empirisoft Corporation (2003). *DirectRT* [computer software]. New York: Empirisoft Corporation.
- Flykt, A. (2005). Visual search with biological threat stimuli: Accuracy, reaction times, and heart rate changes. *Emotion*, *5*, 349–353.
- Giedd, J.N., Snell, J.W., Lange, N., Rajapakse, J.C., Casey, B.J., Kozuch, P.L., Vaituzis, A.C., Vauss, Y.C., Hamburger, S.D., Kaysen, D., & Rapoport, J.L. (1996). Quantitative magnetic resonance imaging of human brain development: Ages 4–18. *Cerebral Cortex*, *6*, 551–560.
- Gilbert, P.E., Campbell, A., & Kesner, R.P. (2003). The role of the amygdala in conditioned flavor preference. *Neurobiology of Learning and Memory*, *79*, 118–121.
- Golan, O., Baron-Cohen, S., Hill, J.J., & Rutherford, M.D. (2006). The ‘Reading the Mind in the Voice’ Test-Revised: A study of complex emotion recognition in adults with and without autism spectrum conditions. *Journal of Autism and Developmental Disorders*, *37*, 1096–1106.
- Grelotti, D.J., Klin, A.J., Gauthier, I., Skudlarski, P., Cohen, D.J., Gore, J.C., Volkmar, F.R., & Schultz, R.T. (2005). fMRI activation of the fusiform gyrus and amygdala to cartoon characters but not to faces in a boy with autism. *Neuropsychologia*, *43*, 373–385.
- Hadjikhani, N., Joseph, R.M., Snyder, J., Chabris, C.F., Clark, J., Steele, S., McGrath, L., Vangel, M., Aharon, I., Feczko, E., Harris, G.J., & Tager-Flusber, H. (2004). Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. *NeuroImage*, *22*, 1141–1150.
- Hannula, D.E., Simons, D.J., & Cohen, N.J. (2005). Imaging implicit perception: Promise and pitfalls. *Nature Reviews Neuroscience*, *6*, 247–255.
- Haznedar, M.M., Buchsbaum, M.S., Wei, T.C., Hof, P.R., Cartwright, C., Bienstock, C.A., & Hollander, E. (2000). Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. *American Journal of Psychiatry*, *157*, 1994–2001.
- Hobson, R.P. & Meyer, J.A. (2005). Foundations for self and other: A study in autism. *Developmental Science*, *8*, 481–491.
- Howard, M.A., Cowell, P.E., Boucher, J., Brooks, P., Mayes, A., Farrant, A., & Roberts, N. (2000). Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. *Neuroreport*, *11*, 2931–2935.
- Humphreys, K., Minshew, N., Leonard, G.L., & Behrmann, M. (2007). A fine-grained analysis of facial expression processing in high-functioning adults with autism. *Neuropsychologia*, *45*, 685–695.
- Johnson, S.A., Yechiam, E., Murphy, R.R., Queller, S., & Stout, J.C. (2006). Motivational processes and autonomic responsivity in Asperger’s disorder: Evidence from the Iowa Gambling Task. *Journal of the International Neuropsychological Society*, *12*, 668–676.
- Kelly, D.J., Quinn, P.C., Slater, A.M., Lee, K., Gibson, A., Smith, M., Ge, L., & Pascalis, O. (2005). Three-month-olds, but not newborns, prefer own-race faces. *Developmental Science*, *8*, F31–F36.
- Killgore, W.D. & Yurgelun-Todd, D.A. (2004). Activation of the amygdala and anterior cingulate during nonconscious processing of sad versus happy faces. *Neuroimage*, *21*, 1215–1223.
- Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry*, *59*, 809–816.
- Larson, C.L., Schaefer, H.S., Seigle, G.J., Jackson, C.A., Anderle, M.J., & Davidson, R.J. (2006). Fear is fast in phobic individuals: Amygdala activation in response to fear-relevant stimuli. *Biological Psychiatry*, *60*, 410–417.
- LeDoux, J.E. (1994). Emotion, memory and the brain. *Scientific American*, *270*, 50–57.
- LeDoux, J.E. (2000). The amygdala and emotion: A view through fear. In J.P. Aggleton (Ed.), *The amygdala: A functional analysis* (2nd ed., pp. 289–310). Oxford: Oxford University Press.
- Lewis, P.A., Critchley, H.D., Rothstein, P., & Dolan, R.J. (2007). Neural correlates of processing valence and arousal in affective words. *Cerebral Cortex*, *17*, 742–748.
- Lord, C., Risi, S., Lambrecht, L., Cook, E.H., Leventhal, B.L., DiLavore, P., Pickles, A., & Rutter, M. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*, *30*, 205–223.
- Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism & Developmental Disorders*, *24*, 659–685.
- Loveland, K. (2001). Toward an ecological theory of autism. In J.A. Burack, T. Charman, N. Yirmiya, & P.R. Zelazo (Eds.), *The development of autism: Perspectives from theory and research*. Mahwah, NJ: Lawrence Erlbaum.
- Merckelbach, H., De Jong, P., Leeuw, I., & van den Hout, M.A. (1995). Startle responses of spider phobics to masked stimuli: A pilot study. *International Journal of Neuroscience*, *81*, 169–175.
- Morris, J.S., Scott, S.K., & Dolan, R.J. (1999). Saying it with feeling: Neural responses to emotional vocalizations. *Neuropsychologia*, *37*, 1155–1163.
- Munson, J., Dawson, G., Abbott, R., Faja, S., Webb, S.J., Friedman, S.D., Shaw, D., Artru, A., & Dager, S.R. (2006). Amygdalar volume and behavioral development in autism. *Archives of General Psychiatry*, *63*, 686–693.
- Nakic, M., Smith, B.W., Busis, S., Vythilingam, M., & Blair, R.J. (2006). The impact of affect and frequency on lexical decision: The role of the amygdala and inferior frontal cortex. *Neuroimage*, *31*, 1752–1761.
- Nelson, C.A., Bloom, F.E., Cameron, J.L., Amaral, D., Dahl, R.E., & Pine, D. (2002). An integrative, multidisciplinary approach to

- the study of brain-behavior relations in the context of typical and atypical development. *Development and Psychopathology*, *14*, 499–520.
- Ohman, A. (2005). The role of the amygdala in human fear: Automatic detection of threat. *Psychoneuroendocrinology*, *30*, 953–958.
- Ohman, A., Flykt, A., & Esteves, F. (2001). Emotion drives attention: Detecting the snake in the grass. *Journal of Experimental Psychology: General*, *130*, 466–478.
- Ohman, A. & Mineka, S. (2001). Fears, phobias, and preparedness: Toward an evolved module of fear and fear learning. *Psychological Review*, *108*, 482–522.
- Pasley, B.N., Mayes, L.C., & Schultz, R.T. (2004). Subcortical discrimination of unperceived objects during binocular rivalry. *Neuron*, *42*, 163–172.
- Paul, R., Augustyn, A., Klin, A., & Volkmar, F.R. (2005). Perception and production of prosody by speakers with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *35*, 205–220.
- Pelphrey, K.A., Sasson, N.J., Reznick, J.S., Paul, G., Goldman, B.D., & Piven, J. (2002). Visual scanning of faces in autism. *Journal of Autism and Developmental Disorders*, *32*, 249–261.
- Phelps, E.A. & LeDoux, J.E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*, *48*, 175–187.
- Pierce, K., Haist, F., Sedaghat, F., & Courschesne, E. (2004). The brain response to personally familiar faces in autism: Findings of fusiform activity and beyond. *Brain*, *127*, 2703–2716.
- Pierce, K., Muller, R.A., Ambrose, J., Allen, G., & Courchesne, E. (2001). Face processing occurs outside the “fusiform face area” in autism: Evidence from functional MRI. *Brain*, *124*, 2059–2073.
- Pine, D.S., Lissek, S., Klein, R.G., Mannuzza, S., Moulton, J.L., III, Guardino, M., & Woldehawariat, G. (2004). Face-memory and emotion: Associations with major depression in children and adolescents. *Journal of Child Psychiatry and Psychology*, *45*, 1199–1208.
- Rauch, S.L., Shin, L.M., & Phelps, E.A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research—past, present, and future. *Biological Psychiatry*, *60*, 376–382.
- Reinders, A.A., Glascher, J., de Jong, J.R., Willemsen, A.T., den Boer, J.A., & Buchel, C. (2006). Detecting fearful and neutral faces: BOLD latency differences in amygdala-hippocampal junction. *Neuroimage*, *33*, 805–814.
- Rutherford, M.D., Young, G.S., Hepburn, S., & Rogers, S.J. (2006). A longitudinal study of pretend play in autism. *Journal of Autism and Developmental Disorders*, *37*, 1024–1039.
- Sabatelli, D., Bradley, M.M., Fitzsimmons, J.R., & Lang, P.J. (2005). Parallel amygdala and inferotemporal activation reflect emotional intensity and fear relevance. *Neuroimage*, *24*, 1265–1270.
- Sabbagh, M.A. (2004). Understanding orbitofrontal contributions to theory-of-mind reasoning: Implications for autism. *Brain and Cognition*, *55*, 209–219.
- Sander, K., Brechmann, A., & Scheich, H. (2003). Audition of laughing and crying leads to right amygdala activation in a low-noise setting. *Brain Research Protocols*, *11*, 81–91.
- Schultz, R.T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience*, *23*, 125–141.
- Schultz, R.T., Gauthier, I., Klin, A., Fulbright, R.K., Anderson, A.W., Volkmar, F., Skudlarski, P., Lacadie, C., Cohen, D.J., & Gore, J.C. (2000). Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. *Archives of General Psychiatry*, *57*, 331–340.
- Schultz, R.T., Grelotti, D.J., Klin, A., Kleinman, J., Van der Gaag, C., Marois, R., & Skudlarski, P. (2003). The role of the fusiform face area in social cognition: Implications for the pathobiology of autism. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*, 415–427.
- Schultz, R.T., Hunyadi, E., Connors, C., & Pasley, B. (2005). *fMRI study of facial expression perception in autism: The amygdala, fusiform face area and their functional connectivity*. Paper presented at the annual meeting of the Organization for Human Brain Mapping, June 12–16, 2005, Toronto, CA.
- Schumann, C.M., Hamstra, J., Goodlin-Jones, B.L., Lotspeich, L.J., Kwon, H., Buonocore, M.H., Lammers, C.R., Reiss, A.L., & Amaral, D.G. (2004). The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. *Journal of Neuroscience*, *24*, 6392–6401.
- Skuse, D., Morris, J., & Lawrence, K. (2003). The amygdala and the development of the social brain. *Annals of the New York Academy of Sciences*, *1008*, 91–101.
- Sotres-Bayon, F., Bush, D.E., & LeDoux, J.E. (2004). Emotional perseveration: An update on prefrontal-amygdala interactions in fear extinction. *Learning and Memory*, *11*, 525–535.
- Sparks, B.F., Friedman, S.D., Shaw, D.W., Aylward, E.H., Echelard, D., Artru, A.A., Maravilla, K.R., Giedd, J.N., Munson, J., Dawson, G., & Dager, S.R. (2002). Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*, *59*, 184–192.
- Speer, L.L., Cook, A.E., McMahon, W.M., & Clark, E. (2007). Face processing in children with autism: Effects of stimulus contents and type. *Autism*, *11*, 265–277.
- Suomi, S.J. & Harlow, H.F. (1971). Abnormal social behavior in young monkeys. In J. Helmuth (Ed.), *The exceptional infant* (Vol. 2). New York: Bruner-Mazel.
- Turati, C., Simion, F., Milani, I., & Umiltà, C. (2002). Newborns’ preference for faces: What is crucial? *Developmental Psychology*, *38*, 875–882.
- van der Geest, J.N., Kemner, C., Camfferman, G., Verbaten, M.N., & van Engeland, H. (2002). Gaze behavior of children with pervasive developmental disorder toward human faces: A fixation time study. *Journal of Child Psychology and Psychiatry*, *43*, 669–678.
- Vollm, B.A., Taylor, A.N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., Deakin, J.F., & Elliot, R. (2006). Neuronal correlates of theory of mind and empathy: A functional magnetic resonance imaging study in a nonverbal task. *Neuroimage*, *20*, 90–98.
- Vuilleumier, P. & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia*, *45*, 174–194.
- Wang, A.T., Dapretto, M., Hariri, A.R., Sigman, M., & Bookheimer, S.Y. (2004). Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*, 481–490.
- Waterhouse, L., Fein, D., & Modahl, C. (1996). Neuro-functional mechanisms in autism. *Psychological Review*, *103*, 457–489.

- Willems, S., Adam, S., & van der Linden, M. (2002). Normal mere exposure effect with impaired recognition in Alzheimer's disease. *Cortex*, *38*, 77–86.
- Winston, J.S., Gottfried, J.A., Kilner, J.M., & Dolan, R.J. (2005). Integrated neural representations of odor intensity and affective valence in human amygdala. *Journal of Neuroscience*, *25*, 8903–8907.
- Zajonc, R.B. (1968). Attitudinal effects of mere exposure. *Journal of Personality and Social Psychology*, *9*, 1–27.
- Zajonc, R.B. (2001). Mere exposure: A gateway to the subliminal. *Current Directions in Psychological Science*, *10*, 224.
- Zirlinger, M. & Anderson, D. (2003). Molecular dissection of the amygdala and its relevance to autism. *Genes, Brain, and Behavior*, *2*, 282–294.