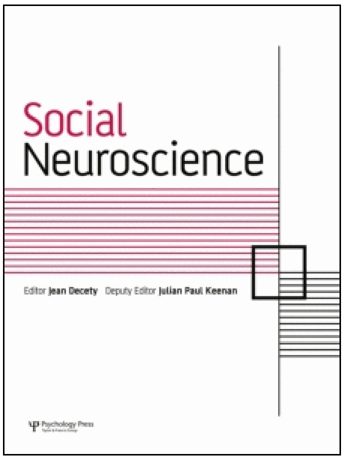

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Levels of emotional awareness and autism: An fMRI study

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Levels of emotional awareness and autism: An fMRI study

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Autism is associated with an inability to identify and distinguish one's own feelings. We assessed this inability using alexithymia and empathy questionnaires, and used fMRI to investigate brain activity while introspecting on emotion. Individuals with high functioning autism/Asperger syndrome (HFA/AS) were compared with matched controls. Participants rated stimuli from the International Affective Picture System twice, once according to the degree of un/pleasantness that the pictures induced, and once according to their color balance. The groups differed significantly on both alexithymia and empathy questionnaires. Alexithymia and lack of empathy were correlated, indicating a link between understanding one's own and others' emotions. For both groups a strong relationship between questionnaire scores and brain activity was found in the anterior insula (AI), when participants were required to assess their feelings to unpleasant pictures. Regardless of self-reported degree of emotional awareness, individuals with HFA/AS differed from controls when required to introspect on their feelings by showing reduced activation in self-reflection/mentalizing regions. Thus, we conclude that difficulties in emotional awareness are related to hypoactivity in AI in both individuals with HFA/AS and controls, and that the particular difficulties in emotional awareness in individuals with HFA/AS are not related to their impairments in self-reflection/mentalizing.

INTRODUCTION

Individuals with high functioning autism and Asperger syndrome (henceforth HFA/AS) often have difficulties in attributing mental states, such as beliefs, desires or intentions to others (see Frith, 2004, for a review). The neurophysiological basis of this ability, often referred to as mentalizing, can be demonstrated in a network of regions, which shows reduced activation in this group (see Frith & Frith, 2006, for a review). However, much less is known of how these high-functioning individuals experience their own bodily and emotional states, although a number of studies

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suggest that this experience is abnormal, with impaired emotional awareness being frequently reported (Ben Shalom et al., 2006; Hill, Berthoz, & Frith, 2004; Hurlburt, Happé, & Frith, 1994; Rieffe, Meerum Terwogt, & Kotronopoulou, 2006). This study aimed to increase this knowledge by investigating emotional awareness in HFA/AS.

Difficulties in emotional awareness characterize the condition known as alexithymia. This is a subclinical phenomenon marked by difficulties in identifying and describing feelings. These include difficulties in distinguishing feelings from the bodily sensations of emotional arousal (Nemiah, Freyberg, & Sifneos, 1976). Alexithymia is thought to characterize 10% of the general population (Linden, Wen, & Paulhaus, 1994; Salminen, Saarijarvi, Aarela, Toikka, & Kauhanen, 1999). However, in recent studies with individuals with HFA/AS severe degrees of alexithymia have been found to affect about 50% of this population (Hill et al., 2004). Given these results, and the well-documented impairments in mentalizing in this group, Hill et al. (2004) suggested a relationship between mentalizing difficulties (impairments in representing mental states of the self) and difficulties in the experience of own emotions. Under this hypothesis the representation of mental states is necessary for emotional awareness.

Lambie and Marcel (2002) have reviewed models of emotional experience and argued for a framework where a distinction is made between the neurophysiological arousal associated with emotions (first-order experience) and the awareness of this arousal, often referred to as interoception (second-order experience). In addition, we need to consider a third level, arising from the requirement to introspect on one's inner experience, an aspect that is particularly relevant for autism. This level involves an awareness of a self who has emotions and can monitor them and is different from a second-order bodily awareness of emotions. If impaired introspection or self-reflection characterizes autism (Kennedy, Redcay, & Courchesne, 2006), then we would expect the self-reflective system to be less active. In individuals with autism who also have a high degree of alexithymia this activity might be reduced still further when they are required to introspect on their emotions.

First-order emotional experience has been associated with increased activity in the amygdala and orbitofrontal cortex in studies of both implicit and explicit emotions in normal individuals (Ochsner & Gross, 2005). In autism there is evidence for reduced activation of this system in the presence of fearful faces (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007). However, there is as yet little evidence about responses to emotionally arousing pictures other than faces. If a lack of neural response to strong emotion is characteristic of autism, then we would predict that amygdala and orbitofrontal cortex would show reduced activation. Even less activation might be expected in individuals with autism who report alexithymic symptoms.

Second-order awareness of bodily states associated with emotions, or interoceptive awareness, is a particularly promising candidate for the explanation of alexithymic symptoms. Several studies have recently focused on the so-called interoceptive cortex (Craig, 2002, 2003) and suggested a crucial role for insular-somatosensory as well as anterior cingulate cortices (ACC) in the processing and representation of the internal arousal and bodily states that may underpin core conscious feeling states (Craig, 2003; Critchley, 2005; Damasio, 1994). In particular, anterior insula activation has been observed in a wide range of imaging studies associated with positive and negative subjective feelings such as perceived unpleasantness of painful stimulation (Craig, Chen, Bandy, & Reiman, 2000). Imaging studies focusing on the relationship between peripheral measures of arousal and brain activity also provide robust evidence for the crucial role of rostral ACC and anterior insular cortices in the representation of internal bodily states of arousal as well as emotional awareness. For example, activity in insula, somatomotor and cingulate cortices was observed when participants were asked to monitor their heartbeat and judge whether concurrent auditory feedback was either synchronous or delayed. Furthermore, both the activity and cortical thickness of the right anterior insula were correlated with performance on the heartbeat monitoring task as well as the participants' subjective rating of their visceral awareness (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). Singer and colleagues have extended these approaches by suggesting that these representations may not only serve the awareness of own feeling states, but may also underlie the capacity to empathize, that is to share the feelings of others who are, for example, in pain or experiencing disgust (Singer et al., 2004; Wicker et al., 2003).

All these findings suggest that the anterior insula and ACC are involved in conscious representation of internal bodily states. Therefore we would expect to observe reduced activation of the anterior insula region in individuals with autism who also have a high degree of alexithymia. Moreover, in view of the critical role of the insula in empathic responses, we would expect, at the behavioral level, a relationship between degree of self-reported alexithymia and degree of self-reported lack of empathy; at the physiological level, we would expect that the amount of insula activation would correlate with the degree of self-reported alexithymia and lack of empathy.

The present study targeted the neurophysiological processes that underlie awareness of strong emotions as elicited by picture stimuli in individuals with, and without, an autistic spectrum disorder and varying degrees of alexithymia. Thus, first, we assessed participants with HFA/AS and controls with both Alexithymia scales and Empathy questionnaires. Second, we carried out an fMRI study using a version of the paradigm developed by Lane, Fink, Chau, and Dolan (1997). Participants viewed picture stimuli from the International Affective Picture System (IAPS) and either rated the emotion evoked in them by the stimuli (Internal task), or judged the black/white color balance present in the stimuli (External task). The contrast between strong negative vs. neutral stimuli, regardless of the task set required, elucidates the presence or absence of neural responses to arousing stimuli (first-order: having an emotional response). The interaction between task set and emotional valence assesses the effect of interoceptive awareness, that is the awareness of bodily sensations in the presence of emotional arousal (second order: being aware of bodily sensations). The contrast between the Internal and the External task reveals processes underlying the task set of introspection (third order: being aware of having emotions).

Thus, the design of the present study allowed two orthogonal questions to be addressed. First, what are the neural systems that relate to the degree of self-reported emotional awareness, e.g., alexithymia and lack of empathy? Second, what are the differences between neural responses to emotional stimuli in individuals with HFA/AS and matched controls?

EXPERIMENTAL PROCEDURES

Participants

Fifteen participants (13 male; 2 female) with autistic disorder (ASD) and fifteen control participants (13 male; 2 female) were recruited for this study. Groups were matched on age (ASD: $M = 36.6$ years, $SD = 11.7$; Control: $M = 33.7$ years, $SD = 10.3$) and IQ as assessed using the Wechsler Adult Intelligence Scale (Wechsler, 1999; HFA/AS: $M = 117.6$, $SD = 13.5$; Control: $M = 119.6$, $SD = 11.4$). All participants in the HFA/AS group were high functioning and had previously received a diagnosis of autism or Asperger syndrome from an independent clinician according to standard criteria (DSM-IV; American Psychiatric Association, 1994). In line with current practice, we used the Autism Diagnostic Observational Schedule (ADOS; Lord et al., 1989) to corroborate the clinical diagnosis. All participants met ADOS criteria for HFA/AS (see Appendix, Figure A1). Control participants were screened for any pre-existing neurological or psychiatric disorders using a questionnaire/interview. Participants gave their informed consent to participate in the study, which was approved by the local ethics committee and conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Questionnaires

The 20-item Toronto Alexithymia Scale (TAS-20; Bagby, Parker, & Taylor, 1994) and the Bermond–Vorst Alexithymia Questionnaire (BVAQ-B; Vorst & Bermond, 2001) were used to index the degree to which participants reported alexithymic tendencies. Individual differences in empathy were assessed with the Davis Interpersonal Reactivity Index (IRI; Davis, 1980).

Stimuli

Participants were presented with full-color pictures selected from the International Affective Picture System (IAPS; Lang, Bagby, & Cuthbert, 1999a). Pictures were projected onto a screen positioned at the head end of the MRI scanner. Participants viewed the screen through a mirror mounted on the head coil. For each picture within this set, standardized valence and arousal scores are available. These scores are expressed on a 9-point scale from low to high arousal and from pleasant to unpleasant (Lang, Bradley, & Cuthbert, 1999b). Pictures were categorized according to their valence into three types of stimuli: unpleasant, pleasant and neutral. In order to prevent stereotyped responses and to elicit deeper introspection on emotions, we excluded pictures on the extremes of the pleasantness–unpleasantness dimension. In order to elicit strong emotional bodily responses, we selected pictures with high arousal ratings. We used 90 unpleasant (valence $M = 3.39$, $SD = 0.59$; arousal $M = 5.96$, $SD = 0.71$), 90 pleasant (valence $M = 6.98$, $SD = 0.36$; arousal $M = 5.79$, $SD = 0.54$) and 90 neutral (valence $M = 4.97$, $SD = 0.22$; arousal $M = 2.58$, $SD = 0.39$) stimuli. The pleasant and unpleasant sets were comparable in terms of their arousal ratings (two-sample t-test; $p = .3$). Unpleasant stimuli were of main interest in the exploration of interoceptive awareness, as highly arousing negative picture stimuli have proved to be capable of evoking body arousal responses more reliably than positive stimuli (Baumgartner, Esslen, & Jancke, 2006; Pollatos, Gramann, & Schandry, 2007).

Behavioral study

In order to establish whether the individuals with HFA/AS understood the tasks in the same way as the controls, and found them of equal difficulty, we carried out a subsequent study outside the scanner. In this study we obtained individual valence ratings as well as RT measures for a parallel set of IAPS pictures, which were matched on arousal and valence ratings with that used in the functional imaging study. We used a parallel set because we wanted to avoid unwanted familiarity effects and possible habituation, which might have distorted the ratings. The set consisted of three subsets of 30 pictures each of positive, negative and neutral emotional content. We used 5 response categories rather than an analogue scale in order to obtain RTs. Accordingly, participants used a 5-button response pad. All other conditions were the same as in the scanner. Thus, participants saw the pictures twice, once using the instructions for the Internal task and once using the instructions for the External task with appropriate counterbalancing.

Functional imaging study

Procedure. The factorial design of the task is presented in Figure 1. There were two tasks, one Internal, one External, and three types of stimuli, unpleasant, neutral, and pleasant. In the Internal task participants were asked to rate the emotion evoked by the stimulus on a visual analogue scale presented immediately after the stimulus, where the end points of the scale were labeled ‘‘Positive’’ and ‘‘Negative.’’ In the External task, participants were asked to indicate the ratio of black and white colored pixels in the stimulus picture (a physical aspect of the stimulus). Ratings were made on a visual analogue scale, the extremes of which were labeled ‘‘Black’’ and ‘‘White.’’

Testing began with a training session outside of the scanner, in order to familiarize the participants with the tasks to be performed during the scanning session. All sessions were divided into three runs of 15 minutes each with breaks in between. Each trial began with the presentation of the picture for two seconds, followed by a four-second period in which participants indicated their response on a visual analogue scale. A fixation cross presented for one second marked the end of the current trial and the start of the next. Participants responded by moving a pointer along the scale using a response box, where they had to use index and middle finger to press one of two buttons so as to move a cursor on the scale. Labeling of the scale extremes (e.g., positive left, negative right, or vice versa), and the starting position of the pointer was randomly determined on every trial in order to discourage response preparation during the time in which the stimulus was viewed.

Both task and stimulus valence were blocked such that in any one block participants only performed one task and saw one kind of stimulus (unpleasant, pleasant, or neutral). Five pictures were presented in each block, and each block lasted for 35 seconds (see Figure 1). Rest blocks (of the same duration) were also presented in which the participants viewed a white cross in the middle of a black background. Instructions presented before each block informed participants which of the two tasks they were to perform. A total of 9 blocks per type of stimulus (pleasant, unpleasant, and neutral) for the Internal task, 9 blocks per type of stimulus (pleasant, unpleasant, and neutral) for the external task, and 18 blocks of resting period were presented during the three runs of the scanning session. The order of blocks

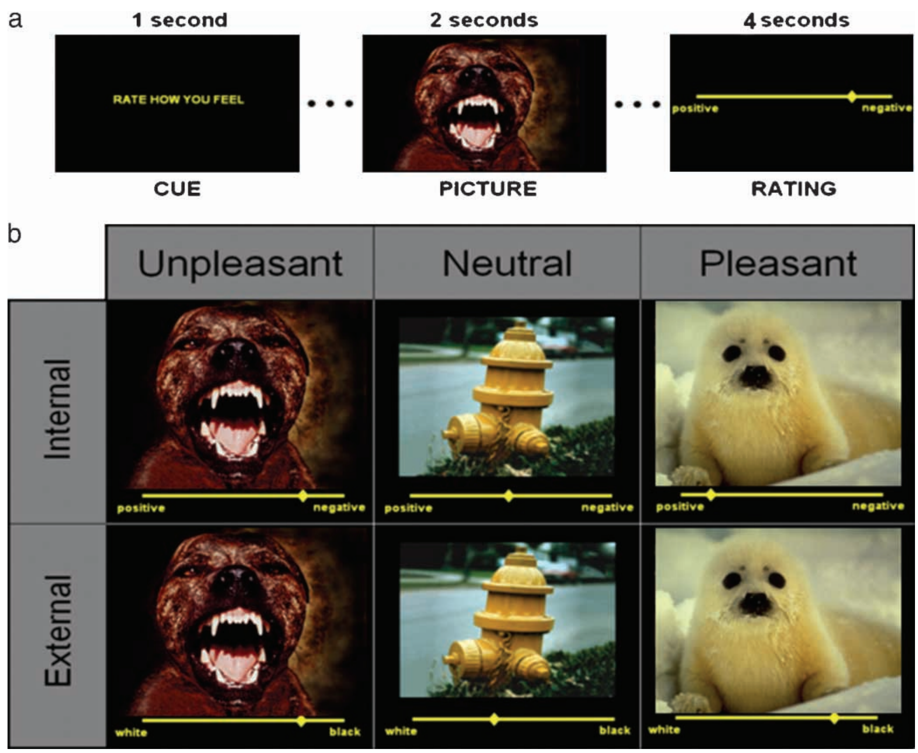

Figure 1. Task design and example stimuli. Participants were asked to view emotional or neutral pictures and either rate the emotion evoked in them by the stimuli (Internal task), or to judge the black/white color balance in the stimuli (External Task), in both cases using an analog scale.

and thus task and stimulus category were randomized within participants.

Imaging data acquisition. MRI brain images were acquired with a 1.5 Tesla system (Siemens Sonata). Structural images were acquired with a T1 sequence using a phased-array headcoil. Functional whole brain data were obtained using a T2* echoplanar sequence sensitive to BOLD contrast (33 slices, 3 mm thickness, gap 1.5 mm, TE 90 ms, TR 2970 ms per volume). Slices were angled in an oblique orientation 5° to the anterior-posterior commissural line. The functional data were acquired in three sessions, the first six volumes of each session were discarded to allow for T1 equilibration effects. Stimulus presentation began after the sixth volume. A total of 795 full-brain volumes for each participant were acquired.

Imaging data analyses. fMRI data were analyzed using SPM 2 (Wellcome Department of Imaging Neuroscience, London, UK). To correct for motion, functional images were realigned to the first volume and then spatially normalized to a standard template with a resampled voxel size of $2 \times 2 \times 2$ mm, and smoothed using a Gaussian kernel with of 10 mm FWHM (Friston et al., 1995a). After preprocessing, functional images were analyzed using an event-related model (Worsley & Friston, 1995), under the general linear model assumption (Friston et al., 1995b). Each stimulus category (pleasant, unpleasant, and neutral) for the Internal and External tasks was modeled as a separate regressor and used to derive contrast images for second-level and correlation analyses. Contrast images coding for: (1) the main effect of introspection ([Internal task – External task]); (2) the main effect of viewing unpleasant stimuli ([Unpleasant – Neutral]); and (3) the interaction effect of interoceptive awareness ([Internal Unpleasant – Internal Neutral] – [External Unpleasant – External Neutral], were entered into one- and two-sample *t*-tests in order to investigate population-level effects and any group differences. These analyses were thresholded at $p < .001$, uncorrected.

The neural basis of the participants' degree of self-reported emotional awareness was investigated in each group by regressing individual scores on the alexithymia and empathy scales onto neural activity (whole brain analysis) when introspecting upon emotion. For regression analyses a threshold of $p < .005$, uncorrected, was used.

RESULTS

Questionnaires

Fourteen HFA/AS (one participant failed to complete the questionnaire) and fifteen control participants completed questionnaires indexing their degree of alexithymia (TAS-20 and BVAQ) and empathy (Interpersonal Reactivity Index; IRI). The individual data are presented in Figure 2. (Appendix Figure A1 presents means and standard deviations for the subscales of the questionnaires.)

Alexithymia. As expected (Hill et al., 2004), the HFA/AS group had a significantly higher total TAS-20 score than controls ($df = 27$; $t = 2.8$; $p < .01$). Their problem was particularly associated with describing feelings (subscale $df = 27$; $t = 3.4$; $p < .01$). On the BVAQ questionnaire the HFA/AS group did not differ from the controls on the total score, but showed poor insight ($df = 27$; $t = 3.2$; $p < .005$) and impaired cognition ($df = 27$; $t = 2.2$; $p < .05$).

Empathy. Overall we found a significant correlation between the perspective-taking subscale and the empathic-concern subscale of the IRI ($r = .593$, $p < .05$), and therefore combined these two subscales and used the combined score in subsequent regression analyses. On the combined score the HFA/AS group scored significantly lower than the control group ($df = 26$; $t = -2.9$; $p < .05$). They also scored significantly lower on the perspective taking subscale alone ($df = 26$; $t = -4.3$; $p < .001$).

Correlations between alexithymia and empathy. In controls, a significant correlation was found between scores on the alexithymia questionnaires (TAS-20) and scores on the empathic-concern and perspective-taking subscales of the IRI (empathic-concern scale, $r = -682$, $p < .01$; and perspective-taking scale, $r = -661$, $p < .01$), supporting the suggested link between alexithymia and empathy. In the HFA/AS group, too, a highly significant correlation was found between the alexithymia and empathy questionnaires, specifically for the empathic-concern scale ($r = -853$, $p < .01$).

Behavioral study

Overall, the pattern of results suggests that the tasks were of equal difficulty for the two groups, at least as indexed by RTs, allowing us to discount unequal task difficulty as an explanation of any group difference in neural activity. RT measures established that for both groups the External task was more difficult, i.e., was performed more slowly, $F(1, 26) = 23.64$, $p < .001$. (Appendix, Figure A2).

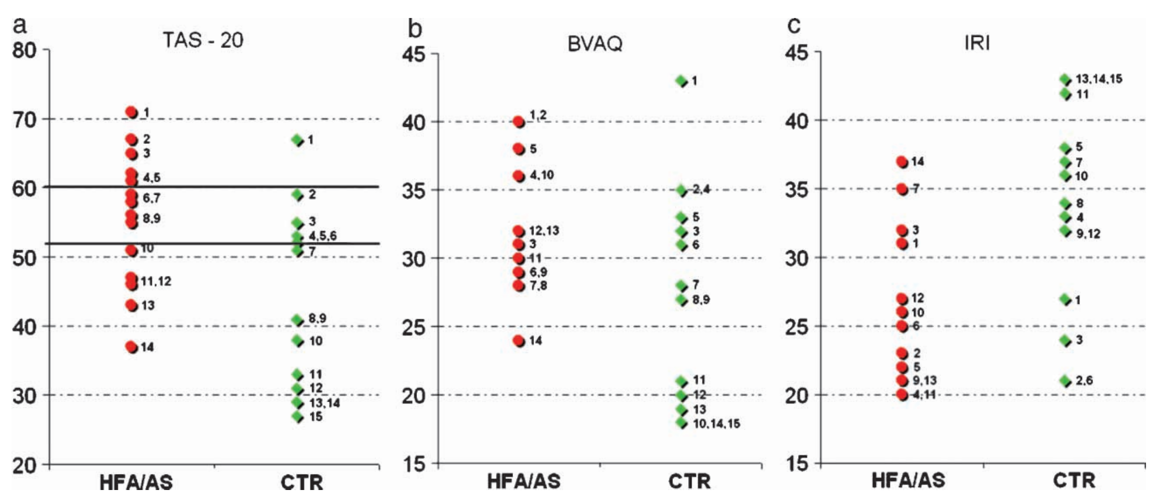

Figure 2. Questionnaire scores. Individual scores for participants with HFA/AS are shown in red and for controls in green. Each participant is identified by the same number to facilitate comparison. (a) Toronto Alexithymia questionnaire. Borderline scores (52–60) are shown between the black lines; scores >60 indicate alexithymia. (b) Bermond–Vorst Alexithymia Questionnaire – Cognitive subscale. (c) Davis Interpersonal Reactivity Index (IRI)—Composite of empathic-concern and perspective-taking subscales.

Interestingly, we found significant, and equal, RT increases when negative stimuli were judged in the external task for both the HFA/AS, $F(1, 26) = 11.59$, $p = .002$, and Control, $F(1, 26) = 9.11$, $p = .006$, groups. This is consistent with the finding that negative affective stimuli interfere with cognitive tasks (Blair et al., 2007; Simpson et al., 2000) and on this evidence both groups view the stimuli as emotional and they do so to an equal extent. In terms of rated valence, the HFA/AS and control groups did not differ, $F(1, 26) < 1$, and there was no correlation between self-reported Alexithymia and rated valence. Hence we assume that all participants were equally able to differentiate between the stimulus categories pleasant, neutral, and unpleasant, and that the stimulus categories were appropriate for participants with HFA/AS.

Functional imaging results

1. Activity associated with emotional awareness and empathy in HFA/AS and Control groups

The neural system underpinning emotional awareness was identified by regressing participants' self-reported degree of alexithymia, and empathy, onto the neural activity when introspecting in the presence of emotional arousal (see Section 2 below) separately for each group. In order to be confident that introspection on emotion was the appropriate condition with which to regress the alexithymia and empathy questionnaire scores, we also regressed the scores onto neural activity when introspecting (irrespective of the emotional content of stimuli) and onto neural activity when presented with unpleasant stimuli (irrespective of task). However, there were no significant correlations with either the alexithymia questionnaire, nor with the empathy questionnaire, in any area using these contrasts. Therefore, we present results from correlations with activity during introspection on emotion only.

Correlations of neural activity with alexithymia and empathy scores. Scores on the alexithymia questionnaires (negatively) and on the empathy questionnaire (positively) were significantly correlated with activity in mid-anterior insula (Figure 3 and Appendix Table A4) bilaterally in both groups, and were also correlated with activity in the left amygdala in the autism group (Figure 4 and Appendix Table A4). In order to elucidate the correlation between anterior insula activity and the combined empathy score we also separately correlated activity with the perspective-taking and empathic-concern subscales. Each showed the same patterns of correlation as the combined score, although at a reduced statistical threshold. The location of the correlation in the mid-anterior insula corresponded with previous functional studies of interoceptive awareness (Critchley et al., 2004). In contrast, none of the questionnaire measures was correlated with activity in the mentalizing system.

The relationship to lack of empathic concern confirms the proposal by Singer and her colleagues that the insula region is not only involved in the conscious perception of one's own bodily sensations and emotions, but is also involved in empathic reactions to the emotions of others (Singer et al., 2004).

2. Comparison between HFA/AS and Control groups

In order to discover any differences in neural activity between individuals with HFA/AS and typically developing control participants we compared group-level activity in response to: the task set of introspection; the presentation of unpleasant stimuli; and introspection in the presence of emotional arousal.

Activation associated with introspection. The comparison of the Internal with the External task showed increased activity in a large network of regions, components of which have previously been identified as being involved in both self-reflection and mentalizing (Frith & Frith, 2006; Ochsner et al., 2004). This network included the MPFC, ACC, precuneus, frontal inferior orbital cortex, bilateral temporal poles and the cerebellum, $p < .001$ (Figure 5a and Appendix Table A1). These same regions were also activated in the autistic participants, although to a reduced statistical and spatial extent (Figure 5b and Appendix Table A1). Group comparisons indicated that the autistic participants showed significantly less activity in MPFC, ACC, precuneus, left temporal pole and cerebellum, and increased activity in more posterior regions such as the parietal and occipital cortex (Figure 5c and Appendix Table A1).

Activation associated with the presentation of unpleasant stimuli. The comparison of neutral and unpleasant pictures regardless of task showed a

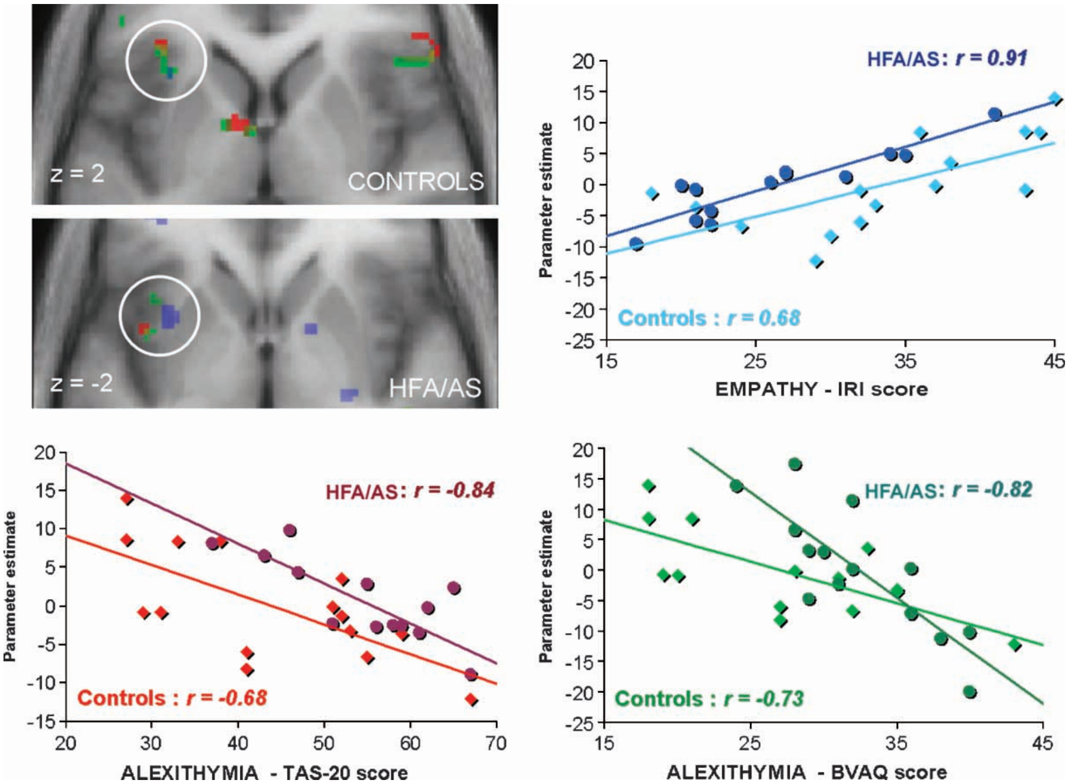

Figure 3. Neural correlates of alexithymia and empathy in HFA/AS and control groups. Activity in the left and right anterior insula correlates with alexithymia (negatively) and empathy (positively). Clusters are superimposed onto an average T1 image derived from all participants and the axial views of the insular cortex are presented. Functional data specific to introspection on negative emotions was used for the correlation analysis. Activity in the left anterior insula cortex: (i) controls (−32, 20, 2) z-score = 2.7, cluster = 9; HFA/AS (−40, 4, 0), z-score = 3.73, cluster = 12 is plotted against participants' scores on the Toronto Alexithymia Scale (TAS–20); (ii) controls (−32, 20, 2), z-score = 3.1, cluster = 5; HFA/AS (−40, 4, −4), z-score = 3.59, cluster = 14 is plotted against participants' scores on the Bermond–Vorst Alexithymia Questionnaire (BVAQ); (iii) controls (−32, 20, 2), z-score = 2.73, cluster = 5; HFA/AS (−34, 10, 2), z-score = 3.86, cluster = 7 is plotted against participants' scores on the Interpersonal Reactivity Index (IRI).

higher response in the amygdala and inferior orbitofrontal regions in both control and HFA/AS participants (Appendix Table A2). These brain regions have previously been reported to show enhanced activity in response to strongly unpleasant stimuli (Phillips, Drevets, Raush, & Lane, 2003; Taylor, Liberzon, & Koeppe, 2000). Group comparisons revealed greater activity in the inferior orbitofrontal cortex, but not amygdala, in control participants, suggesting a stronger basic response to emotions in this group.

Activation associated with interoceptive awareness of unpleasant emotions. Activity in response to introspection on the bodily sensation associated with the feeling of unpleasantness was investigated through the interaction of the task and valence factors. Specifically, we looked for areas that were more active when the Internal task was performed on unpleasant vs. neutral stimuli. Both the autism and control groups showed increased activity in superior frontal and temporal regions. The groups did not show significantly different activity in any region that has been hypothesized to be involved in the processing of emotional stimuli (Appendix Table A3). However, at a lower statistical threshold, control participants showed enhanced activity in insular cortex bilaterally, left AI (−34, 14, 2), z = 2.68; right AI (46, −2, 0), z = 2.45, compared to participants with HFA/AS.

DISCUSSION

To our knowledge this is the first study examining the neural correlates of self-reported awareness of own and other emotions in individuals with HFA/AS. The study also complements existing neuroimaging work on individuals with alexithymia and on interoceptive awareness in otherwise healthy individuals (Berthoz et al., 2002; Lane

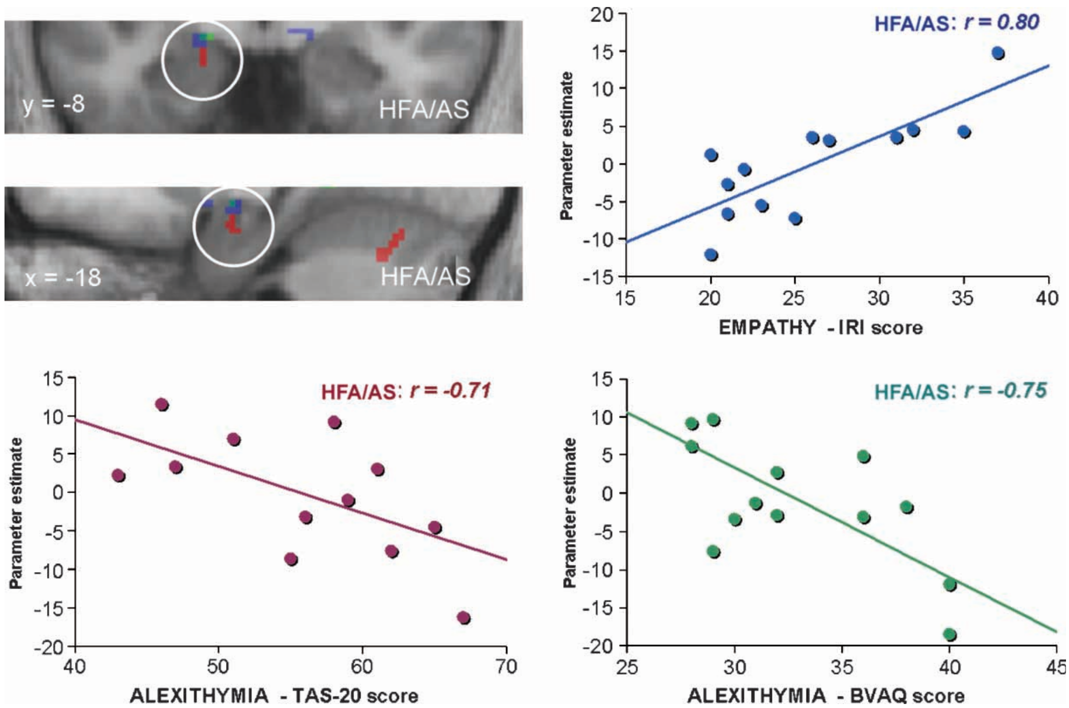

Figure 4. Neural correlates of alexithymia and empathy in the HFA/AS group. Activity in the left amygdala correlates with alexithymia (negatively) and empathy (positively). Clusters are superimposed onto an average T1 image derived from all participants and coronal and axial views of the amygdala are presented. Functional data specific to introspection on negative emotions were used for the correlation analysis. Activity in the left amygdala (−18, −8, −20), *z*-score = 2.87, cluster = 5; (−16, −6, −16), *z*-score = 3.10, cluster = 5; (−20, −10, −16), *z*-score = 3.49, cluster = 15 is plotted against participants' scores on the Toronto Alexithymia Scale (TAS–20), Bermond–Vorst Alexithymia Questionnaire (BVAQ) and Interpersonal Reactivity Index (IRI), respectively.

et al., 1997; Ochsner et al., 2004). However, the study was limited by the relatively small number of participants and the lack of a subgroup of non-autistic volunteers with low emotional awareness and empathic concern. Thus, we hope that further work will build upon these results.

This study adopted a three-level model of emotional experience based on the model of Lambie and Marcel (2002). In this model a distinction is made between the neurophysiological arousal associated with emotions (first-order experience) and the awareness of this arousal, often referred to as interoception (second-order experience). A third level was added to this model, which is reserved for introspection or self-processing, which we referred to as the awareness of having emotions. Brain areas can be mapped to the model so that first-order experience was localized to the amygdala and inferior orbitofrontal cortex, the second level to the anterior insula, and the third level to the mentalizing network.

Reduced emotional awareness as reported in questionnaires could not be explained by a reduced emotional response in the amygdala–orbitofrontal system to presentation of unpleasant stimuli. Thus, the first-order emotional experience of Lambie and Marcel (2002) does not seem to be affected by degree of alexithymia and lack of empathy. Neither could alexithymia and lack of empathy be explained by problems in adopting the task set of introspection. Instead, self-reported poor awareness of own and others' feelings, both in autistic and typically developing individuals, was strongly associated with a reduced response in interoceptive cortex, especially anterior insula (Craig, 2003; Critchley, 2005). Correlational analyses showed that the level of activity in this region correlated significantly and negatively with scores on both alexithymia measures. The higher the alexithymia score the lower the activity. These data suggest that in the condition most relevant to alexithymia, i.e., when the individual's own emotional state must be consciously represented, activity in the insula is associated with the degree to which alexithymia is reported.

This brain response was assessed when participants introspected on their inner experience in the presence of unpleasant stimuli, and this is consistent with the proposal that the function of

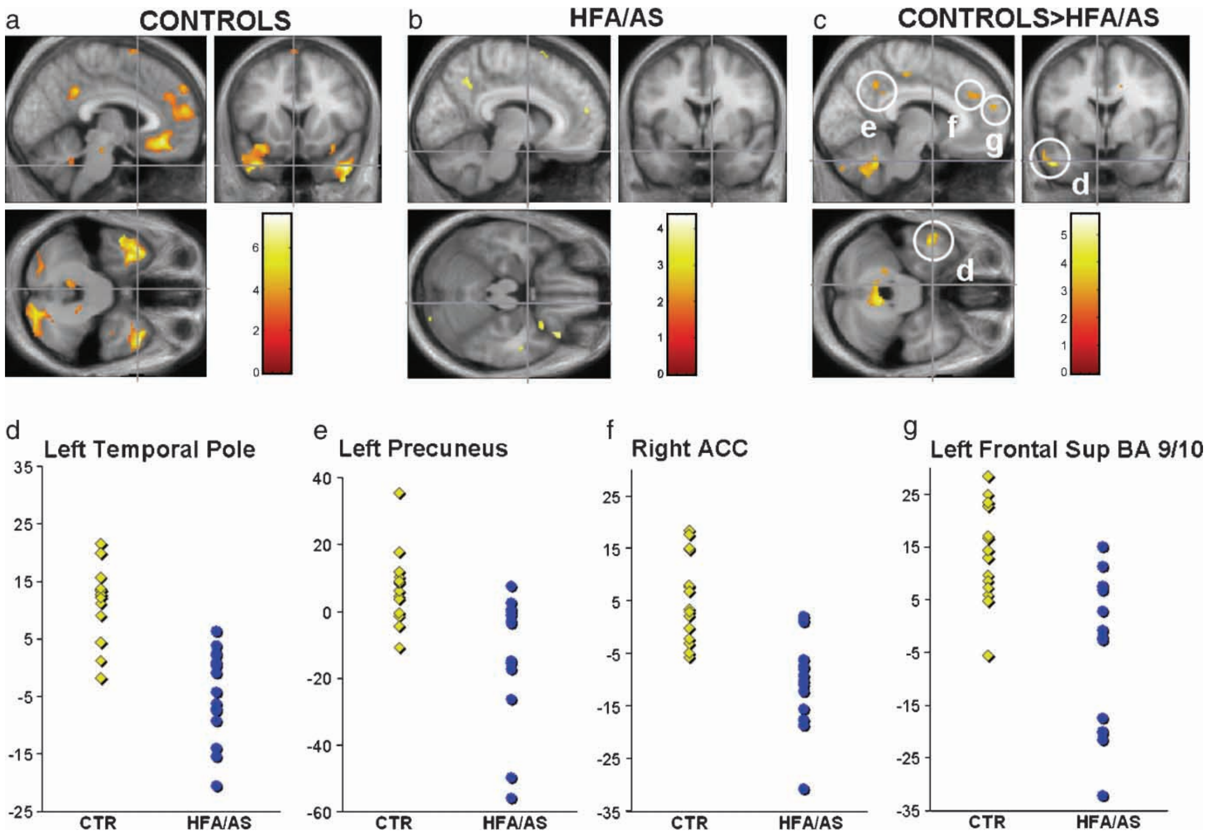

Figure 5. Increase in activity when activation evoked by the Internal task is contrasted with that evoked by the External task (irrespective of stimulus valence) and parameter estimates of this contrast in areas with significant group differences. (a) Increase in activity during the Internal task in controls. (b) Increase in activity during the Internal task in HFA/AS. (c) Difference between control and HFA/AS groups. (d–g) Increase in activity during the Internal task: (d) Left mid/inferior temporal pole (−50, −2, −34), *z*-score = 4.63, cluster = 132; (e) Left precuneus (−10, −54, 38), *z*-score = 3.15, cluster = 46; (f) Right anterior cingulate cortex (10, 38, 32), *z*-score = 4.27, cluster = 239; (g) Left superior frontal gyrus (−14, 56, 32), *z*-score = 3.7, cluster = 73. Color bars represent *t*-statistic values. Clusters are superimposed onto an average T1 image derived from all participants.

the insula is to provide a representation of bodily states that enables conscious awareness of feelings. We suggest it is a lack of conscious awareness of these representations that characterizes alexithymic symptoms in emotional awareness, i.e., an impairment in Lambie and Marcel's second-order emotional experience.

Our findings are consistent with existing models of alexithymia that suggest a "decoupling" of physiological arousal due to an emotional state from the conscious representation of the arousal (Lane & Schwartz, 1987). This raises the possibility that alexithymic symptoms may vary as a function of the degree of physiological arousal evoked by a particular emotional state. This suggestion is in accord with the results of several neuroimaging studies on alexithymic individuals, which showed that patterns of neural activity depend on which emotion is represented (Berthoz et al., 2002; Mantani, Okamoto, Shirao, Okada, & Yamawaki, 2005).

The behavioral measures of self-reported alexithymia and lack of empathy were found to be highly correlated with each other. Moreover, we observed significant correlation between activity in the insula cortex not only with alexithymia scores but also with scores on empathic concern and perspective taking. Thus, the areas where activity was correlated with alexithymia scores were the same areas where activity correlated with empathy scores. In agreement with other theorists (Lane & Schwartz, 1987), we hypothesize that the same neural architecture underlies the conscious representation of emotion in the self and in others. We suggest that the insula subserves this function. More speculatively, our results suggest that conscious representation of bodily and emotional states may be carried out by different networks from those involved in representing mental states such as beliefs, and that empathy as far as it involves the representation of another's emotional state, may be neurologically distinct from the representation of another's belief states (Singer, 2006).

The finding of reduced activation of medial prefrontal, temporal and precuneus regions in HFA/AS participants while introspecting is of particular interest, even though it did not show any relationship to alexithymic symptoms. It is consistent with the recently observed abnormal lack of activation in these regions during rest, and interpreted as an abnormal lack of introspection during rest conditions (Kennedy et al., 2006). Since the same brain regions are activated during mentalizing (Frith & Frith, 2006), it appears that the same network is active when monitoring the mental states of others as when monitoring one's own mental states.

On the basis of a study by Moriguchi et al. (2006) we would have expected that scores on the alexithymia questionnaire, reflecting levels of emotional awareness, to be correlated with activity in the mentalizing system. Alexithymia is described as a deficit in identifying and describing feelings (Nemiah et al., 1976), and our participants were continuously asked to rate their emotion during the Internal task. However, analysis revealed that activity in the introspection/mentalizing system did not vary as a function of the level of alexithymia. Unlike the study of Moriguchi et al., however, our study did not include an explicit test of mentalizing and we did not deliberately seek out participants with extreme scores on the alexithymia scales. Further work addressing the relationship between alexithymia/emotional awareness and mentalizing is therefore needed.

Indeed, our data reveal a dissociation between the task set of introspection, i.e., what we call the third level of emotional awareness and self-reported alexithymia and lack of empathy in our HFA/AS participants. There was a subgroup of participants in the HFA/AS group who did not report alexithymia or show reduced activity in anterior insula when introspecting on the effect of strongly emotional pictures, but still showed reduced activity in the introspection/mentalizing system. We can therefore conclude that lack of awareness of bodily states or impairments in second-order emotional experience are neither necessary nor sufficient for autistic disorder as currently diagnosed. On the other hand third-order emotional experience, knowing that you have emotional experiences, may well be critically associated with autism.

In common with previous reports (Ashwin et al., 2007), we found some evidence of hypoactivity in basic emotional processing areas (inferior orbitofrontal cortex) although not in the amygdala when processing negative stimuli regardless of task. However, activity in these areas did not vary as a function of alexithymia in either group.

One question for the future is why so many individuals with HFA/AS report alexithymic symptoms and a lack of empathy. The only condition where activity was related to questionnaire scores of alexithymia and lack of empathy was when participants were required to introspect on their emotions. Interestingly, in this condition, self-reported emotional awareness was correlated with activity in the anterior insula in the control group but with the anterior insula *and* the amygdala in the HFA/AS group. We have localized first- and second-order emotional response to the amygdala and anterior insula, respectively. Therefore it seems that alexithymic symptoms are normally mediated in the second-order emotional response. In the case of autism, however, a complex interaction between first-, and second-order awareness seems to apply. The specific details of this interaction, and the reason for its prevalence in autism, are yet to be discovered.

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APPENDIX

	Controls (N=15)	HFA/AS (N=14)
Age	33.7 (10.3)	36.9 (11.8)
IQ	119.6 (11.4)	117.6 (13.5)
ADOS	-	9.77 (2.4)
TAS total	43.7 12.7)	55.6 ● (9.7)
TAS dif	14.3 (5.3)	18.5 (6.5)
TAS ddf	11.8 (4.4)	17.2 ● (4.2)
TAS eot	17.6 (5.3)	19.9 (3.1)
BVAQ total	47.0 (11.1)	53.2 (8.7)
BVAQ pv	9.7 (3.5)	11.7 (2.3)
BVAQ pf	10.2 (3.5)	10.6 (2.8)
BVAQ pi	8.9 (2.9)	12.4 ● (3.0)
BVAQ pee	9.8 (2.7)	10.2 (3.9)
BVAQ ct	8.4 (3.1)	8.2 (3.0)
BVAQ cog	27.0 (7.6)	32.4 ● (4.9)
BVAQ em	20.0 (5.4)	20.9 (6.0)
IRI total	59.6 (8.8)	52.8 (11.0)
IRI pt	16.1 (4.5)	9.8 ● (3.1)
IRI fs	14.7 (4.3)	12.2 (5.0)
IRI ec	17.7 (4.2)	16.4 (4.2)
IRI pd	11.3 (5.0)	14.6 (6.3)

Legend

● = significantly different at $p<0.05$

TAS = Toronto Alexithymia Scale
dif = difficulty identifying feelings
ddf = difficulty describing feelings
eot = external oriented thinking

BVAQ = Bermond – Vorst Alexithymia Questionnaire
pv = poor verbalizing
pf = poor fantasies
pi = poor insight
pee = poor emotional excitability
ct = concrete thinking
em = Emotional factor
cog = cognitive factor

IRI = Interpersonal Reactivity Index
pt = perspective taking
fs = fantasy scale
ec = empathic concern
pd = personal distress

Figure A1. Sample description and questionnaire data.

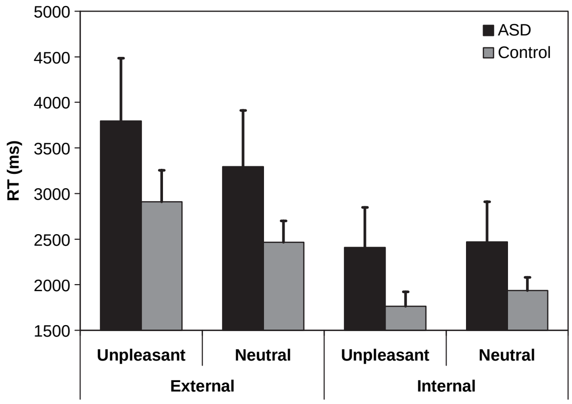

Figure A2. Performance on the behavioral task for the controls and individuals with high-functioning autistics/Asperger syndrome. Reaction times mean and (*SEM*) in the external and internal conditions, for neutral and unpleasant stimuli.

TABLE A1
Internally vs. externally oriented task (at $p < .001$)

		MNI coordinates of peak activation (mm)				
Side		*Brain region*	*x*	*y*	*z*	*Cluster t-value*
Controls						
L	Rectus	−4	36	−14	580	6.65*
L	Frontal sup	−14	54	32	1343	6.08*
L	Frontal sup medial	−6	56	16	1343	4.91*
R	Frontal sup medial	4	52	28	1343	4.47*
L	Frontal mid	−24	50	26	1343	5.52*
L	ACC	−12	40	26	1343	4.93*
R	ACC	8	42	28	1343	4.03*
L	SMA	−4	8	70	28	3.86
L	Precuneus	−4	−46	34	128	4.93
L	Frontal inf orb	−36	16	−18	1369	6.01*
R	Frontal inf orb	30	20	−20	691	4.54*
L	Temporal mid	−58	−4	−22	1369	5.19*
R	Temporal mid	60	−6	−24	691	4.01*
L	Temporal inf	−46	8	−38	1369	5.84*
R	Temporal pole sup	34	8	−18	691	4.73*
L	Temporal pole mid	−40	14	−36	1369	7.02*
R	Temporal pole mid	44	14	−36	691	7.62*
L	Temporal pole inf	−34	6	−36	1369	6.53*
L	Insula	−36	8	−6	15	4.20
L	Angular gyrus	−40	−60	20	33	4.45
R	Parahippocampus	30	−8	−28	249	4.74*
L	Fusiform	−26	−30	−24	69	5.85
L	Cerebellum	−22	−76	−32	66	4.94
R	Cerebellum	18	−80	−34	530	6.15*
HFA/AS						
L	Rectus	−4	42	−16	30	3.94
R	Frontal sup med	8	56	16	15	3.92
L	Frontal mid	−44	10	48	11	4.38
R	Precuneus	8	−56	40	43	3.98
R	Frontal inf orb	36	26	−22	14	4.02
R	Temporal pole mid	46	10	−42	7	3.98
R	Angular gyrus	58	−60	28	8	3.89
R	Lingual	24	−94	−18	39	4.03

TABLE A1 (*Continued*)

		MNI coordinates of peak activation (mm)				
Side		*Brain region*	*x*	*y*	*z*	*Cluster t-value*
Controls > HFA/AS						
L	Rectus	−12	38	−14	10	3.28
L	Frontal sup	−14	56	32	73	4.34
L	Frontal sup medial	−12	56	14	35	3.54
L	Frontal inf	−36	28	24	30	3.69
R	ACC	10	38	32	239	5.13
L	Cingulum mid	−6	−22	50	30	3.30
L	Precuneus	−10	−54	38	46	3.49
L	Temporal inf	−50	−2	−34	132	5.74
L	Temporal pole mid	−56	4	−30	132	7.02
L	Post central	62	−8	34	10	3.49
L	Cerebellum	−6	−50	−30	370	4.72*
R	Cerebellum	6	−54	−34	370	4.07*
HFA/AS > Controls						
L	Precentral	−30	−10	68	38	3.86
R	Precuneus	10	−58	48	17	3.50
L	Parietal inf	−30	−50	50	13	3.57
R	Lingual	8	−40	−6	32	3.76
L	Occipital sup	−20	−78	30	12	3.41
R	Occipital sup	26	−82	30	194	3.70
L	Occipital mid	−26	−96	2	12	3.41
R	Occipital mid	38	−80	32	197	3.91

Note: *Brain regions corrected for cluster level at $p < .05$.

TABLE A2
Emotional vs. neutral stimuli presentation (unpleasant > neutral at $p < .001$)

		MNI coordinates of peak activation (mm)				
Side		*Brain region*	*x*	*y*	*z*	*Cluster t-value*
Controls						
L	Frontal inf orb	−28	34	−14	16	4.64
L	Temporal mid	−46	−40	−20	55	4.48
L	Amygdala	−32	−4	−14	23	3.83
HFA/AS						
L	Rectus	−2	54	−16	27	4.25
L	Precuneus	−8	−60	52	12	3.62
R	Frontal inf	58	20	30	21	3.14
L	Frontal inf orb	−44	48	−12	86	3.84
L	Frontal inf orb/insula	−42	18	−10	33	3.98
L	Temporal mid	−62	−58	14	23	3.70
L	Amygdala	−18	−2	−18	6	3.37
L	Angular gyrus	−42	−54	38	12	3.60
L	Lingual	−22	−80	−10	10	3.68
R	Lingual	16	−84	−8	51	3.59
R	Occipital mid	34	−86	10	140	4.39
L	Occipital in	−44	−74	−6	98	4.90
L	Cerebellum	−12	−86	−20	17	6.00
Controls > HFA/AS						
L	Frontal inf orb	−28	34	−14	17	3.53
R	Cerebellum	6	−84	−40	31	3.57
HFA/AS > Controls						
R	Occipital mid	34	−88	10	98	4.20
R	Calcarine	2	−80	−6	44	3.90

TABLE A3
Internal- vs. external-oriented task during negative vs. neutral stimuli presentation (internal [unpleasant – neutral] > external [unpleasant – neutral] at $p < .001$)

		MNI coordinates of peak activation (mm)				
Side		*Brain region*	*x*	*y*	*z*	*Cluster t-value*
Controls > HFA/AS						
R	Corpus callosum	−2	24	8	23	3.79
HFA/AS > Controls						
	No suprathreshold voxels					

TABLE A4
Regression analyses with questionnaire measures (at $p < .005$ uncorrected)

		MNI coordinates of peak activation (mm)				
Side		*Brain region*	*x*	*y*	*z*	*Cluster t-value*
TAS						
	Controls					
L	Insula/operculum	−34	28	0	8	3.93
	HFA/AS					
L	Insula cortex	−40	4	0	12	5.29*
L	Amygdala	−18	−8	−20	5	3.53
BVAQ						
	Controls					
L	Insula/operculum	−32	20	2	5	3.86*
R	Insula cortex	44	20	−2	5	3.81*
	HFA/AS					
L	Insula cortex	−44	4	−4	14	4.96*
	Insula/operculum	−36	14	0	9	3.89*
R	Insula cortex	48	0	10	52	7.40*
L	Amygdala	−16	−6	−16	5	3.94*
IRI						
	Controls					
L	Insula/operculum	−32	20	2	2	3.25
	HFA/AS					
L	Insula/operculum	−32	10	2	7	5.83*
L	Amygdala	−20	−10	−16	15	4.38*

Note: *Significant at $p < .001$, uncorrected.