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Influence of anxiety and alexithymia on brain activations associated with the perception of others' pain in autism

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Emotional resonance, alexithymia and ASD

Abstract:

The circumstances under which empathy is altered in ASD remain unclear, as previous studies did not systematically find differences in brain activation between ASD and controls in empathy-eliciting paradigms, and did not always monitor whether differences were primarily due to ASD "per se", or to conditions overlapping with ASD, such as alexithymia and anxiety. Here, we collected fMRI data from 47 participants (22 ASD) viewing pictures depicting hands and feet of unknown others in painful, disgusting, or neutral situations. We computed brain activity for painful and disgusting stimuli (vs. neutral) in whole brain and in regions of interest among the brain areas typically activated during the perception of nociceptive stimuli. Group differences in brain activation disappeared when either alexithymia or anxiety – both elevated in the ASD group – were controlled for. Regression analyses indicated that the influence of symptoms was mainly shared between autistic symptomatology, alexithymia and anxiety or driven by unique contributions from alexithymia or anxiety. Our results suggest that affective empathy may be affected in ASD, but that this association is complex. The respective contribution of alexithymia and anxiety to decreased affective empathy of people with ASD may be due to the association of those psychiatric conditions with reduced motor resonance/Theory of Mind.

KEYWORDS: Empathy, ASD, Alexithymia, Anxiety, fMRI

BACKGROUND

Signs of distress in others typically elicit an empathetic response in human observers. Empathy is a fairly recent concept, as the word itself was only translated to English from German (*Einfühlung*: feeling into) a hundred years ago. Although there is no consensual definition of empathy, it can be described as a state of mind that facilitates deep understanding of others' emotions/affect and leads us to attempt to comfort them and alleviate their suffering (Lockwood, 2016). Empathy is multicomponent and requires not only that the empathetic person resonates with the state of another (affective empathy), but also that he/she remains aware that the other is the source of that state (cognitive empathy: de Vignemont & Jacob, 2012). Emotional contagion and emotional arousal are the two critical components of *affective empathy*. The expression of pain is a particularly potent affective signal that automatically attracts prosocial behaviors from others (de C. Williams, 2002). Indeed, seeing others in pain elicits activation in the brain regions typically activated during the experience of pain (Singer et al., 2004), a phenomenon sometimes referred to as *emotional contagion*. Emotional contagion is a process that is thought to rely heavily on motor resonance (Decety & Meyer, 2008), and can be explained by the Perception Action Model (PAM) reflecting "the spontaneous activation of the observer's representations for the target's state" (De Waal & Preston, 2017). The neural network that is activated both when experiencing pain and witnessing it in another includes the inferior frontal gyrus (IFG), the somato-sensory cortices (SI, SII), the supplementary motor area (SMA), the anterior insula (AI), the anterior cingulate cortex (ACC), the periaqueductal gray (PAG), the thalamus and the cerebellum (reviewed in Peyron, Laurent, & García-Larrea, 2000 and Decety, 2011). In addition, perceiving pain in others triggers *emotional arousal*, which is linked with activations in the hypothalamus, the amygdala, the orbito-frontal cortex (OFC), and the hippocampal region (e.g., Decety, 2011). In contrast, *cognitive empathy* refers to mental state

understanding and perspective-taking (Decety & Svetlova, 2012). Cognitive empathy relies on regions of the frontal lobe typically activated during mentalization tasks such as the medial prefrontal cortex (mPFC: Vachon-Presseau et al., 2012; Frith & Frith, 2006, although see Bird et al., 2004 for evidence of preserved mentalization ability in a patient with mPFC damage) and the frontal pole (Jean Decety & Jackson, 2004). Both of those regions are also activated when participants view facial expressions of pain (Vachon-Presseau et al., 2012; Budell, Jackson, & Rainville, 2010).

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by social communication and interaction difficulties and a restricted repertoire of interests and behaviors (American Psychiatric Association, 2013). Cognitive empathy is particularly impaired in people with ASD, who have difficulties representing others' mental states and putting themselves in others' shoes (Levy, Mandell, & Schultz, 2009; Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007; Lombardo et al., 2010). This in turn hinders their ability to successfully navigate complex social situations (Klin et al., 2007) and to respond appropriately to others' needs and distress (Baron-Cohen, 2011). Although diminished empathy is currently believed to be an important feature of ASD (U. Frith & De Vignemont, 2005), the bases for this behavior remain unclear. The results of previous *behavioral studies* have confirmed that adults and children with ASD lacked perspective-taking/cognitive empathy (Dziobek et al., 2008; Jones, Happe, Gilbert, Burnett, & Viding, 2010; Pouw, Rieffe, Oosterveld, Huskens, & Stockmann, 2013; Schwenck et al., 2012). It is unclear however whether *affective* empathy is similar, enhanced or decreased in people with ASD compared to controls. The aforementioned behavioral studies found similar levels of affective empathy in participants with and without ASD. However, some have argued

that affective empathy may be heightened in people with ASD (Smith, 2006, 2009), a hypothesis that is supported by the finding of a greater empathetic facial affect in children with ASD than in controls (Capps, Kasari, Yirmiya, & Sigman, 1993). In addition, it has also been hypothesized that the lack of prosocial concern observed in ASD could also be due to a normal or even heightened affective empathy together with difficulties with cognitive empathy, leading to personal distress at the sight of pain and self-regulating behavior of avoidance (Hadjikhani et al., 2014). In contrast with this view, others have proposed that people with ASD have a reduced ability to embody the affective states of others (emotional resonance) leading to a decreased empathetic response to distress (Gallese, Rochat, & Berchio, 2013). This concept was supported by the results of an electromyography study that found that adults with ASD did not exhibit automatic facial mimicry (an index of emotional contagion) when observing others' emotional expressions (McIntosh, Reichmann-Decker, Winkielman, & Wilbarger, 2006) and by the findings of studies that used subjective measures of empathy in people with and without ASD (S Baron-Cohen & Wheelwright, 2004; Michael V. Lombardo et al., 2007; Rogers, Dziobek, Hassenstab, Wolf, & Convit, 2007; Shamay-Tsoory, Tomer, Yaniv, & Aharon-Peretz, 2002).

Only a few functional magnetic resonance imaging (fMRI) studies to date have attempted to directly investigate whether activation in the brain areas responding to the perception of pain in others is altered in people with ASD (Bird et al., 2010; Fan, Chen, Chen, Decety, & Cheng, 2014; Gu et al., 2015; Hadjikhani et al., 2014; Krach et al., 2015). Bird et al. (2010) found no difference in the brain activation in response to the perception of pain applied to a the hand of a familiar other, and Hadjikhani et al. (2014) found no difference in the brain response to perception of facial expression of pain between participants with and without ASD. Similarly,

Krach et al. (2015) found no group difference in the ACC and AI activation in response to the perception of others' hands/feet in painful situation. Together, those results suggest that affective empathy is intact in ASD. Moreover, Gu et al. (2015) found evidence of enhanced affective empathy in ASD, as they reported increased activation in the AI of their participants with ASD viewing stimuli depicting hands/feet in painful situation. However, although they also used stimuli depicting hands/feet in painful situation, Fan et al. (2014) found *decreased* neural responses in the ACC and AI of participants with ASD relative to controls when viewing injured body parts, suggesting decreased affective resonance in ASD. Decreased activation in the vmPFC and IFG of people with ASD relative to controls presented with stimuli depicting facial expressions was also found in some previous studies (Greimel et al., 2010; Klapwijk et al., 2016; Schulte-Ruther et al., 2011).

Neurodevelopmental diagnoses, such as ASD, are typically demarcated as discrete entities in the diagnostic manuals and in research. However, it has become increasingly clear that neurodevelopmental and psychiatric symptoms are highly overlapping with one other, probably because different symptoms share a general etiology and because some symptoms exist across different diagnoses (Gillberg, 2010; Pettersson, Anckarsäter, Gillberg, & Lichtenstein, 2013). This is also mirrored in clinical practice where "pure" cases of ASD are very rare. Consequently, individuals with ASD and typically developed individuals are very likely to differ on other symptoms besides those that are considered to index ASD "per se". Two traits common among individuals with ASD that might be particularly important for affective empathy are alexithymia and anxiety (Grynberg, Luminet, Corneille, Grèzes, & Berthoz, 2010; Moriguchi et al., 2006; Todd, Forstmann, Burgmer, Brooks, & Galinsky, 2015).

Alexithymia is defined as the inability to identify and discriminate emotion states (Nemiah et al., 1976). It is possible to assess alexithymia both dimensionally and categorically, and it has been shown that clinical levels of alexithymia are present in approximately half of the ASD population (Berthoz & Hill, 2005; Hill, Berthoz, & Frith, 2004) whereas it is much less frequent (~10%) in the general population (Linden, Wen, & Paulhus, 2014; Salminen, Saarijärvi, Äärelä, Toikka, & Kauhanen, 1999). Alexithymia is associated with reduced activity in the AI (Silani et al., 2008). Given that the AI is a region that responds to the perception of pain in others, it would be no surprise that alexithymia affects empathetic experience. Likewise, anxiety has been associated with increased egocentric thinking and reduced empathic concern (Todd et al., 2015).

Sometimes, alexithymia and anxiety are seen as "comorbid" conditions of ASD. From this perspective the application of covariate analyses is warranted to control for the confounding effect of these symptoms in group comparisons. However, this approach has been criticized because it removes important parts of the variance that typically co-occur with ASD, which is well known to represent a spectrum/several spectra of heterogeneous symptoms. As Gillberg noted regarding the overlap of disorders and symptoms more generally, "*so-called 'comorbidity' is a misnomer if ever there was one, as we are usually not dealing with completely separate disorders in the first place"* (Gillberg, 2010). Indeed, many features of alexithymia have been described in ASD (Fitzgerald & Bellgrove, 2006). Likewise, aspects of anxiety – such as severe (di)stress in the face of sudden changes in the physical or social environment – could arguably be seen as integral to ASD. In the current study, we use covariate analyses to explore the "specificity" of the association between ASD and activation in the brain areas responding to the perception of pain in others. Importantly, besides covariate analyses, we also take an analytical

approach where we dimensionally attempt to parse out the unique and shared variance attributable to symptoms of ASD, of alexithymia and of trait anxiety.

It has been hypothesized that the lack of empathetic concern often observed in people with ASD may be due to their comorbid alexithymia rather than to their ASD "per se". This hypothesis was supported by the results of Bird et al. (2010), in a study where they selected a comparison group with the same high level of alexithymia as the ASD group, and demonstrated that the activation of AI correlated with alexithymia in both groups. Furthermore, they found that when alexithymia – as measured by the Toronto Alexithymia Scale (TAS-20: Bagby, Parker, & Taylor, 1994) – was equal between groups, there were no group differences in scores in empathy measured by the Interpersonal Reactivity Index (IRI: Davis, 1983). Given that alexithymia was not measured or accounted for in most of the other aforementioned fMRI studies, a difference in the rate of alexithymia among the included participants with ASD could potentially explain why brain activity in the network supporting affective empathy was either similar between ASD and control participants (Hadjikhani et al., 2014; Krach et al., 2015), increased for participants with ASD (Gu et al., 2015), or decreased for participants with ASD (Fan et al., 2014). It is possible that higher levels of alexithymia are associated with reduced emotional resonance/vicarious experience (Lockwood, Bird, Bridge & Viding, 2013), leading to more difficulties in interpreting stimuli where pain is inflicted on a body part.

The present study used the stimuli developed by Benuzzi et al. (2008) to investigate the brain correlates associated with the perception of painful and disgusting stimuli applied to feet and hands of unknown others, in people with ASD and controls, and to examine the influence of trait alexithymia and anxiety traits on these correlates. Previous studies in which groups were matched on alexithymia levels showed no differences between ASD and control participants when they viewed the feet/hands of known others in painful situation (Bird et al., 2010). No study to date has investigated the contribution of trait anxiety to the empathy deficit of people with ASD. However, given that a large proportion of people with ASD suffer from clinical anxiety (van Steensel, Bogels, & Perrin, 2011) and that anxiety was shown to be associated with decreased empathy (Todd et al., 2015), we hypothesized that anxiety would significantly contribute to the differences of activation in the empathy network between people with and without ASD.

We aimed at investigating whether activation in the brain areas sensitive to empathy-relevant information was correlated with autism symptomatology (as assessed by the Autism-spectrum Quotient [AQ:] and the Autism Diagnosis Observation Schedule [ADOS-2: (Catherine Lord et al., 2000)]), anxiety (as assessed by the State Trait Anxiety Inventory [STAI: (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983)]), and alexithymia (as measured by the Toronto Alexithymia Scale [TAS-20: (Bagby et al., 1994)]), so as to determine the personality/neurodevelopmental traits that affect activation in brain areas sensitive to empathy-relevant information in the sample, and to what extent the influence is unique or shard among all three symptom dimensions.

METHODS

Participants

Forty-seven participants (6 females) were recruited for the study. Among those, 22 (2 females) were clinically diagnosed with ASD using DSM IV-TR criteria as well as the Autism Diagnostic Observation Schedule (ADOS [(Catherine Lord et al., 2000)] in all participants with ASD [module 4]) and the Autism Diagnostic Interview-Revised (ADI-R, [(C Lord, Rutter, & Le Couteur, 1994)]) in 20 participants with ASD. None of the 25 controls had a history of psychiatric/neurological disorders. Participants with ASD were recruited from Lausanne and Brest, while control participants were recruited from Lausanne. Participants were scanned at the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne. Three subjects with ASD (all males) and 5 control subjects (1 female) were excluded from fMRI data analysis because of excessive motion (i.e., movement above a Framewise Displacement [FD] threshold of .9 mm [(Siegel et al., 2014)] more than 20% of time). Importantly, participants with and without ASD did not differ in their head motion (relative mean displacement: $t[33]=.19$, $p=.85$).

A total of 39 participants (19 ASD, see *Table 1* for mean scores on the ADOS [social and communication subscales, all module 4] and on the ADI-R)[1] between the age of 15 and 43 years (mean=24.69, SD=8.12) were included in the final functional analysis. They all completed the Autism-spectrum Quotient (AQ), a self-report questionnaire assessing the level of impairment in cognitive domains affected in ASD (communication, social skills, imagination, attention switching, attention to details). Intelligence Quotient (IQ) scores were obtained using the Wechsler Nonverbal Scale of Ability (WNS [Wechsler and Naglieri, 2006]; 19 participants including 10 with ASD) or the two nonverbal subtests of the Wechsler Abbreviated Scale of Intelligence (WASI [Wechsler, 1999]; 20 participants including 9 with ASD). All participants had an IQ score in the normal range or above. Alexithymia was assessed using the Toronto

[1] 11 were diagnosed with Asperger Syndrome (AS), 6 were diagnosed with Autism Spectrum Disorder (ASD), and 2 were diagnosed with Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)

Alexithymia Scale (TAS-20). Trait anxiety was evaluated with the State-Trait Anxiety Inventory (STAI-T) in 34 participants (18 ASD). Independent sample t-tests (performed using SPSS) were used to test whether the ASD and control groups differed in terms of age, IQ, and scores on the AQ, STAI-T and TAS-20 (*Table 1*). However, comorbid conditions of ASD such as anxiety disorders, Major Depressive Disorder (MDD), and Attention Deficit Hyperactivity Disorder (ADHD) were not assessed.

All procedures were in accordance with the Declaration of Helsinki and were approved by the Lausanne University Hospital ethics committee. Written informed consent was obtained from all adult participants and from all parents of participating adolescents. All adolescent participants also gave their oral assent.

Visual stimuli

The set of video clips used in this study lasted 1s and portrayed body parts of an unknown male actor in three different conditions: neutral (N), painful (P), and disgusting (D). In the neutral condition, the hand/foot was touched by a neutral stimulus (a ball or a pen), that came from the right side of the screen (pen) or fell down from a central location (ball). In the painful condition, the hand/foot was wounded by a knife or a syringe that came from the right side of the screen. In the disgusting condition, the hand/foot was touched by a disgusting stimulus (spider, beetle, earthworm, or grasshopper) that fell down from a central location. The hand and foot were always presented in the allocentric viewpoint. Benuzzi and colleagues (Benuzzi et al., 2008) validated those video-clips in 14 participants (age 21-57 years, mean: 35.1), and we selected

those with the highest ratings for our study.[2] This included 20 neutral stimuli, 20 painful stimuli, and 20 disgusting stimuli (10 representing the right hand and 10 representing the right foot in each category), which resulted in a total of 60 stimuli (degree of visual angle: 12-13°). Examples of those stimuli are shown in Benuzzi and colleagues (Benuzzi et al., 2008).

Experimental Design

The experiment consisted of two runs, presented in a counterbalanced order across participants. In each of those runs, 30 trials (10 painful, 10 disgusting, and 10 neutral) were presented in pseudo-random order. As shown in Figure 1, each trial lasted 6s and consisted of a central fixation cross (1s) followed by a video clip (1s), itself followed by another fixation cross (1s) and a choice slide (3s), on which the words "painful", "neutral", and "disgusting" were displayed (from left to right). We asked participants to look at the video clips and determine whether they thought the stimulus was painful, neutral, or disgusting, by pressing the corresponding button on the button box (leftward button, central button, rightward button) when the choice slide was presented. We collected response time and accuracy in all but 8 subjects[3], for which data was lost due to technical difficulties. An additional analysis for the subgroup of participants with behavioral data is included in the Supplementary Materials.

[2] In Benuzzi et al. (2008), after each experiment, the 14 participants were asked to rate how disgusting (D) and painful (P) the video clips were on two separate 0 –10 point scales; in each trial, the volunteers were asked to rate the perceived unpleasantness (U) of the stimulus. The video clips rated as the most painful or the most disgusting were selected for the present fMRI study. The ratings obtained by Benuzzi et al. (2008) for the stimuli we selected for the present study were the following: painful (mean P:7.98, sd:1.55), disgusting (mean D:4.56, sd:2.01), neutral (mean P:0.12, sd:0.32/ mean D:0.04, sd:0.14).

[3] The behavioral data were not collected in one participant with ASD (female) and 3 control participants (all males), due to the behavioral response not being recorded during the experiment. Among the remaining 35 subjects (17 controls) 4 male subjects (1 with ASD) recognized none of the stimuli, for at least one category. Those were therefore excluded from the behavioral analyses, which included 31 subjects (14 controls).

Data acquisition

fMRI data were collected with a 12-channel radio frequency coil in a Siemens 3T scanner (Siemens Tim Trio, Erlangen, Germany) at the Centre d'Imagerie BioMédicale in Lausanne. The first scanning sequence consisted of Siemens's autoalign scout for the head allowing an automatic positioning and alignment of slices. Anatomical images were acquired using a multi-echo magnetization prepared rapid gradient echo sequence: 176 slices; 256 × 256 matrix; echo time (TE): TE1: 1.64 ms, TE2: 3.5 ms, TE3: 5.36 ms, TE4: 7.22 ms; repetition time (TR): 2530 ms; flip angle 7°, voxel size = 1mm isotropic. The functional data were obtained using an echo planar imaging sequence (47 AC-PC slices, 3 mm thick, 3.12 mm by 3.12 mm in plane resolution, 64 × 64 matrix; field of view: 216; TE: 30 ms; TR: 3000 ms; flip angle 90°) lasting 6 minutes (2 runs of 3 minutes each).

Data analysis

Behavioral data

Percent accuracy rates were calculated for each subject and each condition. Accuracy rates and RTs were analyzed using a mixed 3 (Emotions: Painful, Neutral, Disgusting) x 2 group (participants with ASD, controls) Analysis of Variance (ANOVA). Greenhouse-Geisser corrections were used when assumption of sphericity were violated. Post-hoc t-tests were conducted, using a Bonferroni correction to correct for multiple comparisons. ANCOVAs using TAS-20 or STAI scores as covariates were also run to examine whether effects remained after controlling for alexithymia or anxiety in participants. Data were analyzed with IBM SPSS Statistics for Mac, Version 24.0 (IBM Corp., 2013, Armonk, NY).

Whole brain analysis

fMRI data processing, and preprocessing was carried out using FEAT Version 6.0, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.ul/fsl). Non-brain tissues were removed from high-resolution anatomical images using Christian Gaser's VBM8 toolbox for SPM8 fed into FEAT. Data were motion-corrected using MCFLIRT and motion parameters were added as confound variables to the model. In addition, residual outlier time-points were identified using FSL's motion outlier detection program and integrated as additional confound variables in the first-level general linear model analysis. Preprocessing further included spatial smoothing using a Gaussian kernel of 8 mm, grand-mean intensity normalization and high pass temporal filtering with sigma=50.0 s.

The two runs (treated as fixed effect) from each participant were combined. Subject-level statistical analysis was carried out for the following contrasts (Painful vs. Neutral, Disgusting vs. Neutral) using FILM with local autocorrelation correction. Registration to high-resolution structural images was carried out using FLIRT. Registration to Montreal Neurological Institute (MNI) standard space was then further refined using FNIRT (FMRIB's nonlinear registration tool).

Group-level analyses were performed using FLAME 1&2 (general linear mixed model analysis) with automatic outlier detection. In modeling subject variability, this kind of analysis allows inference about the population from which the subjects are drawn. *Z*-statistic images and tables were obtained using a cluster defining threshold (CDT) of $Z>3.1$ ($p<.001$) and a FWE of $p<0.05$. Images were displayed on a standard brain surface (fsaverage). Within-group activations and between-group differences in activity were assessed using independent *t*-tests available in FSL. We also conducted separate whole brain (WB) analyses covarying for alexithymia, anxiety

or AQ scores at the group level in order to examine the correlations between the contrasts of interests and (1) alexithymia, and (2) anxiety.

ROI analyses

The regions of interest (ROIs) were chosen based on prior knowledge of the regions involved in pain and disgust perception (Benuzzi et al., 2008) and/or empathy (Barak & Feng, 2016; J Decety, 2011; Jean Decety & Jackson, 2004; Peyron et al., 2000): the medial prefrontal cortex (mPFC), the supplementary motor cortex (SMA), the left and right inferior frontal gyrus (IFG, pars opercularis), the thalamus, the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC), the anterior insula (AI), the postcentral gyrus, and the parietal operculum. All the aforementioned structures but the anterior insula were defined anatomically using the Harvard-Oxford probabilistic atlases of FSL. For the anterior insula, the ROI was also defined from the Harvard-Oxford probabilistic atlas and contained insular cortex anterior to y=6 (in MNI coordinates), extracted using fslmaths. For each subject, the mean percentage blood-oxygen-level dependent (BOLD) signal change was extracted for the ten structures and the two contrasts of interest, using the Featquery tool in FSL. For each of the ROIs, a 2 (groups: participants with ASD, controls) by 2 (contrasts: disgusting>neutral, painful>neutral) repeated measure analysis of variance (ANOVA) was performed. The Greenhouse-Geisser correction was used when the assumption of sphericity was violated. When the ANOVA yielded significant interactions, simple effects were investigated with post-hoc t-tests. A Bonferroni correction for multiple comparison was applied to correct for the number of ROIs (10). When a significant group effect was found, we investigated whether it was due to difference in the alexithymia or anxiety level between the groups by conducting an analysis of covariance (ANCOVA), using TAS-20 or STAI scores as covariates. In addition, we conducted Spearman correlations (two-tailed) between the

activity in each of the selected ROIs for the contrasts Disgusting vs. Neutral/ Painful vs. Neutral and (1) AQ scores, (2) STAI-T scores, (3) TAS-20 scores (across groups) and (4) ADOS scores (in the ASD group).

RESULTS

Behavioral results

Accuracy analysis

There was a main effect of emotion [F (1.64, 47.52) =4.17, MSE=1515.34, p=.03, η^2=.13] on percent accuracy such that disgusting stimuli (mean=75.57%, SE=4.07%) were less well recognized overall than neutral stimuli (mean=86.24%, SE=3.10%; p_{bonf}=.05) and painful stimuli (mean=86.89%, SE=2.72%; p_{bonf}=.01).

There was also a main effect of group [F (1,29) = 5.22, MSE=2264.68, p=.03)] with participants with ASD showing a lower emotion recognition accuracy (mean=77.94%, SE=2.92) than control participants (mean= 87.86%, SE=3.21). However, there was no interaction between group and emotion (F=.06, p=.91). To determine whether the group effect on emotion recognition accuracy may be related to alexithymia, we conducted an ANCOVA on accuracy, using TAS-20 score as covariate. When alexithymia or anxiety were controlled for, no effect –including the group effect– was significant (p>.05 for the main effects and interactions).

RT analysis

There was a main effect of emotion [F (2, 58) =4.90, MSE=98888.77, p=.01, η^2=.15] with disgusting stimuli being recognized more slowly than neutral stimuli [mean=807.10ms (SE=47.43) for disgusting stimuli, mean=696.65ms (SE=31.33) for neutral stimuli; p_{bonf}=.02]. However, there was no effect of group [F=.22, p=.64; mean=759.39ms for ASD (SE=43.32) and

mean= 729.30 for controls (SE=47.74)] and only a trend for the interaction between group and emotion [F (2,58) =3.13, MSE=63096.87, p=.051, η^2=.10)]. No effect remained significant when alexithymia or anxiety were controlled for.

Neuroimaging results[4]

Whole brain analysis

Although age did not differ between the two groups, the age range was wide in the present study and emotion perception is known to be affected by age (Somerville, Fani, & McClure-Tone, 2011) perhaps to a different extent in people with and without ASD (Harms, Martin, & Wallace, 2010). Consequently, we conducted an initial analysis, using age as a covariate. However, age did not correlate with whole brain activation for any of the contrasts of interest, and did not affect any of the Within and Between group results. Thus, we report the whole brain activation results without controlling for age.

Within group

The contrast Painful vs. Neutral yielded activation in both ASD and control participants (*Table 2a* and *2b* respectively). The contrast Disgusting vs. Neutral also yielded activation in participants with ASD and controls (*Table 3a* and *3b* respectively).

Between group

[4] Note that we included 39 subjects in this analysis. However, when the analysis was conducted with the 31 subjects included in the behavioral analysis, we obtained similar results (see supplementary materials).

Participants with ASD showed less activation than control participants for the contrasts Painful vs. Neutral in the left inferior and middle frontal gyrus (*Table 4* and *Figure 2*). For the contrast Disgusting vs. Neutral, participants with ASD had less activation than control participants in the left inferior and middle frontal gyrus (*Table 5* and *Figure 3*).

Correlation analyses

Neither the TAS-20 nor the STAI-T correlated with whole brain activation for any of the contrasts of interest. However, it is noteworthy that, when TAS-20 scores were controlled for, the group effects (controls > participants with ASD) for the contrasts Painful vs. Neutral and Disgusting vs. Neutral disappeared, which suggests that the increased brain response of control participants relative to participants with ASD reported above may be related to their increased interoception ability (indexed by a low score on one of the three TAS-20 subscale). This group difference also disappeared, when trait anxiety (indexed by the STAI-T) was controlled for, suggesting that trait anxiety may also play a role in the decreased empathy for pain in ASD.

ROI RESULTS

ANOVAs & ANCOVAs

Left IFG opercularis: There was a main effect of group ($F(1,37)=9.98$, MSE=9867.62, $p=.03$, $\eta^2=.21$) with increased brain activation in the control group (mean:59.23, SE:15.71) relative to the ASD group (mean:-11.86, SE:16.11*; Figure 4*). There was no interaction between group and emotion. This group effect disappeared when alexithymia or anxiety were controlled for.
No other effect was significant for any of the other ROIs of interest.

Correlations

Motivated by a dimensional approach to data analysis, we performed the main correlations analyses in the full sample when the data is available for both groups. For correlations split by group, we refer to the supplementary online material.

AQ scores: We found a significant inverse correlation between the mean activation in the left IFG to the contrast Painful vs. Neutral (r_s=-.34, p=.04); a trend for an inverse correlation between the mean activation in the thalamus to the contrast Painful vs. Neutral (r_s=-.29, *p*=.07) (*Figure 5*).

TAS-20 scores: We found a significant inverse correlation between the mean activation for the contrast Painful vs. Neutral in the left IFG (r_s=-.41, *p*=.02), the thalamus (r_s=-.39, *p*=.02), the mPFC (r_s=-.50, *p*<.01), the anterior insula (r_s=-.37, *p*=.03). There were also trending inverse correlations between the mean activation in the PCC for the contrast Painful vs. Neutral (r_s=-.32, *p*=.06)(*Figure 6*).

STAI-T scores: We found a significant inverse correlation between STAI-T scores and activity in the right IFG (r_s=-.36, *p*=.04), the left IFG (r_s=-.41, *p*=.02), the thalamus (r_s=-.45, *p*=.01), and the mPFC (r_s=-.40, *p*=.02) for the contrast Painful vs. Neutral. For the same contrast, there was also a trending inverse correlation between activity in the anterior insula and the STAI-T scores (r_s=-.31, *p*=.07)(*Figure 7*).

ADOS scores: In the ASD group only, we found a significant correlation between ADOS scores and the mean activation for the contrast Painful vs. Neutral in the right IFG (r_s=-.47, *p*=.04) and anterior insula (r_s=-.47, *p*=.04), as well as a trend for an inverse correlation between ADOS scores and the mean activation in the left IFG (r_s=-.46, *p*=.06)(*Figure 8*).

Hence dimensional measures of autism, alexithymia and anxiety symptoms, assessed across subjects, were all related to brain activation in certain areas of the empathetic brain network, that were found to differ between the ASD and control groups (Thalamus, Left IFG and MPFC). AQ, STAI-T and TAS-20 scores all correlated with activity in the left IFG and the thalamus, therefore we used commonality regression analyses to parse out the unique and shared variance attributable to AQ (as an index of ASD "per se"), STAI-T (as an index of trait anxiety), and TAS-20 (as an index of alexithymia) in the subset of participants who completed the three questionnaires (N=34 including 18 with ASD). The overall variance explained by the model including the three parameters was significant for the thalamus [R2=.29; F(3, 33)=4.07, *p*=.02] and trending toward significance for the left IFG [R2=.21; F(3, 33)=2.59, *p*=.07]. Interestingly, the proportion of shared variance and unique variance for each of the parameters was very different between the left IFG and the thalamus (*Figure 9*). In the thalamus, almost half of the variance was shared between the three parameters (R2=.14), and the unique variance accounted for by TAS-20 scores was the largest (R2=.09), followed by the unique variance accounted for by AQ scores (R2=.06) and STAI-T scores (R2=.01). In contrast, in the left IFG, only about a third of the variance was shared between the three parameters (R2=.08), and most of the variance was uniquely explained by STAI-T scores (R2=.12), while the amount of unique variance explained by AQ and TAS-20 scores was negligible (R2=.001 in both cases).

Given that TAS-20 and STAI-T (but not the AQ) were both correlated with activity in the AI and the mPFC, we also used multiple regression analyses to parse out the unique and shared variance attributable to STAI-T (as an index of trait anxiety) and TAS-20 (as an index of alexithymia) in the subset of participants who completed the two questionnaires (N=34 including 18 with ASD). The model including the two predictors was significant both in the AI (R2=.20;

F(2, 33)=3.76, *p*=.03] and in the mPFC [R2=.17; F(2, 33)=3.24, *p*=.05]. In both regions, more than half of the variance was shared among the two predictors (R2=.12 for AI and R2=.09 for the mPFC), and anxiety uniquely contributed to the overall variance less (3% in the AI and 2% in the mPFC) than alexithymia (5% in the AI and 6% in the mPFC, *see Figure 10*).

DISCUSSION

In this study, we demonstrate that activity in brain regions associated with a specific aspect of affective empathy, i.e., motor resonance (in particular left IFG), were diminished in people with ASD who viewed limbs of others in painful/disgusting situations and had to label the sensation evoked by the stimuli, but that this decreased activation is likely influenced by elevated levels of alexithymia and anxiety which co-occur with ASD, assessed either diagnostically/categorically or dimensionally.

We found decreased brain activity for participants with ASD relative to controls in regions involved in affective empathy/motor resonance, including the inferior/middle frontal gyrus, the precentral gyrus, the frontal orbital cortex and the medial prefrontal cortex (for the contrast Painful vs. Neutral), and the thalamus (for the contrast Disgusting vs. Neutral). In addition, the ROI analysis revealed a group effect (decreased activation for participants with ASD relative to controls) in the left IFG. The IFG is known to be particularly critical for motor resonance (Enticott et al., 2012; Landmann et al., 2011). Interestingly, in a previous study (with a different cohort of participants), Hadjikhani et al. (2006) found cortical thinning of the IFG that was correlated with ADI-R social and communication scores. The IFG is richly connected with the anterior insula, a region supporting emotional simulation (Jabbi & Keysers, 2008). Our present results provide evidence that emotional resonance processing is altered in people with ASD, and

are in line with those of a recent study that also used stimuli featuring limbs of others in painful situation (Fan et al., 2014), where decreased neural responses were found in participants with ASD relative to controls in regions underlying affective empathy/motor resonance. A previous cross-sectional study in which facial expressions were presented reported age-related increase in IFG activation in people with ASD but not in controls, suggesting that the decrease in IFG activation of people with ASD may attenuate with age (Bastiaansen et al., 2011).

A possibility for the inconsistent results of the previous fMRI studies of pain perception, empathy and autism may be the use of very diverse stimuli to elicit an empathic response, both in terms of the body part presented as well as in terms of familiarity with the presented stimulus. In Bird et al. (2010), participants viewed an electric shock being applied to the hand of a close other (partner, friend, familiar experimenter) while in other studies, participants viewed stimuli featuring limbs of unknown others in painful situation (Fan et al., 2014; Gu et al., 2015; Krach et al., 2015) or faces of unknown others experiencing pain (Hadjikhani et al., 2014). While all these stimuli have been shown to elicit activations in the brain areas related to pain perception in typical individuals (Benuzzi, Lui, Duzzi, Nichelli, & Porro, 2008), empathy for the pain of familiar others may be higher than empathy for strangers (Kiat & Cheadle, 2017), and empathy for faces expressing pain may involve different –or additional– mechanisms than empathy for observed pain on limbs (Goubert et al., 2005). Indeed, others' facial expression of pain is a clear indication of their suffering and provokes an automatic empathetic reaction in the observer (Williams, 2002), whereas viewing others' limbs being hurt may be a less clear indication of their suffering (e.g., different people have different pain thresholds), and elicit a weaker empathetic reaction. Indeed, although empathy-eliciting stimuli depicting limbs have never been

systematically compared to empathy-eliciting stimuli depicting faces, facial expressions of pain seem to be the clearest signal of another's suffering (Williams, 2002), and viewing the limb of a familiar other receiving a painful shock elicits more empathy than viewing the limb of an unfamiliar other receiving a painful shock, given the higher empathy elicited by familiar vs. unfamiliar people (Preston & de Waal, 2002; Komeda et al., 2014). An important endeavor for future studies would be to systematically compare the brain responses to different empathy-eliciting stimuli, in people with and without ASD. Nevertheless, differences in the type of stimuli used by previous fMRI experiments investigating empathy-elicited activation in ASD are not sufficient to explain their discrepant results. Indeed, at least three neuroimaging studies using stimuli representing limbs of others in painful situation to investigate empathy in ASD had different results. Gu et al. (2015) found that neural activity linked to affective empathy was increased in ASD, while Fan et al. (2014) found that it was decreased, and Krach et al. (2015) found no group difference. These discrepant results may be attributable to differences in participants' characteristics across those three studies. The present study investigated the respective contributions of two key personality dimensions –alexithymia and anxiety – to the brain response elicited by painful/disgusting stimuli.

In the current study, we took an analytical approach where we, besides categorical group comparisons and covariate analyses, dimensionally attempted to parse out the unique and shared variance attributable to symptoms of ASD, of alexithymia and of trait anxiety. Alexithymia levels were not reported by all previous studies investigating differences in empathy-elicited brain activations between people with and without ASD (Gu et al., 2015; Hadjikhani et al., 2014; Krach et al., 2015). Given that alexithymia is common in ASD, and alters one's ability to

identify emotion in self and others, it could very well be the cause of the decreased empathy-elicited activation sometimes observed in ASD (present results, and Fan et al., 2014). In this study, the group with ASD had a significantly higher alexithymia level than the group without ASD, and this contributed to the observed effects both at the behavioral level and at the neural level. Indeed, at the behavioral level, people with ASD were less accurate than controls in identifying the emotion depicted in the stimuli. However, this group difference was lost when alexithymia levels were controlled for in the analysis. Although controlling for alexithymia may not be entirely warranted in this sample (Miller & Chapman, 2001), this suggests that this difficulty in labeling emotions in people with ASD could be due to their level of alexithymia, rather than to their ASD "per se". These findings are in line with the results of Cook et al. (2013) who showed that facial emotion identification correlates strongly with the level of alexithymia but not with autism severity. It suggests that it would be important to test for co-occurring levels of alexithymia in people receiving an ASD diagnosis, as this symptom dimension might capture much of their difficulty with emotion identification. In addition, in the present study, we found that the differences in empathy-elicited brain activations between people with ASD and controls also disappeared when the level of alexithymia was controlled for. This is in line with Bird et al. (2010) who found that, in groups with and without ASD but with similar alexithymia levels, there were no differences in empathy-elicited activity in the left AI, and that these levels were inversely correlated with alexithymia. In the study by Bird et al. (2010), the selection of control participants was higher than the 10% typically found in the general population. Here we decided to choose a more naturalistic control group in that respect, in order to explore whether we could reproduce these results, and we also found that participants' level of alexithymia was inversely correlated with their AI activation for the contrast Painful vs. Neutral. Our results however are in

contrast with those of Fan et al. (2014), who found no correlation between alexithymia and AI in participants with ASD. This discrepancy may be attributable to their use of different kinds of empathy-eliciting stimuli (social and nonsocial), and to their different task (unpleasantness ratings). In the present study, inverse correlations between alexithymia and brain activity were found in the mPFC, the IFG, and the thalamus for the contrast Painful vs. Neutral. While lower activations in the AI have been shown to be associated with higher levels of alexithymia in previous studies (Rizzolatti & Craighero, 2004; Silani et al., 2008), a relationship has not yet been described between alexithymia levels and activity in the mPFC/ IFG/ thalamus (see Wingbermühle, Theunissen, Verhoeven, Kessels, & Egger, 2012 and Van der Velde et al., 2013 for reviews of the abnormally activated regions in alexithymia). All of these regions are part of the affective empathy network involved in emotional resonance (reviewed in Peyron et al., 2000 and Decety, 2011) and mPFC is also involved in Theory of Mind (ToM: Neubert et al., 2015), indicating that emotional resonance/ToM may be affected by alexithymia levels. Overall, our findings are consistent with the idea that decreased emotion recognition and apparently diminished empathy in ASD may be at least partly due to alexithymia rather than to their ASD per se (see Bird & Cook, 2013). This would appear to have profound implications regarding the diagnosis instruments and the interventions used for ASD. It would be particularly important to further investigate the characteristics of the autism subtype that is not associated with alexithymia so as to ensure it can also be picked up by diagnostic instruments (preferably in a way which does not exclusively rely on self-reports). In addition, it will be important for ASD interventions training emotional skills (e.g., Emotiplay: Fridenson-Hayo et al., 2017) to target people affected by both ASD and alexithymia, as this might moderate the rationale for and outcome of any behavioral intervention.

Difference in anxiety between participants with ASD and controls seems to also be important for the group difference in empathy-elicited neural activity, since the group difference for both contrasts disappeared when anxiety was controlled for. Unfortunately, there is a high degree of clinical anxiety in people with ASD (van Steensel et al., 2011) and the anxiety scores of participants with and without ASD differ in the present study. This makes it challenging to rightfully control for anxiety (Miller & Chapman, 2001), which, much like is the case for alexithymia, arguably be considered to be integral to ASD. Moreover, there was a negative correlation between participants' anxiety scores and activity in the regions of the empathy network (frontal pole, thalamus, IFG, anterior insula) for the contrast Painful vs. Neutral. High anxiety is typically associated with hypersensitivity to negative/threatening stimuli (Koster, Crombez, Verschuere, & De Houwer, 2006; Mogg et al., 2000). It is therefore somewhat surprising that anxiety is negatively correlated with activity in the regions of the empathy network in the present study. It is possible that anxiety enhances activity in the regions of the social brain network, but diminishes activity in the regions of the empathy-elicited network. In fact, this would be in line with the idea that people with autism are overly sensitive to threat signals, and cope with this hypersensitivity by over-regulating their neural response to emotional situations (such as empathy-eliciting stimuli), making them appear insensitive to the suffering of others (Smith, 2009; Lassalle et al., 2017).

One novel aspect of the present study is our investigation of the unique and shared contributions of autistic-like traits, alexithymia and anxiety to the activity in key regions of interest for affective resonance (thalamus, left IFG, AI, frontal pole). We found that the

contribution of those personality dimensions to the activity in regions critical for motor resonance was shared in large part. However, alexithymia is the dimension that contributed most of the activity in the thalamus, AI and frontal pole while anxiety is the dimension that contributed to activity in the IFG. In contrast, autistic-like traits mainly contributed jointly with the other variables in explaining activity levels in those regions. This suggests that the association to ASD is complex, and that co-occurring symptoms of anxiety and alexithymia might be more central than autism "per se" to explain the empathy deficit often observed in people with ASD. It would be important that future studies replicate this finding before it is used as a guide to intervention.

A limitation of the present study concerns the wide age range of participants (15-43 years old). This is comparable to the age range of participants selected for previous neuroimaging studies in which brain difference related to empathy were observed between people with and without ASD (Schulte-Ruther et al., 2011 [18-48 years old]; Fan et al., 2014 [16-29 years old]) but not all (Greimel et al., 2010 [13-17 years old]; Klapwijk et al., 2016 [15-19 years old]). In this study, age was controlled for in all analyses, but future studies may want to restrict the age range, or assess the effect of age on empathy-related activations in people with and without ASD.

CONCLUSIONS

We found that the neural circuit associated with motor resonance/affective empathy was activated to a lesser extent in participants with ASD than in controls, but that this difference disappeared when controlling for levels of alexithymia and anxiety. Decreased emotion recognition in people with ASD relative to controls disappeared when alexithymia or anxiety was controlled for. We also found inverse correlations between the level of alexithymia/anxiety

and activation in the brain regions underlying emotional resonance/ToM (anterior insula, medial prefrontal cortex, thalamus and inferior frontal gyrus) in response to viewing painful stimuli. Regression analyses indicated that the influence of symptoms was mainly shared between autistic symptomatology, alexithymia and anxiety or driven by unique contributions from alexithymia or anxiety. Overall, our findings support the theory that decreased emotion recognition and decreased brain activation to pain and disgust stimuli are reduced ASD, but that the association with ASD is complex. Much seems to reflect a relation between emotional resonance/ToM associated with alexithymia and anxiety rather than to ASD "per se", which has important implications in terms of the diagnostic instruments and interventions used for people on the autism spectrum.

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FIGURES

Figure 1: *Example of the timing of a trial.*

Figure 2: *Map of activation showing the brain areas that are more activated for CON than Participants with ASD, for the contrast Painful>Neutral. (threshold: Z>3.1, FWE: p<.05).*

Figure 3: *Map of activation showing the brain areas that are more activated for CON than Participants with ASD, for the Disgusting>Neutral contrast. (threshold: Z>3.1, FWE: p<.05).*

Figure 4: *Mean Beta activation for participants with Autism Spectrum Disorder (ASD: in orange) and control participants (CON: in blue) for the contrast Disgusting>Neutral (left panel) and Painful>Neutral (right panel) in the left inferior frontal gyrus. Error bars represent standard error of the mean.*

Figure 5: *Spearman correlation between the score of participants with ASD (orange) and CON (blue) on the Autism-spectrum Quotient (AQ) and the mean parameter estimate in the left inferior frontal gyrus (left panel), and the thalamus (right panel).*

Figure 6: *Spearman correlation between the score of participants with ASD (orange) and CON (blue) on the Toronto Alexithymia Scale (TAS-20) and the mean parameter estimate in the mPFC, the thalamus, the anterior insula, the left IFG, and the Posterior Cingulate Cortex.*

Figure 7: *Spearman correlation between the score of participants with ASD (orange) and CON (blue) on the State Trait Anxiety Inventory (STAI-T) and the mean parameter estimate in the mPFC, the thalamus, the anterior insula, the left IFG and the right IFG.*

Figure 8: *Spearman correlation between the score of participants with ASD on the ADOS (Autism Diagnostic Observation Schedule) and the mean parameter estimate in the right Inferior Frontal Gyrus [IFG], the left Inferior Frontal Gyrus and the Anterior Insula.*

Figure 9: *Proportion of unique and shared variance in brain activity (in the thalamus and the left inferior frontal gyrus [IFG]) accounted for by alexithymia, trait anxiety, and autistic-like traits (Painful-Neutral contrast).*

Figure 10: *Proportion of unique and shared variance in brain activity (in the anterior insula [AI] and the mPFC) accounted for by alexithymia and trait anxiety (Painful-Neutral contrast).*

TABLES

Table 1*: Demographic information and test results for participants with Autism Spectrum Disorder (ASD) and control participants (CON). N refers to the sample size, SD to the standard deviation to the mean, F to females. * 3 adolescent AQ scores in each group. ** sum of the social and communication subscales (all module 4).*

Table 2a*: Brain regions activated by participants with Autism Spectrum Disorder for the contrast Painful>Neutral (threshold: Z>3.1, p<0.05).*

Table 2b*: Brain regions activated by participants with Autism Spectrum Disorder for the contrast Disgusting>Neutral (threshold: Z>3.1, p<0.05).*

Table 3a*: Brain regions activated by control participants (CON) for the contrast Painful>Neutral (threshold: Z>3.1, p<0.05).*

Table 3b*: Brain regions activated by control participants (CON) for the contrast Disgusting>Neutral (threshold: Z>3.1, p<0.05).*

Table 4*: Brain regions more activated in control participants than in participants with autism spectrum disorder (CON>ASD) for the contrast Painful>Neutral (threshold: Z>3.1, p<0.05).*

Table 5*: Brain regions more activated in control participants than in participants with autism spectrum disorder (CON>ASD) for the contrast Disgusting>Neutral (threshold: Z>3.1, p<0.05).*

Emotional resonance, alexithymia and ASD

Figure1

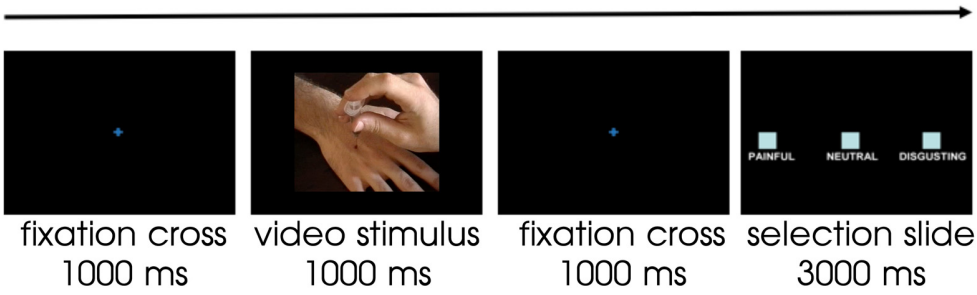

Figure2

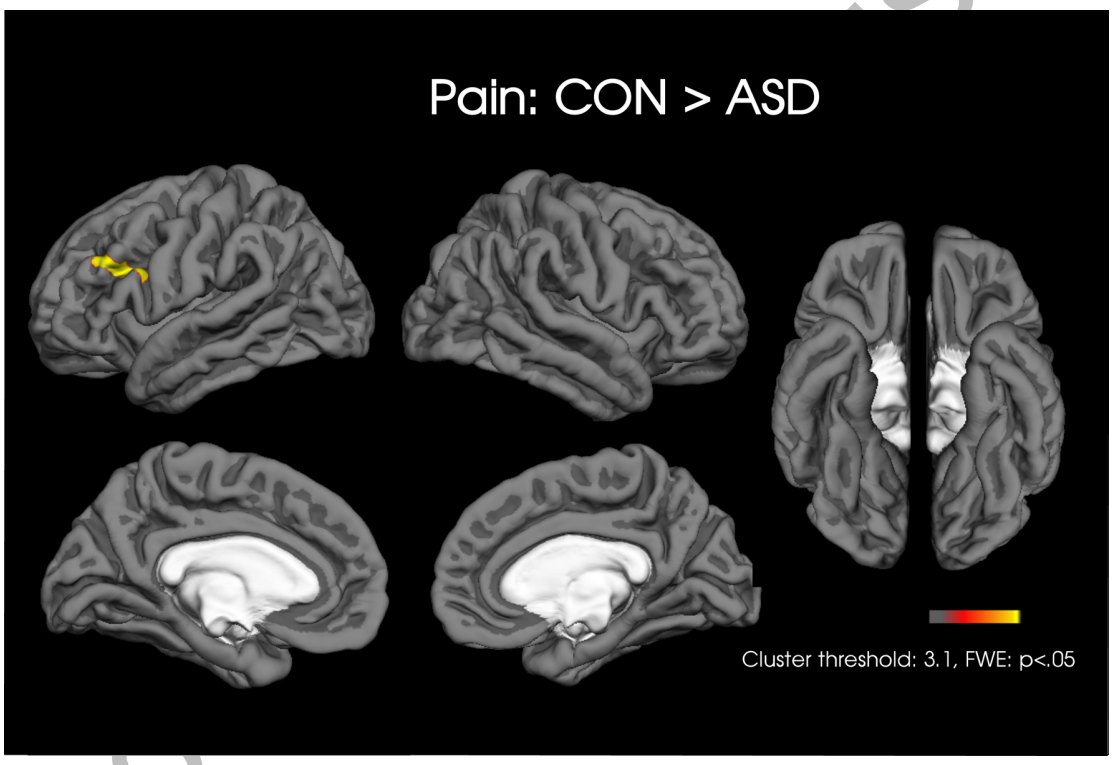

Figure3

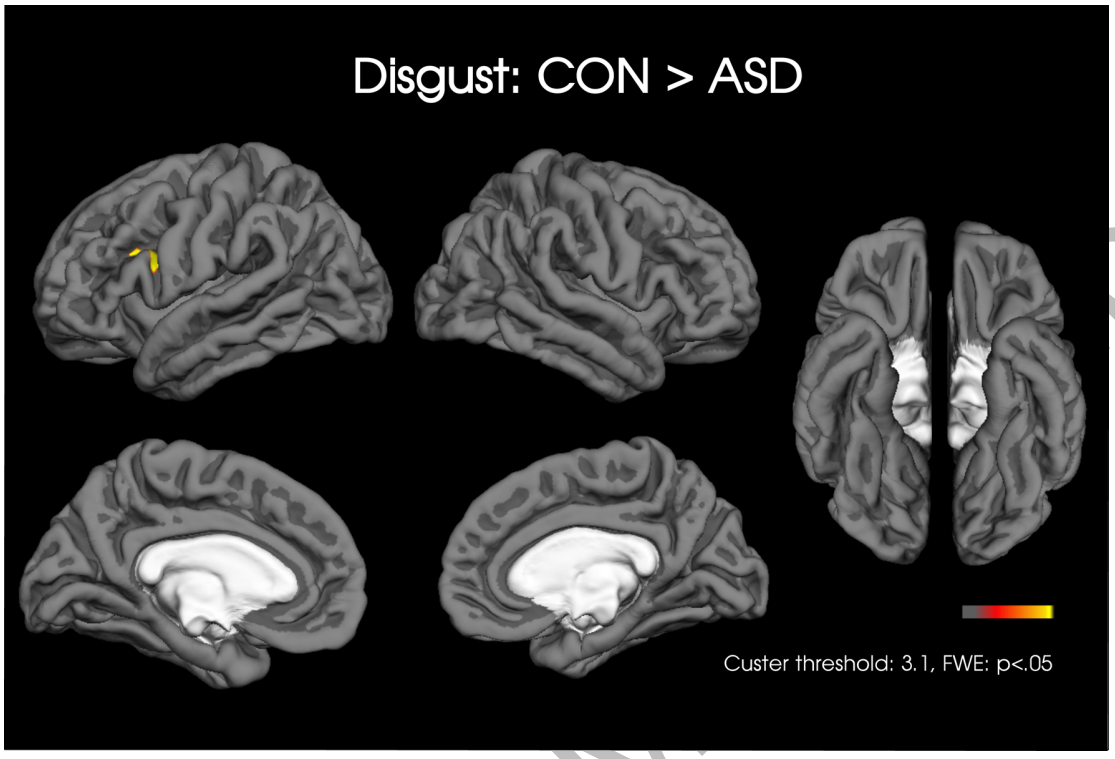

Figure4

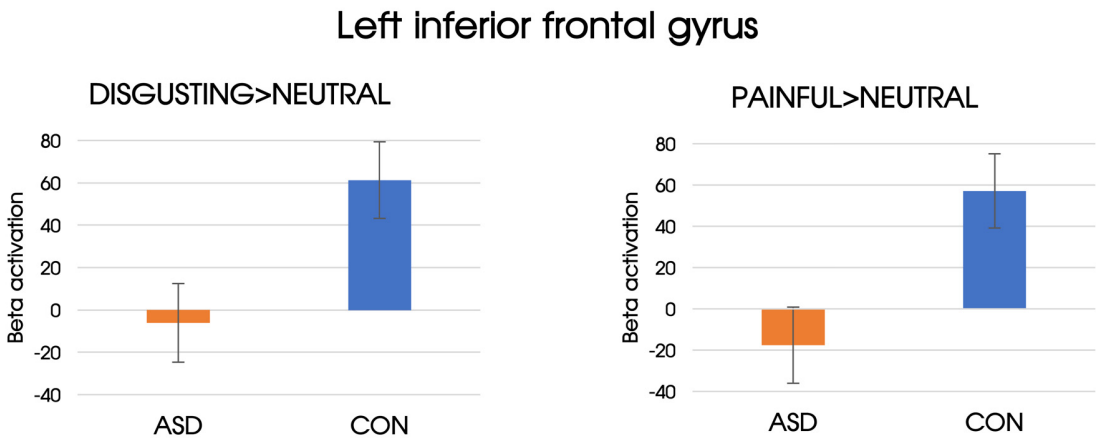

Figure5

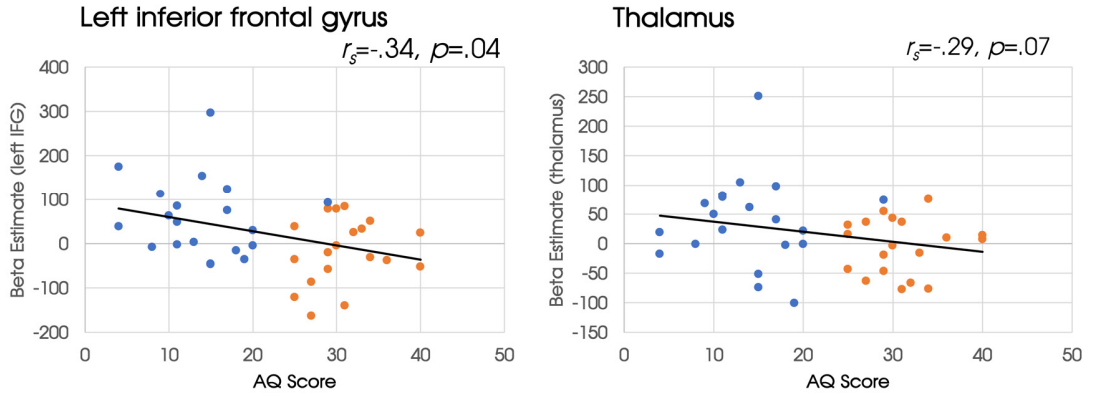

Figure6

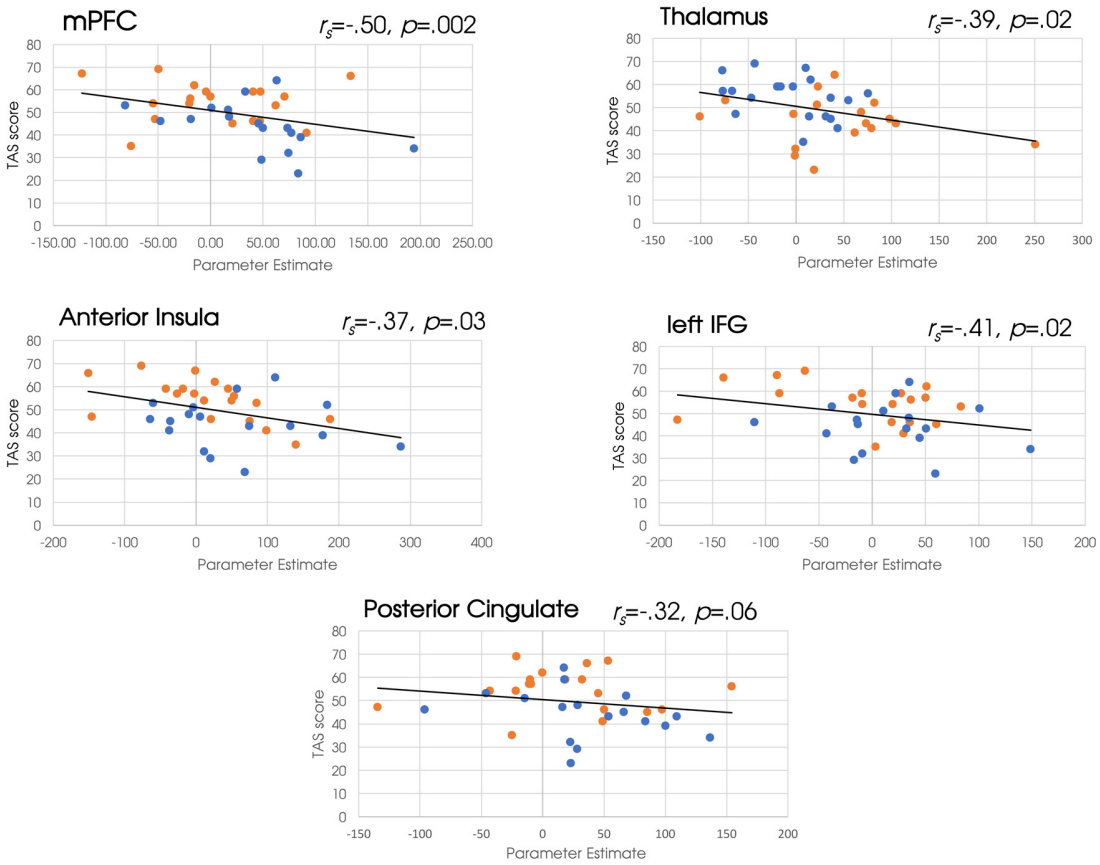

Figure7

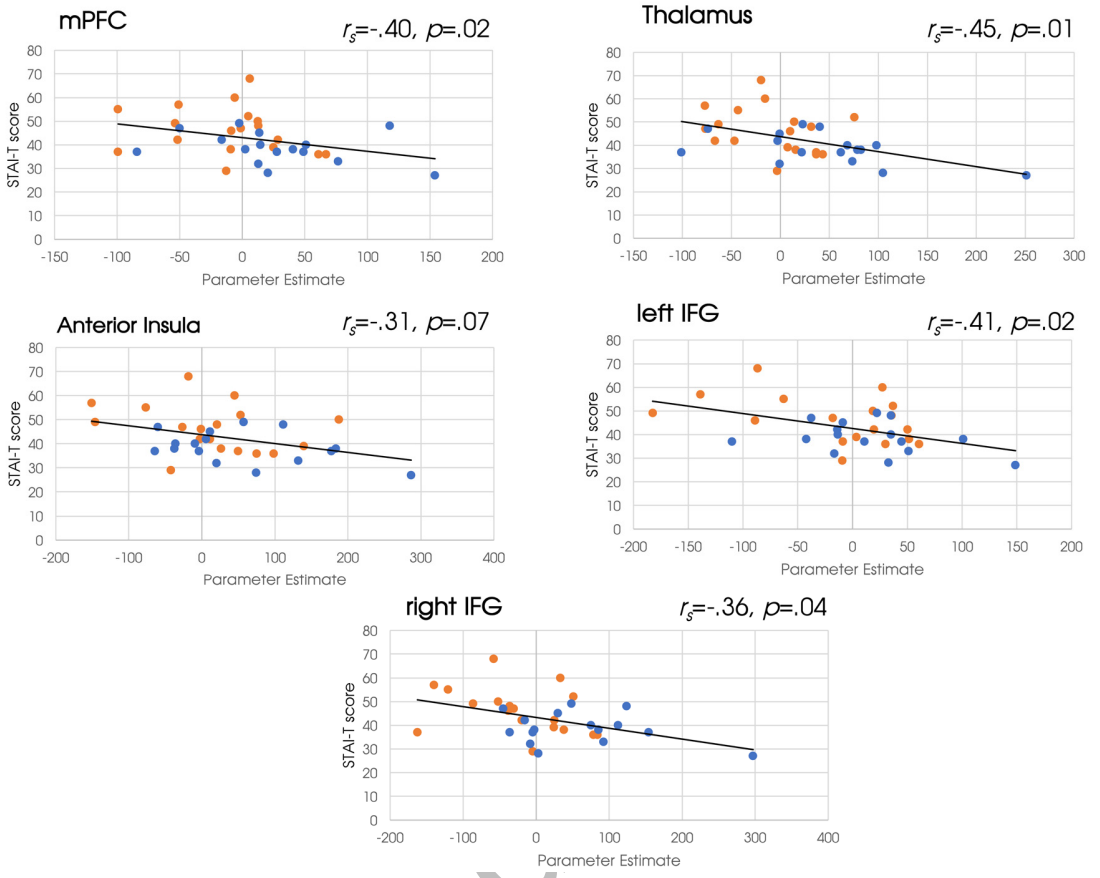

Figure8

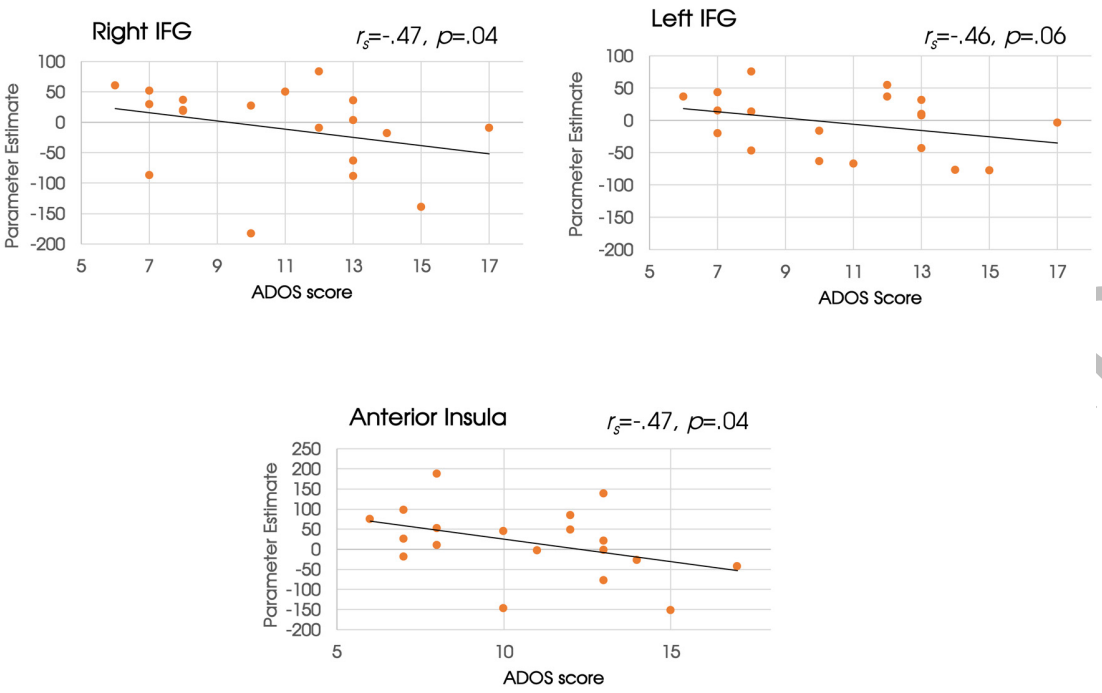
Right IFG
r_s=-.47, p=.04
Parameter Estimate
ADOS score
Left IFG
r_s=-.46, p=.06
Parameter Estimate
ADOS Score
Anterior Insula
r_s=-.47, p=.04
Parameter Estimate
ADOS score

Figure9

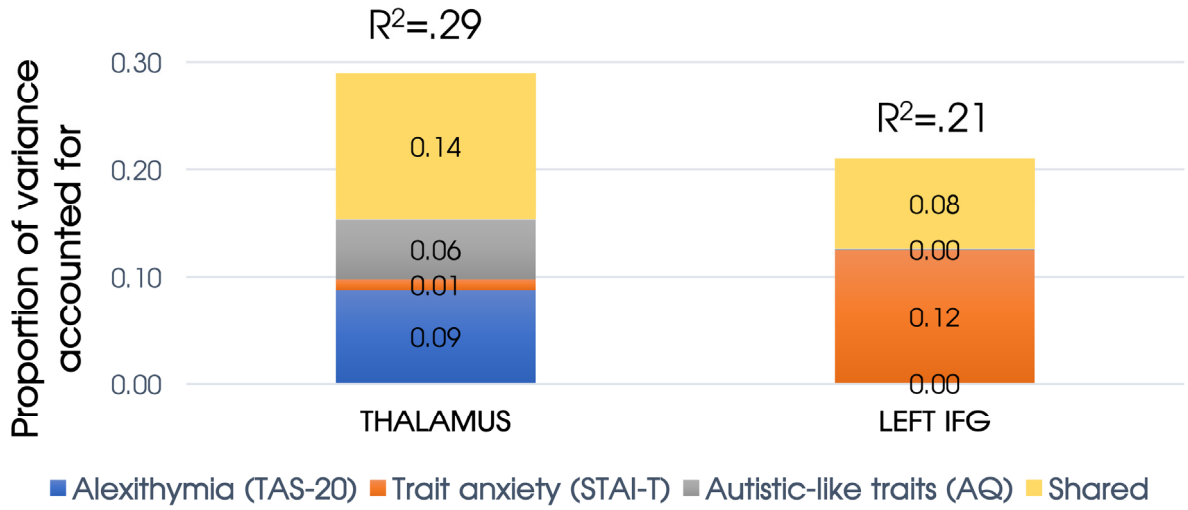
R2=.29
R2=.21
Proportion of variance accounted for
0.14
0.06
0.01
0.09
0.08
0.00
0.12
0.00
THALAMUS
LEFT IFG
Alexithymia (TAS-20)
Trait anxiety (STAI-T)
Autistic-like traits (AQ)
Shared

Figure10

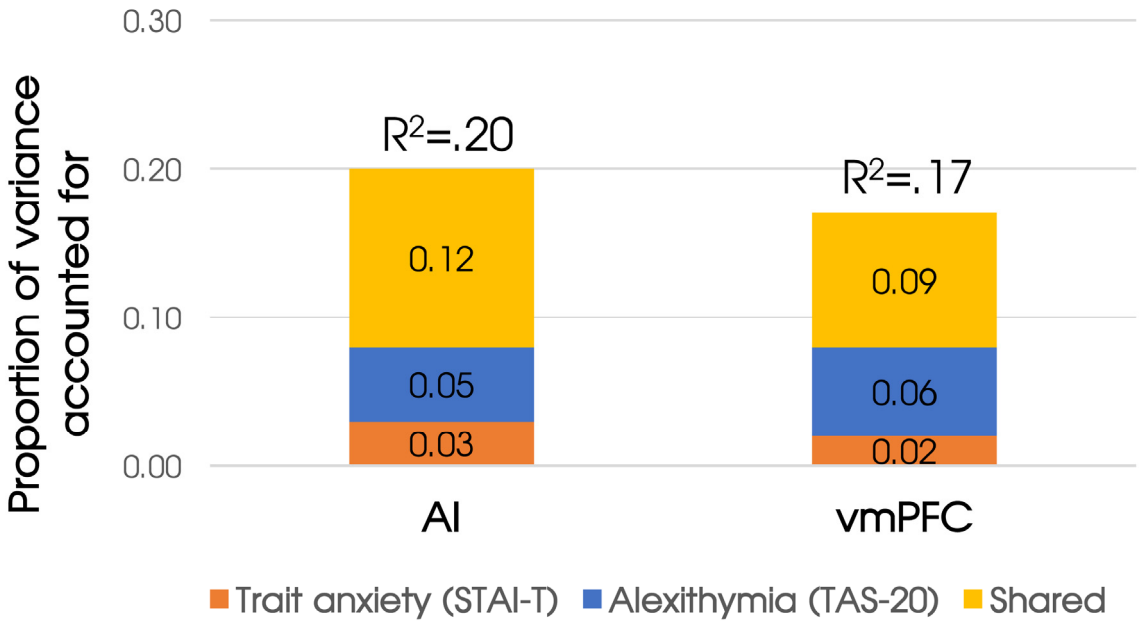

Table 1

	Autism Spectrum Disorders			*Controls*			T-tests
	N	Mean	SD	N	Mean	SD	
Age	19 (2F)	25.27	8.83	20 (3F)	24.15	7.57	t(37)=.43, p=.67
IQ	19 (2F)	111.21	8.83	20 (3F)	111.85	9.15	t(37)=-.17, p=.87
AQ*	19 (2F)	31.11	4.11	20 (3F)	14	5.91	**t(37)=10.01, p<.01**
STAI-T	18 (2F)	46.17	9.89	16 (1F)	38.63	6.6	**t(32)=-2.58, p=.02**
TAS-20	19 (2F)	54.32	9.08	17 (2F)	44.06	10.59	**t(34)=3.13, p<.01**
ADOS**	19 (2F)	10.74	3.16				
ADI-R	17 (2F)	39.28	12.55				

Table 2a

Structure	Side	Cluster size	Z	x	y	z
		1330				
lingual gyrus	L		6.05	-8	-88	-6
occipital pole	L		5.05	-6	-98	-4
occipital fusiform gyrus	L		4.1	-22	-84	-10
		859				
posterior cingulate gyrus	R		5.04	2	-20	36
supplementary motor area	R		3.63	4	4	46
anterior cingulate cortex	R		3.02	4	2	34
	L		3.44	0	-2	32

Table 3a

Structure	Side	Cluster size	Z	x	y	z
		7873				
occipital pole	L		9.22	-6	-90	-4
lingual gyrus	R		3.06	16	-64	-4
	L		9.17	-8	-86	-6
occipital fusiform gyrus	L		7.43	-26	-70	-6
lateral occipital cortex	L		4.65	-22	-88	24
brain-stem			4.61	-4	-32	-4
intracalcarine cortex	R		4.39	8	-84	14
cuneal cortex	R		4.22	12	-84	32
thalamus	L		3.81	-18	-28	0
precuneus cortex	L		3.72	-2	-56	6
temporal occipital fusiform cortex	L		3.64	-30	-54	-8
posterior cingulate gyrus	R		2.95	16	-40	2
	L		3.55	-2	-42	30
parahippocampal gyrus	R		3.31	18	-28	-8
	L		3.47	-12	-40	-6
caudate	L		3.16	-8	2	10
		2925				
superior frontal gyrus	R		4.95	4	48	32
	L		5.02	0	50	34
frontal pole	R		3.48	8	66	14
	L		4.35	-4	62	16

paracingulate gyrus	R		3.64	2	54	16
	L		3.88	0	52	12
anterior cingulate gyrus	L		3.82	-6	34	22
frontal medial cortex	R		3.44	4	46	-16
subcallosal cortex	R		3.25	4	20	-22
	L		2.48	-4	20	-24
		2742				
inferior frontal gyrus	L		4.67	-54	24	10
frontal orbital cortex	L		4.07	-46	22	-12
middle frontal gyrus	L		4.06	-42	8	32
frontal pole	L		3.88	-50	38	6
anterior insula	L		3.59	-28	26	-2
temporal pole	L		3.24	-52	18	-16
		1228				
supramarginal gyrus	L		4.09	-40	-52	16
angular gyrus	L		3.86	-56	-48	32
lateral occipital cortex	L		3.69	-44	-54	26
middle temporal gyrus	L		3.34	-44	-54	6

Table 4

Structure	Side	Cluster size	Z	x	y	z
		1719				
frontal pole	L		4.08	-48	38	6
inferior frontal gyrus	L		3.94	-42	14	22
precentral gyrus	L		3.75	-50	8	20
frontal orbital cortex	L		3.64	-46	34	-8
middle frontal gyrus	L		3.53	-40	16	28
frontal operculum cortex	L		2.74	-42	18	2

Table 5

Structure	Side	Cluster size	Z	x	y	z
		1896				
middle frontal gyrus	L		4.1	-48	26	28
inferior frontal gyrus	L		3.8	-46	10	28
precentral gyrus	L		3.51	-42	8	26
		889				
thalamus	R		3.73	4	-22	4
	L		3.46	-12	-10	0
brain-stem			3.13	2	-26	-4
posterior cingulate gyrus	R		3.11	6	-34	26

Emotional resonance, alexithymia and ASD

SUPPLEMENTARY MATERIALS

Neuroimaging results of the analysis involving only the subjects (N=31, 14 CON) who performed the task accurately.

ROI analyses

Correlations

Spearman correlations (two-tailed) were also conducted between STAI scores/TAS-20 scores and the mean activation in the selected regions of interest for each group separately, for the contrast Painful vs. Neutral.

Correlations with TAS				
	ASD		CON	
	r	p	r	p
mPFC	-0.08	0.74	-0.68	0.004
thalamus	-0.44	0.06	-0.08	0.74
anterior insula	-0.67	0.002	-0.18	0.49
left IFG	-0.39	0.09	-0.1	0.73
posterior cingulate	-0.08	0.73	-0.46	0.07
Correlation with STAI				
mPFC	-0.18	0.47	-0.32	0.21
thalamus	-0.39	0.1	-0.39	0.12
anterior insula	-0.32	0.19	-0.32	0.21
left IFG	-0.39	0.11	-0.24	0.37
right IFG	-0.43	0.08	-0.12	0.64