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Title: Brain correlates of emotional prosodic change detection in Autism Spectrum Disorder

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Abstract

Autism Spectrum Disorder (ASD) is currently diagnosed by the joint presence of social impairments and restrictive, repetitive patterns of behaviors. While the co-occurrence of these two categories of symptoms is at the core of the pathology, most studies investigated only one dimension to understand underlying physiopathology. In this study, we analyzed brain hemodynamic responses in neurotypical adults (CTRL) and adults with autism spectrum disorder during an oddball paradigm allowing to explore brain responses to vocal changes with different levels of saliency (deviancy or novelty) and different emotional content (neutral, angry).

Change detection relies on activation of the supratemporal gyrus and insula and on deactivation of the lingual area. The activity of these brain areas involved in the processing of deviancy with vocal stimuli was modulated by saliency and emotion. No group difference between CTRL and ASD was reported for vocal stimuli processing or for deviancy/novelty processing, regardless of emotional content.

Findings highlight that brain processing of voices and of neutral/ emotional vocal changes is typical in adults with ASD. Yet, at the behavioral level, persons with ASD still experience difficulties with those cues. This might indicate impairments at latter processing stages or simply show that alterations present in childhood might have repercussions at adult age.

Keywords : autism spectrum disorder, change detection, fMRI, emotion, voice, novelty

Introduction

Physical and social adaptation typically challenges the impaired skills of individuals with Autism Spectrum Disorder (ASD), as it requires efficiently detecting and reacting to biologically essential stimulations. This orienting response towards potentially relevant events involves automatic attentional mechanisms that are unconscious and stimulus driven (Corbetta and Shulman, 2002; Sokolov, 1963). Such automatic orientation of attention would be elicited mainly by two classes of evolutionary important stimulations: signal stimuli (usually emotional and critical for the individual, such as danger) and novel stimuli (unknown or unexpected in a particular environment) (Carretié et al., 2004; Öhman et al., 2001). Two automatic attention systems operating either on emotional stimuli or on unexpected events and involving both common and distinct brain structures have thus been depicted. Both attentional systems would be impaired in individuals with ASD, leading to difficulties to apprehend social stimuli such as voices and to atypical behaviors in response to change. While the co-occurrence of these two categories of symptoms is at the core of ASD, most studies investigate only one dimension to understand underlying physiopathology.

On the one hand, in the social dimension, people with ASD fail to automatically orient their attention towards social stimuli and to react to their emotional nature. For example, people with ASD generally do not display the classical preference for vocal stimuli (Klin, 1991; Kuhl et al., 2005) and do not recognize the humanness in natural voices compared to robotic voices (Kuriki et al., 2016). Few studies have investigated the neural processing of vocal stimuli in people with ASD in order to figure out if behavioral difficulties could be related to low-level impairment in response to voice. Decreased activation in several brain areas was reported in high-risk infants compared to low-risk infants (Blasi et al., 2015) and in children with ASD compared to controls (Abrams et al., 2019) suggesting a potential delay in the specialization for human voice processing. In adults, mixed results were observed with two studies highlighting a reduced activation in ASD compared to controls especially over temporal voice areas (Gebauer et al., 2014; Gervais et al., 2004) while other groups did not show any group difference for vocal processing (Hoffmann et al., 2016; Schelinski et al., 2016). Even more contradictory results arise when vocal stimuli carried an affective prosody. In typically developing people, emotional stimuli tend to have “priority processing” underlined by an emotional attention network (Vuilleumier, 2005). Though mainly studied in the visual modality, emotional stimuli have been found to evoke earlier and stronger responses both in the limbic areas, such as the amygdala and orbitofrontal cortex, in the traditional sensory areas (Vuilleumier and Pourtois, 2007), as well as in the fronto-parietal attention regions (Pourtois et al., 2005). ERPs studies even showed that the emotional value of the stimuli can be encoded before categorical encoding (non social/ social) of the stimuli themselves as it

modulates early visual sensory components during emotional faces (Batty and Taylor, 2003) or words (Ortigue et al., 2004) processing. The same emotional attention model applies to the auditory modality, though less documented, as confirmed by the enhanced brain responses in auditory regions during exposure to vocal emotional stimuli (Grandjean et al., 2005; Mitchell et al., 2003). In Autism Spectrum Disorder, at the behavioral level, some studies showed lower performances on tasks of emotional prosody perception in people with ASD compared to controls (Globerson et al., 2015; Hesling et al., 2010; Kujala et al., 2005; Rosenblau et al., 2016; Stewart et al., 2013) while others described small alterations or even no differences with controls (Baker et al., 2010; Heikkinen et al., 2010; Hubbard et al., 2017; Le Sourn-Bissaoui et al., 2013; Martzoukou et al., 2017). Yet, alteration of prosodic production in ASD populations remains a recurrent finding (Paul et al., 2005; Peppé et al., 2007). At the neuronal level, studies showed either smaller (Blasi et al., 2015; Eigsti et al., 2012) or greater activation (Eigsti et al., 2012; Hesling et al., 2010; Wang et al., 2006) in ASD than in controls or no significant group differences in response to emotional prosody (Gebauer et al., 2014; Rosenblau et al., 2016). Thereafter, the integrity of the processing of (emotional) vocal stimuli still remains debated in ASD.

On the other hand, in the “sameness dimension” originally described by Kanner, intolerance to change has been associated with an atypical processing of deviancy (Gomot et al., 2011, 2002). Auditory deviancy and novelty detection have been extensively studied in controls especially for non-vocal sounds (e.g. tones, complex sounds) and involves several brain areas whose activity is modulated by the saliency of change (Doeller et al., 2003; Opitz et al., 2002; Rinne et al., 2005; Schönwiesner et al., 2007). These brain areas were frequently localized in temporal (Cacciaglia et al., 2015; Gomot et al., 2008, 2006; Jääskeläinen et al., 2004; Laufer et al., 2008; Linden et al., 1999; Mathiak et al., 2002; Molholm et al., 2005; Sabri et al., 2004; Williams et al., 2007) and frontal regions (Deouell et al., 2007; Doeller et al., 2003; Downar et al., 2002; Rinne et al., 2005; Schall et al., 2003; Schönwiesner et al., 2007; Vouloumanos et al., 2001) even if activations were also mentioned in parietal (Celsis et al., 1999; Crottaz-Herbette and Menon, 2006; Kiehl et al., 2001; Laurens et al., 2005), occipital (Bekinschtein et al., 2009; Deouell et al., 2007; Kiehl et al., 2005b; Müller et al., 2003) and extracortical regions (basal ganglia, brainstem, cerebellum; Kiehl et al., 2001; Müller et al., 2003; Stevens et al., 2005a; Yoshiura et al., 1999). All these brain areas probably encompass the activity of a large fronto-temporo-parietal network. Indeed, the salience network (insula, anterior cingulate cortex), the ventral fronto-parietal attention network (temporo-parietal junction, inferior frontal gyrus, anterior insula) and some temporal areas appeared involved in the processing of deviancy. In ASD, people differently activate this deviancy processing network compared to typically-developing individuals. Indeed, for auditory deviancy detection, children with autism spectrum disorder showed reduced activation of the left anterior cingulate gyrus, the

left medial orbitofrontal region and the left inferior frontal gyrus compared to controls (Gomot et al., 2006). For novelty detection, decreased activation was found in ASD in bilateral inferior parietal lobule and posterior STG (Superior Temporal Gyrus), in the left anterior cingulate gyrus and in the right IFG (Inferior Frontal Gyrus), medial frontal gyrus, anterior cerebellum (Gomot et al., 2006). In another investigation while change was actively attended (Gomot et al., 2008), an increased activation in ASD compared to controls was reported in right superior/middle and inferior frontal gyrus, in the right pre- and post-central gyri and in the left inferior parietal lobule. Hence, some of the behaviors specific to the sameness dimension such as stereotyped and repetitive behaviors could arise from atypical change detection. This proposed link between ASD symptomatology and the ability to process changes is coherent with the Bayesian theory of brain functions recently invoked in ASD (Pellicano and Burr, 2012). This Bayesian theory proposes that the brain extracts sensory regularities in order to build up predictions (priors) from past sensations, to optimally adapt to the ever-changing environment (Friston, 2005). In ASD, an imbalance in the contribution of priors relatively to sensory inputs would induce an altered perception of the environment leading to difficulties in daily life adaption (Gomot and Wicker, 2012; Lawson et al., 2017; Van de Cruys et al., 2014).

Overall several behaviors specific to the pathology (difficulties to apprehend social environments, intolerance of change) could arise from an atypical functioning of the brain networks dedicated to changing and emotional events processing. To date, no fMRI study has been performed to assess emotional deviancy detection in ASD in response to vocal stimuli in order to simultaneously address the two symptomatologic dimensions at the heart of ASD. However, such investigation has already been realized in electrophysiology with recordings of two neural components- the mismatch negativity (MMN) and the P3a, reflecting respectively, automatic detection of change in a regular environment and orientation of attention toward change (Näätänen et al., 2007). The few investigations on these electrophysiological cues revealed that in response to deviancy in vocal stimuli, adults with ASD showed atypical responses (EEG studies; Charpentier et al., 2018a; Kasai et al., 2005; Kujala et al., 2007; Lepistö et al., 2007). When deviancy was also emotional, group differences were characterized by several modifications of MMN and P3a responses. For example, a reduction of MMN amplitude (EEG; Fan and Cheng, 2014; Kujala et al., 2005) in ASD compared to CTRL was shown as well as shorter/ delayed MMN response (EEG; Charpentier et al., 2018a; Kujala et al., 2005) and atypical P3a amplitudes (EEG; Charpentier et al., 2018a; Fan and Cheng, 2014). Overall, event-related potential (ERP) studies likely indicate an impaired detection of vocal deviancy. fMRI studies in control participants indicated that processing of vocal deviancy mainly activated temporal cortices (Celsis et al., 1999; Laufer et al., 2008; Leff et al., 2009; Schirmer et al., 2008; Shtyrov et al., 2008; Szycik et al., 2013; Vouloumanos

et al., 2001) even if activations in supramarginal gyrus (Celsis et al., 1999), precentral gyrus (Laufer et al., 2008) and IFG (Vouloumanos et al., 2001) were also reported. In these studies, the effect of emotion on the vocal deviancy processing was only poorly explored and it did not reveal any difference between neutral and emotional deviant processing (Demenescu et al., 2015; Schirmer et al., 2008). Even if the functioning of both auditory sensory regions implicated in vocal processing and preattentive fronto-parietal networks is likely to be impaired in ASD, the precise location of brain regions involved in the atypical vocal deviancy processing in ASD remains unknown.

At the sight of previous behavioral and neurophysiological findings, we proposed that the difficulties in adequately detecting and reacting to prosodic cues in everyday life in ASD might be underlined by an atypical detection of deviancy in (emotional) vocal streams. In order to better characterize the brain network involved in this atypical vocal deviancy processing in ASD, and its modulation by emotional prosody or deviance magnitude (e.g. saliency), event-related fMRI responses were recorded for neutral and emotional deviant and novel stimuli in both controls and ASD.

Material and methods

Participants

Fifteen adults with ASD were recruited through the Autism Resource Centre of Centre Val de Loire (Tours; <https://www.cra-centre.org/>). One adult was removed from the analysis group due to excessive movement artifacts. The characteristics of the remaining ASD participants are presented in Table 1 (mean age \pm standard error: 27.9 years \pm 6.4; 13 right-handed; 13 males). An experienced team of clinicians diagnosed subjects according to DSM-IV-TR criteria (American Psychiatric Association, 2000) with ADI-R and ADOS tools (results displayed in Table 1; Lord et al., 2000, 1994). Sixteen healthy adults with similar age (two-sided t-test; $p > .05$) also participated in the study as control subjects (CTRL; mean age: 26.4 years \pm 7.5; 13 right-handed; 12 males). None of the CTRL reported any developmental difficulties in language or sensorimotor acquisition. For all subjects, audition was deemed normal after evaluation with an audiometer. No epilepsy or other disease (immune, metabolic and neurological) was reported. Only one adult with ASD was medicated at the time of the study (neuroleptic and antidepressant). Intellectual skills were assessed in all subjects with psychometric tests (WAIS-IV: full version in ASD, four subtests in CTRL (Vocabulary, Similarities, Cubes and Matrix) to estimate verbal and performance IQ; Wechsler, 2011). Autistic traits and empathy were also evaluated in all participants with the Autism Quotient (Baron-Cohen et al., 2001) and the Empathy Quotient (Baron-Cohen and Wheelwright, 2004).

Two-tailed t-tests were used to determine if verbal and performance IQ, Autism Quotient and Empathy Quotient differed between CTRL and ASD. Verbal IQ scores were lower in the ASD than in the CTRL population ($p=.01$; Table 1) while performance IQ was similar between groups ($p>.05$). Autistic traits were significantly higher in ASD than in CTRL ($p<.001$) whereas empathy was significantly lower ($p<.001$). These results along with ADI-R and ADOS scores (Table1) confirmed socio-emotional impairments or at least difficulties in ASD participants of the present study.

Informed written consent was obtained from all adult participants or from their legal guardian when needed. The protocol was approved by the Ethics Committee (CCP) of the University Hospital of Tours and complied with the principles of the Declaration of Helsinki.

----- Insert Table 1 around here -----

Stimuli

Stimuli were female voices with different prosodies extracted from the Montreal Affective Voices (Belin et al., 2008) or recorded in a soundproofed room of the laboratory. The standard stimulus (neutralStd) was the sound [a] uttered with neutral prosody by a female speaker 'A'. Deviants were the sound [a] produced by different women (female speaker 'B' and 'C') with either a neutral prosody (neutralDev) or an emotional angry prosody (emotionalDev), respectively. Stimuli validation procedure was performed on an independent sample of adults ($n=16$; for more details please refer to Charpentier et al., 2018a). The three selected stimuli (neutralStd, neutralDev and emotionalDev) displayed similar mean fundamental frequency (for an acoustic characterization of these stimuli, please refer to Charpentier et al., 2018b). The average mean fundamental frequency of novels was at $294\text{Hz} \pm 90$, [197-500] (mean \pm sd, [min-max]). All the stimuli of the experiment were played at the same intensity and had the same duration (400ms) in order to limit the influence of acoustic parameters variations on hemodynamic responses (Wiethoff et al., 2008). Neutral novel stimuli (neutralNovel), used in the oddball sequence, were four neutral vowels ([o], [y], [ə], [e]) all pronounced by five different females and novel emotional stimuli (emotionalNovel) were four [a] uttered with happy, fearful, disgust and sad prosodies by five different females. Novels displayed a higher level of change compared to deviants because (1) their acoustic frequencies differed from the standard contrary to deviants, (2) they have a lower probability of occurrence ($p=0.024$ for novels vs. $p=0.042$ for deviants) and (3) because of their rarity (neutral and emotional novels are conditions composed of various different stimuli instead of

only one stimulus repeated several times for deviants. Thus, each novel stimulus appeared only one time while both deviants were presented several times during the oddball sequence).

----- Insert Figure 1 around here -----

Design (Figure 1)

The oddball sequence was composed of the standard stimulus (probability of occurrence of $p=0.868$), the neutral and emotional deviants ($p=0.042$ for each), and neutral and emotional novel stimuli ($p=0.024$ for each). Stimulus onset asynchrony was 700ms. In the oddball sequence, two oddball stimuli (e.g., deviants and novels) were separated by 4 to 15 standard stimuli (= 2.8 to 10.5s). The total number of stimuli in this oddball sequence was 849. This sequence allowed studying brain responses to different prosody (neutral and emotional) and levels of saliency (deviancy and novelty). An additional sequence (equiprobable sequence where all stimuli had the same probability of occurrence) was also presented to participants (**data not analyzed in this study**). This equiprobable sequence was composed of standard and deviant stimuli from the oddball sequence and five new stimuli expressing emotional prosodies.

Subjects were asked not to pay attention to the auditory stimuli and to watch a movie during the experiment. The sequences were split in two and used in two functional runs. In each run, a different half of the oddball and equiprobable sequences was presented. A run always started with the oddball sequence. A rest period (10 TR) during which no sound was presented was acquired within functional runs between stimulation periods and at the end of the functional acquisition.

fMRI acquisition

Functional images covering the whole brain (field of view [FOV]: 192 mm; 36 slices; interleaved; in-plane resolution 3x3mm; slice thickness: 3mm) were acquired on a 3-T Tim Trio Scanner (Siemens) using an echoplanar imaging (EPI) sequence (repetition time [TR]: 2.05s, echo time [TE]: 30 ms, flip angle: 90°). Two runs of about 245 volumes were acquired. High-resolution T1-weighted images (structural scan; FOV: 256 mm, 192 slices, voxel size: 1x1x1 mm, flip angle: 9°, TR: 1.9 s, TE: 2.48ms) were acquired between the 2 functional runs.

fMRI data preprocessing

Data were analyzed using the SPM12 toolbox (Wellcome Department of Imaging Neuroscience; <http://www.fil.ion.ucl.ac.uk/spm>) running in Matlab 2015. First, the anatomical scan was AC-PC centered; this correction was applied to all EPI images. Functional images were then temporally-corrected (reference slice: 36) and spatially realigned: all scans were aligned to the first scan of the run closest to the anatomical acquisition, and a mean image was created. The within session anatomical scan was coregistered to the mean image and segmented. The anatomical scan and the functional images were then normalized to the Montréal Neurological Institute (MNI) template using the parameters issued from the segmentation with a voxel resolution of 1x1x1 and 3x3x3, respectively. Functional images were then smoothed with a Gaussian function with a full-width at half-maximum of 8 x 8 x 8 mm. The first 5 volumes of each session were not included in the analysis of the data to allow for stabilization of the scanner. Gray and white matter as well as cerebrospinal fluid images, issued from the segmentation, were combined in order to create a brain mask which was used as an explicit mask in the first-level analysis.

fMRI data analysis

EPI time series were analyzed using the general linear model as implemented in SPM12. Functional data were analyzed in a two-level random-effects design. At the first level, onsets were defined as the presentation of an auditory stimulus. For each run, we modelled the onsets of neutralStd, neutralDev, emotionalDev, neutralNov, emotionalNov (oddball sequence), equiNeutral2 (\approx neutralDev but in the equiprobable sequence) and equiEmotional (\approx emotionalDev but in the equiprobable sequence). Finally, a regressor of no interest regrouped the onsets of the first three standard stimuli (neutralStd) of a sequence, the first two neutralStd following a deviant or a novel stimulus as well as all the stimuli of the equiprobable sequence excluding equiNeutral2 and equiEmotional. In addition, to account for residual motion artifacts, the design matrix also included realignment parameters as nuisance covariates. Thus, the design matrix included 8 regressors per run (7 conditions of interests, plus one regressor of no interest), which contained boxcar functions representing the onset of the stimulation convolved with a canonical hemodynamic response function. For each participant, betas estimates were calculated for each of the 7 conditions and used to create several contrast images: 1) the deviancy response corresponding to deviants (neutralDev, emotionalDev) minus standard stimulus (neutralStd), 2) the novelty response corresponding to novels (neutralNovel, emotionalNovel) minus standard stimulus (neutralStd), 3) neutral deviancy response response (neutralDev minus neutralStd), 4) emotional deviancy response

(emotionalDev minus neutralStd), 5) neutral novelty response (neutralNov minus neutralStd), and 6) emotional novelty response (emotional Nov minus neutralStd).

Statistical analyses

All statistical analyses on fMRI data were performed with the GLMFlex Software (Version June 1st, 2014).

First, the integrity of vocal processing in ASD was evaluated with t-tests with groups on standard stimuli (neutralStd vs rest). T-tests with groups were also used on contrasts 1 and 2 to assess cerebral networks involved in deviancy and novelty processing and to determine their integrity in the ASD population.

Finally, contrasts 3, 4, 5 and 6 were all entered into mixed-design ANOVA (Prosody - 2 levels (neutral vs. emotional) x Saliency - 2 levels (deviancy response vs. novelty response)) with Group (CTRL, ASD) as between-subject factor. This analysis aimed to evaluate the influence of saliency, emotion and group and of their interaction on automatic change processing. Results are reported at an uncorrected cluster-defining threshold of $p < 0.001$ at the voxel level with a 5% FWE-corrected cluster threshold. Only activations/ deactivations occurring in the two cerebral hemispheres were reported in this paper.

Results

Standard response (Figure 2; Table 2)

For the entire population, the brain response to vocal standard stimuli (vs. rest) is characterized by a significant bilateral activation of superior temporal gyrus (STG) extending to the right postcentral gyrus (*one-sample Ttest* $T(1,28) > 3.41$; *FWEc*; corresponding to a $k = 1002$) and by a deactivation of the occipital cortex (bilateral superior and middle occipital gyri, calcarine sulcus, right cuneus; *one-sample Ttest* $T(1,28) > -3.41$; *FWEc*; corresponding to a $k = 1057$). No significant group difference between CTRL and ASD was observed for this response.

----- Insert Table 2 and Figure 2 around here -----

Deviancy response (Figure 3; Table 2)

The deviancy response (neutral and emotional deviants vs. standard) was characterized by a bilateral activation of STG extending to the supramarginal gyrus and the insula in the right hemisphere (*one-sample Ttest* $T(1,28) > 3.41$; *FWEc*; corresponding to a $k = 128$). Deactivation of the lingual cortex was also reported (*one-sample Ttest* $T(1,28) > -3.41$; *FWEc*; corresponding to a $k = 471$). No region showed a significant group difference regarding the deviancy response.

----- Insert Figure 3 around here -----

Novelty response (Figure 3; Table 2)

The novelty response (neutral and emotional novels vs. standard) activated several clusters over temporal, parietal and occipital lobes. Activations were observed in bilateral STG and insula but also in the right supramarginal gyrus and in the inferior occipital gyrus (*one-sample Ttest* $T(1,28) > 3.41$; *FWEc*; corresponding to a $k = 110$). Deactivation was again observed in a lingual cluster (*one-sample Ttest* $T(1,28) > -3.41$; *FWEc*; corresponding to a $k = 124$). No significant group difference was observed.

Saliency, prosody and group: what effect on brain responses to change? (Figure 4 and Table 3)

----- Insert Table 3 and Figure 4 around here -----

In order to investigate these effects, a mixed-design ANOVA was performed with Saliency (deviancy and novelty responses) and Prosody (neutral and emotional) as within-subject factors and Group (CTRL, ASD) as between-subject factor. This analysis evidenced a main effect of Saliency ($\text{abs}(T(1,28)) > 3.41$; $\text{FWEc} = 125$) with a modulation of brain activity by the level of change. Larger change was associated with larger bilateral activation of superior temporal gyrus, left calcarine sulcus and right occipital areas (calcarine sulcus, lingual gyrus and inferior occipital gyrus).

A main effect of Prosody ($\text{abs}(T(1,28)) > 3.41$; $\text{FWEc} = 158$) was found due to a larger activation for emotional than for neutral prosody in right STG and to a reduced deactivation

during emotional compared with neutral prosody processing in a bilateral occipital cluster (lingual gyrus, fusiform gyrus, middle occipital gyrus and calcarine sulcus).

A Saliency by Prosody interaction ($\text{abs}(F(1,28)) > 13.50$; $\text{FWEc} = 441$) was present in left calcarine sulcus. This result is related to an absence of deactivation for the emotional novelty response while brain deactivations were observed for the neutral novelty response and for both neutral and emotional deviancy responses.

No group effect nor interaction involving group was found.

Discussion

The present study evaluated the processing of vocal deviancy in CTRL and ASD. The main goals were 1) to identify the brain regions responsible for the processing of vocal deviancy in ASD and 2) to assess if their activity could be modulated by saliency or emotion. Beforehand, the integrity of auditory vocal processing was checked in ASD.

No group difference between CTRL and ASD was reported for vocal stimuli processing nor for the deviancy/ novelty processing, regardless of emotional content. However, the activity of brain areas involved in the processing of deviancy with vocal stimuli was modulated by saliency and emotion.

Brain response to voice in autism spectrum disorder

Presentation of vocal stimuli activated the superior temporal gyrus in both hemispheres for the entire population. STG is well-known for its involvement in social cognition (Deen et al., 2015) and more especially for voice processing (Belin et al., 2000; Pernet et al., 2015). Indeed, it includes the Temporal Voice Areas (TVA), which display stronger activity for vocal than environmental sounds (Belin et al., 2000). This voice-specific response in TVA appeared somehow relatively independent from acoustics, as it cannot be reproduced with acoustically equivalent non-vocal stimuli (i.e. auditory chimeras; Agus et al., 2017). In a preliminary study conducted in adults with ASD, brain activation to voice was smaller in ASD than in CTRL (Gervais et al., 2004). Investigations in infants at high familial risk of autism spectrum disorder (Blasi et al., 2015) and in children with ASD (Abrams et al., 2019) also evidenced atypical neural responses to voice. At the opposite, no deficit of activation to voice nor any link with autism traits were observed in two studies in adults with ASD (Hoffmann et al., 2016; Schelinski et al., 2016). Our work conducted in adults with ASD is congruent with the latest investigations, as activation maps to vocal stimuli did not differ

between CTRL and ASD. Moreover, individual data distribution appeared very similar between groups. Taken together these results suggest age-related normalization of low-level brain response to voice at adulthood in people with autism spectrum disorder as previously shown in vocal ERP studies (Charpentier et al., 2018a).

Brain responses to deviancy and novelty

In the present work, deviancy and novelty induced the same functional maps: activation in the superior temporal gyrus and in the insula and de-activation in the lingual area.

Lingual cortex involvement has been rather limited in previous investigations. Yet, an ERP study showed activation of bilateral lingual gyri in response to non-social deviancy (Justen and Herbert, 2018). Authors suggested that the lingual gyri activation might have been triggered by the processing of salient acoustic stimuli. Hence, the more salient the deviancy is, the more lingual activation should be observed. The results of the present study with two levels of deviancy (low-medium for deviants and medium-high for novels) contradicts this idea. Indeed, the lingual cortex is deactivated for the majority of acoustic deviancy conditions (neutral and emotional deviants and neutral novels). It is only weakly activated in response to high deviancy such as emotional novels. This finding might suggest that the lingual cortex plays the role of regulator for the effective detection of deviance. When the deviancy is low, it might deactivate in order to increase the signal to noise ratio in the other brain regions dedicated to the deviancy detection while it would play little or no role when the deviancy level is high. Such crossmodal interactions have repeatedly been reported to happen between auditory and visual regions, in particular decreased visual responses to auditory stimulus presentations (Amaral and Langers, 2013; Johnson and Zatorre, 2005; Mozolic et al., 2008; Weissman et al., 2004). The present findings are in line with those showing that cross-modal deactivations occur to compensate processing difficulty, possibly playing the role of an intrinsic filter for irrelevant information (Hairston et al., 2008).

Contrary to lingual deactivation, temporal activation was consistently evidenced in all investigations of brain responses to vocal deviancy (Celsis et al., 1999; Demenescu et al., 2015; Laufer et al., 2008; Leff et al., 2009; Schirmer et al., 2008; Shtyrov et al., 2008; Szyck et al., 2013; Vouloumanos et al., 2001; Zvyagintsev et al., 2020). The implication of the superior temporal cortex for unconscious processing of irregularities appeared clearly established by fMRI studies in accordance with the location of neuronal sources of deviance-elicited electrophysiological components (i.e. mismatch negativity and P3a; Gomot et al., 2006; Opitz et al., 2002; Recasens et al., 2014; Sabeti et al., 2016). The present work validates once more the key role of the STG for deviancy detection.

The only other brain area activated by deviancy in the current study is the insula. In the literature, the insular activation was mostly observed for speech deviants (Laufer et al., 2008; Vouloumanos et al., 2001). The anterior part of the insula belongs to the saliency network (with the anterior cingulate cortex), which underlies the detection, integration and filtering of internal and environmental stimuli to achieve conscious or unconscious rankings of elements to attend to (Menon and Uddin, 2010; Sridharan et al., 2008). Both social and complex stimuli are able to activate the saliency network. However, Vouloumanos et al. (2001) observed an activation of the insula in a non-sense speech vs. tones contrast but not in a complex sounds vs. tones contrast, highlighting the strong role of social information for insula activation. This might explain why the insula is mainly implicated in social deviancy paradigms.

Overall, our results are consistent with a recent neurophysiological model of passive auditory deviance detection which was established after the analysis of EEG source localization data (Justen and Herbert, 2018). In this work, the authors showed that the deviancy response was characterized by activation in right STG around N1/MMN latency and in bilateral insulae around P3 latency. Hence, authors concluded to the involvement of STG and auditory cortex (from the ventral attention network) for the stimulus-driven deviance detection and the insula (from the salience network) for salience detection (Justen and Herbert, 2018).

In conclusion, the deviancy response relies on brain regions involved in the discrimination and evaluation of change relevance while at the same time, the lingual cortex deactivates in order to decrease the interaction and potential interference with regions specifically dedicated to deviancy processing (Downar et al., 2000; Gaebler et al., 2015).

The novelty response involved the same brain areas with additional activations in inferior occipital and supramarginal gyrus. These regions were already cited in change detection protocols but most of the time, studies included a target detection task or a multimodal audio-visual integration (Beer et al., 2013; Crottaz-Herbette and Menon, 2006; Deouell et al., 2007; Downar et al., 2002; Kiehl et al., 2001; Kiehl and Liddle, 2001; Linden et al., 1999; Stevens et al., 2000; Williams et al., 2007). A specialization of the supramarginal gyrus for phonological changes was also previously reported and could explain the present activation for neutral novels especially (Celsis et al., 1999; Turkeltaub and Coslett, 2010).

Effects of saliency and emotion on deviancy and novelty responses

Larger activations were observed in several brain areas (superior temporal gyrus, right calcarine sulcus, lingual gyrus and inferior occipital gyrus) for novelty compared to deviancy.

This saliency effect differed somewhat from findings of the literature because previous studies presented their deviant and novel during an active task requiring the detection of a target: the deviant. Thereafter, it appeared difficult to differentiate effects of saliency and level of attention in these investigations, which reported more widespread activity for the deviant target compared to novels (Kiehl et al., 2005b, 2005a, 2001; Kiehl and Liddle, 2001; Laurens et al., 2005; Stevens et al., 2005b, 2005a). In another three-stimuli active oddball task, Gomot et al. (2008) observed a more widespread network for the novel target than for deviancy processing. In the passive version of the same paradigm, the authors (Gomot et al., 2006) also showed more widespread activation for novelty than for deviancy, though no direct comparison allowed the assessment of the potential saliency effect. Some fMRI studies performed such comparisons but they did not use novels and deviants but rather three deviants with different saliencies (Doeller et al., 2003; Opitz et al., 2002; Schönwiesner et al., 2007). Doeller (2003) and Schönwiesner (2007) reported stronger temporal activation when the saliency increased. In the investigation of Opitz et al. (2002), temporal activation also tended to be stronger for large saliency. Moreover, they observed activation in fronto-opercular area for large and medium deviants but not for small deviant. These studies tend to confirm a main effect of saliency especially over temporal areas as shown in the present work. However, no firm conclusion can be drawn regarding the origin of this effect. It might be related to the large acoustic difference but it could also reflect an adaptive response with a primary reflex to a potential danger (surprising rare events).

Temporal activation also increased as a function of the emotional prosody. Larger activation was found for emotional compared to neutral prosody in the right hemisphere. This result was commonly reported in previous studies investigating the emotional modulation on sensory processing (Blasi et al., 2011; Ethofer et al., 2009; Grandjean et al., 2005; Kotz et al., 2003; Liebenthal et al., 2016; Mitchell et al., 2003; Shultz et al., 2012; Zhang et al., 2018), which also observed right-hemispheric lateralization (Alba-Ferrara et al., 2012; Beaucousin et al., 2007; Eigsti et al., 2012; Mitchell et al., 2003; Wartenburger et al., 2007). These studies reported the implication of several other brain areas for the emotional sensory processing (e.g. hippocampus, insula, inferior frontal gyrus). A main difference with these studies is the absence of activation in limbic structures such as amygdala in the present work. This result can seem a bit odd as amygdala is a well-known emotional brain area. Nevertheless, it should be underlined that the present study did not compare brain responses to emotional vs neutral voice but brain responses to emotional vs neutral vocal change. Therefore, the focus of the current investigation was not the affective network per se. In two investigations conducted in healthy adults (Demenescu et al., 2015; Schirmer et al., 2008) on the contrast (emotional vs neutral vocal change), no additional activation was reported in the amygdala for the emotional change. These concordant results might indicate that contrary to emotional sensory

processing, emotional change processing does not rely on the recruitment of additional brain areas. Thus, an emotional change appearance would only modulate the activity of pre-existing brain networks related to change processing.

An effect of prosody was also observed in a large bilateral occipital cluster where deactivation was smaller for emotional than neutral change. This finding appears rational if we consider as previously stated, that the occipital cluster deactivation would allow to modulate brain interferences during change processing. Indeed, the more different the deviant appears, the more the detection and processing of the deviancy would be easy and therefore, deactivation of occipital areas useless. An interaction between saliency and prosody in a left calcarine cluster seemed to confirm this idea. In this region, the more easily discernable change (i.e. emotional novel) did not deactivate this brain area while all other conditions did.

What about deviancy and novelty processing in autism spectrum disorder?

In this study, no group difference was reported in adults for brain responses involved in the processing of prosodic deviancy or novelty. In the literature, only three studies, performed in children, evaluated the integrity of similar mechanisms in autism spectrum disorder, but these were in response to non-vocal change. Without task, children with ASD showed reduced activation of frontal regions and left anterior cingulate cortex for novelty processing while the reduced activity was only present in left anterior cingulate cortex during deviance detection (Gomot et al., 2006). During a novel auditory detection paradigm (Gomot et al., 2008), results differed completely with increased activations in children with ASD compared to controls in frontal and parietal areas. Lastly, a decreased activation of the left STG was reported for MMF (Mismatch Fields) amplitude recorded with MEG in children with ASD (Yoshimura et al., 2017). To conclude, until now, brain activations involved in change detection in children with autism spectrum disorder differed from controls regardless of the level of attention. These findings differed with results of the present study conducted in adults where all studied brain responses were found to be typical. In an EEG investigation on same deviancy processes, more atypical brain responses was observed in children compared to adults with ASD (Charpentier et al., 2018a). Overall, this discrepancy between age groups could be explained by a normalization of atypical responses between childhood and adulthood. This hypothesized normalization could be related to learning/ acquisition of social expertise or to brain maturation. Of course, a longitudinal study would be necessary to confirm this age-related normalization.

The absence of group difference between CTRL adults and adults with ASD could also be explained by stimulus type or by the group size of the present study, which is rather small. However, it is worth noting that a similar paradigm applied in event-related potentials on a larger sample (Charpentier et al., 2018a) did not report major group difference on MMN amplitude response at adulthood. Only a latency difference, which could not be observed with fMRI recording parameters, was reported. Moreover, even if individual variability was observed in ASD data in concordance with previous works (Latinus et al., 2019; Otto-Meyer et al., 2018), in this study a large number of participants with autism spectrum disorder displayed brain activations similar to CTRL. Individual data observation thus tends to exclude the group size as a potential factor explaining the absence of group difference. Nevertheless, further investigations should include a larger number of subjects to confirm the absence of group difference but also to represent the ASD spectrum as best as possible. [In order to determine the adequate number of subjects necessary to detect a potential group effect, future studies should consider performing preliminary experiments to obtain pre-study power calculation indicating the adequate number of subjects \(Szucs and Ioannidis, 2020\).](#) Finally, while Empathy Quotient and scores of ADI-R/ ADOS confirmed impaired social abilities in adults with ASD in this study, further works should be considered to acquire behavioral measures to evaluate emotion recognition and emotional change detection in explicit and implicit ways (questionnaires and emotion contagion evaluation for example). Such evaluations may help to decipher different ASD profiles based on combined information from behavioral and fMRI tests.

Conclusion

Brain processing of voice and deviancy/ novelty appears typical in adults with autism spectrum disorder. No group difference was noticed between cerebral activations/ deactivations of CTRL and ASD. Yet, at the behavioral level, adults with ASD still experience several difficulties with both receptive and expressive prosody and with emotional change. These abnormalities might be a consequence of the alterations observed at childhood. Indeed, atypical processing of changes in social information in children with ASD could hamper an appropriate interpretation of social cues and reverberate at adulthood even if cerebral processing normalized meanwhile.

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Figure captions

Figure 1: Schematic of the experimental protocol.

2-column fitting image

Figure 2: Brain response to auditory standard stimuli (standard vs. rest) for all subjects (top), and in CTRL and in ASD (bottom). Red/ orange represents activation and blue/green deactivation. Cluster statistics FWE-corrected at $p=.05$, voxel value $p=.001$. Mean betas values (\pm standard error mean) are displayed for some clusters through histograms while individual data are exhibited with stars on the histograms. CTRL data are represented in blue and ASD in red.

2-column fitting image

Figure 3: Deviancy and novelty responses to prosodic stimuli (deviants vs. standard and novels vs. standard respectively) for all participants. Red/ orange represents activation and blue/green deactivation. Cluster statistics FWE-corrected at $p=.05$, voxel value $p=.001$. Mean betas values (\pm standard error mean) are displayed for some clusters through histograms while individual data are exhibited with stars on the histograms. CTRL data are represented in blue and ASD in red.

Single column fitting image

Figure 4: Brain areas sensitive to saliency, prosody or both during the oddball paradigm for all participants. Cluster statistics FWE-corrected at $p=.05$, voxel value $p=.001$. Mean betas values (\pm standard error mean) are displayed for some clusters through histograms while individual data are exhibited with stars on the histograms. CTRL data are represented in blue and ASD in red. Moreover, the neutral condition appears in light colors while the emotional condition is in dark colors.

2-column fitting image

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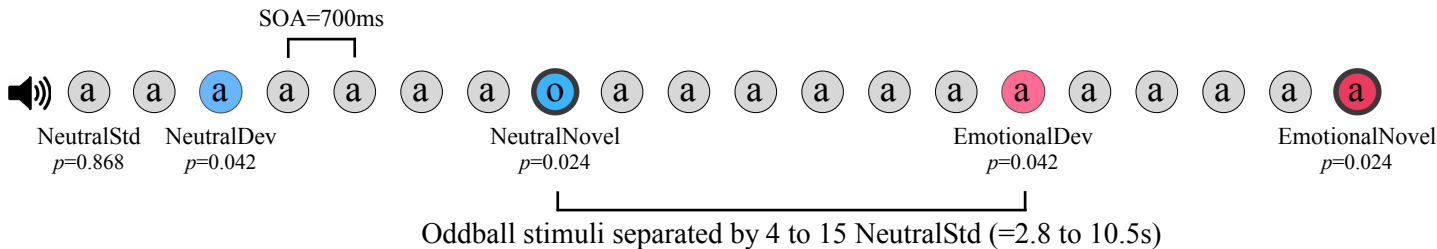
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NeutralStd ([a] uttered by a female speaker 'A')

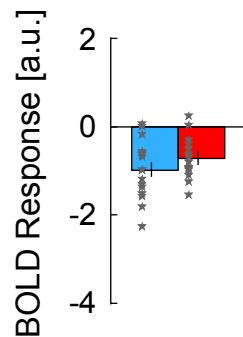
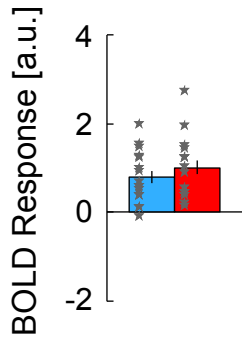
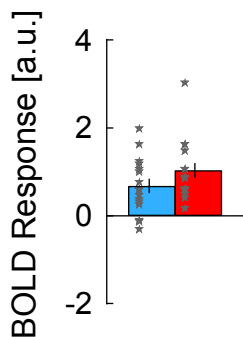
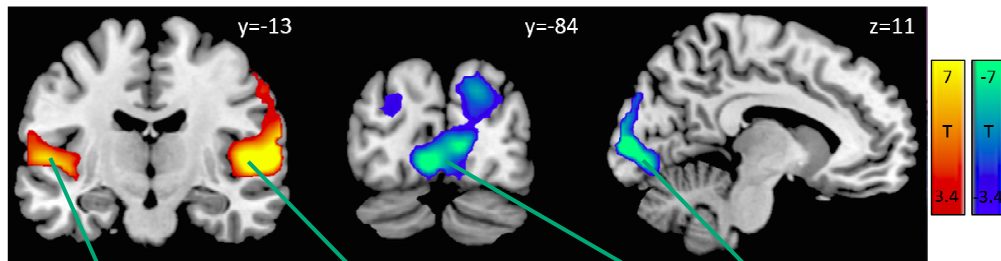
NeutralDev ([a] uttered by a different female speaker 'B')

EmotionalDev ([a] pronounced with an angry prosody by a female speaker 'C')

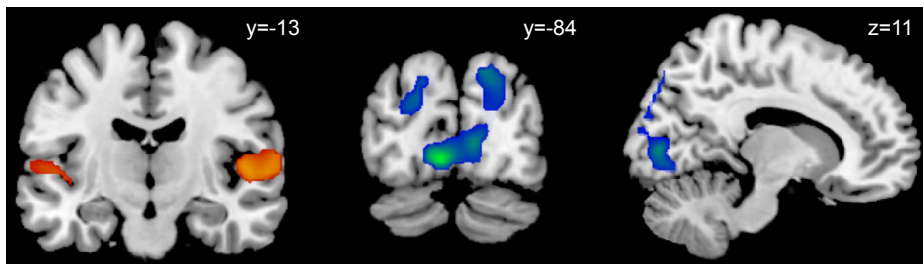
NeutralNovel ([o], [y], [ə], [e] uttered by different female speakers)

EmotionalNovel ([a] pronounced with an happy, fearful, disgusted and sad prosody by different female speakers)

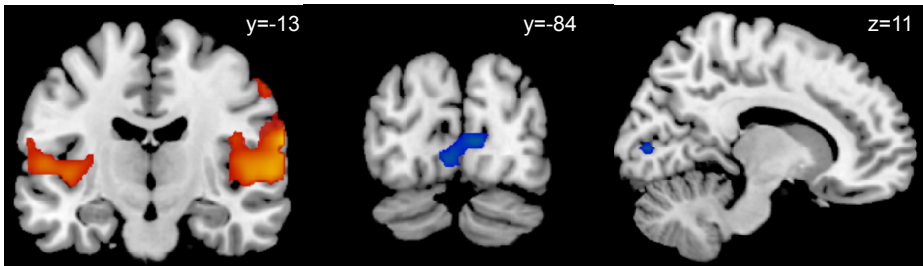
Standard Response (All Subjects)



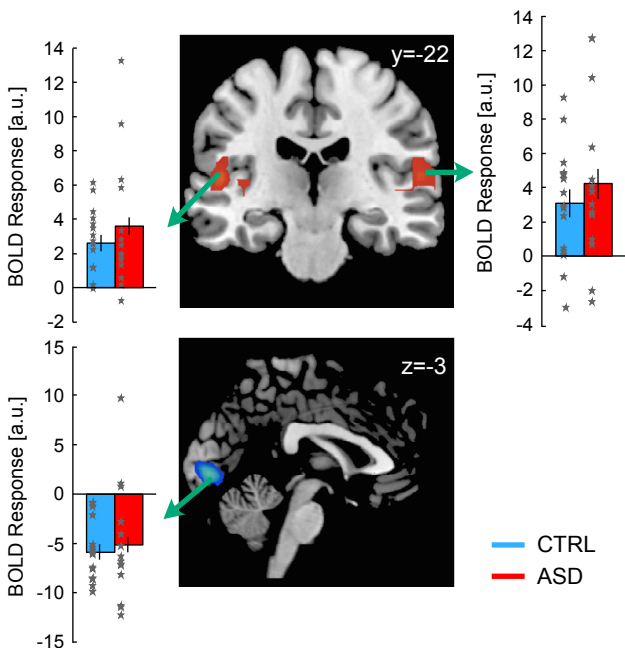
Standard Response (CTRL)



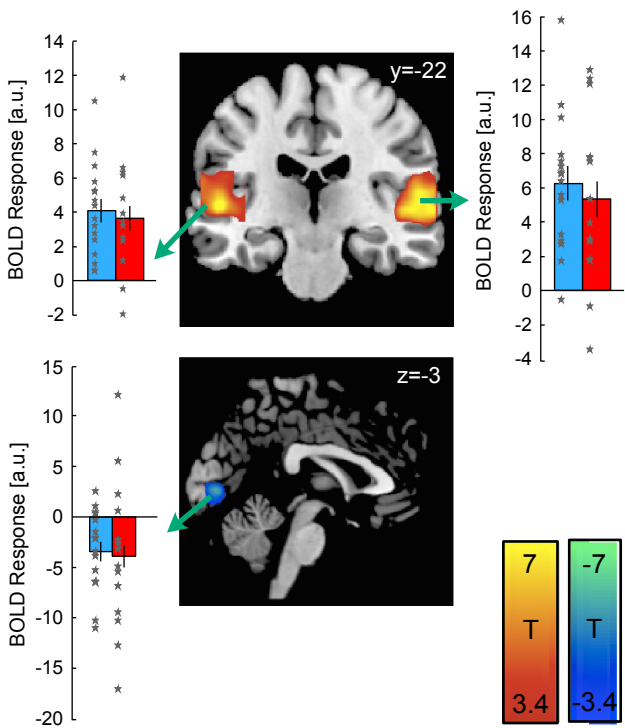
Standard Response (ASD)



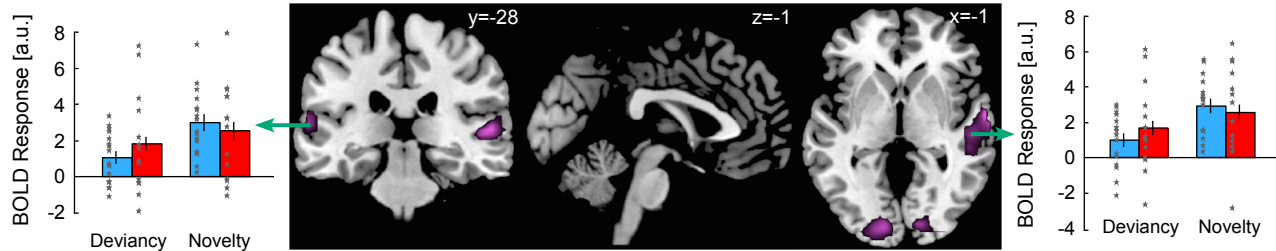
DEVIANCY RESPONSE



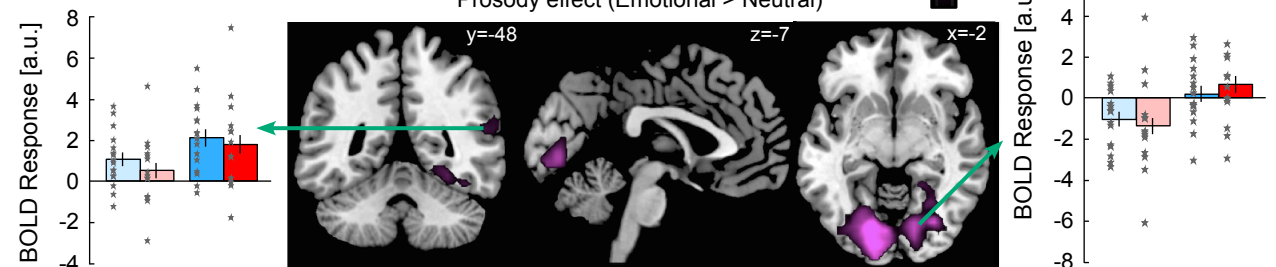
NOVELTY RESPONSE



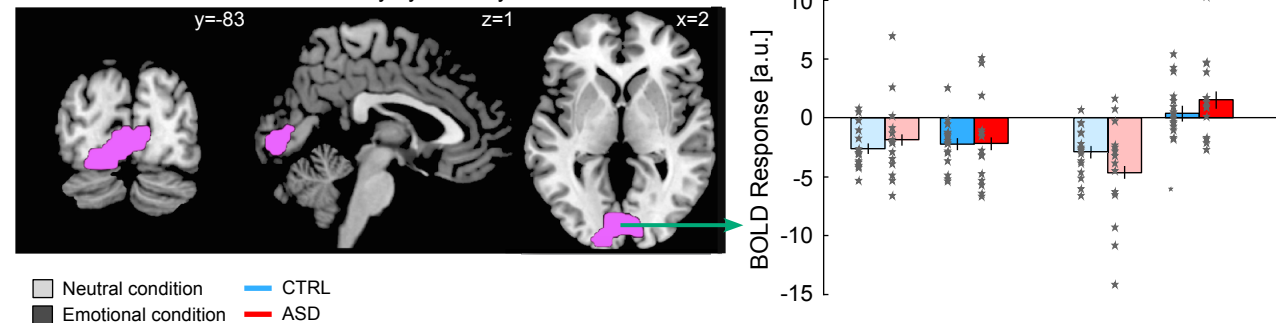
Saliency effect (Novelty response > Deviancy response)



Prosody effect (Emotional > Neutral)



Interaction Saliency by Prosody effect



| | CTRL (n=16) | ASD (n=14) |
|---------------------------------|-------------------------------|------------------------|
| Age (mean \pm sd) (age range) | 26.4 \pm 7.5 (18-41) | 27.9 \pm 6.4 (20-37) |
| Gender (male/ female) | 12/4 | 13/1 |
| Handedness (right/ left-handed) | 13/3 | 13/1 |
| Verbal IQ ^{*a} | 118 \pm 14 | 100 \pm 22 |
| Performance IQ | 111 \pm 14 | 105 \pm 16 |
| Autism Quotient ^{*b} | 12 \pm 6 | 31 \pm 7 |
| Empathy Quotient ^{*c} | 41 \pm 10 | 23 \pm 8 |
| ADI scores | Social interaction domain | - |
| | Communication domain | - |
| | Restricted, repetitive domain | - |
| ADOS scores | Social interactions | - |
| | Communication | - |

Table 1: Population characteristics.

Mean \pm Standard Deviation; * Statistically significant (two-sided t-test; $< p = .05$) ^a $p = .01$; ^b $p < .001$; ^c $p < .001$. ADI cut-off scores for autism: social 10, communication 8, restricted and repetitive domain 3. ADOS cut-off scores for autism: social 6, communication 3.

Data is missing for one adult with ASD for the Autism Quotient, the Empathy Quotient and ADI scores.

CTRL= control adults, ASD= adults with Autism Spectrum Disorder, ADI= Autism Diagnostic Interview, ADOS= Autism Diagnostic Observation Schedule.

| Brain response to standard stimuli | Peak values | | | | | MNI coordinates (mm) | | |
|---------------------------------------|-------------------------------------|------------------|-----------------|------------|------------|-------------------------|-----|----|
| | Regions | Brodmann area | Cluster size | T value | z score | x | y | z |
| Standard>Rest (activation) | Right temporal cluster | | 1157 | | | | | |
| | Right superior temporal gyrus | 22 | | 9.3 | 6.2 | 54 | -4 | -1 |
| | Right postcentral gyrus | 4 | | 4.6 | 3.9 | 57 | -13 | 41 |
| | Left superior temporal gyrus | 41 | 1002 | 8.4 | 5.9 | -39 | -31 | 11 |
| Standard<Rest (deactivation) | Occipital cluster | | 1057 | | | | | |
| | Left occipital superior gyrus | 18 | | -11.1 | 6.8 | -9 | -94 | 2 |
| | Right occipital superior gyrus | 19 | | -6.4 | 5.0 | 18 | -88 | 32 |
| | Left middle occipital gyrus | 18 | | -7.7 | 5.6 | -18 | -94 | 17 |
| | Right middle occipital gyrus | 19 | | -5.0 | 4.2 | 36 | -73 | 23 |
| | Left calcarine sulcus | 18 | | -8.3 | 5.8 | -6 | -85 | -4 |
| | Right calcarine sulcus | 17 | | -7.2 | 5.4 | 12 | -82 | 5 |
| | Right cuneus | 19 | | -5.8 | 4.6 | 9 | -88 | 29 |
| Group difference | - | | | | | | | |

| Deviancy response | Peak values | | | | | MNI coordinates (mm) | | |
|-----------------------------------|------------------------------|---------------|--------------|---------|---------|----------------------|-----|----|
| | Regions | Brodmann area | Cluster size | T value | z score | x | y | z |
| Deviants>Standard (activation) | Left superior temporal gyrus | 22 | 631 | 5.6 | 4.5 | -63 | -34 | 17 |

| | Right temporal cluster | | 191 | | | | | |
|-------------------------------------|---|---------------|--------------|-------------|---------|----------------------|-----|-----|
| | Right superior temporal gyrus | 22 | | 4.4 | 3.8 | 54 | -13 | -4 |
| | Right insula | 13 | | 3.7 | 3.3 | 42 | -10 | 2 |
| | Right STG extending to supramarginal | 39 | 128 | 5.0 | 4.2 | 63 | -49 | 20 |
| Deviants<Standard (deactivation) | Bilateral lingual gyrus | 18 | 471 | -6.2 | 4.9 | 9 | -82 | -7 |
| Group difference | - | | | | | | | |
| Novelty response | Regions | Brodmann area | Cluster size | Peak values | | MNI coordinates (mm) | | |
| | | | | T value | z score | x | y | z |
| Novels>Standard (activation) | Left temporal cluster | | 896 | | | | | |
| | Left superior temporal gyrus | 22 | | 8.6 | 6.0 | -63 | -34 | 14 |
| | Left insula | 13 | | 3.6 | 3.2 | -39 | -10 | -4 |
| | Right tempo-parietal cluster | | 988 | | | | | |
| | Right superior temporal gyrus | 22 | | 8.0 | 5.7 | 54 | -13 | -4 |
| | Right insula | 13 | | 5.7 | 4.6 | 42 | -4 | -10 |
| | Right supramarginal gyrus | 40 | | 5.3 | 4.4 | 66 | -40 | 32 |
| | Right inferior occipital gyrus | 18 | 110 | 4.5 | 3.9 | 27 | -91 | -10 |
| Novels<Standard (deactivation) | Left lingual gyrus | 17 | 124 | -5.9 | 4.7 | 3 | -81 | 1 |
| Group difference | - | | | | | | | |

Table 2: T-tests results. Voxel value $p=.001$, cluster statistics FWE-corrected at $p=.05$.

| ANOVA Saliency by Prosody | Regions | Brodmann area | Cluster size | Peak values | | MNI coordinates (mm) | | |
|--|--------------------------------|------------------|-----------------|--------------|---------|-------------------------|-----|-----|
| | | | | T/F value | z score | x | y | z |
| <u>Saliency effect</u> | | | | | | | | |
| Novelty response> Deviancy response | Right superior temporal gyrus | 41 | 341 | -7.3 | 5.4 | 63 | -7 | -1 |
| | Left superior temporal gyrus | 41 | 125 | -5.6 | 4.6 | -63 | -25 | 8 |
| | Left calcarine sulcus | 18 | 220 | -6.1 | 4.8 | -12 | -91 | -1 |
| | Right occipital cluster | | 136 | | | | | |
| | Right calcarine sulcus | 17 | | -5.7 | 4.6 | 15 | -88 | -1 |
| | Right lingual gyrus | 18 | | -4.8 | 4.1 | 21 | -85 | -7 |
| | Right inferior occipital gyrus | 18 | | -3.8 | 3.4 | 33 | -94 | -1 |
| Novelty response< Deviancy response | - | | | | | | | |
| <u>Prosody effect</u> | | | | | | | | |
| Emotional change> Neutral change | Bilateral occipital cluster | | 2452 | | | | | |
| | Left lingual gyrus | 18 | | 8.9 | 6.1 | -17 | -79 | -12 |
| | Right lingual gyrus | 18 | | 6.8 | 5.2 | 15 | -76 | -13 |
| | Left fusiform gyrus | 18 | | 8.4 | 5.9 | -24 | -73 | -13 |
| | Right fusiform gyrus | 19 | | 6.5 | 5.1 | 27 | -73 | -10 |
| | Left middle occipital gyrus | 18 | | 8.1 | 5.8 | -15 | -88 | -7 |
| | Right middle occipital gyrus | 18 | | 5.8 | 4.7 | 33 | -91 | 5 |
| | Left calcarine sulcus | 17 | | 5.1 | 4.3 | -12 | -76 | 11 |
| | Right calcarine sulcus | 18 | | 8.6 | 6.0 | 18 | -94 | 5 |

| | | | | | | | | |
|-------------------------------------|--------------------------------------|----|-----|------|-----|----|-----|----|
| | Right superior temporal gyrus | 22 | 158 | 4.8 | 4.1 | 51 | -43 | 14 |
| Emotional change< Neutral change | - | | | | | | | |
| <u>Group effect</u> | - | | | | | | | |
| <u>Saliency by Prosody</u> | Left calcarine sulcus | 18 | 441 | 40.1 | 4.8 | -6 | -88 | -7 |

Table 3: ANOVA results. Voxel value $p=.001$, cluster statistics FWE-corrected at $p=.05$.