Tactile Hypersensitivity and GABA Concentration in the Sensorimotor Cortex of Adults with Autism

Laurie-Anne Sapey-Triomphe, Franck Lamberton, Sandrine Sonié, Jeremie Mattout, Christina Schmitz

Tactile hypersensitivity and GABA concentration in the sensorimotor cortex of adults with autism

Running title: GABA and tactile hypersensitivity in autism

Authors: Laurie-Anne Sapey-Triomphe[1,2], Franck Lamberton[3,4], Sandrine Sonié[1,5,6], Jérémie Mattout[1], Christina Schmitz[1]

1. Lyon Neuroscience Research Center, Brain Dynamics and Cognition team, INSERM UMRS 1028, CNRS UMR 5292, Université Claude Bernard Lyon 1, Université de Lyon, F-69000, Lyon, France.

2. Laboratory of Experimental Psychology, Department of Brain & Cognition, KU Leuven, Belgium.

3. SFR East Lyon Health, CNRS UMS 3453, INSERM US7, Lyon 1 University, Lyon, France.

4. CERMEP, Imagerie du Vivant, Lyon, France.

5. Centre de Ressource Autisme Rhône-Alpes, Centre Hospitalier Le Vinatier, Bron, France.

6. Hôpital Saint-Jean-de-Dieu, Lyon, France.

Correspondence concerning this article should be addressed to Laurie-Anne Sapey-Triomphe

Email: laurieanne.sapeytriomphe@kuleuven.be

Acknowledgements

We would like to thank all of the participants for their time and participation. This study was supported by a Scientific Research Council grant (CSR-G07) from the Vinatier Hospital Center and by the LABEX CORTEX (ANR-11-LABX-0042) of Université de Lyon, within the program "Investissements d'Avenir" (ANR-11-IDEX-0007) operated by the French National Research Agency (ANR).

LAY SUMMARY

People with autism spectrum disorder (ASD) often experience tactile hypersensitivity. Here, our goal was to highlight a link between tactile hypersensitivity and the concentration of GABA (an inhibitory neurotransmitter) in the brain of adults with ASD. Indeed, self-reported hypersensitivity correlated with reduced GABA levels in brain areas processing touch. Our study suggests that this neurotransmitter may play a key role in tactile hypersensitivity in autism.

ABSTRACT

Sensory hypersensitivity is frequently encountered in autism spectrum disorder (ASD). GABA has been hypothesized to play a role in tactile hypersensitivity. The aim of the present study was twofold. First, as children with ASD have decreased GABA concentrations in the sensorimotor cortex [Puts et al., 2016], we aimed at determining whether the GABA reduction remained in adults with ASD. For this purpose, we used magnetic resonance spectroscopy to measure GABA concentration in the sensorimotor cortex of neurotypical adults (n=19) and ASD adults (n=18). Second, we aimed at characterizing correlations between GABA concentration and tactile hypersensitivity in ASD. GABA concentration in the sensorimotor cortex of adults with ASD was lower than in neurotypical adults (decrease by 17%). Interestingly, GABA concentrations were positively correlated with self-reported tactile hypersensitivity in adults with ASD (r = .50, p = .01), but not in neurotypical adults. In addition, GABA concentrations were negatively correlated with the intra-individual variation during threshold measurement, both in neurotypical adults (r = -.47, p = .04) and in adults with ASD (r = -.59, p = .01). In other words, in both groups, the higher the GABA level, the more precise the tactile sensation. These results highlight the key role of GABA in tactile sensitivity, and suggest that atypical GABA modulation contributes to tactile hypersensitivity in ASD. We discuss the hypothesis that hypersensitivity in ASD could be due to suboptimal predictions about sensations.

Keywords: Autism Spectrum Disorder, gamma-Aminobutyric Acid, Hypersensitivity, Magnetic Resonance Spectroscopy, Somatosensory Cortex, Touch.

INTRODUCTION

A challenging aspect to understand autism spectrum disorder (ASD) is that symptoms observed at the behavioral level are hardly related to abnormalities at the molecular level. The behavioral symptoms of ASD are heterogeneous and are thought to emerge from complex genetic, environmental and/or epigenetic interactions. The core symptoms of ASD are impairments in social interaction and communication, as well as restricted interests and repetitive patterns of behaviors. Sensory processing abnormalities have been recently added to ASD symptoms: *"hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment"* [American Psychiatric Association, 2013]. Hypersensitivity and hyposensitivity have been reported in every sensory modality in ASD [Kern et al., 2007; Marco et al., 2011; Zachor & Ben-Itzchak, 2013; Baum et al., 2015; Foxe et al., 2015]. Hypersensitivity corresponds to increased reactivity to sensory stimulations. Studies investigating tactile sensitivity in ASD remain relatively scarce, even though the first reports on autism already mentioned an atypical tactile sensitivity [Kanner, 1943; Asperger, 1944; Frith, 1991]. Abnormal tactile sensitivity has been evidenced in ASD [Blakemore et al., 2006; Cascio et al., 2008; Puts et al., 2014; Takayama et al., 2014; Tavassoli et al., 2016], but behavioral measurements are quite inconsistent [Mikkelsen et al., 2016]. Importantly, hypersensitivity to tactile stimuli affects many aspects of the daily-life of individuals with ASD, to a larger extent than hyposensitivity. This is translated by difficulties ranging from finding clothes to wear that do not trigger this hypersensitivity, to avoiding social interactions that may require social touch. A recent study conducted in a large sample of adults with ASD suggested that social dysfunction was primarily mediated by hyper-responsiveness to touch in adults with ASD [Lundqvist, 2015]. It therefore appears crucial to better understand the mechanisms underlying tactile hypersensitivity in ASD.

Recent studies have successfully related behavioral measurements of tactile sensitivity to molecular measurements in ASD and neurotypical (NT) individuals. Indeed, GABA (gamma-aminobutyric acid) concentration in the sensorimotor cortices is negatively correlated to the tactile frequency discrimination threshold (i.e. minimum difference in frequency to discriminate two vibrotactile stimulations) in NT children and NT adults, and to the tactile detection threshold (i.e.

minimum intensity to detect a tactile stimulation) in children with ASD [Puts et al., 2011, 2016]. Genetic results also suggest a link between tactile sensitivity and GABA. Indeed, genetic variations in the *GABRB3* gene (an autism candidate gene encoding a subunit of $GABA_A$ receptors) have been associated with modulations of tactile sensitivity in the human general population [Tavassoli et al., 2012], as well as in a mouse model of ASD [DeLorey et al., 2011; Orefice et al., 2016].

GABA plays multiple roles in the developing and mature brain. During early development, it is excitatory and regulates neurogenesis processes, such as neural proliferation or differentiation [Wu & Sun, 2015]. In the mature brain, GABA is the main inhibitory neurotransmitter and is present in cortical and white matter interneurons [Wu & Sun, 2015]. GABA inhibits glutamatergic neurons, through lateral inhibition, which sharpens the tuning of cortical neurons [Isaacson & Scanziani, 2011]. Interestingly, the neuronal excitatory/inhibitory balance, mostly relying on glutamate (excitatory) and GABA (inhibitory), has been hypothesized to be increased in ASD [Hussman, 2001; Rubenstein & Merzenich, 2003; Lam et al., 2006; Yizhar et al., 2011; Rosenberg et al., 2015], which may lead to cortical hyper-reactivity and behavioral hypersensitivity in ASD [Markram & Markram, 2010]. This balance controls the endogenous neural noise level, which might be either decreased [Davis & Plaisted-Grant, 2015] or increased [Simmons et al., 2007, 2009] in ASD. Several findings suggest an increased glutamate/GABA ratio in ASD, which could induce glutamate excitotoxicity and contribute to abnormal brain development [Bittigau & Ikonomidou, 1997; Lam et al., 2006; El-Ansary & Al-Ayadhi, 2014]. One of the potential causes for an increased ratio in ASD would be a reduced level of glutamate acid decarboxylase, which is the enzyme converting glutamate into GABA [Fatemi et al., 2002]. A decreased GABAergic action in ASD could also be induced by a reduced number of GABA receptors in the frontal cortex [Fatemi et al., 2014], by genetic variations in GABA receptor genes [Shao et al., 2003; Ma et al., 2005; Piton et al., 2013], by disrupted inhibitory action due to altered minicolumn organization [Casanova et al., 2002, 2003] or by immature GABA neurons [Ben-Ari et al., 2012]. Interestingly, promoting GABA neuron maturation would reduce symptoms in children with ASD [Lemonnier & Ben-Ari, 2010; Du et al., 2015; Lemonnier et al., 2017]. Furthermore, increasing GABAergic inhibition in mice models of ASD decreased autistic-like symptoms [Han et

al., 2014]. Finally, computational models simulating the behavioral consequences of a GABA diminution account for many of the autistic symptoms [Rosenberg et al., 2015].

Currently, the only non-invasive technique offering the opportunity to measure direct, *in vivo* GABA concentrations is GABA-edited magnetic resonance spectroscopy (MRS) [Edden et al., 2009; Puts et al., 2011, 2016; Puts & Edden, 2012]. MRS studies in children with ASD have shown that GABA concentrations were either decreased or unchanged, depending on the brain region. In children with ASD, GABA levels were reduced in the prefrontal cortex [Harada et al., 2011], in auditory regions [Gaetz et al., 2014], in sensorimotor regions [Gaetz et al., 2014; Puts et al., 2016], in the cerebellum and in the anterior cingulate cortex [Ito et al., 2017], and were unchanged in other regions, such as the occipital cortex [Gaetz et al., 2014]. GABA-edited MRS studies performed in adults with ASD showed no group difference in GABA levels between NT and ASD in the occipital lobe [Robertson et al., 2016] nor in the superior temporal sulcus [Kirkovski et al., 2018]. In the sensorimotor cortex, GABA levels are reduced in children with ASD [Puts et al., 2016], yet it is not clear whether adults with ASD also show this reduction [Robertson et al., 2016]. As ASD is a neurodevelopmental disorder, whether the GABA reduction remains across development until adulthood might be questioned.

GABA concentration in the sensorimotor cortex has been correlated to tactile detection thresholds in children with ASD [Puts et al., 2016]. Note that measurements of tactile detection thresholds do not consistently show hypersensitivity in ASD [Mikkelsen et al., 2016], despite self-reported tactile hypersensitivity in ASD [Takayama et al., 2014; Tavassoli et al., 2014, 2017; Ward et al., 2017]. It is therefore worth investigating the correlations between self-reported measures of tactile hypersensitivity and GABA concentration. Tactile hypersensitivity can be assessed using the Glasgow Sensory Questionnaire (GSQ) [Robertson & Simmons, 2013; Sapey-Triomphe et al., 2018], which measures the frequency of atypical sensory experiences in daily-life.

The main objective of the present study was to relate *in vivo* GABA concentrations in the sensorimotor cortex to tactile hypersensitivity in adults with ASD. Precisely, we aimed (1) at determining whether adults with ASD present with a reduction in GABA concentration in the sensorimotor cortex, as children with ASD do, (2) at investigating correlations between GABA level

and self-reported tactile hypersensitivity, (3) and at examining correlations between GABA concentration and sensory precision on tactile sensations. For these purposes, GABA concentration was measured in the sensorimotor cortices of NT and ASD adults, using edited MRS. Subjective individual evaluations of tactile hypersensitivity were obtained with the GSQ score of tactile hypersensitivity. Objective individual evaluations of tactile hypersensitivity included measurements of tactile detection thresholds and of their precision (as reflected by intra-individual variations in the measurements) during a staircase procedure, as well as tactile frequency discrimination thresholds. We expected increased sensitivity and precision to be associated with higher GABA concentrations, as previous findings showed that lower tactile thresholds were associated with higher GABA concentrations [Puts et al., 2011, 2016] and because increased GABAergic inhibition should sharpen the neural response [Isaacson & Scanziani, 2011]. More precisely, we hypothesized that GABA levels should be negatively correlated with the detection thresholds and frequency discrimination thresholds. GABA levels should be positively correlated with the precision of measurements of detection thresholds and with the self-reported hypersensitivity score.

METHODS

Participants

Twenty-one NT adults and 20 adults with ASD participated in the MRS study, but two NT and two ASD participants were discarded from the analyses due to movements during the MRS acquisition (leading to fully distorted spectra during the MRS acquisition that cannot be corrected by preprocessing, and therefore leading to poor averaging). The remaining groups of 19 NT and 18 ASD participants were matched in age, gender ratio, education level and intellectual quotient. Demographic data are summarized in Table 1. Inclusion criteria were being between 18 and 50 years old, having had an IQ test (WAIS IV) less than 4 years ago and being affiliated to the French social security system. Exclusion criteria were having an IQ below 70, presenting with any contraindication to MRI, having received a diagnosis of psychiatric or neurological disorder (other than ASD for ASD participants), and being under current use of neuropsychiatric medication. ASD participants met criteria for ASD

according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [American Psychiatric Association 2013] and all scored above threshold at the ADOS (Autism Diagnosis Observation Schedule [Lord et al., 1989]). They were diagnosed by experienced psychiatrists specialized in ASD, in the regional Resources Centre for Autism. Handedness was measured using the Edinburgh handedness inventory. All participants completed the Autism-spectrum Quotient [Baron-Cohen et al., 2001].

Participants gave their written informed consent beforehand. Approval was obtained from the local ethics committee (South East IV Committee for the Protection of Persons).

Please, insert Table 1 here

Self-reported sensitivity: Glasgow Sensory Questionnaire

Every participant completed the French version of the Glasgow Sensory Questionnaire (GSQ) [Robertson and Simmons, 2013; Sapey-Triomphe et al., 2018]. The GSQ is a self-administered questionnaire assessing the frequency of atypical sensory processing events in adults. The GSQ consists of 42 questions and investigates sensory sensitivity in seven sensory modalities, including the tactile modality. In each of the seven sensory modality, three questions assess hypersensitivity and three questions assess hyposensitivity. The GSQ evaluates how frequently some sensory events are experienced by the participant (e.g., "*Do you cut the labels out of your clothes?*"). Participants answer using the scale: *never* (0 point), *rarely* (1 point), *sometimes* (2 points), *often* (3 points) or *always* (4 points). The subscale assessing total hypersensitivity can range from 0 to 84, and the subscale assessing tactile hypersensitivity can range from 0 to 12. High GSQ scores of hypersensitivity correspond to frequent experiences of hypersensitivity.

Tactile stimuli

Tactile stimulations were delivered on the internal face of the third phalanx of the left second finger, using a piezo-electric tactile stimulator (mPTS, Dancer Design, http://www.dancerdesign.co.uk). The stimulator was housed in a machined ceramic case 67mm long x 20mm wide x 5mm thick. The case was placed in a hand-support. The vibrating surface was a 6mm

diameter flat aluminum probe. The third phalanx of the left second finger was resting on the probe, and the hand was immobilized. Stimulations were composed of 5 ms-long boxcar pulses, repeated at a given frequency. Tactile stimuli were generated using Matlab 2013b and were displayed using Presentation ® software (Version 17.1, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

Dynamic tactile detection thresholds

Dynamic detection thresholds were measured with tactile stimulations at frequencies of 30 Hz and 200 Hz, outside of the MR scanner. We chose to use these two frequencies based on a study showing hypersensitivity at 200 Hz but not at 30 Hz in adult participants with ASD [Blakemore et al., 2006]. The tactile detection threshold was estimated in each subject using a staircase procedure (method of limits). The amplitude of the tactile stimulations started at zero and progressively increased. Participants had to click on the left button of the computer mouse using their right hand to indicate when they could detect the sensation. After the participant's response indicating the detection of the sensation, the amplitude kept on increasing by 50%, before starting to decrease. The amplitude progressively decreased until zero, and participants were asked to click using their right hand to indicate when they could not detect the sensation any more. This procedure (i.e. progressive increase and decrease) was repeated four times successively. Every 1000 ms, the amplitude of the stimulation increased/decreased by steps of 28.75 mV in the 30 Hz condition and by steps of 14.37 mV in the 200Hz condition (same difference in steps between the 30 Hz and 200 Hz conditions, as in a former study [Blakemore et al., 2006]). The order of measurement of the tactile detection thresholds (30 Hz and 200 Hz) was counterbalanced between participants. We assessed both the detection of the sensation (i.e. during the increase) and the disappearance of the sensation (i.e. during the decrease) to collect a maximum number of measurements to estimate the precision of the response. We measured both the mean detection threshold (average of the eight measurements) and the intra-individual variability in detection threshold measurement (i.e. standard deviation of the eight measurements of the detection threshold).

Tactile frequency discrimination task

In this task, the amplitude of tactile stimulations was adjusted for each participant (as three times the threshold measured at 30Hz). Participants performed a tactile frequency discrimination task with frequencies delivered on average at 30Hz on their left second finger (same position as in the detection threshold measurement). Two 500 ms tactile stimulations were delivered successively, separated by a 2000 ms interval. A response screen showing plus and minus signs was displayed right after the second stimulation. Participants had to click on the left or right side of the computer mouse to indicate whether the second stimulation was higher (*plus* sign) or lower (*minus* sign) in frequency than the first one. The inter-trial interval lasted for 1800 ms (±300 ms). The side of the plus and minus signs was counterbalanced between participants. Participants used their right second or third finger to answer.

The first stimulation was always delivered at 30 Hz, while the second stimulation was 1 to 8 Hz higher or lower than the first stimulation, therefore ranging from 22 Hz to 38 Hz. The tactile discrimination task consisted of 64 trials. Each pair of frequencies (30 Hz – 22 Hz, …, 30 Hz – 38 Hz) was presented four times.

Prior to this task, participants performed a short training session including 16 trials providing feedback after each trial (“correct” or “incorrect”).

In the frequency discrimination task, we calculated the mean level of accuracy, together with the minimum difference between the two frequencies (1 to 8 Hz) to accurately discriminate the frequencies in 75% of the trials. To estimate the frequency discrimination threshold, we fitted psychometric functions on the percentage of response “2^{nd} stimulus higher” as a function of the intensity (-8 Hz to +8 Hz of difference between the first and second stimuli). We measured the intercepts of the fitted curve at 25% and 75% of response “higher”. The threshold was calculated as the mean of the absolute value of these two intercepts.

MRI and MRS acquisitions

MRI and MRS data were acquired on a 3 Tesla Siemens Magnetom Prisma scanner, with a 64-channel head-neck coil.

MRI acquisition

A 3D whole brain T1-weighted anatomical image was obtained for each subject, using a MPRAGE sequence (TR = 3500 ms; echo time TE = 3.42 ms; FOV = 224 mm; 192 slices; voxel size = 0.9 x 0.9 x 0.9 mm^3).

MRS acquisition

Single voxel MR spectra were acquired from two 3 x 3 x 3 cm^3 volumes of interest located in the right sensorimotor cortex (s-VOI) and in the median occipital cortex, as a control region (o-VOI) (Figure 1). The s-VOI was centered on the hand region of the right postcentral gyrus and was parallel to the cortical surface. Because of the VOI size and the postcentral gyrus shape, the s-VOI overlapped some regions belonging to the precentral gyrus. The o-VOI was set in the occipital lobe, in the median region, dorsal to the cerebellum, avoiding the venous sinus. Its posterior limit was the superior sagittal sinus.

Prior to the MRS acquisition, shims were adjusted using the automatic GRE shim sequence, and we ensured that shimming for the full width at maximum of water signal was less than 16 Hz. We ran a short quality-check MRS acquisition (4 excitations) beforehand in order to ensure that the water signal was correctly suppressed and that the lipids did not contaminate the spectrum.

MR spectra were collected using the MEGA-PRESS spectral editing sequence [Mescher et al., 1998] that combines two MRS acquisitions, each ones with a different frequency-selective pulse at 1.9 ppm for ON-scans and 7.5 ppm for OFF-scans (i.e. symmetrically disposed about the water frequency), used to refocus differently the J evolution of the GABA triplet signal at 3.02 ppm. The TE was set at 68 ms in order to maximize the phase difference of the two GABA signals at this resonance before their subtraction. Other parameters of the sequence were: TR = 2000 ms, 160 pairs of interleaved spectra, 2048 data points, 5 kHz spectral width and center frequency set to the peak position of creatine at -1.7 ppm relative to the water, 21.5 ms Gaussian editing pulses (55 Hz) applied in alternating spectral lines. Note that even if the bandwidth of the editing pulses was minimized, none of the existing methods such as, for example, longer TE or symmetric editing with an OFF-scans acquired with the editing pulses centered at 1.5 ppm were used to reduce a signal contamination from

macromolecules. Consequently, co-editing of macromolecules is expected. In this article, GABA+ therefore corresponds to GABA + macromolecules [Edden et al., 2012].

An additional localized unsuppressed water scan was acquired in order to have a fully relaxed water measurement, with TE = 30 ms, TR = 10 000 ms and four averages. The overall acquisition time per VOI was around 14 minutes.

Please, insert Figure 1 here

MRS data analysis

Data preprocessing

MRS original data (*.dat*) were preprocessed using the automatic pipeline *run_megapressproc_auto.m* available in the FID-A package [Simpson et al., 2017]. This preprocessing pipeline includes seven steps: (1) multi-coil combination, (2) removing motion corrupted averages, with a criteria of more than 3 standard deviations from the mean, (3) realignment of averages after frequency and phase drift corrections, (4) removing points before and after TE, (5) zero-order phase correction using the creatine peak, (6) alignment of the edit-ON and edit-OFF spectra, (7) subtraction of edit-ON and edit-OFF spectra. Each individual fit was carefully inspected. As previously mentioned, the fits of two NT and two ASD subjects were not satisfying, suggesting lipid contaminations, probably due to movements during the MRS acquisition. These four participants were discarded from the analyses. On average, eleven pairs of scans were removed after step 2 (22 ±14 scans in the NT group, 22 ±12 scans in the ASD group).

GABA+ quantification

The preprocessed data were saved as Matlab structures to be processed using Gannet 2.0 [Edden et al., 2014]. As the data were already preprocessed using FID-A, Gannet 2.0 was modified so as to remove the preprocessing steps. The unsuppressed water scan was used as water reference. GABA+ concentrations are given in institutional units (*iu*). GABA+ concentrations were corrected for tissue fractions using the segmentation and quantification steps implemented in Gannet 2.0 [Harris et al., 2015]. These steps included tissue segmentation in SPM (SPM8, Wellcome Trust Center for Neuroimaging) to estimate the fractions in grey matter f_{GM}, white matter f_{WM} and cerebrospinal fluid

f_{CSF}. We used the latest tissue correction with $\alpha = 0.5$ [Harris et al., 2015] : $[GABA]_{\alpha corr} = [GABA] / (f_{GM} + \alpha.f_{WM})$.

Statistical analyses

We used parametric tests as all the variables of interest followed a normal distribution (assessed using Kolmogorov-Smirnov test). In addition, the variances of the measures of interest were not statistically different between groups (assessed using Fisher test), except for GABA+ concentration in the s-VOI, where there was a tendency toward a difference of variance ($p = .047$, ratio of variance = 2.7). GABA+ concentrations, GSQ scores, AQ scores and frequency discrimination thresholds in the tactile discrimination task were compared between groups using Student t-tests. A two-way ANOVA with the factors group (NT and ASD) and frequency (30 Hz and 200 Hz) was performed on the mean tactile detection thresholds and on the intra-individual variation of the tactile detection measurements. Within each group, correlation tests between GABA+ concentrations and behavioral measures (i.e. GSQ scores, tactile detection thresholds, intra-individual standard deviation and frequency discrimination thresholds) were performed using Pearson correlation tests. All statistical analyses were performed using R (version 2.15.3, http://www.r-project.org/). The threshold for statistical significance was set at $p < .05$.

RESULTS

MRS measures

Quality checks

In the s-VOI and o-VOI, tissue fractions did not differ between groups (Table 2). GABA+ fit errors did not differ either between groups (Table 2). Additionally, we visually ensured that every fit was close to the expected fit aspect. The total frequency drift [Near et al., 2015] is reported in Table 2 and did not differ between groups.

Please, insert Table 2 here

GABA+ concentration

In the s-VOI, GABA+ concentrations were 2.85 (±0.86) *iu* in the NT group and 2.37 (±0.52) *iu* in the ASD group (Figure 2). In the control region, the o-VOI, GABA+ concentrations were 2.22 (±0.51) *iu* in the NT group and 2.35 (±0.67) *iu* in the ASD group.

The ANOVA investigating the effect of group (NT and ASD) and VOI (s-VOI and o-VOI) on the concentration of GABA+ revealed a significant effect of the factor VOI ($F(1,34) = 4.49$, $p < .05$) and an interaction between group and VOI ($F(1,34) = 4.92$, $p < .05$). Post-hoc t-tests showed a significant group difference in the s-VOI (t (30) = 2.1, $p < .05$) but not in the o-VOI. In the s-VOI, GABA+ concentration was 17% lower in the ASD group compared to the NT group.

Please, insert Figure 2 here

Behavioral measures

Self-reported hypersensitivity

The GSQ score of total hypersensitivity (i.e. across the seven sensory modalities) was 20.8 (±9.4) in the NT group and 39.3 (±13.7) in the ASD group (Figure 3.A). These scores significantly differed between groups (t (30) = 4.5, $p < .0001$). The GSQ score of tactile hypersensitivity was 3.4 (±2.3) in NT and 6.0 (±2.9) in ASD, and this score was higher in ASD than in NT (t (31) = 2.5, $p = .02$) (Figure 3.A).

Consistently with previous studies using the GSQ [Robertson and Simmons, 2013; Sapey-Triomphe et al., 2018], the GSQ total score of hypersensitivity was positively correlated with the AQ (2 groups: $r = .72$, $p < .0001$, NT group: $r = .33$, $p > .1$, ASD group: $r = .56$, $p = .01$).

Tactile detection threshold

At 30 Hz, the average detection threshold was 250 mV (±103) in the NT group and 189 mV (±78) in the ASD group (Figure 3.B). At 200 Hz, the average detection threshold was 153 mV (±65) in NT and 125 mV (±61) in ASD. The ANOVA revealed a group effect (F (1,42) = 23.6, $p < .0001$) and a frequency effect (F (1,42) = 75.8, $p < .0001$), and a trend toward an interaction between group and frequency (F (1,42) = 3.2, $p = .08$). Pairwise t-test revealed a lower threshold at 200 Hz than at 30 Hz in the NT group (t (18) = 6.4, $p < .0001$) and in the ASD group (t (17) = 5.3, $p < .0001$). The group

effect corresponded to ASD participants having lower thresholds than NT, with a trend toward lower thresholds at 30 Hz (t (34) = 1.9, p = .06).

At 30 Hz and 200 Hz, the intra-individual standard deviations on threshold measurements were respectively 0.07 (±0.04) and 0.04 (±0.02) in the NT group, and 0.06 (±0.03) and 0.04 (±0.02) in the ASD group (Figure 3.B). One participant with ASD was discarded from the analysis on intra-individual standard deviations, as he appeared to be an outlier (away from the group mean by more than three standard deviations). An ANOVA of the factors group and frequency on intra-individual standard deviations only revealed a frequency effect (F (1,34) = 18.9, p < .001). Pairwise t-tests revealed lower intra-individual standard deviations at 200 Hz than at 30 Hz in the NT group (t (18) = 3.4, p < .01) and in the ASD group (t (16) = 2.7, p = .02).

Please, insert Figure 3 here

Tactile frequency discrimination task

The mean percentage of correct answers was 84.6% (±10.0) in the NT group and 76.7% (±13.8) in the ASD group (no significant group difference). Psychometric curves were fitted on individual data across the range of frequencies used (Figure 3.C). The fit was poor in two of the ASD subjects who did not reach the 75% criteria, and who were therefore considered as outliers. The mean tactile frequency threshold was 3.3 Hz (±2.7) in the NT group and 4.3 Hz (±3.2) in the ASD group (no significant group difference).

Correlations between GABA+ concentrations and behavioral measures

Correlations with self-reported hypersensitivity

In the NT group, no significant correlations were found between GABA+ concentrations and GSQ scores. In the ASD group, GABA+ concentrations in the s-VOI were positively correlated with the GSQ scores of total hypersensitivity (r = .56, p = .01) and of tactile hypersensitivity (r = .50, p = .03) (Figure 4). GABA+ concentrations in the o-VOI were not correlated with the GSQ scores in any group.

Please, insert Figure 4 here

Correlations with tactile detection threshold

The average dynamic tactile detection thresholds (at 30 Hz or 200 Hz) did not correlate with GABA+ concentrations in any group.

The intra-individual standard deviations during threshold measurements at 30 Hz were negatively correlated with GABA+ concentrations in the s-VOI in the two groups (r = -.40, p = .01), in the NT group (r = -.47, p = .04) and in the ASD group (r = -.59, p = .01) (Figure 5). Note that in the NT group only, the intra-individual standard deviations at 30 Hz were also correlated with GABA+ concentrations measured in the o-VOI (r = -.62, p < .01). The intra-individual standard deviations at 200 Hz did not show any significant correlations in any group.

Please, insert Figure 5 here

Correlations with accuracy in the frequency discrimination task

The percentages of correct answers in the tactile frequency discrimination task were not significantly correlated with GABA+ concentrations in any group.

DISCUSSION

Using MRS, we aimed at investigating the relationships between *in vivo* GABA+ concentrations and tactile hypersensitivity in ASD. As compared to NT adults, lower GABA+ concentrations were found in adults with ASD in the sensorimotor cortex, but not in the occipital cortex. Within the ASD group only, higher GABA+ concentrations in the sensorimotor cortex were associated with higher self-reported tactile hypersensitivity. In both groups, higher GABA+ levels were associated with higher tactile precision (i.e. lower intra-individual variation during the tactile detection threshold measurement). Finally, GABA+ concentrations did not correlate with the dynamic tactile detection thresholds or with the tactile frequency discrimination thresholds in any group.

Decreased GABA+ concentration in the sensorimotor cortex of adults with ASD

GABA+ concentration in the sensorimotor cortex was lower in adults with ASD than in NT. Decreased GABA concentration, as measured using MRS, may reflect decreased inhibition by

GABAergic interneurons in the brain [Puts et al., 2011]. GABA+ concentration is decreased by 8% in children with ASD compared to NT children [Puts et al., 2016], while we found a decrease by 17% in adults with ASD compared to NT adults. In ASD, the lower concentrations of GABA+ found in both children [Puts et al., 2016] and adults (present study) suggest that this reduction remains across development. Longitudinal MRS studies conducted in individuals with ASD should confirm these results. An evolution in GABA concentration in the somatosensory cortex across development could be associated with changes in tactile hypersensitivity across life. At the behavioral level, it remains unclear whether and how sensory hypersensitivity would evolve in ASD from childhood to adulthood [Ben-Sasson et al., 2009; McCormick et al., 2016].

In the present study, GABA+ concentrations in the occipital lobe did not differ between NT and ASD adults. Similar results were found in adults with ASD [Robertson et al., 2016] and in children with ASD [Gaetz et al., 2014; Puts et al., 2016]. These findings might sound surprising as visual sensitivity is atypical in ASD [Simmons et al., 2009]. Interestingly, in a binocular rivalry task, GABA+ concentration in the occipital region was positively correlated with the proportion of perceptual suppression in NT adults, but not in adults with ASD [Robertson et al., 2016]. The authors concluded on a disruption in inhibitory signaling in the occipital lobe of adults with ASD, despite normal GABA levels [Robertson et al., 2016]. These results suggest that GABA reduction in ASD might be region-specific, and that the links between GABA level and sensitivity might show a sensory modality specificity.

Atypical self-reported hypersensitivity but typical objective sensitivity in ASD

Consistently with previous studies using the GSQ [Takayama et al., 2014; Ward et al., 2017], adults with ASD reported more frequent tactile hypersensitivity experiences than NT adults. Given this higher self-reported tactile hypersensitivity, we could have expected behavioral measurements of tactile sensitivity to show lower detection thresholds or lower frequency discrimination thresholds in the ASD group. However, there was just a non-significant trend toward lower detection thresholds in the ASD group at 30 Hz, and the two groups presented with the same abilities to discriminate tactile frequencies. Note that, in the frequency discrimination task, the participants might have used intensity

rather than frequency to perform the task, as higher frequencies are perceived as stronger than lower frequencies [LaMotte & Mountcastle, 1975]. The dynamic tactile detection thresholds did not differ either between groups, consistently with previous studies [Mikkelsen et al., 2016]. One study found lower tactile detection thresholds at 200 Hz in a group of ASD participants (n = 10) compared to NT [Blakemore et al., 2006], whereas, in the present study, the ASD group did not differ from NT at 200 Hz. This suggests that the activation thresholds of both Pacinian corpuscles (activated at 200 Hz) and Meissner corpuscles (activated at 30 Hz) would not be atypical in ASD. The fact that people with ASD experience tactile hypersensitivity in their daily life, despite typical activation thresholds of tactile receptors, suggests that their hypersensitivity might be context-dependent and might be influenced by top-down processes. It also suggests that hyper-responsiveness to tactile stimuli would not be systematically associated with a more "accurate" or sensitive system to process tactile information (i.e. better or enhanced discrimination of tactile inputs). Indeed, the enhanced brain responses to tactile stimulations in the somatosensory cortex of children or adolescents with ASD [Green et al., 2015; Kaiser et al., 2016] mostly suggest a hyper-responsiveness to tactile stimuli (as measured by questionnaires), rather than sharper mechanisms to process tactile information.

Interestingly, a recent study showed increased skin conductance response to tactile stimuli in adults with ASD compared to NT, despite no differences in tactile detection thresholds [Fukuyama et al., 2017]. The skin conductance response was positively correlated with sensory sensitivity in daily living, as well as with social difficulties [Fukuyama et al., 2017], as measured by the Social Responsiveness Scale [Constantino & Gruber, 2012]. Tactile hypersensitivity could therefore enhance the difficulties encountered by people with ASD during social interactions [Lundqvist 2015; Mikkelsen et al., 2016].

GABA concentration is correlated to the precision of tactile sensations in NT and ASD

Tactile precision, assessed during the tactile detection threshold measurements, was positively correlated with GABA+ concentration in both groups (i.e., negative correlation between the intra-individual variability and GABA+ levels). In other words, the higher the GABA concentration, the more precise the tactile sensation. Increased GABAergic inhibition should reduce the amount of

neuronal noise and therefore sharpen the cortical response [Isaacson & Scanziani, 2011]. Indeed, lateral inhibition would sharpen the tuning of cortical neurons, which would be more sensitive and selective to certain stimulations. Increased GABAergic inhibition would lead to an increased precision at the neural level, which could be measured at the behavioral level. This is consistent with the correlation found in the present study, but such a relationship would also predict lower precision in the ASD group given their lower GABA+ levels, which was not observed. Hence, other mechanisms might be at play in ASD to explain the absence of group difference on tactile precision.

Besides, GABA+ concentration was correlated with the intra-individual standard deviation of the tactile threshold at 30 Hz but not at 200 Hz. The absence of such a correlation at 200 Hz either might be explained by a reduced dispersal of values between participants, preventing from revealing significant correlations (standard deviation twice lower at 200 Hz than at 30 Hz) or might indicate that GABA inhibits differently the afferent fibers of Pacinian and Meissner corpuscles.

Grounded on previous results from Puts and colleagues [Puts et al., 2011], we initially hypothesized that GABA+ concentration in the s-VOI would be negatively correlated with the tactile frequency discrimination thresholds in NT adult participants. In our study the absence of such correlations may be due to differences in the methods used to measure thresholds (e.g. different duration or intensity of the stimulations) or to differences in the populations tested (e.g. differences in age range).

GABA+ concentration is correlated to self-reported tactile hypersensitivity in ASD only

Increased GABA+ concentrations should sharpen the cortical signal [Isaacson & Scanziani, 2011], which could be associated with a higher sensitivity. This relationship would be consistent with the results showing a positive correlation between the self-reported tactile hypersensitivity score and GABA+ concentration in the sensorimotor cortex of ASD participants. However, this relationship would not explain the fact that the ASD group show higher tactile hypersensitivity than the NT group.

In ASD, altered GABA-mediated tactile functions might reflect a reduced ability of the cortex to filter or habituate to sensory information [Puts et al., 2016]. In addition, a recent study in a mouse model of ASD, suggested that a downregulation of presynaptic GABAergic inhibition in peripheral

sensory neurons led to tactile hypersensitivity. It suggests that a decreased GABA inhibition in the peripheral nervous system can also contribute to hypersensitivity in ASD [Orefice et al., 2016].

Contrary to behavioral measurements objectively assessing the precision, the GSQ provides a subjective measure of tactile hypersensitivity. The GSQ assesses hypersensitivity in a daily-life context, it therefore estimates sensitivity in multi-sensory contexts where sensory inputs might be unexpected. As the correlation between GABA+ levels and self-reported tactile hypersensitivity is specific to the ASD group (whereas correlations with objective measures were found in both groups), we can hypothesize that altered GABA modulation might contribute to increased sensory hyper-reactivity in multisensory and/or unexpected contexts in ASD. Indeed, individuals with ASD would have more difficulties in dealing with unpredictable sensations and in adjusting the precision of incoming sensory inputs compared to predictive ones [Pellicano & Burr, 2012; Lawson et al., 2014; Van de Cruys et al., 2014, 2017]. Interestingly, tactile sensations can be attenuated by top-down predictions [Blakemore et al., 2000], but these predictions might be too loose or suboptimal in ASD according to the recent Bayesian hypotheses of ASD [Brock, 2012; Pellicano & Burr, 2012; Lawson et al., 2014; Van de Cruys et al., 2014, 2017; Palmer et al., 2017]. Following these hypotheses, tactile sensations would be more often perceived as being unpredicted in ASD, leading to sensory hypersensitivity. The weight of predictions (relatively to sensory information) has been hypothesized to be modulated by GABA [Lawson et al., 2014; Rosenberg et al., 2015]. Hence, these results highlight the potential role of GABA in attenuating tactile sensations depending on their predictability.

GABA levels do not account entirely for tactile hypersensitivity in ASD

Interestingly, GABA+ levels were reduced in the sensorimotor region of ASD participants compared to NT, but the two groups did not differ in the dynamic detection threshold nor in the frequency discrimination threshold, and these measurements were not correlated with GABA levels. Conversely, some participants with ASD presented with GABA levels in the typical range, but reported frequent sensations of tactile hypersensitivity (see Figure 3). It therefore suggests that the concentration of GABA only, as measured with MRS, cannot account entirely for the tactile hypersensitivity reported in ASD. Alternative mechanisms at play may include other abnormalities of

the GABAergic system in ASD (such as, the reduced number of GABA receptors [Fatemi et al., 2014]) or other neurotransmitters (such as, increased glutamate levels due to reduced level of glutamate acid decarboxylase [Fatemi et al., 2002]).

Limitations

One of the limitations of MRS studies is that measurements are performed in large brain regions (e.g., in our study, the volume of interest centered on the somatosensory cortex overlapped parts of the precentral gyrus and of the inferior parietal gyrus). It also remains difficult to draw a direct link between edited MRS measurements and synaptic inhibition. In addition, we cannot exclude a contamination of the edited GABA signal with co-edited macromolecules [Henry et al., 2001; Edden et al., 2012], whose concentrations could differ between the two studied populations.

Besides, the present study has a relatively limited number of participants (18 in the ASD group and 19 in the NT group), but note that the ASD group appeared to be relatively homogeneous (e.g. Figure 5.A). Finally, we correlated GABA+ concentrations with five behavioral measurements, out of which three were significant. As we did not correct for multiple comparisons, there may be some false positives. The correlation between GABA+ levels and the GSQ score of tactile hypersensitivity within the ASD group would not survive correction for multiple comparison (i.e., with $p < .01$). Yet, interestingly, this correlation with the GSQ score of tactile hypersensitivity in ASD was specific to the sensorimotor cortex (i.e., no correlation with GABA+ levels in the occipital region). Replication studies are needed to assess the strength of these results.

Conclusion

Our results highlight the key role of GABA in tactile sensitivity, and suggest that atypical GABAergic modulation contributes to tactile hypersensitivity in ASD. We relate our findings to the recent Bayesian theories, which suggest that atypical sensitivity in ASD would be due to suboptimal predictions about sensations. Within this framework, GABA has been hypothesized to modulate the relative weights of sensory inputs and predictions. The correlations between GABA and self-reported hypersensitivity in ASD would therefore be consistent with this hypothesis.

Abbreviations: AQ: Autism-Spectrum Quotient, ASD: Autism Spectrum Disorders, GABA+: Gamma-AminoButyric Acid + macromolecules, GSQ: Glasgow Sensory Questionnaire, MRS: Magnetic Resonance Spectroscopy, NT: Neurotypical, VOI: Volume Of Interest (s-VOI: sensorimotor VOI, o-VOI: occipital VOI).

REFERENCES

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders V, DSM Library.

Asperger, H. (1944). Die 'Autistischen Psychopathen' im Kindesalter. Archiv für Psychiatrie und Nervenkrankheim. 117, 76–136.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J Autism Dev Disord. 31:5–17.

Baum, S.H., Stevenson, R.A., Wallace, M.T. (2015). Behavioral, perceptual, and neural alterations in sensory and multisensory function in autism spectrum disorder. Prog Neurobiol. 134:140–160.

Ben-Ari, Y., Khalilov, I., Kahle, K.T., Cherubini, E. (2012). The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. Neurosci Rev J Bringing Neurobiol Neurol Psychiatry. 18:467–486.

Ben-Sasson, A., Hen, L., Fluss, R., Cermak, S.A., Engel-Yeger, B., Gal, E. (2009). A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. J Autism Dev Disord. 39:1–11.

Bittigau, P., Ikonomidou, C. (1997). Glutamate in neurologic diseases. J Child Neurol. 12:471–485.

Blakemore, S.J., Tavassoli, T., Calò, S., Thomas, R.M., Catmur, C., Frith, U., Haggard, P. (2006). Tactile sensitivity in Asperger syndrome. Brain Cogn. 61:5–13.

Blakemore, S.J., Wolpert, D., Frith, C. (2000). Why can't you tickle yourself? Neuroreport. 11:R11-16.

Brock, J. (2012). Alternative Bayesian accounts of autistic perception: comment on Pellicano and Burr. Trends Cogn Sci. 16:573–574.

Casanova, M.F., Buxhoeveden, D.P., Switala, A.E., Roy, E. (2002). Minicolumnar pathology in autism. Neurology. 58:428–432.

Casanova, M.F., Buxhoeveden, D.P., Gomez, J. (2003). Disruption in the Inhibitory Architecture of the Cell Minicolumn: Implications for Autisim. The Neuroscientist. 9:496–507.

Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K.A., Essick, G. (2008). Tactile Perception in Adults with Autism: a Multidimensional Psychophysical Study. J Autism Dev Disord. 38:127–137.

Constantino, J.N., Gruber, C.P. (2012). The Social Responsiveness Scale Manual, Second Edition (SRS-2).

Davis, G., Plaisted-Grant, K. (2015). Low endogenous neural noise in autism. Autism Int J Res Pract. 19:351–362.

DeLorey, T.M., Sahbaie, P., Hashemi, E., Li, W.-W., Salehi, A., Clark, J.D. (2011). Somatosensory and Sensorimotor Consequences Associated with the Heterozygous Disruption of the Autism Candidate Gene, Gabrb3. Behav Brain Res. 216:36–45.

Du, L., Shan, L., Wang, B., Li, H., Xu, Z., Staal, W.G., Jia, F. (2015). A Pilot Study on the Combination of Applied Behavior Analysis and Bumetanide Treatment for Children with Autism. J Child Adolesc Psychopharmacol. 25:585–588.

Edden, R.A.E., Muthukumaraswamy, S.D., Freeman, T.C.A., Singh, K.D. (2009). Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. J Neurosci Off J Soc Neurosci. 29:15721–15726.

Edden, R.A.E., Puts, N.A.J., Barker, P.B. (2012). Macromolecule-suppressed GABA-edited magnetic resonance spectroscopy at 3T. Magn Reson Med. 68:657–661.

Edden, R.A.E., Puts, N.A.J., Harris, A.D., Barker, P.B., Evans, C.J. (2014). Gannet: A batch-processing tool for the quantitative analysis of gamma-aminobutyric acid–edited MR spectroscopy spectra. J Magn Reson Imaging JMRI. 40:1445–1452.

El-Ansary, A., Al-Ayadhi, L. (2014). GABAergic/glutamatergic imbalance relative to excessive neuroinflammation in autism spectrum disorders. J Neuroinflammation. 11:189.

Fatemi, S.H., Halt, A.R., Stary, J.M., Kanodia, R., Schulz, S.C., Realmuto, G.R. (2002). Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. Biol Psychiatry. 52:805–810.

Fatemi, S.H., Reutiman, T.J., Folsom, T.D., Rustan, O.G., Rooney, R.J., Thuras, P.D. (2014). Downregulation of GABAA Receptor Protein Subunits α6, β2, δ, ε, γ2, θ, and ρ2 in Superior Frontal Cortex of Subjects with Autism. J Autism Dev Disord. 44:1833–1845.

Foxe, J.J., Molholm, S., Del Bene, V.A., Frey, H.-P., Russo, N.N., Blanco, D., Saint-Amour, D., Ross, L.A. (2015). Severe multisensory speech integration deficits in high-functioning school-aged children with Autism Spectrum Disorder (ASD) and their resolution during early adolescence. Cereb Cortex N Y N 1991. 25:298–312.

Frith, U. (1991). Autism and Asperger Syndrome. Cambridge University Press.

Fukuyama, H., Kumagaya, S.-I., Asada, K., Ayaya, S., Kato, M. (2017). Autonomic versus perceptual accounts for tactile hypersensitivity in autism spectrum disorder. Sci Rep. 7:8259.

Gaetz, W., Bloy, L., Wang, D.J., Port, R.G., Blaskey, L., Levy, S.E., Roberts, T.P.L. (2014). GABA estimation in the brains of children on the autism spectrum: measurement precision and regional cortical variation. NeuroImage. 86:1–9.

Green, S. A., Hernandez, L., Tottenham, N., Krasileva, K., Bookheimer, S. Y., & Dapretto, M. (2015). Neurobiology of Sensory Overresponsivity in Youth With Autism Spectrum Disorders. JAMA psychiatry, 72(8), 778–786.

Han, S., Tai, C., Jones, C.J., Scheuer, T., Catterall, W.A. (2014). Enhancement of inhibitory neurotransmission by GABAA receptors having α2,3-subunits ameliorates behavioral deficits in a mouse model of autism. Neuron. 81:1282–1289.

Harada, M., Taki, M.M., Nose, A., Kubo, H., Mori, K., Nishitani, H., Matsuda, T. (2011). Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 tesla instrument. J Autism Dev Disord. 41:447–454.

Harris, A.D., Puts, N.A.J., Edden, R.A.E. (2015). Tissue correction for GABA-edited MRS: Considerations of voxel composition, tissue segmentation, and tissue relaxations. J Magn Reson Imaging JMRI. 42:1431–1440.

Harris, A. D., Singer, H. S., Horska, A., Kline, T., Ryan, M., Edden, R. a. E., & Mahone, E. M. (2016). GABA and Glutamate in Children with Primary Complex Motor Stereotypies: An 1H-MRS Study at 7T. *AJNR. American journal of neuroradiology*, *37*(3), 552–557.

Henry, P.G., Dautry, C., Hantraye, P., Bloch, G. (2001). Brain GABA editing without macromolecule contamination. Magn Reson Med. 45:517–520.

Hussman, J.P. (2001). Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. J Autism Dev Disord. 31:247–248.

Isaacson, J.S., & Scanziani, M. (2011). How inhibition shapes cortical activity. Neuron, 72(2), 231–243.

Ito, H., Mori, K., Harada, M., Hisaoka, S., Toda, Y., Mori, T., Goji, A., Abe, Y., Miyazaki, M., Kagami, S. (2017). A Proton Magnetic Resonance Spectroscopic Study in Autism Spectrum Disorder Using a 3-Tesla Clinical Magnetic Resonance Imaging (MRI) System: The Anterior Cingulate Cortex and the Left Cerebellum. J Child Neurol. 883073817702981.

Kaiser, M. D., Yang, D. Y.-J., Voos, A. C., Bennett, R. H., Gordon, I., Pretzsch, C., et al. (2016). Brain Mechanisms for Processing Affective (and Nonaffective) Touch Are Atypical in Autism. Cerebral Cortex (New York, N.Y.: 1991), 26(6).

Kanner, L. (1943). Autistic disturbances of affective contact. Nervous Child:2, 3, 217–250.

Kern, J.K., Trivedi, M.H., Grannemann, B.D., Garver, C.R., Johnson, D.G., Andrews, A.A., Savla, J.S., Mehta, J.A., Schroeder, J.L. (2007). Sensory correlations in. Autism. 11:123–134.

Kirkovski, M., Suo, C., Enticott, P. G., Yücel, M., & Fitzgerald, P.B. (2018). Short communication: Sex-linked differences in gamma-aminobutyric acid (GABA) are related to social functioning in autism spectrum disorder. Psychiatry Research. Neuroimaging, 274, 19–22.

Lam, K.S.L., Aman, M.G., Arnold, L.E. (2006). Neurochemical correlates of autistic disorder: a review of the literature. Res Dev Disabil. 27:254–289.

LaMotte, R.H., & Mountcastle, V.B. (1975). Capacities of humans and monkeys to discriminate vibratory stimuli of different frequency and amplitude: a correlation between neural events and psychological measurements. Journal of Neurophysiology, 38(3), 539–559.

Lawson, R.P., Rees, G., Friston, K.J. (2014). An aberrant precision account of autism. Front Hum Neurosci. 8:302.

Lemonnier, E., Ben-Ari, Y. (2010). The diuretic bumetanide decreases autistic behaviour in five infants treated during 3 months with no side effects. Acta Paediatr Oslo Nor 1992. 99:1885–1888.

Lemonnier, E., Villeneuve, N., Sonie, S., Serret, S., Rosier, A., Roue, M., Brosset, P., Viellard, M., Bernoux, D., Rondeau, S., Thummler, S., Ravel, D., Ben-Ari, Y. (2017). Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders. Transl Psychiatry. 7:e1056.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., Schopler, E. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. J Autism Dev Disord. 19:185–212.

Lundqvist, L.-O. (2015). Hyper-responsiveness to touch mediates social dysfunction in adults with autism spectrum disorders. Res Autism Spectr Disord. 9:13–20.

Ma, D.Q., Whitehead, P.L., Menold, M.M., Martin, E.R., Ashley-Koch, A.E., Mei, H., Ritchie, M.D., DeLong, G.R., Abramson, R.K., Wright, H.H., Cuccaro, M.L., Hussman, J.P., Gilbert, J.R., Pericak-Vance, M.A. (2005). Identification of Significant Association and Gene-Gene Interaction of GABA Receptor Subunit Genes in Autism. Am J Hum Genet. 77:377–388.

Marco, E.J., Hinkley, L.B.N., Hill, S.S., Nagarajan, S.S. (2011). Sensory Processing in Autism: A Review of Neurophysiologic Findings: Pediatr Res. 69:48R-54R.

Markram, K., & Markram, H. (2010). The Intense World Theory – A Unifying Theory of the Neurobiology of Autism. Frontiers in Human Neuroscience, 4.

McCormick, C., Hepburn, S., Young, G.S., Rogers, S.J. (2016). Sensory symptoms in children with autism spectrum disorder, other developmental disorders and typical development: A longitudinal study. Autism Int J Res Pract. 20:572–579.

Mescher, M., Merkle, H., Kirsch, J., Garwood, M., Gruetter, R. (1998). Simultaneous in vivo spectral editing and water suppression. NMR Biomed. 11:266–272.

Mikkelsen, M., Wodka, E.L., Mostofsky, S.H., Puts, N.A.J. (2016). Autism spectrum disorder in the scope of tactile processing. Dev Cogn Neurosci.

Near, J., Edden, R., Evans, C.J., Paquin, R., Harris, A., Jezzard, P. (2015). Frequency and phase drift correction of magnetic resonance spectroscopy data by spectral registration in the time domain. Magn Reson Med. 73:44–50.

Orefice, L.L., Zimmerman, A.L., Chirila, A.M., Sleboda, S.J., Head, J.P., Ginty, D.D. (2016). Peripheral Mechanosensory Neuron Dysfunction Underlies Tactile and Behavioral Deficits in Mouse Models of ASDs. Cell. 166:299–313.

Palmer, C.J., Lawson, R.P., Hohwy, J. (2017). Bayesian approaches to autism: Towards volatility, action, and behavior. Psychol Bull. 143:521–542.

Pellicano, E., Burr, D. (2012). When the world becomes “too real”: a Bayesian explanation of autistic perception. Trends Cogn Sci. 16:504–510.

Piton, A., Jouan, L., Rochefort, D., Dobrzeniecka, S., Lachapelle, K., Dion, P.A., Gauthier, J., Rouleau, G.A. (2013). Analysis of the effects of rare variants on splicing identifies alterations in GABAA receptor genes in autism spectrum disorder individuals. Eur J Hum Genet. 21:749–756.

Puts, N.A.J., Edden, R.A.E. (2012). In vivo magnetic resonance spectroscopy of GABA: a methodological review. Prog Nucl Magn Reson Spectrosc. 60:29–41.

Puts, N.A.J., Edden, R.A.E., Evans, C.J., McGlone, F., McGonigle, D.J. (2011). Regionally Specific Human GABA Concentration Correlates with Tactile Discrimination Thresholds. J Neurosci. 31:16556–16560.

Puts, N.A.J., Wodka, E.L., Harris, A.D., Crocetti, D., Tommerdahl, M., Mostofsky, S.H., Edden, R.A.E. (2016). Reduced GABA and altered somatosensory function in children with autism spectrum disorder. Autism Res Off J Int Soc Autism Res.

Puts, N.A.J., Wodka, E.L., Tommerdahl, M., Mostofsky, S.H., Edden, R.A.E. (2014). Impaired tactile processing in children with autism spectrum disorder. J Neurophysiol. 111:1803–1811.

Robertson, A.E., Simmons, D.R.. (2013). The Relationship between Sensory Sensitivity and Autistic Traits in the General Population. J Autism Dev Disord. 43:775–784.

Robertson, C.E., Ratai, E.-M., Kanwisher, N. (2016). Reduced GABAergic Action in the Autistic Brain. Curr Biol CB. 26:80–85.

Rosenberg, A., Patterson, J.S., Angelaki, D.E. (2015). A computational perspective on autism. Proc Natl Acad Sci U S A. 112:9158–9165.

Rubenstein, J.L.R., Merzenich, M.M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav. 2:255–267.

Sapey-Triomphe, L.-A., Moulin, A., Sonié, S., Schmitz, C. (2018). The Glasgow Sensory Questionnaire: Validation of a French Language Version and Refinement of Sensory Profiles of People with High Autism-Spectrum Quotient. J Autism Dev Disord. 48:1549–1565.

Shao, Y., Cuccaro, M.L., Hauser, E.R., Raiford, K.L., Menold, M.M., Wolpert, C.M., Ravan, S.A., Elston, L., Decena, K., Donnelly, S.L., Abramson, R.K., Wright, H.H., DeLong, G.R., Gilbert, J.R., Pericak-Vance, M.A. (2003). Fine Mapping of Autistic Disorder to Chromosome 15q11-q13 by Use of Phenotypic Subtypes. Am J Hum Genet. 72:539–548.

Simmons, D.R., McKay, L., McAleer, P., Toal, E., Robertson, A., Pollick, F.E. (2007). Neural noise and autism spectrum disorders. Perception. 36:119–120.

Simmons, D.R., Robertson, A.E., McKay, L.S., Toal, E., McAleer, P., Pollick, F.E. (2009). Vision in autism spectrum disorders. Vision Res. 49:2705–2739.

Simpson, R., Devenyi, G.A., Jezzard, P., Hennessy, T.J., Near, J. (2017). Advanced processing and simulation of MRS data using the FID appliance (FID-A)-An open source, MATLAB-based toolkit. Magn Reson Med. 77:23–33.

Takayama, Y., Hashimoto, R., Tani, M., Kanai, C., Yamada, T., Watanabe, H., Ono, T., Kato, N., Iwanami, A. (2014). Standardization of the Japanese version of the Glasgow Sensory Questionnaire (GSQ). Res Autism Spectr Disord. 8:347–353.

Tavassoli, T., Auyeung, B., Murphy, L.C., Baron-Cohen, S., Chakrabarti, B. (2012). Variation in the autism candidate gene GABRB3 modulates tactile sensitivity in typically developing children. Mol Autism. 3:6.

Tavassoli, T., Bellesheim, K., Tommerdahl, M., Holden, J.M., Kolevzon, A., Buxbaum, J.D. (2016). Altered tactile processing in children with autism spectrum disorder. Autism Res Off J Int Soc Autism Res. 9:616–620.

Tavassoli, T., Miller, L.J., Schoen, S.A., Brout, J., Sullivan J., Baron-Cohen S. (2017). Sensory reactivity, empathizing and systemizing in autism spectrum conditions and sensory processing disorder. Dev Cogn Neurosci.

Tavassoli, T., Miller, L.J., Schoen, S.A., Nielsen, D.M., Baron-Cohen, S. (2014). Sensory over-responsivity in adults with autism spectrum conditions. Autism Int J Res Pract. 18:428–432.

Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., Wagemans, J. (2014). Precise minds in uncertain worlds: Predictive coding in autism. Psychol Rev. 121:649–675.

Van de Cruys, S., Van der Hallen, R., Wagemans, J. (2017). Disentangling signal and noise in autism spectrum disorder. Brain Cogn. 112:78–83.

Ward, J., Hoadley, C., Hughes, J.E.A., Smith, P., Allison, C., Baron-Cohen, S., Simner, J. (2017). Atypical sensory sensitivity as a shared feature between synaesthesia and autism. Sci Rep. 7:41155.

Wu, C., & Sun, D. (2015). GABA receptors in brain development, function, and injury. Metabolic brain disease, 30(2), 367–379.

Yizhar, O., Fenno, L.E., Prigge, M., Schneider, F., Davidson, T.J., O'Shea, D.J., Sohal, V.S., Goshen, I., Finkelstein, J., Paz J.T., Stehfest, K., Fudim, R., Ramakrishnan, C., Huguenard, J.R., Hegemann, P., Deisseroth, K. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature. 477:171–178.

Zachor, D.A., Ben-Itzchak, E. (2013). The Relationship Between Clinical Presentation and Unusual Sensory Interests in Autism Spectrum Disorders: A Preliminary Investigation. J Autism Dev Disord.

TABLES

	NT	ASD	*p*
Number	19	18	-
Males / Females	14 / 5	13 / 5	*ns*
Age (years)	33.2 (±8.4)	35.0 (±10.2)	*ns*
Educational level (years)	16.0 (±2.2)	15.5 (±2.5)	*ns*
WAIS IV	126.4 (±12.0)	124.6 (±20.1)	*ns*
AQ score	12.4 (±5.4)	35.0 (±7.0)	**

Table 1. Participant characteristics

Values correspond to the NT and ASD group means (± standard deviations). Educational level: number of years of formal education. AQ: Autism-spectrum Quotient.

p-values were obtained from Student t-tests between the two groups (*ns*: *not significant*, ** $p < .001$).

	NT	ASD	*p*
Sensorimotor volume of interest (s-VOI)			
Tissue fractions			
Grey matter	33% (±3)	31% (±4)	*ns*
White matter	58% (±5)	61% (±5)	*ns*
Cerebrospinal fluid	9% (±3)	8% (±3)	*ns*
GABA fit error	5.6 (±1.5)	6.4 (±2.7)	*ns*
Total frequency drift (Hz)	3.2 (±0.8)	3.6 (±1.6)	*ns*
Occipital volume of interest (o-VOI)			
Tissue fractions			
Grey matter	60% (±3)	60% (±2)	*ns*
White matter	32% (±3)	32% (±3)	*ns*
Cerebrospinal fluid	7% (±1)	7% (±2)	*ns*
GABA fit error	4.7 (±1.2)	4.8 (±1.2)	*ns*
Total frequency drift (Hz)	3.0 (±0.9)	3.8 (±1.8)	*ns*

Table 2. Parameters of the MRS measurements

Values correspond to the NT and ASD group means (± standard deviations). *p*-values were obtained from t-tests between the two groups and were all non-significant (*ns*).

FIGURE LEGENDS

Figure 1: MRS voxel locations and spectra from all participants

Location of the sensorimotor MRS voxel (s-VOI, top) and of the occipital MRS voxel (o-VOI, bottom), and individual spectra of the NT and ASD participants in the s-VOI (top) and in the o-VOI (bottom).

Figure 2: GABA+ concentration in the NT and ASD groups

GABA+ concentrations (in institutional units) in the sensorimotor volume of interest (s-VOI) and in the occipital volume of interest (o-VOI) in the NT group (blue) and in the ASD group (orange).

Error bars correspond to standard deviations. * $p < .05$ (Student t-test).

Figure 3: Behavioral measurements of tactile hypersensitivity

A. Results of the Glasgow Sensory Questionnaire, measuring self-reported total hypersensitivity (left) and tactile hypersensitivity (right) in the ASD group (orange) and NT group (blue). * $p < .05$, ** $p < .001$.

B. Results of the measurements of the dynamic tactile detection thresholds with vibrotactile stimulations at 30 Hz and 200 Hz: mean detection threshold (left) and intra-individual variation during the detection threshold measurement (right).

C. Results of the frequency discrimination task, with a standard frequency of 30 Hz, in a two-alternative forced choice task in the ASD group (left, orange) and NT group (right, blue).

Figure 4: GABA+ concentrations and self-reports of tactile hypersensitivity

Correlations between GABA+ concentrations in the sensorimotor volume of interest and self-reported tactile hypersensitivity GSQ scores in the ASD group (A) and in the NT group (B). High tactile hypersensitivity GSQ scores indicate frequent experiences of tactile hypersensitivity in daily-life. GABA+ concentrations are given in institutional units. The correlation was significant in the ASD group ($p < .05$, Pearson correlation test), but there was no correlation in the NT group.

Figure 5: GABA+ concentrations and precision during tactile threshold measurements

Correlations between GABA+ concentrations in the sensorimotor VOI and intra-individual standard deviations during threshold measurements at 30 Hz in the ASD group (A) and in the NT group (B). A low intra-individual standard deviation corresponds to a high precision in the measurement of tactile detection threshold. GABA+ concentrations are given in institutional units. These correlations were significant both in the ASD group and in the NT group ($p < .05$, Pearson correlation tests).

Figure 1 :

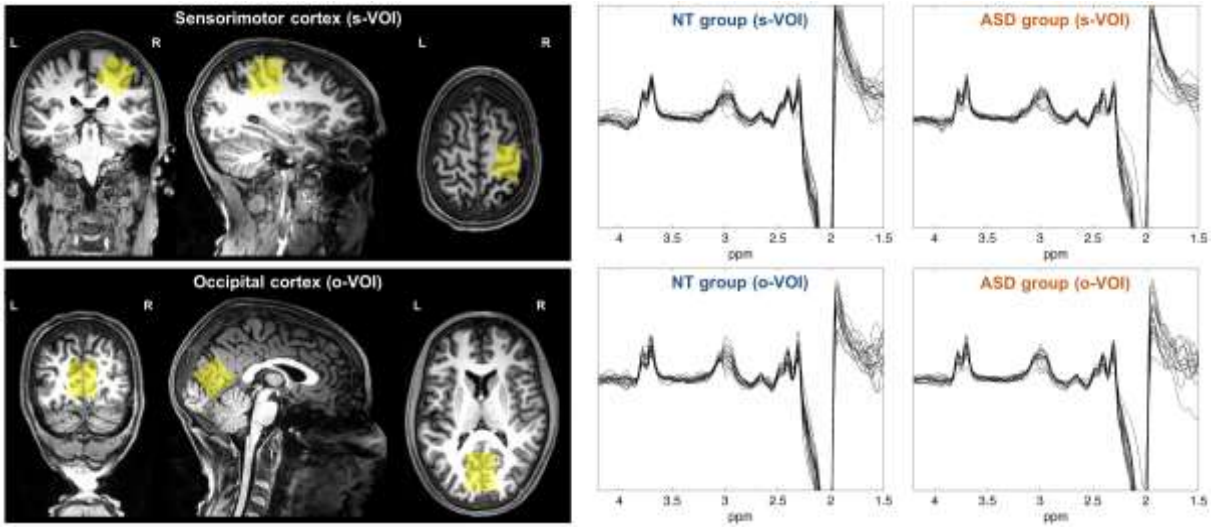

Figure 2 :

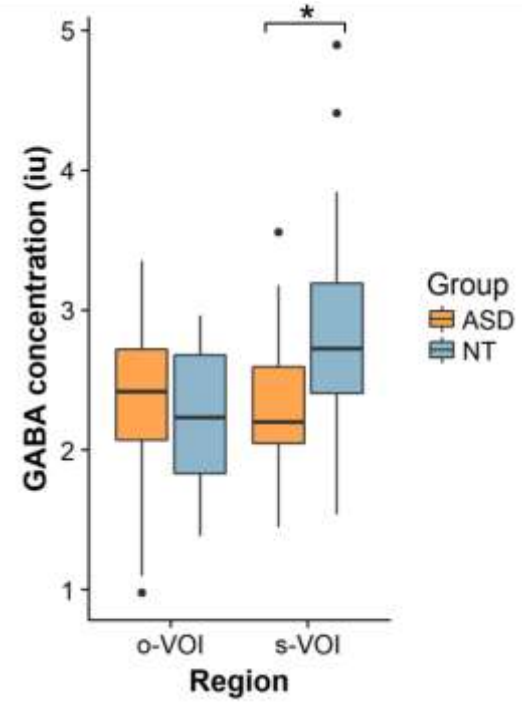

Figure 3 :

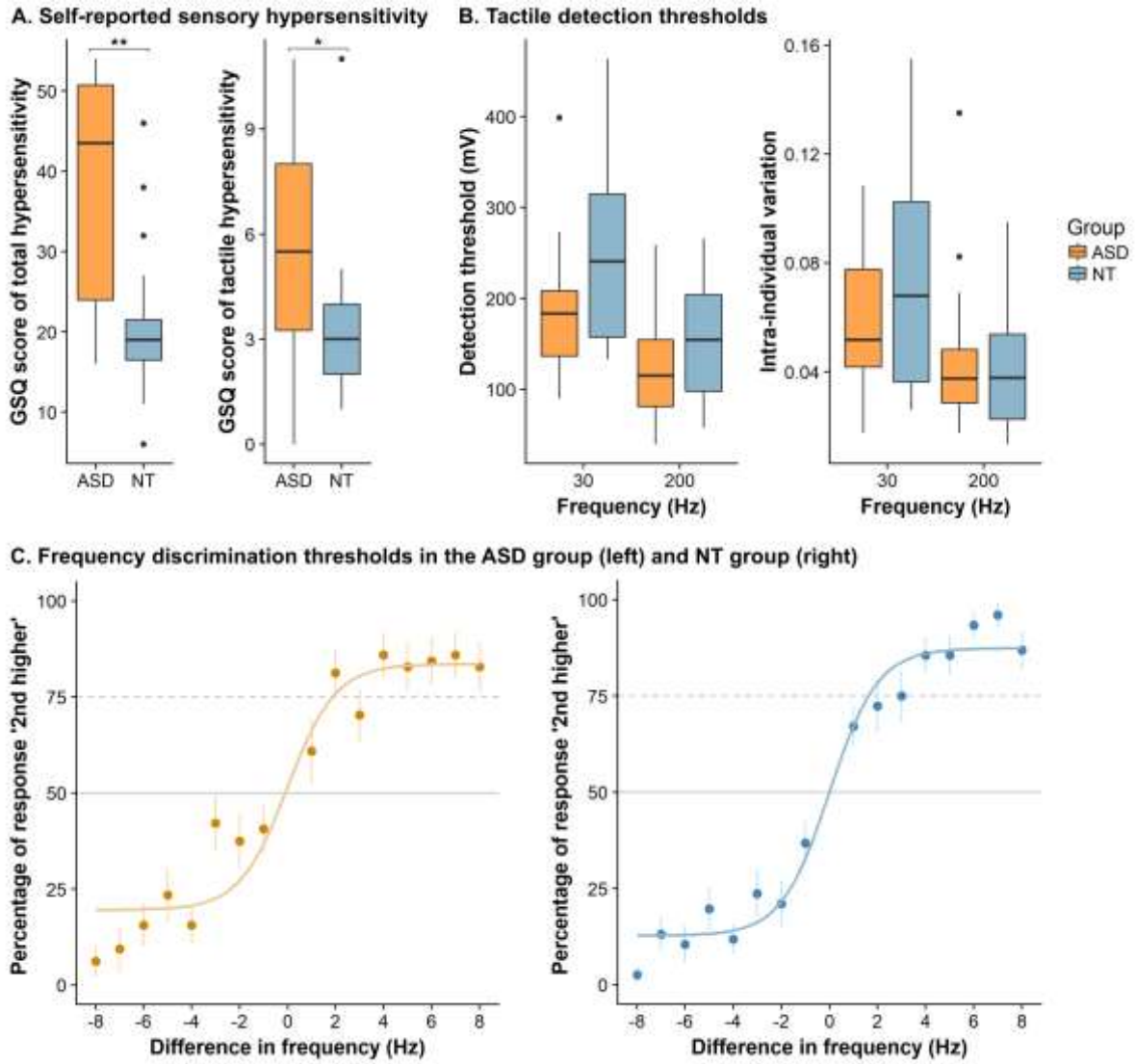
A. Self-reported sensory hypersensitivity
B. Tactile detection thresholds
GSQ score of total hypersensitivity
GSQ score of tactile hypersensitivity
Detection threshold (mV)
Intra-individual variation
ASD
NT
Frequency (Hz)
Group
C. Frequency discrimination thresholds in the ASD group (left) and NT group (right)
Percentage of response '2nd higher'
Difference in frequency (Hz)

Figure 4 :

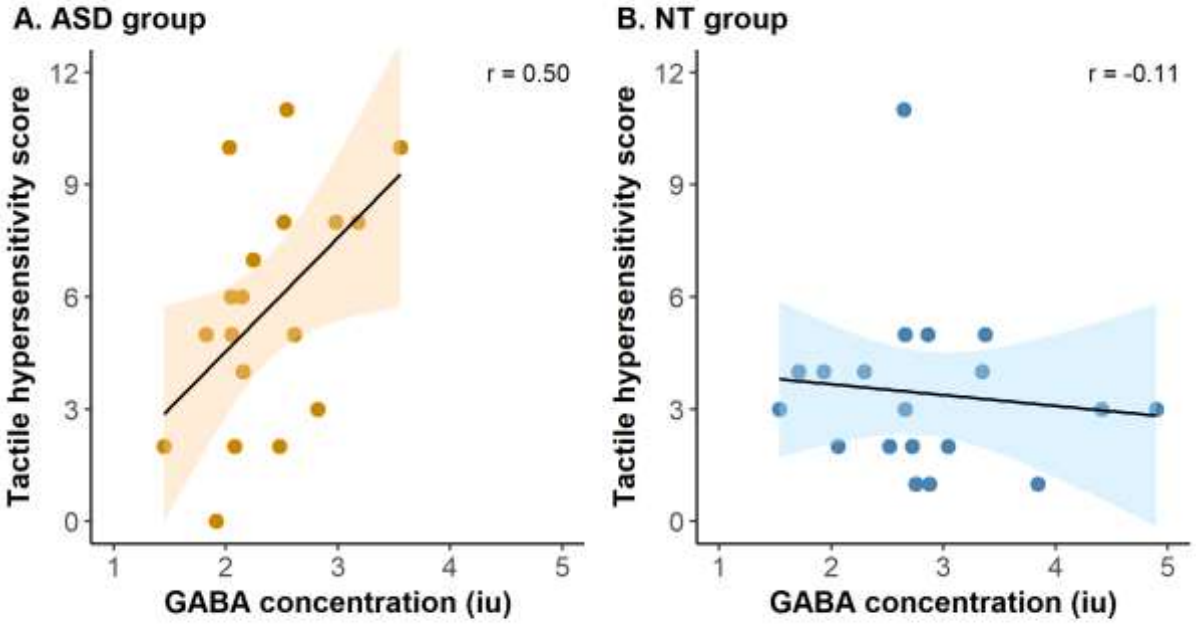

Figure 5 :