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RESEARCH ARTICLE

Tackling hypo and hyper sensory processing heterogeneity in autism: From clinical stratification to genetic pathways

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Abstract

As an integral part of autism spectrum symptoms, sensory processing issues including both hypo and hyper sensory sensitivities. These sensory specificities may result from an excitation/inhibition imbalance with a poorly understood of their level of convergence with genetic alterations in GABA-ergic and glutamatergic pathways. In our study, we aimed to characterize the hypo/hyper-sensory profile among autistic individuals. We then explored its link with the burden of deleterious mutations in a subset of individuals with available whole-genome sequencing data. To characterize the hypo/hyper-sensory profile, the differential Short Sensory Profile (dSSP) was defined as a normalized and centralized hypo/hypersensitivity ratio from the Short Sensory Profile (SSP). Including 1136 participants (533 autistic individuals, 210 first-degree relatives, and 267 controls) from two independent study samples (PARIS and LEAP), we observed a statistically significant dSSP mean difference between autistic individuals and controls, driven mostly by a high dSSP variability, with an intermediated profile represented by relatives. Our genetic analysis tended to associate the dSSP and the hyposensitivity with mutations of the GABAergic pathway. The major limitation was the dSSP difficulty to discriminate subjects with a similar quantum of hypo- and hyper-sensory symptoms to those with no such symptoms, resulting both in a

Richard Delorme and Guillaume Dumas contributed equally to this work.

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similar ratio score of 0. However, the dSSP could be a relevant clinical score, and combined with additional sensory descriptions, genetics and endophenotypic substrates, will improve the exploration of the underlying neurobiological mechanisms of sensory processing differences in autism spectrum.

Lay Summary

To explore the hypo/hyper-sensory profile among autistic individuals and its link with genetic alterations in GABA-ergic and glutamatergic pathways, we constructed the differential Short Sensory Profile (dSSP) from the Short Sensory Profile (SSP) of 1136 participants (533 autistic individuals, 210 relatives, and 267 controls). Groups differed in the mean dSSP, which tended to be associated with mutations of the GABAergic pathway highlighting the interest of combining dSSP with additional sensory descriptions, genetics and endophenotypic substrates to explore ASD's sensory differences.

KEYWORDS

autism spectrum disorder, clinical marker, excitation and inhibition balance, GABA/glutamatergic pathway, sensory profile

INTRODUCTION

Alongside differences in social communication and restricted, repetitive behaviors, sensory issues are now considered as being a core defining diagnostic feature of the autism spectrum (DSM-5; American Psychiatric Association, 2013). Reported in up to 87% of autistic individuals, sensory processing sensitivities have been emphasized as a critical feature for characterizing and understanding autism spectrum (Dellapiazza et al., 2018; Uljarević et al., 2017). However, the sensory profiles described among autistic individuals are heterogeneous, hampering progress to understand their biological substrates (Charman, 2015; Robertson & Baron-Cohen, 2017). Sensory sensitivities symptoms are manifested as hyposensitivity, hypersensitivity, avoidance of sensory stimuli, and/or unusual sensory interests, affecting the visual, auditory, gustatory, olfactory, tactile, vestibular, proprioceptive and interoceptive modalities (Sinclair et al., 2017). Sensory processing differences are associated with social communication differences, restricted and repetitive behaviors, but also with specific cognitive patterns, emerging sometimes as an earlier marker of autism spectrum (Schulz & Stevenson, 2019; Uljarević et al., 2016).

According the neural systems processing sensory information, and social behavior, both involving in autism spectrum, the excitation/inhibition (E/I) imbalance model was hypothesized in some forms of autism spectrum (Haider et al., 2013; Rubenstein & Merzenich, 2003). Despite the difficulty to predict the effect of neurotransmitters on the E/I balance (Levin & Nelson, 2015), this E/I imbalance could be linked to a disequilibrium between glutamatergic (principal excitatory neurotransmitter) and GABAergic (principal inhibitory neurotransmittor) activity (Dickinson et al., 2016; Sears & Hewett, 2021; Sohal & Rubenstein, 2019). Such disequilibrium could be at the origin of imbalance of sensory processing. Preliminary studies on animal models carrying mutations in GABAergic or glutamatergic pathway related genes associated with autism spectrum are starting to support such link between E/I imbalance and sensory processing alterations (Balasco et al., 2022; Chen et al., 2020; Gogolla et al., 2014; He et al., 2017; Orefice et al., 2019). The E/I imbalance might disrupt the neural homeostasis in individuals at risk for autism spectrum and thus participate in their phenotypic diversity—such as the occurrence of epileptic seizures, or the diversity of social communication symptoms (Dickinson et al., 2016). Also, the E/I imbalance may affect the gating and gain control of sensory inputs and result in sensory processing differences reported in autistic individuals (LeBlanc & Fagiolini, 2011; Mikkelsen et al., 2018; Ward, 2019). For example, individuals carrying deleterious mutations in genes associated with autism spectrum and involved the E/I homeostasis showed anomalous event-related potentials (ERP) with auditory deviance detection (Williams et al., 2021) such as those with *NLGN4* (Bonnet-Brilhault et al., 2016) or *FMRP* mutations (Hall et al., 2015; Knoth et al., 2014) or in Fragile X syndrome (MacCullagh et al., 2020).

To improve the characterization of sensory processing differences in autism spectrum and facilitate the exploration of their biological substrates, we sought to determine a score summarizing the sensory symptom directions and heterogeneity, which could be secondarily related to autism spectrum E/I imbalance. We aimed to construct a summarizing score as a normalized and centralized ratio of the hypo- to hyper-sensitivity derived from the short sensory profile (SSP), a commonly used questionnaire to explore the sensory symptoms frequently reported in autistic individuals from childhood to adulthood. The SSP used by large-scale projects in the field (autism speaks autism treatment network Lajonchere et al., 2012; EU-AIMS Longitudinal European Autism Project

Charman et al., 2017) was constructed with 38 items representing a heterogeneous combination of subconstructs (McIntosh et al., 1999). Despite its validity to dissect sensitivity symptoms (Williams et al., 2018) the SSP items are unequally distributed across both sensory modalities and subtypes of sensory processing differences. For example, the SSP taps constructs of visual hyper-responsiveness, auditory hyper-responsiveness, and auditory hypo-responsiveness, but not visual hypo-responsiveness. We therefore have reconsidered the diversity of the sensitivity symptoms by splitting them in a two dimensional perspective hypo- versus hyper-sensitivity. Additional questionnaires may have been more efficient to explore the hypo- and hyper-sensitivity in autism spectrum but none of them better account for the unequal distribution between the two sensory modalities and the subtypes of sensory processing dysfunction. The Sensory Experience Questionnaire explores mainly hypo or hyper aspects but is not adapted to all ages (child ages 2–12 years; Version 3.0; SEQ; Baranek et al., 2006). To date, there are still no studies highlighting the sensory patterns of individuals across all the sensory domains in terms of hypo and hyper-sensitivity. However, recent evidence supports the coexistence of both hypo- and hyper-sensitivity in autism spectrum among the different domains with an impact on social functioning (Thye et al., 2018). We reconsidered the diversity of the sensitivity symptoms by splitting the SSP items in a two-dimensional perspective hypo- versus hyper-sensitivity. The literature described an association between hypersensitivity and an increase in the E/I ratio (Sapey-Triomphe et al., 2019), suggesting conversely that hyposensitivity could be more driven by a decrease of the E/I ratio. We thus hypothesized that the differential SSP score (dSSP), when different from 0, would indirectly reflect at the brain level the function imbalance related to the glutamatergic and the GABAergic neuromodulators disequilibrium (Rubenstein & Merzenich, 2003; Sohal & Rubenstein, 2019). To achieve the first goal of this study, we empirically defined the hypo- or hyper- sensory processing type of each item of the SSP questionnaire to calculate the dSSP score. We then tested the relevance of the dSSP score by quantifying and exploring its distribution in two independent samples of autistic individuals and with typical development from the PARIS and the EU-AIMS study samples ($n = 1136$). We also challenged the empirical construct of the dSSP score to a more data-driven procedure based on a clustering approach of all the SSP questionnaire items. The second step of our study was to explore if the dSSP score could facilitate the exploration of the biological background involved in the sensory sensitivities reported in the autistic individuals. As a very preliminary study, we aimed to conduct a genetic study exploring in a modest sample of participants the relationship between the dSSP score and the burden of deleterious mutations affecting genes of the glutamatergic and the GABAergic pathways. We hypothesized the variability of the dSSP score would be correlated with the load of deleterious mutations affecting the glutamatergic and GABAergic equilibrium.

METHODS

Participants

In total, 1136 participants were enrolled in the study from two independent study samples. The Paris Autism Research International Sibpair (PARIS) study sample included 165 autistic individuals, their 210 unaffected first-degree relatives and 97 individuals with typical development at the Child and Adolescent Psychiatry Department, Robert Debre Hospital, Paris (France) between April 2013 and September 2016. The EU-AIMS Longitudinal European Autism Project (LEAP) sample study was composed of 384 autistic individuals and 280 individuals with typical development included between January 2014 and August 2016 (Loth et al., 2017). The demographic and clinical descriptions of the individuals enrolled in both samples are reported in Table 1. The clinical characterization of the participants from the PARIS and LEAP study were included following the method described elsewhere (Charman et al., 2017; Lefebvre et al., 2021; Loth et al., 2017). As a summary, the diagnosis of autism spectrum was based on DSM-IV-TR/5 criteria and made by summing the information from the Autism Diagnosis Interview-Revised (ADI-R), the Autism Diagnostic Observation Scale-second edition (ADOS-2), and clinical reports from experts in the field. The cognitive abilities of individuals were also assessed using the Wechsler Intelligence Scales adapted to the age of individuals.

The PARIS and the LEAP study samples were granted approval by their local Ethics Committee. They were carried out in accordance with Good Clinical Practice (ICH GCP) standards. Written informed consent was obtained from all participants. For the patients who were unable to consent for themselves, a parent or legal guardian consented to the study on their behalf.

Sensory profile of individuals included in the study

The sensory profile of all participants included in the study was assessed with the Short Sensory Profile (McIntosh et al., 1999). Each item of this 38-item questionnaire is scored on a 5-point Likert scale (1 = always, 2 = frequently, 3 = occasionally, 4 = seldom, and 5 = never). The 38 items—SSP is a shortened form of the Sensory Profile questionnaire (Dunn & Westman, 1997), which demonstrated the highest discriminatory power of divergent sensory processing. The SSP questionnaire is composed of 7 subscales including tactile sensitivity,

TABLE 1 Clinical and demographic descriptions of the individuals enrolled in the study

	PARIS study sample				LEAP study sample		
	AS	Relatives	TD	$F(p, \eta^2)$	AS	TD	$t(p, d)$
N	165	210	97		384	280	
Males (%)	138 (84)	110 (52)	49 (50)	26 (<0.001, 0.1)	330 (43)	204 (27)	1.72 (0.05, 0.06)
Age (SD)	15.4 (9.8)	31.8 (18.1)	22.9 (13.9)	82 (<0.001, 0.3)	14.2 (4.6)	16.3 (5.7)	4.3 (<0.001, 0.03)
Nonverbal IQ (SD)	93 (22)	115 (16)	108 (16)	46 (<0.001, 0.2)	97 (22)	101 (22)	1.59 (0.1, 0.05)
SRS-2 total score (*t*-score)	73.9 (11.6)	50.1 (13.6)	43.3 (5.9)	210 (<0.001, 0.5)	72.1 (11.7)	48.2 (9.4)	0.5 (<0.001, 0.05)
ADI-R subdomains							
Social behavior	19.4 (6.1)				16.7 (6.8)		
Communication behavior	14.6 (6.2)				13.4 (5.7)		
Repetitive behavior	6.1 (2.8)				4.3 (2.6)		
ADOS-2 CSS*							
Social communication	6.5 (2.5)				6.1 (2.6)		
Repetitive behaviors	5.8 (1.4)				4.7 (2.7)		

Note: For continuous variables, data are mean ± standard deviation (SD). AS, autism spectrum; TD, typically developing; *N*, number of participants, Age in years; IQ, intelligence quotient; ADI-R, autism diagnostic interview-revised; ADOS-2 CSS, autism diagnostic observation schedule—second version—calibrated severity score. ADOS-2 CSS are the Calibrated Severity Scores; see Charman et al., 2017 for a description.

taste/smell sensitivity, movement sensitivity, visual/auditory sensitivity, under-responsive/seeks sensation, auditory filtering, and low energy/weak. Lower scores indicate more sensory issues. The SSP measure has been psychometrically validated in autistic individuals aged 3–18-year old (Williams et al., 2018). For the present study, we reversed-scored each item to allow a more direct comparison with the summarizing score we built (Figures 1A and 2A). Concerning the PARIS sample study, the SSP was collected for autistic individuals at T0, month 3 and year 1 and 2 for all subjects of the autistic group. Testing the stability among the development of the dSSP, we performed a two-way analysis of variance (ANOVA) with repeated measures to compare results at different time points.

Building of the dSSP score

We constructed a summarizing score as a normalized and centralized ratio of the hypo- to hyper-sensitivity derived from the SSP questionnaire. We first asked four senior clinical experts in the field of autism spectrum (A.L., A.B., A.M., and F.A.) and blind to the hypothesis of this study to determine which items of the scale were dedicated to the exploration of hyper-, hypo- sensitivity or which seemed to be related to both hyper- and hypo- sensitivity. We then split the 38 items into three subgroups, depending on their ability to explore sensory features related to hyper- ($n = 19$), hypo- ($n = 16$) sensitivities or uncertain ($n = 3$; Table S1). Hypo- and hyper-characterization corresponded to an agreement of at least ¾ of the raters for one of these two characterizations. If only half of the raters were agreed, the item was defined by the "uncertain" characterization. Since the "uncertain" item did not discriminate between hypo and hyper sensory, it was not considered in the calculation of the dSSP. We quantified inter-observer stability using Kendall rank correlation (Table S2). We finally calculated the dSSP score for each individual, a centralized and normalized score reflecting the ratio between the average scores of items related to hypersensitivity (e.g., hyper-sensory score; $n = 19$) and to hyposensitivity (e.g., hypo-sensory score; $n = 16$; Table 2). A positive dSSP score represented a tendency to hyper- sensitivity and a negative one a tendency of hypo-sensitivity. Whereas the dSSP score combined information from two component scores (hypo- and hyper-sensory scores), we improved our analysis by exploring separately the hypo- and hyper-sensory scores.

Clustering distribution of the SSP questionnaire items

To validate the clinical-driven clusters (hypo, hyper and uncertain), we compared our clusters with data-driven clusters. We explored the link between the dSSP score

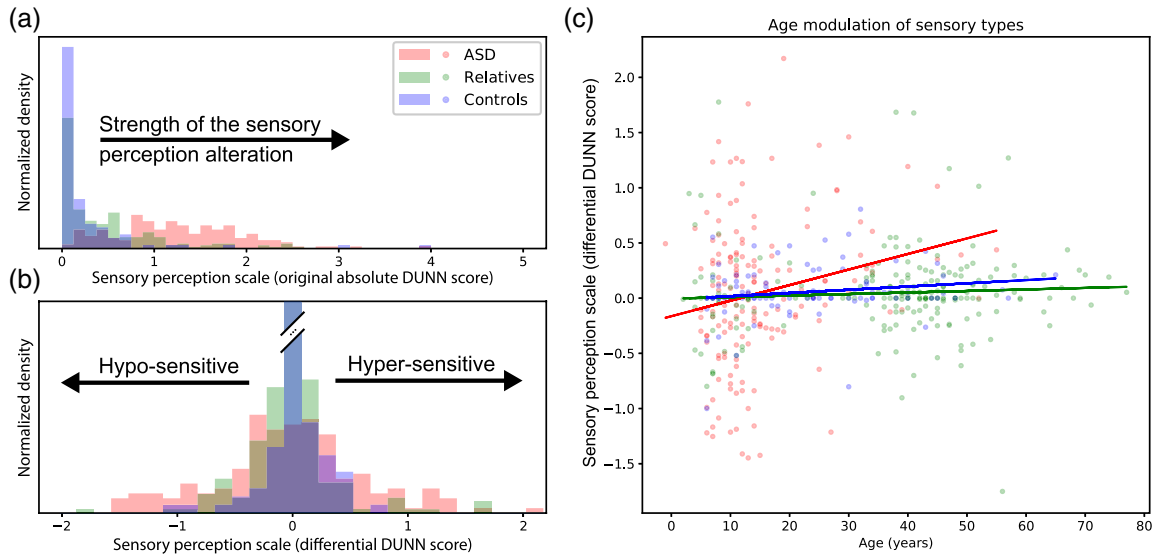

FIGURE 1 Sensory short profile scores within the PARIS sample. (b) Distribution of mean total original SPP score per item for autistic participants (red), their first-degree relatives (green) and for control participants (blue). A higher SPP score meant stronger anomalies of sensory processing. (b) Distribution of the mean differential SPP score on the same participants; here, negative and positive scores respectively represented hypo- and hyper-sensory profiles. Relatives appeared with an intermediate distribution between patients and controls in both (a) and (b). (c) Evolution of the differential SPP score with age for the same participants. Linear regression showed an effect of age only for patients: a significant regression equation of the sensory profile with age ($-0.12 + 0.01$ x age, $p = 0.02$, uncorrected) with an $R^2 = 0.03$ in the group with ASD was obtained. This significant regression was not found in either the relative group ($-0.05 + 0.01$ x age, $R^2 = 0.01$, $p = 0.1$) or the typically developing group ($-0.03 + 0.01$ x age, $R^2 = 0.04$, $p = 0.06$).

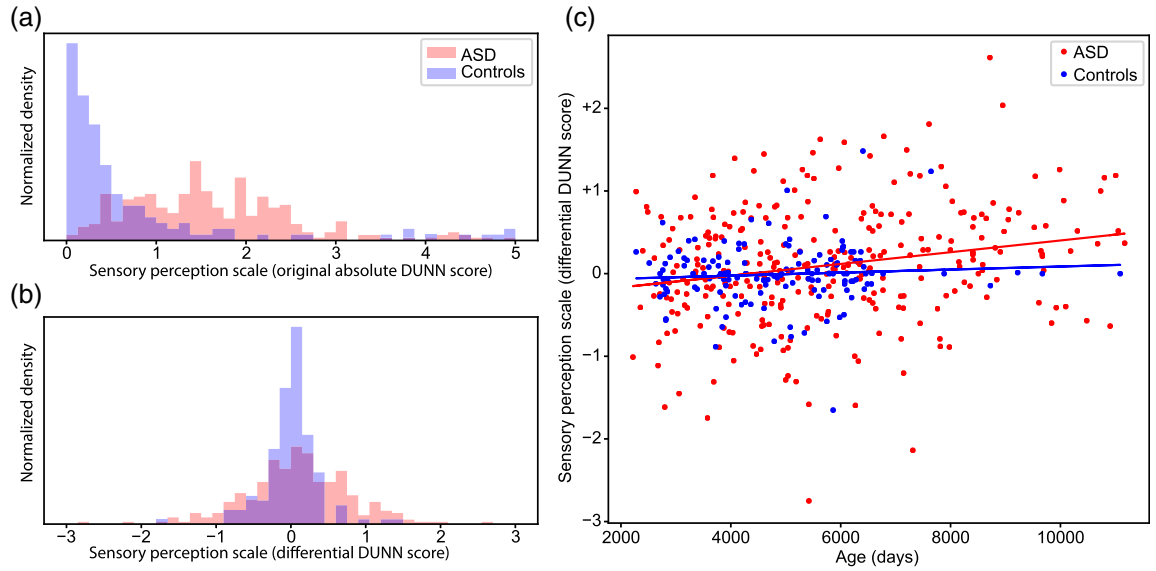

FIGURE 2 Sensory short profile scores within the LEAP cohort. (a) Distribution of mean total original SPP score per item for autistic participants (red) and for participants controls (blue). A higher SPP score meant stronger anomalies of sensory processing. (b) Distribution of the mean differential SPP score on the same participants; here, negative and positive scores respectively represented hypo- and hyper-sensory profiles. (c) Evolution of the differential SPP score with age for the same participants. Linear regression showed an effect of age only for patients. As observed in the PARIS cohort, we replicated a significant regression equation of the sensory profile with age ($-0.28 + 0.02$ x age, $p = 0.0005$, uncorrected) with an $R^2 = 0.03$ in the autism spectrum group. This significant regression was not found in the typically developing group (-0.5, $15 + 0.0008$ x age, $R^2 = 0.007$, $p = 0.28$).

and the sensory processing modalities using the VARCLUS procedure that divides a set of numeric variables into clusters (JMP software; SAS Institute, Inc. 2017). The VACLUS provides no overlapped components unlike the factor analysis. Although the factor analysis allowing components must be interpreted by considering the correlations between the factors, the Varclus allows a simpler interpretation of the results. This iterative

TABLE 2 Hyper-, hypo-sensory or uncertain scores and differential SSP scores in the PARIS and LEAP cohorts

	PARIS cohort				LEAP cohort		
	AS mean (SD)	Relatives mean (SD)	TD mean (SD)	F (p-value, η^2)	AS mean (SD)	TD mean (SD)	t (p-value, d)
Hyper-sensory score[a]	1.28 (0.77)	0.41 (0.56)	0.26 (0.56)	105 (<0.0001, 0.31)	1.66 (0.96)	0.69 (1.15)	9.28 (<0.0001, 0.74)
Hypo-sensory score[b]	1.21 (0.76)	0.38 (0.54)	0.21 (0.60)	99 (<0.0001, 0.30)	1.56 (1.06)	0.69 (1.16)	7.74 (<0.0001, 0.74)
Uncertain score[c]	1.37 (0.85)	0.56 (0.68)	0.31 (0.64)	80 (<0.0001, 0.25)	1.62 (1.02)	0.75 (1.02)	8.16 (<0.0001, 0.78)
Differential SSP score	0.07 (0.65)	0.04 (0.37)	0.04 (0.24)	0.21 (0.81, 0.001)	0.08 (0.03)	−0.05 (0.04)	2.28 (0.02, 3.67)
				Z (p-value, d)			
Differential SSP score (AS—Relatives)				0.94 (0.34, 0.04)			
Differential SSP score (AS—TD)				−0.29 (0.77, 0.02)			
Differential SSP score (Relatives—TD)				1.10 (0.27, 0.01)			
Hyper-sensory score (AS—Relatives)				−11.83 (<0.0001, 0.87)			
Hyper-sensory score (AS—TD)				−11.88 (<0.0001, 1.01)			
Hyper-sensory score (Relatives—TD)				−2.08 (0.06, 0.14)			
Hypo-sensory score (AS—Relatives)				−11.47 (<0.0001, 0.83)			
Hypo-sensory score (AS—TD)				−11.32 (<0.0001, 0.83)			
Hypo-sensory score (Relatives—TD)				−2.26 (0.04, 0.16)			

Note: For continuous variables, data are F-value (p-value, eta squared), considering ANOVA analyses and t-ratio (p-value, Cohen's d) considering t-Student analyses, Z-value (p-value, d-Cohen's d) considering Wilcoxon analyses.

[a]The hyper-, [b]hypo-, and [c]uncertain sensory scores were first explored in order to support the construction and use of the dSSP score. We observed differences of mean and variances between groups, with higher hypo and hyper sensory sensitivities in the autistic group in the two cohorts (Table 2).

method extracted oblique components to identify one-dimensional clusters of mutually correlated variables (Woolston et al., 2012). We used the SSP items scores reported by the autistic participants from the PARIS and the LEAP study samples and then explored the items gathering in each cluster (e.g., item XX from cluster Y was categorized as hyper- or hypo- sensitivities or uncertain). We used a Chi^2 test to test for a significant relationship between variables and a Cramer's V test, which was a post hoc test indicating how significant this relationship is (scoring from 0 for the low association to 1 for the high association). Using Python script (Python Software Foundation, version 3.7), we calculated the silhouette score (scoring from −1 to 1; Rousseeuw, 1987) to interpret and validate the consistency within clusters and the Fowlkes–Mallows similarity score (Fowlkes & Mallows, 1983) to assess the similarity between PARIS and LEAP sample clustering (scoring from 0 to 1).

Genetic profiles

To explore if the dSSP score could facilitate the exploration of the biological background involved in sensory sensitivities reported in autistic individuals, we conducted a genetic study exploring the relationship between the dSSP score and the burden of deleterious mutations affecting the glutamatergic and the GABAergic pathways. We thus performed this exploratory analysis only in a subset of individuals from the PARIS study samples for which whole-genome sequencing (WGS) data were available. For variant calling analysis, the pre-processing steps were as followed: sequence reads were aligned to the human reference genome GRCh37.75 using the Burrows-Wheeler Aligner BWA, then PicardTools was used for removing PCR duplicates, and GATK 3.8.1 was used for small insertion/deletion variants (Indels) realignment and base recalibration. Single Nucleotide Variants (SNV) and Indels were called with the GATK 3.8.1's

HaplotypeCaller on each sample alignment file. We produced a Variant Call Format (VCF) file with all the SNV and Indel calls for the cohort. Variants were then functionally annotated with Variant Effect Predictor (VEP; using Ensembl 92; McLaren et al., 2016). Additionally, we annotated the variants for their frequency in the population from the gnomAD database version 2.1.1 (Karczewski et al., 2020) and for their Combined Annotation Dependent Depletion score (CADD version 1.3; Kircher et al., 2014) to evaluate their deleteriousness. We then queried all variants with a minor allele frequency (MAF) ≤ 10% in the gnomAD database, which were either likely gene disruptive (LGD) variants (i.e., stop gain, stop loss, start loss, splice acceptor, splice donor or frameshift) or missense mutations with a CADD score ≥30 (MIS30). SNVs with a CADD PHRED-scaled score >30 were at the top 0.01% across all potential ~9 billion SNVs and were therefore considered as having a high likelihood to impact protein structure/function (Rentzsch et al., 2019). To control population structure, we performed a PCA analysis using PLINK 1.9 (Purcell et al., 2007), and we used the first four components as covariables for all the burden analysis. We used GRAVITY (http://gravity.pasteur.fr), an open-source Cytoscape app that allowed an efficient visualization and analysis of all the exonic variants stored in a database by mapping them on protein–protein interaction (PPI). Variants of interest were manually curated by visualization of aligned sequencing data (BAM files) using IGV (Thorvaldsdóttir et al., 2013). We used admixture to ascertain the ancestry of the participants (Alexander & Lange, 2011). In our sample, 86% of the participants were from European descent. We finally ascertained the genetic variants related to the GABAergic and glutamatergic pathways by using the KEGG database (Table S3; Kanehisa et al., 2016; Kanehisa & Goto, 2000). We considered the GABAergic synapse pathway (entry I04727) and the Glutamatergic synapse pathway (entIhsa04724) and scored the number of deleterious mutations found in respectively the two pathways. At the end, to explore the link between the dSSP score and the burden of genetic mutations in the GABAergic and/or glutamatergic pathways, we built a linear model with separately the dSSP, hypo- and hyper-sensory scores and the carrier of variants within the GABAergic and Glutamatergic pathways. We also used the bootstrap method and reported median p-values and Cohen-d obtained across 2000 re-sampling. Although the association of the GABAergic and Glutamatergic pathways with sensory processing differences (Puts et al., 2017) and hypersensitivity (Sapey-Triomphe et al., 2019) are suggested in literature, no direct relationship between the GABA/Glutamate ratio imbalance and a clinical hyposensitivity have been reported. To explore these associations, we thus run linear models exploring the number of deleterious variants within the GABAergic and Glutamatergic pathways considering the hypo-, and hyper-sensory scores and their interactions as variables of adjustment.

RESULTS

dSSP scores in the PARIS study and LEAP study samples

In accordance with our hypothesis, the variance of the dSSP scores significantly differed between autistic individuals and controls in the PARIS study samples with a trend for a more hypersensitive sensory pattern in the autistic group than in controls. Despite a moderate sample size, the intergroup comparison (pair by pair: proband, first-degree relatives and controls) did not reach significance with tiny effect sizes ($\eta^2 < 0.04$; Table 2). We however observed a high heterogeneity in the variance of the dSSP scores between the three groups (Browne–Forsythe test: $F = 39.9$, $p = 1.0 \times 10^{-18}$; Figure 1B,C). Autistic individuals had a more extreme sensory pattern on both sides of the distribution when compared to the other groups of individuals. The first-degree relatives appeared with an intermediate distribution profile between autistic and typically developing participants. We then built a linear model for the dSSP scores including group status (autistic participants, first-degree relatives, or controls), sex, age, and their interactions (age, sex, group). A significant positive regression equation was found ($F = 1.7$, $R^2 = 0.05$, $p = 0.001$). We observed positives significant effects of age ($F = 12.1$, $p = 0.0006$, $\eta^2 = 0.02$), sex ($F = 7.9$, $p = 0.005$, $\eta^2 = 0.02$), age x group interaction ($F = 4.31$, $p = 0.01$, $\eta^2 = 0.018$) and a tendency of group status effect ($F = 6.1$, $p = 0.05$, $\eta^2 = 0.03$). The dSSP increased with an increase of age, with higher rates in males versus females and in the group of autism spectrum versus relatives versus controls. No statistically significant interaction effect was found for sex x group status ($F = 0.82$, $p = 0.44$, $\eta^2 = 0.003$), sex x age ($F = 1.64$, $p = 0.20$, $\eta^2 = 0.003$), sex x group x age ($F = 1.87$, $p = 0.15$, $\eta^2 = 0.008$). ANOVAs with repeated measures (at baseline, month 3 and Year 1 and 2) of the SSP and the dSSP scores did not show any developmental effect ($F = 1.3$, $p = 0.29$).

To replicate our findings, we performed a similar analysis on the LEAP study sample. We also observed a more hypersensitive sensory pattern in autistic individuals than in controls (t-value = 2.28, dof = 436, $p = 0.02$, Cohen's $d = 3.67$; Table 2). Building a linear model similar to the one used on the PARIS cohort, we also observed a significant regression equation ($F = 4.46$, $R^2 = 0.05$, $p < 0.0001$). We also reported a higher dSSP scores variance in autistic participants compared to controls (Brown–Forsythe test: $F = 51.3$, $p = 3.4 \times 10^{-12}$; Figure 2B,C) and significative positives effects of age ($F = 6.6$, $p = 0.01$, $\eta^2 = 0.01$), sex ($F = 5.8$, $p = 0.02$,

$\eta^2 = 0.01$) and group status ($F = 4.6$, $p = 0.03$, $\eta^2 = 0.007$). The dSSP increased with an increase of age, with higher rates in males versus females and in the autistic group versus controls. No statistically significant interaction effect was found for sex x group status ($F = 0.31$, $p = 0.57$, $\eta^2 = 0.0005$), sex x age ($F = 0.04$, $p = 0.83$, $\eta^2 = 0.0008$), age x group ($F = 1.92$, $p = 0.17$, $\eta^2 = 0.003$), and sex x group x age interaction ($F = 0.20$, $p = 0.65$, $\eta^2 = 0.0003$).

Items-based clustering

The VARCLUS procedure based on the item scores of the SSP scale reported in the autistic participants of the PARIS study sample, converged into 9 clusters with 60.5% of variance explained (Table S4; silhouette score = 0.11, bootstrap empirical p-value <0.0001). The clusters we obtained were not similarly distributed in items considering the hypo-, hyper- sensitivities or uncertain [Chi^2 (dof = 16, $N = 165$) = 31.2, $p = 0.01$, Cramer's $V = 0.64$] (Table S5). We re-ran the analysis on the LEAP study sample. We found seven clusters which explained 63% of variance (Table S6; silhouette score = −0.08; bootstrap empirical p-value <0.0001). The clusters showed also a statistically significant difference in frequency of the items considering the hypo-, hyper- sensitivities or uncertain (Chi^2 (dof = 12, $N = 384$) = 35.9, $p = 0.0003$, Cramer's $V = 0.69$; Table S7).

We then compared the clustering of the SSP items obtained among the autistic participants of the LEAP study sample to the one obtained on the Paris sample. Clusters derived from both PARIS and LEAP study samples were similar (Fowlkes–Mallows similarity score = 0.56, $p < 0.0001$). Within each cluster, one item was more representative than the others (Tables S4 and S6). Interestingly, two SSP items were described as the most representative of their own clusters in both PARIS and LEAP study samples: item 17 which was related to hypo-sensitivity and item 36 related to hyper-sensitivity.

dSSP score correlated with GABA and/or glutamatergic pathway mutation enrichments in the autistic group

We investigated if differences in dSSP scores were associated with a distinct burden of deleterious variations affecting genes related to the GABA and/or Glutamatergic pathways. We only considered for each subject the Likely Gene Disrupting (LGD) and predicted deleterious missense mutations (CADD>30) (Figure S1). We first built a linear model for the dSSP score including the burden of gene mutations in GABAergic and/or the glutamatergic pathways, and their interactions. In autistic participants ($n = 135$), our analysis reported a trend for a positive association with a burden of gene mutations in the GABAergic pathway but not in the glutamatergic pathway, nor in the both pathways ($R^2 = 0.05$, $F = 2.18$, $p = 0.09$; GABA: $F = 3.36$, $p = 0.06$, $\eta^2 = 0.02$; Glutamate: $F = 0.08$, $p = 0.77$, $\eta^2 = 0.0008$; both pathways: $F = 2.68$, $p = 0.11$, $\eta^2 = 0.02$ (Figure S1). Spearman's rank correlation was computed to assess the relationship between the hypo-, hyper-sensory & dSSP scores and the burden of gene mutations in the GABAergic pathway and highlighted a trend for a positive relation r (133) = 0.33, $p = 0.05$). We then performed a bootstrap analysis -across 2000 resampling- to explore further the relationship between the dSSP score and the burden of deleterious mutations in the GABA pathway. We observed autistic individuals and with a high dSSP score indeed reported a significant enrichment of deleterious mutations in the GABAergic gene pathway ($p = 0.004$, $d = 1.15$). We finally ran a similar analysis only in individuals from European ancestry (based on the results of the admixture analysis) and we obtained a similar trend.

Hypo-, hyper-sensory scores

In PARIS and LEAP study samples, the hypo-sensory score was significantly different between the autistic group and the others groups (PARIS: first-degree relatives and controls groups: $R^2 = 0.3$, $F = 93.45$, $p < 0.0001$, $h^2 = 0.30$; LEAP: t-ratio = 7.74, ddl = 436, $p < 0.0001$, Cohen's $d = 0.74$), with a higher heterogeneity in the autistic group (PARIS: Brown–Forsythe test: $F = 18.28$, $p < 0.0001$; LEAP: Brown-Forsythe test: $F = 6.56$, $p = 0.01$).

Similarly, the hyper-sensory score was significantly different in the autistic group compared to the others groups (PARIS: first-degree relatives and controls groups, $R^2 = 0.31$, $F = 96.54$, $p < 0.0001$, $h^2 = 0.31$; LEAP: controls group, t-ratio = 9.28, ddl = 436 $p < 0.0001$, Cohen's $d = 0.74$), with a higher heterogeneity in the autistic group in the PARIS study sample (Brown–Forsythe test: $F = 19.30$, $p < 0.0001$), not found in the LEAP study sample (Brown–Forsythe test: $F = 3.55$, $p = 0.06$). Results figure in Table 2.

The relation of the hypo- and hyper-scores with a distinct burden of deleterious variations affecting genes related to the GABA and/or Glutamatergic pathways by considering for each subject the Likely Gene Disrupting (LGD) and predicted deleterious missense mutations (CADD >30) was explored. Despite an absence of statistical significance, the GABA F-value showed a trend for a negative association of the hypo-sensory score and the burden of gene mutation in the GABAergic pathway ($R^2 = 0.03$, $F = 1.25$, $p = 0.29$; GABA: $F = 3.21$, $p = 0.08$, $\eta^2 = 0.03$; Glutamate: $F = 0.24$, $p = 0.63$, $\eta^2 = 0.002$; both pathways: $F = 0.01$, $p = 0.92$, $\eta^2 = 0.0001$). However, no hyper-sensory score relation was observed with the with GABA and/or Glutamatergic

pathway mutation enrichments ($R^2 = 0.02$, $F = 0.88$, $p = 0.45$; GABA: $F = 0.02$, $p = 0.89$, $\eta^2 = 0.0002$; Glutamate: $F = 1.10$, $p = 0.29$, $\eta^2 = 0.01$; both pathways: $F = 1.53$, $p = 0.22$, $\eta^2 = 0.01$).

Exploring distinctly the two pathways and their relation with the sensory processing atypicalities (i.e., hypo, hyper sensory processing and their interaction), the linear models also found no significant results, but an interesting trend for a negative association of the hypo-sensory score and the burden of gene mutation in the GABAergic pathway (GABA: $R^2 = 0.05$, $F = 2.06$, $p = 0.11$; interaction: $F = 1.15$, $p = 0.3$, $\eta^2 = 0.009$; hypo-sensory score: $F = 4.36$, $p = 0.04$, $\eta^2 = 0.03$; hyper-sensory score $F = 1.85$, $p = 0.18$, $\eta^2 = 0.01$; Glutamatergic pathway: $R^2 = 0.01$, $F = 0.5$, interaction $F = 0.23$, $p = 0.63$, $\eta^2 = 0.002$, hypo-sensory score: $F = 0.05$, $p = 0.82$, $\eta^2 = 0.0004$; Hyper-sensory score: $F = 0.68$, $p = 0.41$, $\eta^2 = 0.005$). Spearman's rank correlation was computed to assess the relationship between the hypo-sensory score and the burden of gene mutations in the GABAergic pathway and highlighted a trend for a negative relation $r(133) = -0.38$, $p = 0.06$. These results suggested that the increase of mutations in the GABAergic genes would be related to the decrease of the hypo sensory score.

DISCUSSION

Through our study, we aimed to further characterize sensory processing divergences in autism spectrum and improve our ability to explore their potential underlying neurobiological mechanisms (Siemann et al., 2020). We thus built a summarizing score—the dSSP score—which showed that, on average, autistic individuals displayed a trend for a hyper-sensitivity profile, reaching only significance in the LEAP sample (through its power to detect significant results). This association may be driven by the load of comorbidity reported in the autistic individuals, since previous studies reported higher levels of sensory reactivity in those severity of associated comorbidities (Kreiser & White, 2015; Tillmann et al., 2020). This association was observed in individuals with comorbid anxiety or depressive symptoms (MacLennan et al., 2021; Rossow et al., 2022) but also somatic complaints (Lefter et al., 2020). Previous findings in the literature also reported a hyper- sensitivity profile in autistic children. This hyper-sensitivity profile was previously associated with the severity of expressive language deficit (Rossow et al., 2022) but also with early stages of their developmental trajectory (Ben-Sasson et al., 2019; Green et al., 2012)—as we reported both in the PARIS and the LEAP samples. In our study, we reported a significant positive interaction (i.e., in favor of hyper-sensitivity) between dSSP score and chronological age of the participants, which is coherent with the literature (Lane et al., 2022), with a dSSP score stability across child development described by repeated measures on the PARIS study. Although the sensory differences appear early in the development, the dSSP stability appears as a good biomarker candidate of autism spectrum (Aronson & Ferner, 2017; Baranek et al., 2013; Estes et al., 2015; O Miguel et al., 2017).

In our study, we also observed a larger dSSP score variability in autistic individuals than in controls, which is in line with the heterogeneity reported in autism spectrum in many research areas, such as brain imaging (Masi et al., 2017). Our results stressed further the need for partial phenotypes beyond categorical diagnosis to help in patients' stratification and delineate more homogeneous subgroups (Proff et al., 2021; Wolfers et al., 2019). The dSSP score may offer a relevant setting to explore the heterogeneity in autism spectrum (Lombardo et al., 2019). It could also pave new ways to determine the biological mechanisms associated with sensory sensitivities in autism. Although our results need to be replicated in larger samples and combined with additional dimensions, the dSSP score may help to uncover new sub-groups with more coherent neurobiological mechanisms (Bruining et al., 2020; Uljarević et al., 2016). Interestingly, the intermediate dSSP score distribution we observed in the first-degree relatives between autistic individuals or those with typical development, suggested a determination of the dSSP score by inherited biological substrates (Neufeld et al., 2021), which was in line with our initial hypothesis.

To validate the empirical construct of the dSSP score, we performed a data driven approach of the hypo- and hyper-sensory symptoms related items. The cluster analysis revealed a very similar distribution of the items encompassed in the data-driven clusters compared to those included in the two dimensions we empirically built. While it does not give two clusters, the automated analysis still support that this two-dimensional perspective on sensory sensitivities in autism spectrum (hypo-, hyper-sensitivity dimensions; Baranek et al., 2006) is statistically relevant on top of being clinically easier to interpret. The data-driven analysis revealed that two items that emerged as being highly representative of both clusters were identified, whatever the PARIS or the LEAP cohort we considered: item 17 (Table S1: Item17—"Becomes overly excitable during movement activity") drove mainly the variability of the hypo-sensitivity related cluster, and item 36 (Table S1: Item 36—"Is bothered by bright lights after others have adapted to the light") the variability of the hyper-sensitivity related cluster. Beyond the simple dichotomy of sensitivity anomalies in autism spectrum, the dSSP score integrated the personal sensory processing impairment into a ratio score facilitating for example the indirect exploration of the relationship between these symptoms and the E/I imbalance (Pierce et al., 2021).

We finally performed an exploratory analysis to explore the relationship between the dSSP score and the load of deleterious mutations affecting the genes of

glutamatergic & GABAergic pathways (Table S3). Individuals with a high dSSP score, that is, those with an excess of hyper-sensory processing sensitivities, displayed a significant trend for the enrichment of deleterious gene mutations in the GABAergic pathway. Our results were in accordance with numerous reports describing the association between genes affecting directly (such as *GABRA4*, *GRIN1*) or indirectly (such *CACNA1C*, *SHANK1*-3, *CNTN3-6*) the GABAergic pathway homeostasis and sensory processing divergences in autism spectrum (Hartig et al., 2021; Leblond et al., 2014; Mercati et al., 2017; Tavassoli et al., 2021). The excess load of deleterious mutations affecting the genes of GABAergic pathway reported in our study may reduce the GABAergic tone (Ferguson & Gao, 2018)—as previously showed (Sapey-Triomphe et al., 2019)—and may explain the hypersensitivity observed in autism spectrum. Furthermore, our result suggested an association between these deleterious mutations affecting the genes of GABAergic pathway is associated with "less hypo-sensitivity." These results concord with the effect of the sensory experience in early life on the brain, as highlighted by the supranormal sensitivity reported after visual stimulation occurring following a period of dark rearing at the peak of the critical period for plasticity (Hensch, 1998). Our study supports the hypothesis of a potential link between GABAergic pathway and hypo-sensitivity.

LIMITATIONS

One major limitation of the results we obtained was the difficulty of the dSSP score to discriminate participants with a similar quantum of hypo- and hyper-sensory symptoms resulting in a ratio score of 0 to those with no such symptoms but also resulting in a similar ratio score of 0.

Additional questionnaires such as the Sensory Experience Questionnaire may have been more efficient to explore the hypo- and hyper-sensitivity in autism spectrum, but none of them better account for the unequal distribution between the two sensory modalities and the subtypes of sensory processing differences. Moreover, the SSP is robustly employed in large-scale projects in the field of autism (Autism Speaks Autism Treatment Network, Lajonchere et al., 2012; EU-AIMS Longitudinal European Autism Project, Charman et al., 2017). The SSP allows to split these symptoms into two distinct dimensions we aimed to consider in our study. However, our results must be considered with caution since SSP items are unequally distributed across sensory modalities and subtypes of sensory processing differences. Moreover, the clinicians may have been influenced by the theory relating hyposensitivity and seeking when rating the items 15–21 (including the item 17) related to the hypo-sensitivity. However, this theory is not confirmed in the literature (MacLennan et al., 2022). The "uncertain" item 13 rating could also be discussed. Item 13 relates to the fear of heights and heights. Hypo-sensitivity to vestibular sensation would generally present as an absence of fear and the clusters on PARIS and LEAP classified item 13 with hyper items. However, this item was associated with hypo-sensory by half of the raters, probably related to anticipatory anxiety of mismanagement of danger due to the hyposensitivity. This discordant classification could be the result of understanding item bias. Nevertheless, as both items resulted in a discordant classification between raters, they were not considered in constructing the dSSP. This exclusion must be considered when interpreting the dSSP score, which provides additional information to the SSP score but must not be interpreted according to the SSP score. The Kendall rank correlation coefficients for inter-rater agreement were relatively low (Akoglu, 2018), but acceptable considering the number of items ($n = 36$), and of raters ($n = 4$). Despite our cluster analyses trending to validate the empirical construct of the dSSP score, the validation of this two mains dimensions construction (hypo- and hyper-sensitivity dimensions) as coherent constructs from the SSP need further analyses in future studies.

On the other hand, our results add support to a potential association between hypo-sensory alterations and deleterious mutations in GABAergic genes; however, those findings have to be taken with caution and would require replication on a larger population. Specifically, the sample size of the molecular analysis was very limited but should be considered as a highlight of the opportunity to use the dSSP score as a tool to dissect the biology of autism spectrum. The lack of power of this sub-analysis in our study requested the use of a MAF below 10%, which was not a standard in such similar molecular studies but with larger sample sizes. Obviously, those results are calling for a replication of the association between the dSSP and the hypo-sensory scores, as well as with the increased numbers of deleterious mutations in GABAergic genes in autism spectrum. Subsets within the data could also have reduced the power offered for multiple comparisons, more focused analysis would be done in further research. Furthermore, the highlighting of the hypo sensory score when exploring the sensory processing disabilities in ASD questioned the hypothesis of increased sensory precision which is currently gaining more traction in the literature explaining sensory differences in ASD by impairments of Bayesian inference (Karvelis et al., 2018; Palmer et al., 2017). Actually, this overrepresentation of the hyper-sensitivity compared to the hypo-sensitivity in the descriptions of autism spectrum could be the consequence of a reporting bias. This reporting bias stress out the need of quantitative

methods to explore sensory sensitivities and to complete the available questionnaires such as SSP based on observational, non-quantitative scales (Schaaf & Lane, 2015; Yamasaki et al., 2014).

CONCLUSION

In conclusion, the dSSP score we built in this study may facilitate the exploration of hypo- vs. hyper-sensory processing heterogeneity in autism and the identification of the associated neuro-biological mechanisms. One further step would be to estimate the E/I imbalance in autism spectrum by using electroencephalography (Bruining et al., 2020), and explore its correlation with the ratio of hypo- versus hyper-sensitivity processing patterns summarized by the dSSP score.

AUTHOR CONTRIBUTIONS

Aline Lefebvre, Freddy Cliquet, Julian Tillmann, Frederique Amsellem, Anita Beggiato, Anna Maruani, David Germanaud, Anouck Amestoy, Myriam Ly-Le Moal, Manuel Bouvard, Marion Leboyer, Tony Charman, Thomas Bourgeron, Richard Delorme, Guillaume Dumas designed the study. Aline Lefebvre, Frederique Amsellem, Anita Beggiato, Anna Maruani, Anouck Amestoy, AG, Manuel Bouvard, Richard Delorme, and the EU-AIMS LEAP group collected the data. Guillaume Dumas and Aline Lefebvre conducted the analyses. Guillaume Dumas and Richard Delorme were the initiators of the study project and asked for the blind rating of the items. Aline Lefebvre, Anita Beggiato, Anna Maruani, Frederique Amsellem rated the items of the SSP as related to hypo- or hyper-sensitivity for the construction of the dSSP. Aline Lefebvre, Freddy Cliquet, Julian Tillmann, Tony Charman, Thomas Bourgeron, Richard Delorme, and Guillaume Dumas made substantial contributions to the interpretation of the data. Aline Lefebvre, Richard Delorme, and Guillaume Dumas wrote the first and final draft of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All participants (where appropriate) and their parent/legal guardian provided written informed consent.

The Paris Autism Research International Sibpair (PARIS) study sample was granted approval by the local Ethics Committee or "Comité de Protection des Personnes" on 2008 November 14th, authorized by the French authorities (ANSM B80738-70 on 2008, August 11th), and registered in a public trial registry (NCT02628808).

Ethical approval for the EU-AIMS Longitudinal European Autism Project (LEAP) sample study was obtained through ethics committees at each sites Site, Ethics committee, ID/reference no: KCL & UCAM, London Queen Square Health Research Authority

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REFERENCES

Akoglu, H. (2018). User's guide to correlation coefficients. *Turkish Journal of Emergency Medicine*, *18*(3), 91–93. https://doi.org/10.1016/j.tjem.2018.08.001

Alexander, D. H., & Lange, K. (2011). Enhancements to the ADMIXTURE algorithm for individual ancestry estimation. *BMC Bioinformatics*, *12*, 246.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Aronson, J. K., & Ferner, R. E. (2017). Biomarkers—A general review. *Current Protocols in Pharmacology*, *76*, 1–17. https://doi.org/10.1002/cpph.19

Balasco, L., Pagani, M., Pangrazzi, L., Chelini, G., Viscido, F., Chama, A., Galbusera, A., Provenzano, G., Gozzi, A., & Bozzi, Y. (2022). Somatosensory cortex hyperconnectivity and impaired whisker-dependent responses in Cntnap2−/− mice. *Neurobiology of Disease*, *169*, 105742. https://doi.org/10.1016/j.nbd.2022.105742

Baranek, G. T., David, F. J., Poe, M. D., Stone, W. L., & Watson, L. R. (2006). Sensory experiences questionnaire: Discriminating sensory features in young children with autism, developmental delays, and typical development. *Journal of Child Psychology and Psychiatry*, *47*(6), 591–601. https://doi.org/10.1111/j.1469-7610.2005.01546.x

Baranek, G. T., Watson, L. R., Boyd, B. A., Poe, M. D., David, F. J., & McGuire, L. (2013). Hyporesponsiveness to social and nonsocial sensory stimuli in children with autism, children with developmental delays, and typically developing children. *Development and Psychopathology*, *25*(2), 307–320. https://doi.org/10.1017/S0954579412001071

Ben-Sasson, A., Gal, E., Fluss, R., Katz-Zetler, N., & Cermak, S. A. (2019). Update of a meta-analysis of sensory symptoms in ASD: A new decade of research. *Journal of Autism and Developmental Disorders*, *49*(12), 4974–4996. https://doi.org/10.1007/s10803-019-04180-0

Bonnet-Brilhault, F., Alirol, S., Blanc, R., Bazaud, S., Marouillat, S., Thépault, R. A., Andres, C. R., Lemonnier, É., Barthélémy, C., Raynaud, M., Toutain, A., Gomot, M., & Laumonnier, F. (2016). GABA/glutamate synaptic pathways targeted by integrative genomic and electrophysiological explorations distinguish autism from intellectual disability. *Molecular Psychiatry*, *21*(3), 411–418. https://doi.org/10.1038/mp.2015.75

Bruining, H., Hardstone, R., Juarez-Martinez, E. L., Sprengers, J., Avramiea, A. E., Simpraga, S., Houtman, S. J., Poil, S. S., Dallares, E., Palva, S., Oranje, B., Matias Palva, J., Mansvelder, H. D., & Linkenkaer-Hansen, K. (2020). Measurement of excitation-inhibition ratio in autism spectrum disorder using critical brain dynamics. *Scientific Reports*, *10*(1), 9195. https://doi.org/10.1038/s41598-020-65500-4

Charman, T. (2015). The new genetics of autism: A translational opportunity? *The Lancet. Psychiatry*, *2*(10), 856–857. https://doi.org/10.1016/S2215-0366(15)00389-2

Charman, T., Loth, E., Tillmann, J., Crawley, D., Wooldridge, C., Goyard, D., Ahmad, J., Auyeung, B., Ambrosino, S., Banaschewski, T., Baron-Cohen, S., Baumeister, S., Beckmann, C., Bölte, S., Bourgeron, T., Bours, C., Brammer, M., Brandeis, D., Brogna, C., de Bruijn, Y., … Buitelaar, J. K. (2017). The EU-AIMS Longitudinal European Autism Project (LEAP): Clinical characterisation. *Molecular Autism*, *8*, 27. https://doi.org/10.1186/s13229-017-0145-9

Chen, Q., Deister, C. A., Gao, X., Guo, B., Lynn-Jones, T., Chen, N., Wells, M. F., Liu, R., Goard, M. J., Dimidschstein, J., Feng, S., Shi, Y., Liao, W., Lu, Z., Fishell, G., Moore, C. I., & Feng, G. (2020). Dysfunction of cortical GABAergic neurons leads to sensory hyper-reactivity in a Shank3 mouse model of ASD. *Nature Neuroscience*, *23*(4), 520–532. https://doi.org/10.1038/s41593-020-0598-6

Dellapiazza, F., Vernhet, C., Blanc, N., Miot, S., Schmidt, R., & Baghdadli, A. (2018). Links between sensory processing, adaptive behaviours, and attention in children with autism spectrum disorder: A systematic review. *Psychiatry Research*, *270*, 78–88. https://doi.org/10.1016/j.psychres.2018.09.023

Dickinson, A., Jones, M., & Milne, E. (2016). Measuring neural excitation and inhibition in autism: Different approaches, different findings and different interpretations. *Brain Research*, *1648*, 277–289.

Dunn, W., & Westman, K. (1997). The sensory profile: The performance of a national sample of children without disabilities. *The American Journal of Occupational Therapy*, *51*(1), 25–34. https://doi.org/10.5014/ajot.51.1.25

Estes, A., Zwaigenbaum, L., Gu, H., St John, T., Paterson, S., Elison, J. T., Hazlett, H., Botteron, K., Dager, S. R., Schultz, R. T., Kostopoulos, P., Evans, A., Dawson, G., Eliason, J., Alvarez, S., Piven, J., & IBIS Network. (2015). Behavioral, cognitive, and adaptive development in infants with autism spectrum disorder in the first 2 years of life. *Journal of Neurodevelopmental Disorders*, *7*(1), 24. https://doi.org/10.1186/s11689-015-9117-6

Ferguson, B. R., & Gao, W. J. (2018). PV interneurons: Critical regulators of E/I balance for prefrontal cortex-dependent behavior and psychiatric disorders. *Frontiers in Neural Circuits*, *12*, 37. https://doi.org/10.3389/fncir.2018.00037

Fowlkes, E. B., & Mallows, C. L. (1983). A method for comparing two hierarchical clusterings. *Journal of the American Statistical Association*, *78*(383), 553–569. https://doi.org/10.1080/01621459.1983.10478008

Gogolla, N., Takesian, A. E., Feng, G., Fagiolini, M., & Hensch, T. K. (2014). Sensory integration in mouse insular cortex reflects GABA circuit maturation. *Neuron*, *83*(4), 894–905. https://doi.org/10.1016/j.neuron.2014.06.033

Green, S. A., Ben-Sasson, A., Soto, T. W., & Carter, A. S. (2012). Anxiety and sensory over-responsivity in toddlers with autism spectrum disorders: Bidirectional effects across time. *Journal of Autism and Developmental Disorders*, *42*(6), 1112–1119. https://doi.org/10.1007/s10803-011-1361-3

Haider, B., Häusser, M., & Carandini, M. (2013). Inhibition dominates sensory responses in the awake cortex. *Nature*, *493*(7430), 97–100. https://doi.org/10.1038/nature11665

Hall, J., Trent, S., Thomas, K. L., O'Donovan, M. C., & Owen, M. J. (2015). Genetic risk for schizophrenia: Convergence on synaptic pathways involved in plasticity. *Biological Psychiatry*, *77*(1), 52–58. https://doi.org/10.1016/j.biopsych.2014.07.011

Hartig, R., Wolf, D., Schmeisser, M. J., & Kelsch, W. (2021). Genetic influences of autism candidate genes on circuit wiring and olfactory decoding. *Cell and Tissue Research*, *383*(1), 581–595. https://doi.org/10.1007/s00441-020-03390-8

He, C. X., Cantu, D. A., Mantri, S. S., Zeiger, W. A., Goel, A., & Portera-Cailliau, C. (2017). Tactile defensiveness and impaired adaptation of neuronal activity in the *Fmr1* knock-out mouse model of autism. *The Journal of Neuroscience*, *37*(27), 6475–6487. https://doi.org/10.1523/JNEUROSCI.0651-17.2017

Hensch, T. K. (1998). Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science*, *282*(5393), 1504–1508. https://doi.org/10.1126/science.282.5393.1504

Kanehisa, M., & Goto, S. (2000). KEGG: Kyoto encyclopedia of genes and genomes. *Nucleic Acids Research*, *28*(1), 27–30. https://doi.org/10.1093/nar/28.1.27

Kanehisa, M., Sato, Y., Kawashima, M., Furumichi, M., & Tanabe, M. (2016). KEGG as a reference resource for gene and protein annotation. *Nucleic Acids Research*, *44*(D1), D457–D462. https://doi.org/10.1093/nar/gkv1070

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alföldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., … MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*, *581*(7809), 434–443. https://doi.org/10.1038/s41586-020-2308-7

Karvelis, P., Seitz, A. R., Lawrie, S. M., & Seriès, P. (2018). Autistic traits, but not schizotypy, predict increased weighting of sensory information in Bayesian visual integration. *eLife*, *7*, e34115. https://doi.org/10.7554/eLife.34115

Kircher, M., Witten, D. M., Jain, P., O'Roak, B. J., Cooper, G. M., & Shendure, J. (2014). A general framework for estimating the relative pathogenicity of human genetic variants. *Nature Genetics*, *46*(3), 310–315. https://doi.org/10.1038/ng.2892

Knoth, I. S., Vannasing, P., Major, P., Michaud, J. L., & Lippé, S. (2014). Alterations of visual and auditory evoked potentials in fragile X syndrome. *International Journal of Developmental Neuroscience*, *36*, 90–97. https://doi.org/10.1016/j.ijdevneu.2014.05.003

Kreiser, N. L., & White, S. W. (2015). ASD traits and co-occurring psychopathology: The moderating role of gender. *Journal of Autism and Developmental Disorders*, *45*(12), 3932–3938. https://doi.org/10.1007/s10803-015-2580-9

Lajonchere, C., Jones, N. E., Coury, D. L., & Perrin, J. M. (2012). Leadership in health care, research, and quality improvement for children and adolescents with autism spectrum disorders: Autism treatment network and autism intervention research network on physical health. *Pediatrics*, *130*, S62–S68.

Lane, A. E., Simpson, K., Masi, A., Grove, R., Moni, M. A., Montgomery, A., Roberts, J., Silove, N., Whalen, O., Whitehouse, A., & Eapen, V. (2022). Patterns of sensory modulation by age and sex in young people on the autism spectrum. *Autism Research*, *15*(10), 1840–1854. https://doi.org/10.1002/aur.2762

LeBlanc, J. J., & Fagiolini, M. (2011). Autism: A "critical period" disorder? *Neural Plasticity*, *2011*, 921680. https://doi.org/10.1155/2011/921680

Leblond, C. S., Nava, C., Polge, A., Gauthier, J., Huguet, G., Lumbroso, S., Giuliano, F., Stordeur, C., Depienne, C., Mouzat, K., Pinto, D., Howe, J., Lemière, N., Durand, C. M., Guibert, J., Ey, E., Toro, R., Peyre, H., Mathieu, A., … Bourgeron, T. (2014). Meta-analysis of SHANK mutations in autism spectrum disorders: A gradient of severity in cognitive impairments. *PLoS Genetics*, *10*(9), e1004580. https://doi.org/10.1371/journal.pgen.1004580

Lefebvre, A., Cohen, A., Maruani, A., Amsellem, F., Beggiato, A., Amestoy, A., Moal, M. L., Umbricht, D., Chatham, C., Murtagh, L., Bouvard, M., Leboyer, M., Bourgeron, T., & Delorme, R. (2021). Discriminant value of repetitive behaviors in families with autism spectrum disorder and obsessional compulsive disorder probands. *Autism Research*, *14*(11), 2373–2382. https://doi.org/10.1002/aur.2570

Lefter, R., Ciobica, A., Timofte, D., Stanciu, C., & Trifan, A. (2020). A descriptive review on the prevalence of gastrointestinal disturbances and their multiple associations in autism spectrum disorder. *Medicina*, *56*(1), 11. https://doi.org/10.3390/medicina56010011

Levin, A. R., & Nelson, C. A. (2015). Inhibition-Based Biomarkers for Autism Spectrum Disorder. *Neurotherapeutics*, *12*(3), 546–552. https://doi.org/10.1007/s13311-015-0350-1

Woolston, A., Tu, Y.-K., Baxter, P. D., & Gilthorpe, M. S. (2012). A comparison of different approaches to unravel the latent structure within metabolic syndrome. *PLoS One*, *7*(4), e34410. https://doi.org/10.1371/journal.pone.0034410

Lombardo, M. V., Lai, M.-C., & Baron-Cohen, S. (2019). Big data approaches to decomposing heterogeneity across the autism spectrum. *Molecular Psychiatry*, *24*(10), 1435–1450. https://doi.org/10.1038/s41380-018-0321-0

Loth, E., Charman, T., Mason, L., Tillmann, J., Jones, E., Wooldridge, C., Ahmad, J., Auyeung, B., Brogna, C., Ambrosino, S., Banaschewski, T., Baron-Cohen, S., Baumeister, S., Beckmann, C., Brammer, M., Brandeis, D., Bölte, S., Bourgeron, T., Bours, C., … Buitelaar, J. K. (2017). The EU-AIMS longitudinal European autism project (LEAP): Design and methodologies to identify and validate stratification biomarkers for autism spectrum disorders. *Molecular Autism*, *8*, 24. https://doi.org/10.1186/s13229-017-0146-8

MacCullagh, E. A., Rotschafer, S. E., Auerbach, B. D., Klug, A., Kaczmarek, L. K., Cramer, K. S., Kulesza, R. J., Jr., Razak, K. A., Lovelace, J. W., Lu, Y., Koch, U., & Wang, Y. (2020). Mechanisms underlying auditory processing deficits in fragile X syndrome. *FASEB Journal*, *34*(3), 3501–3518. https://doi.org/10.1096/fj.201902435R

MacLennan, K., O'Brien, S., & Tavassoli, T. (2022). In our own Words: The complex sensory experiences of autistic adults. *Journal of Autism and Developmental Disorders*, *52*, 3061–3075. https://doi.org/10.1007/s10803-021-05186-3

MacLennan, K., Rossow, T., & Tavassoli, T. (2021). The relationship between sensory reactivity, intolerance of uncertainty and anxiety subtypes in preschool-age autistic children. *Autism*, *25*(8), 2305–2316. https://doi.org/10.1177/13623613211016110

Masi, A., DeMayo, M. M., Glozier, N., & Guastella, A. J. (2017). An overview of autism spectrum disorder, heterogeneity and treatment options. *Neuroscience Bulletin*, *33*(2), 183–193. https://doi.org/10.1007/s12264-017-0100-y

McIntosh, D. N., Miller, L. J., Shyu, V., & Dunn, W. (1999). Development and validation of the short sensory profile. *Sensory Profile Manual*, *61*, 59–73.

McLaren, W., Gil, L., Hunt, S. E., Riat, H. S., Ritchie, G. R. S., Thormann, A., Flicek, P., & Cunningham, F. (2016). The Ensembl variant effect predictor. *Genome Biology*, *17*(1), 122. https://doi.org/10.1186/s13059-016-0974-4

Mercati, O., Huguet, G., Danckaert, A., André-Leroux, G., Maruani, A., Bellinzoni, M., Rolland, T., Gouder, L., Mathieu, A., Buratti, J., Amsellem, F., Benabou, M., Van-Gils, J., Beggiato, A., Konyukh, M., Bourgeois, J. P., Gazzellone, M. J., Yuen, R. K., Walker, S., … Bourgeron, T. (2017). CNTN6 mutations are risk factors for abnormal auditory sensory perception in autism spectrum disorders. *Molecular Psychiatry*, *22*(4), 625–633. https://doi.org/10.1038/mp.2016.61

Mikkelsen, M., Wodka, E. L., Mostofsky, S. H., & Puts, N. A. J. (2018). Autism spectrum disorder in the scope of tactile processing.

Developmental Cognitive Neuroscience, *29*, 140–150. https://doi.org/10.1016/j.dcn.2016.12.005

Neufeld, J., Taylor, M. J., Lundin Remnélius, K., Isaksson, J., Lichtenstein, P., & Bölte, S. (2021). A co-twin-control study of altered sensory processing in autism. *Autism*, *25*(5), 1422–1432. https://doi.org/10.1177/1362361321991255

O Miguel, H., Sampaio, A., Martínez-Regueiro, R., Gómez-Guerrero, L., López-Dóriga, C. G., Gómez, S., Carracedo, Á., & Fernández-Prieto, M. (2017). Touch processing and social behavior in ASD. *Journal of Autism and Developmental Disorders*, *47*(8), 2425–2433. https://doi.org/10.1007/s10803-017-3163-8

Orefice, L. L., Mosko, J. R., Morency, D. T., Wells, M. F., Tasnim, A., Mozeika, S. M., Ye, M., Chirila, A. M., Emanuel, A. J., Rankin, G., Fame, R. M., Lehtinen, M. K., Feng, G., & Ginty, D. D. (2019). Targeting peripheral somatosensory neurons to improve tactile-related phenotypes in ASD models. *Cell*, *178*(4), 867–886.e24. https://doi.org/10.1016/j.cell.2019.07.024

Palmer, C. J., Lawson, R. P., & Hohwy, J. (2017). Bayesian approaches to autism: Towards volatility, action, and behavior. *Psychological Bulletin*, *143*(5), 521–542. https://doi.org/10.1037/bul0000097

Pierce, S., Kadlaskar, G., Edmondson, D. A., McNally Keehn, R., Dydak, U., & Keehn, B. (2021). Associations between sensory processing and electrophysiological and neurochemical measures in children with ASD: An EEG-MRS study. *Journal of Neurodevelopmental Disorders*, *13*(1), 5. https://doi.org/10.1186/s11689-020-09351-0

Proff, I., Williams, G. L., Quadt, L., & Garfinkel, S. N. (2021). Sensory processing in autism across exteroceptive and interoceptive domains. *Psychology & Neuroscience*, *15*, 105–130. https://doi.org/10.1037/pne0000262

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A. R., Bender, D., Maller, J., Sklar, P., de Bakker, P. I. W., Daly, M. J., & Sham, P. C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*, *81*(3), 559–575.

Puts, N., Wodka, E. L., Harris, A. D., Crocetti, D., Tommerdahl, M., Mostofsky, S. H., & Edden, R. (2017). Reduced GABA and altered somatosensory function in children with autism spectrum disorder. *Autism Research*, *10*(4), 608–619. https://doi.org/10.1002/aur.1691

Rentzsch, J., Thoma, L., Gaudlitz, K., Tänzer, N., Gallinat, J., Kathmann, N., Ströhle, A., & Plag, J. (2019). Reduced sensitivity to non-fear-related stimulus changes in panic disorder. *Neuropsychobiology*, *78*(1), 31–37. https://doi.org/10.1159/000498867

Robertson, C. E., & Baron-Cohen, S. (2017). Sensory perception in autism. *Nature Reviews Neuroscience*, *18*(11), 671–684. https://doi.org/10.1038/nrn.2017.112

Rossow, T., MacLennan, K., & Tavassoli, T. (2022). The predictive relationship between sensory reactivity and depressive symptoms in young autistic children with few to no words. *Journal of Autism and Developmental Disorders*, 1–11. Advance online publication. https://doi.org/10.1007/s10803-022-05528-9

Rousseeuw, P. J. (1987). Silhouettes: A graphical aid to the interpretation and validation of cluster analysis. *Journal of Computational and Applied Mathematics*, *20*, 53–65. https://doi.org/10.1016/0377-0427(87)90125-7

Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior*, *2*, 255–267. https://doi.org/10.1034/j.1601-183X.2003.00037.x

Sapey-Triomphe, L.-A., Lamberton, F., Sonié, S., Mattout, J., & Schmitz, C. (2019). Tactile hypersensitivity and GABA concentration in the sensorimotor cortex of adults with autism. *Autism Research*, *12*, 562–575. https://doi.org/10.1002/aur.2073

Schaaf, R. C., & Lane, A. E. (2015). Toward a best-practice protocol for assessment of sensory features in ASD. *Journal of Autism and Developmental Disorders*, *45*(5), 1380–1395. https://doi.org/10.1007/s10803-014-2299-z

Schulz, S. E., & Stevenson, R. A. (2019). Sensory hypersensitivity predicts repetitive behaviours in autistic and typically-developing children. *Autism*, *23*(4), 1028–1041. https://doi.org/10.1177/1362361318774559

Sears, S. M., & Hewett, S. J. (2021). Influence of glutamate and GABA transport on brain excitatory/inhibitory balance. *Experimental Biology and Medicine (Maywood, N.J.)*, *246*(9), 1069–1083. https://doi.org/10.1177/1535370221989263

Siemann, J. K., Veenstra-VanderWeele, J., & Wallace, M. T. (2020). Approaches to understanding multisensory dysfunction in autism spectrum disorder. *Autism Research*, *13*(9), 1430–1449. https://doi.org/10.1002/aur.2375

Sinclair, D., Oranje, B., Razak, K. A., Siegel, S. J., & Schmid, S. (2017). Sensory processing in autism spectrum disorders and fragile X syndrome-from the clinic to animal models. *Neuroscience and Biobehavioral Reviews*, *76*, 235–253. https://doi.org/10.1016/j.neubiorev.2016.05.029

Sohal, V. S., & Rubenstein, J. L. R. (2019). Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. *Molecular Psychiatry*, *24*, 1248–1257. https://doi.org/10.1038/s41380-019-0426-0

Tavassoli, T., Layton, C., Levy, T., Rowe, M., George-Jones, J., Zweifach, J., Lurie, S., Buxbaum, J. D., Kolevzon, A., & Siper, P. M. (2021). Sensory reactivity phenotype in Phelan-McDermid syndrome is distinct from idiopathic ASD. *Genes*, *12*(7), 977. https://doi.org/10.3390/genes12070977

Thorvaldsdóttir, H., Robinson, J. T., & Mesirov, J. P. (2013). Integrative genomics viewer (IGV): High-performance genomics data visualisation and exploration. *Briefings in Bioinformatics*, *14*(2), 178–192. https://doi.org/10.1093/bib/bbs017

Thye, M. D., Bednarz, H. M., Herringshaw, A. J., Sartin, E. B., & Kana, R. K. (2018). The impact of atypical sensory processing on social impairments in autism spectrum disorder. *Developmental Cognitive Neuroscience*, *29*, 151–167. https://doi.org/10.1016/j.dcn.2017.04.010

Tillmann, J., Uljarevic, M., Crawley, D., Dumas, G., Loth, E., Murphy, D., Buitelaar, J., Charman, T., the AIMS-2-TRIALS LEAP group, Ahmad, J., Ambrosino, S., Auyeung, B., Baumeister, S., Beckmann, C., Bourgeron, T., Bours, C., Brammer, M., Brandeis, D., Brogna, C., … Zwiers, M. P. (2020). Dissecting the phenotypic heterogeneity in sensory features in autism spectrum disorder: A factor mixture modelling approach. *Molecular Autism*, *11*, 67. https://doi.org/10.1186/s13229-020-00367-w

Uljarević, M., Baranek, G., Vivanti, G., Hedley, D., Hudry, K., & Lane, A. (2017). Heterogeneity of sensory features in autism spectrum disorder: Challenges and perspectives for future research. *Autism Research*, *10*(5), 703–710. https://doi.org/10.1002/aur.1747

Uljarević, M., Lane, A., Kelly, A., & Leekam, S. (2016). Sensory subtypes and anxiety in older children and adolescents with autism spectrum disorder: Sensory subtypes and anxiety in autism. *Autism Research*, *9*(10), 1073–1078. https://doi.org/10.1002/aur.1602

Ward, J. (2019). Individual differences in sensory sensitivity: A synthesizing framework and evidence from normal variation and developmental conditions. *Cognitive Neuroscience*, *10*(3), 139–157. https://doi.org/10.1080/17588928.2018.1557131

Williams, Z. J., Failla, M. D., Gotham, K. O., Woynaroski, T. G., & Cascio, C. (2018). Psychometric evaluation of the short sensory profile in youth with autism Spectrum disorder. *Journal of Autism and Developmental Disorders*, *48*, 4231–4249. https://doi.org/10.1007/s10803-018-3678-7

Williams, Z. J., He, J. L., Cascio, C. J., & Woynaroski, T. G. (2021). A review of decreased sound tolerance in autism: Definitions, phenomenology, and potential mechanisms. *Neuroscience and Biobehavioral Reviews*, *121*, 1–17. https://doi.org/10.1016/j.neubiorev.2020.11.030

Wolfers, T., Floris, D. L., Dinga, R., van Rooij, D., Isakoglou, C., Kia, S. M., Zabihi, M., Llera, A., Chowdanayaka, R.,

Kumar, V. J., Peng, H., Laidi, C., Batalle, D., Dimitrova, R., Charman, T., Loth, E., Lai, M.-C., Jones, E., Baumeister, S., … Beckmann, C. F. (2019). From pattern classification to stratification: Towards conceptualising the heterogeneity of autism spectrum disorder. *Neuroscience & Biobehavioral Reviews*, *104*, 240–254. https://doi.org/10.1016/j.neubiorev.2019.07.010

Yamasaki, T., Maekawa, T., Takahashi, H., Fujita, T., Kamio, Y., & Tobimatsu, S. (2014). Electrophysiology of visual and auditory perception in autism spectrum disorders. In V. Patel, V. Preedy, C. Martin (Eds.), *Comprehensive Guide to Autism* (pp. 791-808). Springer. https://doi.org/10.1007/978-1-4614-4788-7_39

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