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1 **Tackling hypo and hyper sensory processing heterogeneity in Autism: from clinical**
2 **stratification to genetic pathways**

3
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45 **LAY SUMMARY**

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

53

54

55 **ABSTRACT**

56 **Background:** As an integral part of autism spectrum symptoms, sensory processing issues
57 including both hypo and hyper sensory sensitivities. These sensory specificities may result
58 from an excitation/inhibition imbalance with a poorly understood of their level of convergence
59 with genetic alterations in GABA-ergic and glutamatergic pathways. **Aims:** In our study, we

60 aimed to characterize the hypo/hyper-sensory profile among autistic individuals. We then
61 explored its link with the burden of deleterious mutations in a subset of individuals with
62 available whole-genome sequencing data. **Methods** To characterize the hypo/hyper-sensory
63 profile, the differential Short Sensory Profile (dSSP) was defined as a normalized and
64 centralized hypo/hypersensitivity ratio from the Short Sensory Profile (SSP). **Results:**
65 Including 1136 participants (533 autistic individuals, 210 first-degree relatives, and 267
66 controls) from two independent study samples (PARIS and LEAP), we observed a statistically
67 significant dSSP mean difference between autistic individuals and controls, driven mostly by
68 a high dSSP variability, with an intermediated profile represented by relatives. Our genetic
69 analysis tended to associate the dSSP and the hyposensitivity with mutations of the GABAergic
70 pathway. **Conclusion:** The major limitation was the dSSP difficulty to discriminate subjects
71 with a similar quantum of hypo- and hyper-sensory symptoms to those with no such symptoms,
72 resulting both in a similar ratio score of 0. However, the dSSP could be a relevant clinical score,
73 and combined with additional sensory descriptions, genetics and endophenotypic substrates,
74 will improve the exploration of the underlying neurobiological mechanisms of sensory
75 processing differences in autism spectrum.

76

77 **KEY-WORDS:** Autism Spectrum Disorder, sensory profile, clinical marker,
78 GABA/Glutamatergic pathway, excitation and inhibition balance

79 INTRODUCTION

80 Alongside differences in social communication and restricted, repetitive behaviours, sensory
81 issues are now considered as being a core defining diagnostic feature of the autism spectrum
82 (DSM-5, American Psychiatric Association, 2013). Reported in up to 87% of autistic
83 individuals, sensory processing sensitivities have been emphasized as a critical feature for
84 characterizing and understanding autism spectrum (Dellapiazza et al., 2018; Uljarević et al.,

85 2017). However, the sensory profiles described among autistic individuals are heterogeneous,
86 hampering progress to understand their biological substrates (Charman, 2015; Robertson &
87 Baron-Cohen, 2017). Sensory sensitivities symptoms are manifested as hyposensitivity,
88 hypersensitivity, avoidance of sensory stimuli, and/or unusual sensory interests, affecting the
89 visual, auditory, gustatory, olfactory, tactile, vestibular, proprioceptive and interoceptive
90 modalities (Sinclair et al., 2017). Sensory processing differences are associated with social
91 communication differences, restricted and repetitive behaviours, but also with specific
92 cognitive patterns, emerging sometimes as an earlier marker of autism spectrum (Uljarević et
93 al., 2016, Schulz & Stevenson, 2019).

94 According the neural systems processing sensory information, and social behavior, both
95 involving in autism spectrum, the excitation/inhibition (E/I) imbalance model was
96 hypothesized in some forms of autism spectrum (Haider et al., 2013, Rubenstein & Merzenich
97 et al. 2003). Despite the difficulty to predict the effect of neurotransmitters on the E/I balance
98 (Levin & Nelson, 2015), this E/I imbalance could be linked to a disequilibrium between
99 glutamatergic (principal excitatory neurotransmitter) and GABAergic (principal inhibitory
100 neurotransmitter) activity (Sears & Hewett, 2021, Sohal & Rubenstein, 2019, Dickinson et al.,
101 2016). Such disequilibrium could be at the origin of imbalance of sensory processing.
102 Preliminary studies on animal models carrying mutations in GABAergic or glutamatergic
103 pathway related genes associated with autism spectrum are starting to support such link
104 between E/I imbalance and sensory processing alterations (Gorgolla et al., 2014, ; He et al.,
105 2020; Orefice et al. 2019, Chen et al. 2020, Balasco et al. 2022). The E/I imbalance might
106 disrupt the neural homeostasis in individuals at risk for autism spectrum and thus participate in
107 their phenotypic diversity - such as the occurrence of epileptic seizures, or the diversity of
108 social communication symptoms (Dickinson et al., 2016). Also, the E/I imbalance may affect
109 the gating and gain control of sensory inputs and result in sensory processing differences

110 reported in autistic individuals (LeBlanc & Fagiolini, 2011; Mikkelsen et al., 2018, Ward et
111 al., 2019). For example, individuals carrying deleterious mutations in genes associated with
112 autism spectrum and involved the E/I homeostasis showed anomalous event-related potentials
113 (ERP) with auditory deviance detection (Williams et al., 2021) such as those with *NLGN4*
114 (Bonnet-Brilhault et al., 2016) or *FMRP* mutations (Knoth et al., 2014; Hall et al., 2015) or in
115 Fragile X syndrome (McCullagh et al., 2020).

116 To improve the characterization of sensory processing differences in autism spectrum and
117 facilitate the exploration of their biological substrates, we sought to determine a score
118 summarizing the sensory symptom directions and heterogeneity, which could be secondarily
119 related to autism spectrum E/I imbalance. We aimed to construct a summarizing score as a
120 normalized and centralized ratio of the hypo- to hyper- sensitivity derived from the Short
121 Sensory Profile (SSP), a commonly used questionnaire to explore the sensory symptoms
122 frequently reported in autistic individuals from childhood to adulthood. The SSP used by large-
123 scale projects in the field (Autism Speaks Autism Treatment Network (Lajonchere, Jones,
124 Coury & Perrin, 2012), EU-AIMS Longitudinal European Autism Project (Charman et al.,
125 2017)) was constructed with 38 items representing a heterogeneous combination of sub-
126 constructs (McIntosh et al., 1999). Despite its validity to dissect sensitivity symptoms
127 (Williams et al., 2018) the SSP items are unequally distributed across both sensory modalities
128 and subtypes of sensory processing differences. For example the SSP taps constructs of visual
129 hyperresponsiveness, auditory hyperresponsiveness, and auditory hyporesponsiveness, but not
130 visual hyporesponsiveness. We therefore have reconsidered the diversity of the sensitivity
131 symptoms by splitting them in a two dimensional perspective hypo- vs. hyper- sensitivity.
132 Additional questionnaires may have been more efficient to explore the hypo- and hyper-
133 sensitivity in autism spectrum but none of them better account for the unequal distribution
134 between the two sensory modalities and the subtypes of sensory processing dysfunction. The

135 Sensory Experience Questionnaire explores mainly hypo or hyper aspects but is not adapted to all ages
136 (child ages 2-12 years) (Version 3.0; SEQ; Baranek, David, Poe, Stone, & Watson, 2006). To date,
137 there are still no studies highlighting the sensory patterns of individuals across all the sensory
138 domains in terms of hypo and hyper sensitivity. However, recent evidence supports the
139 coexistence of both hypo- and hyper sensitivity in autism spectrum among the different
140 domains with an impact on social functioning (Thye et al., 2018). We reconsidered the diversity
141 of the sensitivity symptoms by splitting the SSP items in a two-dimensional perspective hypo-
142 vs. hyper- sensitivity. The literature described an association between hypersensitivity and an
143 increase in the E/I ratio (Sapey Triomphe et al., 2019), suggesting conversely that
144 hyposensitivity could be more driven by a decrease of the E/I ratio. We thus hypothesized that
145 the differential SSP score (dSSP), when different from 0, would indirectly reflect at the brain
146 level the function imbalance related to the glutamatergic and the GABAergic neuromodulators
147 disequilibrium (Rubenstein & Merzenich, 2003, Sohal & Rubenstein, 2019). To achieve the
148 first goal of this study, we empirically defined the hypo- or hyper- sensory processing type of
149 each item of the SSP questionnaire to calculate the dSSP score. We then tested the relevance
150 of the dSSP score by quantifying and exploring its distribution in two independent samples of
151 autistic individuals and with typical development from the PARIS and the EU-AIMS study
152 samples (n=1136). We also challenged the empirical construct of the dSSP score to a more
153 data-driven procedure based on a clustering approach of all the SSP questionnaire items. The
154 second step of our study was to explore if the dSSP score could facilitate the exploration of the
155 biological background involved in the sensory sensitivities reported in the autistic individuals.
156 As a very preliminary study, we aimed to conduct a genetic study exploring in a modest sample
157 of participants the relationship between the dSSP score and the burden of deleterious mutations
158 affecting genes of the glutamatergic and the GABAergic pathways. We hypothesized the

159 variability of the dSSP score would be correlated with the load of deleterious mutations
160 affecting the glutamatergic and GABAergic equilibrium.

161

162

163 **METHODS**

164 *Participants*

165 In total, 1,136 participants were enrolled in the study from two independent study samples. The
166 Paris Autism Research International Sibpair (PARIS) study sample included 165 autistic
167 individuals, their 210 unaffected first-degree relatives and 97 individuals with typical
168 development at the Child and Adolescent Psychiatry Department, Robert Debre Hospital, Paris
169 (France) between April 2013 and September 2016. The EU-AIMS Longitudinal European Autism
170 Project (LEAP) sample study was composed of 384 autistic individuals and 280 individuals
171 with typical development included between January 2014 and August 2016 (Loth et al., 2017).
172 The demographic and clinical descriptions of the individuals enrolled in both samples are
173 reported in Table 1. The clinical characterization of the participants from the PARIS and LEAP
174 study were included following the method described elsewhere (Lefebvre et al. 2021; Charman
175 et al., 2017; Loth et al., 2017). As a summary, the diagnosis of autism spectrum was based on
176 DSM-IV-TR/5 criteria and made by summing the information from the Autism Diagnosis
177 Interview-Revised (ADI-R), the Autism Diagnostic Observation Scale - second edition
178 (ADOS-2), and clinical reports from experts in the field. The cognitive abilities of individuals
179 were also assessed using the Wechsler Intelligence Scales adapted to the age of individuals.
180 The PARIS and the LEAP study samples were granted approval by their local Ethics
181 Committee. They were carried out in accordance with Good Clinical Practice (ICH GCP)
182 standards. Written informed consent was obtained from all participants. For the patients who

183 were unable to consent for themselves, a parent or legal guardian consented to the study on
184 their behalf.

185

186 ***Sensory profile of individuals included in the study***

187 The sensory profile of all participants included in the study was assessed with the Short Sensory
188 Profile (McIntosh et al., 1999). Each item of this 38-item questionnaire is scored on a 5-point
189 Likert scale (1=always, 2=frequently, 3=occasionally, 4=seldom, and 5=never). The 38 items
190 - SSP is a shortened form of the Sensory Profile questionnaire (Dunn & Westman, 1997), which
191 demonstrated the highest discriminatory power of divergent sensory processing. The SSP
192 questionnaire is composed of 7 subscales including tactile sensitivity, taste/smell sensitivity,
193 movement sensitivity, visual/auditory sensitivity, under-responsive/seeking sensation, auditory
194 filtering, and low energy/weak. Lower scores indicate more sensory issues. The SSP measure
195 has been psychometrically validated in autistic individuals aged 3–18-year-old (Williams et al.,
196 2018). For the present study, we reversed-scored each item to allow a more direct comparison
197 with the summarizing score we built (Figures 1.A & 2.A). Concerning the PARIS sample study,
198 the SSP was collected for autistic individuals at T0, month 3 and year 1 and 2 for all subjects
199 of the autistic group. Testing the stability among the development of the dSSP, we performed
200 a two-way analysis of variance (ANOVA) with repeated measures to compare results at
201 different time points.

202

203 ***Building of the dSSP score***

204 We constructed a summarizing score as a normalized and centralized ratio of the hypo- to
205 hyper- sensitivity derived from the SSP questionnaire. We first asked four senior clinical
206 experts in the field of autism spectrum (AL, AB, AM, FA) and blind to the hypothesis of this
207 study to determine which items of the scale were dedicated to the exploration of hyper-, hypo-

208 sensitivity or which seemed to be related to both hyper- and hypo- sensitivity. We then split
209 the 38 items into three subgroups, depending on their ability to explore sensory features related
210 to hyper- (n=19), hypo- (n=16) sensitivities or uncertain (n=3) (Supplementary Table 1). Hypo-
211 and hyper characterization corresponded to an agreement of at least $\frac{3}{4}$ of the raters for one of
212 these two characterizations. If only half of the raters were agreed, the item was defined by the
213 ‘uncertain’ characterization. Since the ‘uncertain’ item did not discriminate between hypo and
214 hyper sensory, it was not considered in the calculation of the dSSP. We quantified inter-
215 observer stability using Kendall rank correlation (Supplementary Table 2). We finally
216 calculated the dSSP score for each individual, a centralized and normalized score reflecting the
217 ratio between the average scores of items related to hypersensitivity (e.g. hyper-sensory score)
218 (n=19) and to hyposensitivity (e.g. hypo-sensory score) (n=16) (Table 2). A positive dSSP
219 score represented a tendency to hyper- sensitivity and a negative one a tendency of hypo-
220 sensitivity. Whereas the dSSP score combined information from two component scores (hypo-
221 and hyper-sensory scores), we improved our analysis by exploring separately the hypo- and
222 hyper- sensory scores.

223

224 *Clustering distribution of the SSP questionnaire items*

225 To validate the clinical-driven clusters (hypo, hyper and uncertain), we compared our clusters
226 with data-driven clusters. We explored the link between the dSSP score and the sensory
227 processing modalities using the VARCLUS procedure that divides a set of numeric variables
228 into clusters (JMP software; SAS Institute Inc. 2017). The VACLUS provides no overlapped
229 components unlike the factor analysis. Although the factor analysis allowing components must
230 be interpreted by considering the correlations between the factors, the Varclus allows a simpler
231 interpretation of the results. This iterative method extracted oblique components to identify
232 one-dimensional clusters of mutually correlated variables (Woolston et al., 2012). We used the

233 SSP items scores reported by the autistic participants from the PARIS and the LEAP study
234 samples and then explored the items gathering in each cluster (e.g. item XX from cluster Y was
235 categorized as hyper- or hypo- sensitivities or uncertain). We used a Chi2 test to test for a
236 significant relationship between variables and a Cramer's V test, which was a post-hoc test
237 indicating how significant this relationship is (scoring from 0 for the low association to 1 for
238 the high association). Using Python script (Python Software Foundation, version 3.7), we
239 calculated the silhouette score (scoring from -1 to 1) (Rousseeuw, 1987) to interpret and
240 validate the consistency within clusters and the Fowlkes-Mallows similarity score (Fowlkes &
241 Mallows, 1983) to assess the similarity between PARIS and LEAP sample clustering (scoring
242 from 0 to 1).

243

244 *Genetic profiles*

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

257 functionally annotated with Variant Effect Predictor (VEP) (using Ensembl 92) (McLaren et
258 al., 2016). Additionally, we annotated the variants for their frequency in the population from
259 the gnomAD database version 2.1.1 (Karczewski et al., 2019) and for their Combined
260 Annotation Dependent Depletion score (CADD version 1.3) (Kircher et al., 2014) to evaluate
261 their deleteriousness. We then queried all variants with a minor allele frequency (MAF) $\leq 10\%$
262 in the gnomAD database, which were either likely gene disruptive (LGD) variants (*i.e.* stop
263 gain, stop loss, start loss, splice acceptor, splice donor or frameshift) or missense mutations
264 with a CADD score ≥ 30 (MIS30). SNVs with a CADD PHRED-scaled score > 30 were at the
265 top 0.01% across all potential ~ 9 billion SNVs and were therefore considered as having a high
266 likelihood to impact protein structure/function (Rentzsch et al., 2019). To control population
267 structure, we performed a PCA analysis using PLINK 1.9 (Purcell et al., 2007), and we used
268 the first four components as covariables for all the burden analysis. We used GRAVITY
269 (<http://gravity.pasteur.fr>), an open-source Cytoscape app that allowed an efficient visualization
270 and analysis of all the exonic variants stored in a database by mapping them on protein-protein
271 interaction (PPI). Variants of interest were manually curated by visualization of aligned
272 sequencing data (BAM files) using IGV (Thorvaldsdóttir et al., 2013). We used admixture to
273 ascertain the ancestry of the participants (Alexander & Lange, 2011). In our sample, 86% of
274 the participants were from European descent. We finally ascertained the genetic variants related
275 to the GABAergic and glutamatergic pathways by using the KEGG database (Supplementary
276 Table 3) (Kanehisa et al., 2016; Kanehisa & Goto, 2000). We considered the GABAergic
277 synapse pathway (entry I04727) and the Glutamatergic synapse pathway (entlhsa04724) and
278 scored the number of deleterious mutations found in respectively the two pathways. At the end,
279 to explore the link between the dSSP score and the burden of genetic mutations in the
280 GABAergic and/or glutamatergic pathways, we built a linear model with separately the dSSP,
281 hypo- and hyper-sensory scores and the carrier of variants within the GABAergic and

282 Glutamatergic pathways. We also used the bootstrap method and reported median p-values and
283 Cohen-d obtained across 2000 re-sampling. Although the association of the GABAergic and
284 Glutamatergic pathways with sensory processing differences (Puts et al., 2017) and hyper-
285 sensitivity (Sapey-Triomphe et al, 2019) are suggested in literature, no direct relationship
286 between the GABA/Glutamate ratio imbalance and a clinical hypo-sensitivity have been
287 reported. To explore these associations, we thus run linear models exploring the number of
288 deleterious variants within the GABAergic and Glutamatergic pathways considering the hypo-
289 , and hyper- sensory scores and their interactions as variables of adjustment.

290

291 **RESULTS**

292

293 *dSSP scores in the PARIS Study and LEAP Study Samples*

294 In accordance with our hypothesis, the variance of the dSSP scores significantly differed
295 between autistic individuals and controls in the PARIS study samples with a trend for a more
296 hypersensitive sensory pattern in the autistic group than in controls. Despite a moderate sample
297 size, the intergroup comparison (pair by pair: proband, first-degree relatives and controls) did
298 not reach significance with tiny effect sizes ($\eta^2 < 0.04$) (Table 2). We however observed a high
299 heterogeneity in the variance of the dSSP scores between the three groups (Browne-Forsythe
300 test: $F=39.9$, $p=1.0 \times 10^{-18}$) (Figures 1.B & C). Autistic individuals had a more extreme sensory
301 pattern on both sides of the distribution when compared to the other groups of individuals. The
302 first-degree relatives appeared with an intermediate distribution profile between autistic and
303 typically developing participants. We then built a linear model for the dSSP scores including
304 group status (autistic participants, first-degree relatives, or controls), sex, age, and their
305 interactions (age, sex, group). A significant positive regression equation was found ($F=1.7$,
306 $R^2=0.05$, $p=0.001$). We observed positives significant effects of age ($F=12.1$, $p=0.0006$,

307 $\eta^2=0.02$), sex ($F=7.9$, $p=0.005$, $\eta^2=0.02$), age x group interaction ($F=4.31$, $p=0.01$, $\eta^2=0.018$)
308 and a tendency of group status effect ($F=6.1$, $p=0.05$, $\eta^2=0.03$). The dSSP increased with an
309 increase of age, with higher rates in males vs females and in the group of autism spectrum vs
310 relatives vs controls. No statistically significant interaction effect was found for sex x group
311 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
312 ($F=1.87$, $p=0.15$, $\eta^2=0.008$). ANOVAs with repeated measures (at baseline, month 3 and Year
313 1 and 2) of the SSP and the dSSP scores did not show any developmental effect ($F=1.3$,
314 $p=0.29$).

315 To replicate our findings, we performed a similar analysis on the LEAP study sample. We also
316 observed a more hypersensitive sensory pattern in autistic individuals than in controls (t -
317 value=2.28, dof=436, $p=0.02$, Cohen's $d=3.67$) (Table 2). Building a linear model similar to
318 the one used on the PARIS cohort, we also observed a significant regression equation ($F=4.46$,
319 $R^2=0.05$, $p<0.0001$). We also reported a higher dSSP scores variance in autistic participants
320 compared to controls (Brown-Forsythe test: $F=51.3$, $p=3.4 \times 10^{-12}$) (Figures 2.B & C) and
321 significant positive effects of age ($F=6.6$, $p=0.01$, $\eta^2=0.01$), sex ($F=5.8$, $p=0.02$, $\eta^2=0.01$)
322 and group status ($F=4.6$, $p=0.03$, $\eta^2=0.007$). The dSSP increased with an increase of age, with
323 higher rates in males vs females and in the autistic group vs controls. No statistically significant
324 interaction effect was found for sex x group status ($F=0.31$, $p=0.57$, $\eta^2=0.0005$), sex x age
325 ($F=0.04$, $p=0.83$, $\eta^2=0.0008$), age x group ($F=1.92$, $p=0.17$, $\eta^2=0.003$), and sex x group x age
326 interaction ($F=0.20$, $p=0.65$, $\eta^2=0.0003$).

327

328

329 *Items-based Clustering*

330 The VARCLUS procedure based on the item scores of the SSP scale reported in the autistic
331 participants of the PARIS study sample, converged into 9 clusters with 60.5% of variance

332 explained (Supplementary Table 4; silhouette score=0.11, bootstrap empirical p-
333 value<0.0001). The clusters we obtained were not similarly distributed in items considering
334 the hypo-, hyper- sensitivities or uncertain [Chi² (dof=16, N=165)=31.2, p=0.01, Cramer's
335 V=0.64] (Supplementary Table 5). We re-ran the analysis on the LEAP study sample. We
336 found 7 clusters which explained 63% of variance (Supplementary Table 6; silhouette score=-
337 0.08; bootstrap empirical p-value <0.0001). The clusters showed also a statistically significant
338 difference in frequency of the items considering the hypo-, hyper- sensitivities or uncertain
339 (Chi² (dof=12, N=384)=35.9, p=0.0003, Cramer's V=0.69) (Supplementary Table 7).
340 We then compared the clustering of the SSP items obtained among the autistic participants of
341 the LEAP study sample to the one obtained on the Paris sample. Clusters derived from both
342 PARIS and LEAP study samples were similar (Fowlkes-Mallows similarity score=0.56, p <
343 0.0001). Within each cluster, one item was more representative than the others (Supplementary
344 Tables 4 & 6). Interestingly, two SSP items were described as the most representative of their
345 own clusters in both PARIS and LEAP study samples: item 17 which was related to hypo-
346 sensitivity and item 36 related to hyper-sensitivity.

347

348 ***dSSP score correlated with GABA and/or Glutamatergic pathway mutation enrichments in***
349 ***the autistic group***

350 We investigated if differences in dSSP scores were associated with a distinct burden of
351 deleterious variations affecting genes related to the GABA and/or Glutamatergic pathways. We
352 only considered for each subject the Likely Gene Disrupting (LGD) and predicted deleterious
353 missense mutations (CADD>30) (Supplementary Figure). We first built a linear model for the
354 dSSP score including the burden of gene mutations in GABAergic and/or the glutamatergic
355 pathways, and their interactions. In autistic participants (n=135), our analysis reported a trend
356 for a positive association with a burden of gene mutations in the GABAergic pathway but not

357 in the glutamatergic pathway, nor in the both pathways ($R^2=0.05$, $F=2.18$, $p=0.09$; GABA:
358 $F=3.36$, $p=0.06$, $\eta^2=0.02$; Glutamate: $F=0.08$, $p=0.77$, $\eta^2=0.0008$; both pathways: $F=2.68$,
359 $p=0.11$, $\eta^2=0.02$ (Supplementary Figure). Spearman's rank correlation was computed to assess
360 the relationship between the hypo-, hyper sensory & dSSP scores and the burden of gene
361 mutations in the GABAergic pathway and highlighted a trend for a positive relation
362 $r(133)=0.33$, $p=0.05$). We then performed a bootstrap analysis -across 2000 resampling- to
363 explore further the relationship between the dSSP score and the burden of deleterious mutations
364 in the GABA pathway. We observed autistic individuals and with a high dSSP score indeed
365 reported a significant enrichment of deleterious mutations in the GABAergic gene pathway
366 ($p=0.004$, $d=1.15$). We finally ran a similar analysis only in individuals from European ancestry
367 (based on the results of the admixture analysis) and we obtained a similar trend.

368

369 ***Hypo-, hyper- sensory scores:***

370 In PARIS and LEAP study samples, the hypo-sensory score was significantly different between
371 the autistic group and the others groups (PARIS: first-degree relatives and controls groups:
372 $R^2=0.3$, $F=93.45$, $p<0.0001$, $h^2=0.30$; LEAP: $t\text{-ratio}=7.74$, $ddl=436$, $p<0.0001$, Cohen's
373 $d=0.74$), with a higher heterogeneity in the autistic group (PARIS: Brown-Forsythe test:
374 $F=18.28$, $p<0.0001$; LEAP: Brown-Forsythe test: $F=6.56$, $p=0.01$).

375 Similarly, the hyper-sensory score was significantly different in the autistic group compared to
376 the others groups (PARIS: first-degree relatives and controls groups, $R^2=0.31$, $F=96.54$,
377 $p<0.0001$, $h^2=0.31$; LEAP: controls group, $t\text{-ratio}=9.28$, $ddl=436$ $p<0.0001$, Cohen's- $d=0.74$),
378 with a higher heterogeneity in the autistic group in the PARIS study sample (Brown-Forsythe
379 Test: $F=19.30$, $p<0.0001$), not found in the LEAP study sample (Brown-Forsythe test: $F=3.55$,
380 $p=0.06$). Results figure in Table 2.

381 The relation of the hypo- and hyper- scores with a distinct burden of deleterious variations
382 affecting genes related to the GABA and/or Glutamatergic pathways by considering for each
383 subject the Likely Gene Disrupting (LGD) and predicted deleterious missense mutations
384 (CADD>30) was explored. Despite an absence of statistical significance, the GABA F-value
385 showed a trend for a negative association of the hypo-sensory score and the burden of gene
386 mutation in the GABAergic pathway ($R^2=0.03$, $F=1.25$, $p=0.29$; GABA: $F=3.21$, $p=0.08$,
387 $\eta^2=0.03$; Glutamate: $F=0.24$, $p=0.63$, $\eta^2=0.002$; both pathways: $F=0.01$, $p=0.92$, $\eta^2=0.0001$).
388 However, no hyper-sensory score relation was observed with the with GABA and/or
389 Glutamatergic pathway mutation enrichments ($R^2=0.02$, $F=0.88$, $p=0.45$; GABA: $F=0.02$,
390 $p=0.89$, $\eta^2=0.0002$; Glutamate: $F=1.10$, $p=0.29$, $\eta^2=0.01$; both pathways: $F=1.53$, $p=0.22$,
391 $\eta^2=0.01$).

392 Exploring distinctly the two pathways and their relation with the sensory processing
393 atypicalities (i.e. hypo-, hyper sensory processing and their interaction), the linear models also
394 found no significant results, but an interesting trend for a negative association of the hypo-
395 sensory score and the burden of gene mutation in the GABAergic pathway (GABA: $R^2=0.05$,
396 $F=2.06$, $p=0.11$; interaction: $F=1.15$, $p=0.3$, $\eta^2=0.009$; Hypo-sensory score: $F=4.36$, $p=0.04$,
397 $\eta^2=0.03$; Hyper-sensory score $F=1.85$, $p=0.18$, $\eta^2=0.01$; Glutamatergic pathway: $R^2=0.01$,
398 $F=0.5$, interaction $F=0.23$, $p=0.63$, $\eta^2=0.002$, Hypo-sensory score: $F=0.05$, $p=0.82$, $\eta^2=0.0004$;
399 Hyper-sensory score: $F=0.68$, $p=0.41$, $\eta^2=0.005$). Spearman's rank correlation was computed
400 to assess the relationship between the hypo-sensory score and the burden of gene mutations in
401 the GABAergic pathway and highlighted a trend for a negative relation $r(133)=-0.38$, $p=0.06$).
402 These results suggested that the increase of mutations in the GABAergic genes would be related
403 to the decrease of the hypo sensory score.

404

405

406 **DISCUSSION**

407 Through our study, we aimed to further characterize sensory processing divergences in autism
408 spectrum and improve our ability to explore their potential underlying neurobiological
409 mechanisms (Sieman et al., 2020). We thus built a summarizing score - the dSSP score - which
410 showed that, on average, autistic individuals displayed a trend for a hyper-sensitivity profile,
411 reaching only significance in the LEAP sample (through its power to detect significant results).
412 This association may be driven by the load of comorbidity reported in the autistic individuals,
413 since previous studies reported higher levels of sensory reactivity in those severity of associated
414 comorbidities (Kreiser & White, 2015, Tillmann et al., 2020). This association was observed
415 in individuals with comorbid anxiety or depressive symptoms (MacLennan, Rossow, et
416 Tavassoli, 2021; Rossow et MacLennan, 2021) but also somatic complaints (Lefter et al.,
417 2020). Previous findings in the literature also reported a hyper- sensitivity profile in autistic
418 children. This hyper- sensitivity profile was previously associated with the severity of
419 expressive language deficit (Rossow et MacLennan, 2021 but also with early stages of their
420 developmental trajectory (Green et al., 2012, Ben-Sasson, Gal, Fluss, Katz-Zetler et Cermak,
421 2019) - as we reported both in the PARIS and the LEAP samples. In our study, we reported a
422 significant positive interaction (i.e. in favor of hyper-sensitivity) between dSSP score and
423 chronological age of the participants, which is coherent with the literature (Lane et al., 2022),
424 with a dSSP score stability across child development described by repeated measures on the
425 PARIS study. Although the sensory differences appear early in the developpement, the dSSP
426 stability appears as a good biomarker candidate of autism spectrum (Baranek et l., 2013, Estes
427 et al., 2015, Miguel et al., 2017, Aronson et Ferner, 2017).

428 In our study, we also observed a larger dSSP score variability in autistic individuals
429 than in controls which is in line with the heterogeneity reported in autism spectrum in many
430 research areas, such as brain imaging (Masi et al., 2017). Our results stressed further the need

431 for partial phenotypes beyond categorical diagnosis to help in patients' stratification and
432 delineate more homogeneous subgroups (Wolfers et al., 2019, Proff et al., 2021). The dSSP
433 score may offer a relevant setting to explore the heterogeneity in autism spectrum (Lombardo
434 et al, 2019). It could also pave new ways to determine the biological mechanisms associated
435 with sensory sensitivities in autism. Although our results need to be replicated in larger samples
436 and combined with additional dimensions, the dSSP score may help to uncover new sub-groups
437 with more coherent neurobiological mechanisms (Uljarević et al., 2016; Bruinning et al., 2020).
438 Interestingly, the intermediate dSSP score distribution we observed in the first-degree relatives
439 between autistic individuals or those with typical development, suggested a determination of
440 the dSSP score by inherited biological substrates (Neufeld et al, 2021), which was in line with
441 our initial hypothesis.

442 To validate the empirical construct of the dSSP score, we performed a data driven
443 approach of the hypo- and hyper- sensory symptoms related items. The cluster analysis
444 revealed a very similar distribution of the items encompassed in the data-driven clusters
445 compared to those included in the two dimensions we empirically built. While it does not give
446 two clusters, the automated analysis still support that this two-dimensional perspective on
447 sensory sensitivities in autism spectrum (hypo-, hyper- sensitivity dimensions) (Baranek, David,
448 Poe, Stone, & Watson, 2006) is statistically relevant on top of being clinically easier to interpret.
449 The data-driven analysis revealed that two items that emerged as being highly representative
450 of both clusters were identified, whatever the PARIS or the LEAP cohort we considered: item
451 17 (Supplementary Table 1: Item17 - "Becomes overly excitable during movement activity")
452 drove mainly the variability of the hypo- sensitivity related cluster, and item 36 (Supplementary
453 Table 1 : Item 36 - "Is bothered by bright lights after others have adapted to the light") the
454 variability of the hyper- sensitivity related cluster. Beyond the simple dichotomy of sensitivity
455 anomalies in autism spectrum, the dSSP score integrated the personal sensory processing

456 impairment into a ratio score facilitating for example the indirect exploration of the relationship
457 between these symptoms and the E/I imbalance (Pierce et al., 2021).

458 We finally performed an exploratory analysis to explore the relationship between the
459 dSSP score and the load of deleterious mutations affecting the genes of glutamatergic &
460 GABAergic pathways (Supplementary Table 3). Individuals with a high dSSP score i.e., those
461 with an excess of hyper sensory processing sensitivities, displayed a significant trend for the
462 enrichment of deleterious gene mutations in the GABAergic pathway. Our results were in
463 accordance with numerous reports describing the association between genes affecting directly
464 (such as *GABRA4*, *GRIN1*) or indirectly (such *CACNA1C*, *SHANK1-3*, *CNTN3-6*) the
465 GABAergic pathway homeostasis and sensory processing divergences in autism spectrum
466 (Leblond et al, 2014; Mercati et al, 2017; Tavassoli et al, 2021, Hartig et al., 2021). The excess
467 load of deleterious mutations affecting the genes of GABAergic pathway reported in our study
468 may reduce the GABAergic tone (Ferguson and Gao, 2018) - as previously showed (Sapey-
469 Triomphe et al., 2019) - and may explain the hypersensitivity observed in autism spectrum.
470 Furthermore, our result suggested an association between these deleterious mutations affecting
471 the genes of GABAergic pathway are associated with “less hypo-sensitivity”. These results
472 concord with the effect of the sensory experience in early life on the brain, as highlighted by
473 the supranormal sensitivity reported after visual stimulation occurring following a period of
474 dark rearing at the peak of the critical period for plasticity (Hensch, 1998). Our study supports
475 the hypothesis of a potential link between GABAergic pathway and hypo-sensitivity.

476

477 **LIMITATIONS**

478 One major limitation of the results we obtained was the difficulty of the dSSP score to
479 discriminate participants with a similar quantum of hypo- and hyper- sensory symptoms

480 resulting in a ratio score of 0 to those with no such symptoms but also resulting in a similar
481 ratio score of 0.

482 Additional questionnaires such as the Sensory Experience Questionnaire may have
483 been more efficient to explore the hypo- and hyper- sensitivity in autism spectrum, but none of
484 them better account for the unequal distribution between the two sensory modalities and the
485 subtypes of sensory processing differences. Moreover, the SSP is robustly employed in large-
486 scale projects in the field of autism (Autism Speaks Autism Treatment Network (Lajonchere,
487 Jones, Coury & Perrin, 2012), EU-AIMS Longitudinal European Autism Project (Charman et
488 al., 2017)). The SSP allows to split these symptoms into 2 distinct dimensions we aimed to
489 consider in our study. However, our results must be considered with caution since SSP items
490 are unequally distributed across sensory modalities and subtypes of sensory processing
491 differences. Moreover, the clinicians may have been influenced by the theory relating
492 hyposensitivity and seeking when rating the items 15-21 (including the item 17) related to the
493 hypo-sensitivity. However, this theory is not confirmed in the literature (MacLennan, O'Brien
494 & Tavassoli, 2022). The "uncertain" item 13 rating could also be discussed. Item 13 relates to
495 the fear of heights and heights. Hypo-sensitivity to vestibular sensation would generally present
496 as an absence of fear and the clusters on PARIS and LEAP classified item 13 with hyper items.
497 However, this item was associated with hypo-sensory by half of the raters, probably related to
498 anticipatory anxiety of mismanagement of danger due to the hyposensitivity. This discordant
499 classification could be the result of understanding item bias. Nevertheless, as both items
500 resulted in a discordant classification between raters, they were not considered in constructing
501 the dSSP. This exclusion must be considered when interpreting the dSSP score, which provides
502 additional information to the SSP score but must not be interpreted according to the SSP score.
503 The Kendall rank correlation coefficients for inter-rater agreement were relatively low
504 (Akoglu, 2018), but acceptable considering the number of items (n=36), and of raters (n=4).

505 Despite our cluster analyses trending to validate the empirical construct of the dSSP score, the
506 validation of this two mains dimensions construction (hypo- and hyper- sensitivity dimensions)
507 as coherent constructs from the SSP need further analyses in future studies.

508 On the other hand, our results add support to a potential association between hypo-
509 sensory alterations and deleterious mutations in GABAergic genes; however, those findings
510 have to be taken with caution and would require replication on a larger population. Specifically,
511 the sample size of the molecular analysis was very limited but should be considered as a
512 highlight of the opportunity to use the dSSP score as a tool to dissect the biology of autism
513 spectrum. The lack of power of this sub-analysis in our study requested the use of a MAF below
514 10% which was not a standard in such similar molecular studies but with larger sample sizes.
515 Obviously, those results are calling for a replication of the association between the dSSP and
516 the hypo-sensory scores, as well as with the increased numbers of deleterious mutations in
517 GABAergic genes in autism spectrum. Subsets within the data could also have reduced the
518 power offered for multiple comparisons, more focused analysis would be done in further
519 research. Furthermore, the highlighting of the hypo sensory score when exploring the sensory
520 processing disabilities in ASD questioned the hypothesis of increased sensory precision which
521 is currently gaining more traction in the literature explaining sensory differences in ASD by
522 impairments of bayesian inference (Palmer et al. 2017, Karvelis et al., 2018). Actually, this
523 overrepresentation of the hyper-sensitivity compared to the hypo-sensitivity in the descriptions
524 of autism spectrum could be the consequence of a reporting bias. This reporting bias stress out
525 the need of quantitative methods to explore sensory sensitivities and to complete the available
526 questionnaires such as SSP based on observational, non-quantitative scales (Yamazaki et al.,
527 2014, Shaaf & Lane, 2015)

528

529

530 **CONCLUSION**

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

537

538 **AVAILABILITY OF DATA AND MATERIALS**

539 The datasets generated and/or analyzed during the current study are not publicly available due
540 to an embargo period but are available from the corresponding author on reasonable request.

541

542 **ABBREVIATIONS**

543 ADI-R: Autism Diagnosis Interview-Revised

544 ADOS-2: Autism Diagnostic Observation Scale - second edition

545 ADOS-2 CSS: Autism diagnostic observation schedule -second edition - calibrated severity
546 score.

547 AS: Autism Spectrum

548 BAM: Binary alignment map

549 DSM: Diagnostic and statistical manual of mental disorders

550 CADD score: Combined Annotation Dependent Depletion score

551 dSSP: differential short sensory profile

552 EU-AIMS: European Autism Interventions – A Multicenter Study for Developing New
553 Medications

554 GABA: Gamma – aminobutyric acid

555 IQ: Intellectual quotient
556 KEGG: Kyoto Encyclopedia of genes and genomes
557 LEAP: Longitudinal European Autism Project
558 LGD: Likely gene disruptive
559 MAF: Minor allele frequency
560 MIS30: Missense mutations with a CADD score ≥ 30
561 PARIS: Paris Autism Research International Sibpair
562 PCA: Principal component analysis
563 PCR: Polymerase chain reaction
564 PPI: protein-protein interaction
565 SSP: short sensory profile
566 SNV: Single Nucleotide Variants
567 TD: Typically developing
568 VEP: Variant Effect Predictor

569

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895

896 **AUTHOR CONTRIBUTIONS**

897 **Contributions**

898 AL, FC, JT, FA, AB, AM, DG, AA, AG, FB, GH, CB, MLLM, MB, ML, TC, TB, RD, GD
899 designed the study. AL, FA, AB, AM, AA, AG, MB, RD, and the EU-AIMS LEAP group
900 collected the data. GD and AL conducted the analyses. GD and RD were the initiators of the
901 study project and asked for the blind rating of the items. AL, AB, AM, FA rated the items of
902 the SSP as related to hypo- or hyper- sensitivity for the construction of the dSSP. AL, FC, JT,
903 TC, TB, RD, and GD made substantial contributions to the interpretation of the data. AL, RD,
904 and GD wrote the first and final draft of the manuscript. All author(s) read and approved the
905 final manuscript.

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908

909 **ETHICS DECLARATIONS**

910 **Ethics approval and consent to participate**

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

913 The Paris Autism Research International Sibpair (PARIS) study sample was granted approval
914 by the local Ethics Committee or "Comité de Protection des Personnes" on 2008 November
915 14th, authorised by the French authorities (ANSM B80738-70 on 2008, August 11th), and
916 registered in a public trial registry (NCT02628808).

917 Ethical approval for the EU-AIMS Longitudinal European Autism Project (LEAP) sample
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929 **Consent for publication**

930 Consent for publication was obtained from all participants prior to the study.

931 **Competing interests**

932 The authors have no competing interests to declare

933

934

935

936 **Table 1. Clinical and demographic descriptions of the individuals enrolled in the study.**

	PARIS study sample				LEAP study sample		
	AS	Relativ es	TD	F (p, η^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 /	19.4 (6.1)				16.7 (6.8)		
Communication /	14.6 (6.2)				13.4 (5.7)		
Repetitive behaviours	6.1 (2.8)				4.3 (2.6)		
ADOS-2 CSS*							
Social communication	6.5 (2.5)				6.1 (2.6)		
Repetitive behaviours	5.8 (1.4)				4.7 (2.7)		

937

938 For continuous variables, data are mean \pm standard deviation (SD). AS: Autism Spectrum ; TD:
939 typically developing; N: number of participants; Age in years; IQ: Intelligence quotient; ADI-
940 R: Autism diagnostic interview-revised; ADOS-2 CSS: Autism diagnostic observation
941 schedule - second version - calibrated severity score. ADOS-2 CSS are the Calibrated Severity
942 Scores; see Charman et al. 2017 for a description.

943

944

945 **Table 2.** Hyper-, hypo- sensory or uncertain scores and differential SSP scores in the PARIS

946 and LEAP cohorts

947

PARIS cohort				LEAP Cohort		
AS mean(SD)	Relative s mean (SD)	TD mean(S D)	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)
-------------------------------------	--------------------

948

949 For continuous variables, data are F-value (p-value, eta squared), considering ANOVA
950 analyses and t-ratio (p-value, cohen's d) considering t-student analyses, Z-value (p-value, d-
951 cohen's d) considering Wilcoxon analyses.

952 ^aThe hyper-, ^bhypo-, and ^cuncertain sensory scores were first explored in order to support the
953 construction and use of the dSSP score. We observed differences of mean and variances
954 between groups, with higher hypo and hyper sensory sensitivities in the autistic group in the
955 two cohorts (Table 2).

956

957 **FIGURE LEGEND**

958 **Figure 1.** Sensory Short Profile scores within the PARIS sample.

959 **A-** Distribution of mean total original SPP score per item for autistic participants (red), their
960 first-degree relatives (green) and for control participants (blue). A higher SPP score meant
961 stronger anomalies of sensory processing. **B-** Distribution of the mean differential SPP score
962 on the same participants; here, negative & positive scores respectively represented hypo- and
963 hyper-sensory profiles. Relatives appeared with an intermediate distribution between patients
964 and controls in both A & B. **C-** Evolution of the differential SPP score with age for the same

965 participants. Linear regression showed an effect of age only for patients: a significant
966 regression equation of the sensory profile with age ($-0.12 + 0.01 \times \text{age}$, $p=0.02$, uncorrected)
967 with an $R^2=0.03$ in the group with ASD was obtained. This significant regression was not found
968 in either the relative group ($-0.05 + 0.01 \times \text{age}$, $R^2=0.01$, $p=0.1$) or the typically developing
969 group ($-0.03 + 0.01 \times \text{age}$, $R^2=0.04$, $p=0.06$).

970 **Figure 2.** Sensory Short Profile scores within the LEAP Cohort.

971 **A-** Distribution of mean total original SPP score per item for autistic participants (red) and for
972 participants controls (blue). A higher SPP score meant stronger anomalies of sensory
973 processing. **B-** Distribution of the mean differential SPP score on the same participants; here,
974 negative & positive scores respectively represented hypo- and hyper-sensory profiles. **C-**
975 Evolution of the differential SPP score with age for the same participants. Linear regression
976 showed an effect of age only for patients. As observed in the PARIS cohort, we replicated a
977 significant regression equation of the sensory profile with age ($-0.28 + 0.02 \times \text{age}$, $p=0.0005$,
978 uncorrected) with an $R^2=0.03$ in the autism spectrum group. This significant regression was not
979 found in the typically developing group ($-0.5,15 + 0.0008 \times \text{age}$, $R^2=0.007$, $p=0.28$).

980

981

982 **SUPPLEMENTARY FIGURE LEGEND**

983

984 **Supplementary Figure.** Distribution of autistic participants with mutations considering the
985 dSSP score.

986 The mutations were explored in the GABA and glutamatergic pathways. Only the variants with
987 Major Allele Frequency (MAF) $<10\%$ were considered. LGD: Likely Gene Disrupting
988 Missense CADD PHRED > 30 .

989

990

991 **SUPPLEMENTARY MATERIAL**

992

993 **Supplementary Table 1.** The 38 items of the SPP split into hyper-sensitivity and hypo-
994 sensitivity.

995

996 **Supplementary Table 2.** Kendall rank correlation coefficient between the four raters.

997

998 **Supplementary Table 3.** List of explored genes related to the GABAergic and glutamatergic
999 pathways.

1000

1001 **Supplementary Table 4.** Clusters obtained among autistic participants in the PARIS sample
1002 study.

1003

1004 **Supplementary Table 5.** Description of clusters obtained among autistic participants in the
1005 PARIS sample study.

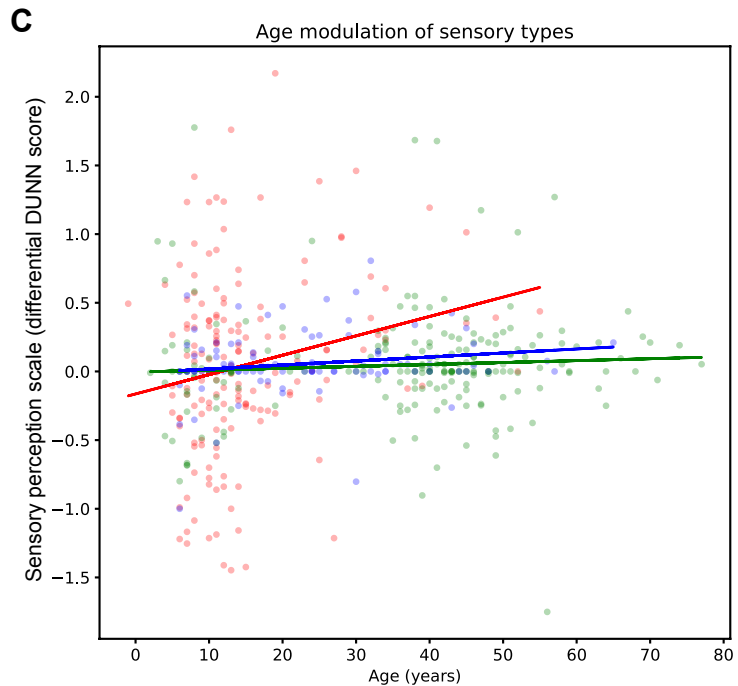
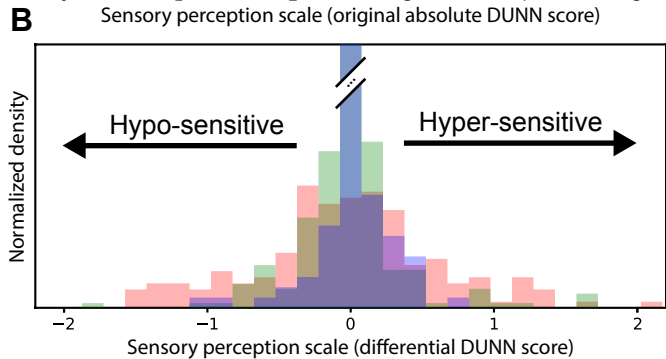
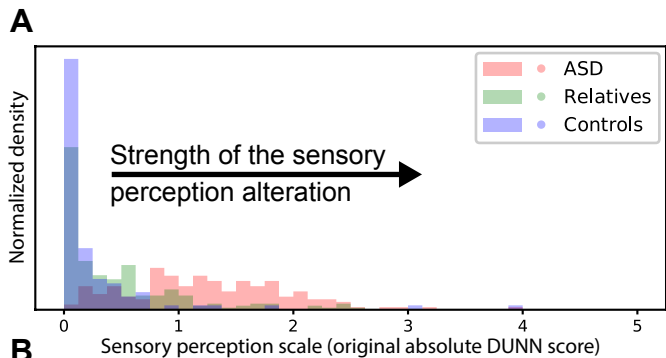
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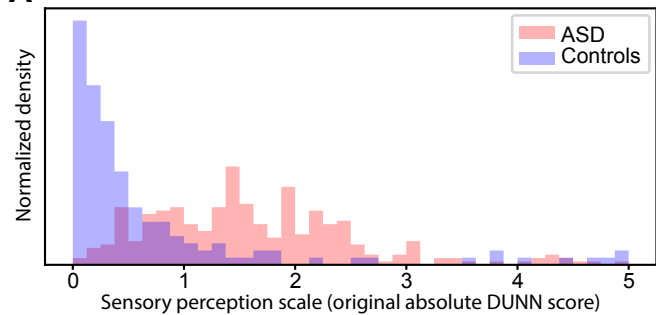
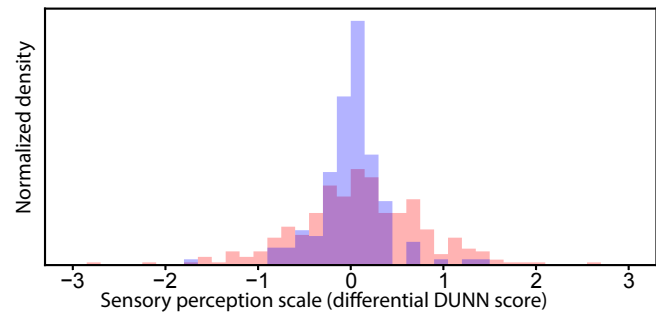
1007 **Supplementary Table 6.** Cluster obtained among only autistic participants in the LEAP
1008 sample study.

1009

1010 **Supplementary Table 7.** Description of clusters obtained among autistic participants in the
1011 LEAP sample study.

1012



A**B****C**