

1 **Title: The human pupil and face encode sound affect and provide objective signatures of**  
2 **tinnitus and auditory hypersensitivity disorders**

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20 **Summary**

21 Sound is jointly processed along acoustic and emotional dimensions. These dimensions can become  
22 distorted and entangled in persons with sensory disorders, producing a spectrum of loudness  
23 hypersensitivity, phantom percepts, and – in some cases – debilitating sound aversion. Here, we  
24 looked for objective signatures of disordered hearing (DH) in the human face. Pupil dilations and micro  
25 facial movement amplitudes scaled with sound valence in neurotypical listeners but not DH participants  
26 with chronic tinnitus (phantom ringing) and sound sensitivity. In DH participants, emotionally evocative  
27 sounds elicited abnormally large pupil dilations but blunted and invariant facial reactions that jointly  
28 provided an accurate prediction of individual tinnitus and hyperacusis questionnaire handicap scores.  
29 By contrast, EEG measures of central auditory gain identified steeper neural response growth functions  
30 but no association with symptom severity. These findings highlight dysregulated affective sound  
31 processing in persons with bothersome tinnitus and sound sensitivity disorders and introduce  
32 approaches for their objective measurement.

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35 **Introduction**

36 Damage or degeneration of peripheral sensory organs causes reduced sensitivity to  
37 environmental stimuli. It can also precipitate the opposite outcome: a hypersensitivity to environmental  
38 stimuli along with the perception of phantom stimuli that have no physical source in the environment.  
39 Sensory phantoms occur in all modalities but are more often heard than seen, tasted, felt, or smelled.  
40 Approximately 12% of adults hear an indefatigable phantom sound every day of their waking life.  
41 Tinnitus typically manifests as a continuous ringing, whooshing, roaring, or sizzling phantom sound that  
42 is often accompanied by a generalized sensitivity and discomfort with moderately intense  
43 environmental sounds<sup>1,2</sup>. Most evidence suggests that disinhibition in auditory processing centers of the  
44 brain is a proximal cause of tinnitus and sound sensitivity<sup>3-7</sup>. Central auditory disinhibition related to  
45 tinnitus and sound sensitivity can arise from normal aging<sup>8,9</sup>, as a compensatory response to hearing  
46 loss and auditory nerve degeneration<sup>10-19</sup>, from traumatic injury of the brain or cervical ganglia<sup>20-22</sup>, or  
47 simply from the abrupt cessation of prescription GABA agonists<sup>23,24</sup>. Whatever the source, the Excess

48 Central Gain model posits that disinhibition has the knock-on effect of increasing the synchrony and  
49 activity rate of local excitatory neurons in silence (the basis of the phantom sound) as well as  
50 disproportionately strong responses to moderately intense sound (the basis of loudness  
51 hypersensitivity)<sup>25-29</sup>. As expected, boosting levels of central inhibition through direct activation  
52 protocols in animals or GABA-acting drugs in humans can mitigate tinnitus symptoms<sup>30,31</sup>.

53 In some cases, persons with tinnitus and sound sensitivity also present with an intense  
54 generalized aversion to sound, anxiety about sound exposure, social withdrawal, depression, and even  
55 suicidal ideations<sup>32</sup>. It is unclear how central gain in low-level auditory processing is related to the  
56 anxiety and mood disruptions that can accompany these disorders. One possibility is that the  
57 connection between elevated central gain and affective dysregulation may literally reflect abnormally  
58 strong coupling between auditory forebrain and limbic centers<sup>33</sup>. A recent animal study of auditory  
59 threat learning has shown that a selective plasticity in auditory corticoamygdalar projection neurons  
60 asymmetrically increased corticofugal spike-LFP coupling and sound-evoked activity in the lateral  
61 amygdala<sup>34</sup>, suggesting that increased neural gain in cortical projection neurons can be passed on to  
62 postsynaptic brain regions that regulate affective evaluation of valence and arousal. To this point,  
63 several neuroimaging studies in participants with tinnitus and sound sensitivity have identified  
64 abnormally strong coupling between auditory cortex and the amygdala, insula, anterior cingulate cortex,  
65 and medial prefrontal cortex<sup>33,35-37</sup>. Whereas psychoacoustic and low-level auditory assays were  
66 generally not correlated with extra-auditory features of sound aversion and psychological burden<sup>38-43</sup>,  
67 neuroimaging assays of enhanced coupling with extra-auditory networks have shown stronger  
68 correlations with individual differences in tinnitus and sound sensitivity severity<sup>37,44</sup>.

69 There are no objective measurements for the severity of tinnitus and sound sensitivity disorders.  
70 Instead, assessments rely on subjective self-report questionnaires, which can introduce vulnerabilities  
71 for malingering and false disability claims<sup>39</sup> and offer less insight into the underlying causes and  
72 potential treatments. Here, we hypothesized that involuntary autonomic and behavioral responses may  
73 have untapped potential as non-invasive, objective markers of tinnitus and sound sensitivity severity  
74 that are relatively easily to implement in laboratory and clinical settings. Autonomic responses (e.g.,  
75 pupil dilation and skin conductance) and involuntary facial movements provide a wealth of information  
76 into affective processing of valence and arousal in humans<sup>45-48</sup> as well as other animals<sup>34,49</sup>. Although  
77 human studies have largely relied on visual stimuli, it is clear that speech, music and other sounds  
78 provide a rich medium for conveying valence and arousal cues<sup>50-54</sup>. This led us to ask whether  
79 emotionally evocative sounds elicit autonomic and facial responses that are modulated by perceived  
80 valence. We then evaluated whether these objective measures could identify a bias towards negative  
81 valence and hyper-arousal in persons with tinnitus and sound sensitivity that might more accurately  
82 predict the severity of sound aversion and psychological burden they report.

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84

## 85 Results

86 Of 196 adults recruited to our study, we identified 71 eligible participants with normal hearing  
87 thresholds who completed the full course of testing (**Figure S1A**). An experienced clinician assigned  
88 participants with chronic tinnitus and/or auditory hypersensitivity to the disordered hearing (DH, N=35)  
89 group and participants without tinnitus or auditory hypersensitivity to the neurotypical (NT, N=36) group.  
90 The distribution of age and hearing thresholds were closely matched between DH and NT groups. As  
91 expected, uncomfortable listening level thresholds in DH subjects were significantly lower than NT  
92 subjects (**Figure S1B-C**, description of statistical testing described in the figure legends throughout).

93

## 94 **Increased central gain is not correlated with tinnitus or sound sensitivity burden**

95 The Enhanced Central Gain model posits that disinhibition in the auditory cortex and subcortical  
96 auditory structures produces hypersynchronized and hyperactive population activity among excitatory  
97 neurons in silence and hyperresponsivity to sounds of increasing physical intensity (**Figure 1A**).  
98 Although we could not directly measure the rate or synchrony of spiking, it was possible to measure  
99 auditory neural response gain through an approach that slowly increased and decreased the intensity  
100 of a 40 Hz amplitude modulated tone (**Figure 1B**, top). Scalp EEG recordings revealed a synchronized  
101 envelope following response (EFR) at 40 Hz that increased and decreased in amplitude with the  
102 change in sound intensity (**Figure 1B**, bottom). Gain (i.e., the output per unit step in input) could be  
103 explicitly measured as the slope of the neural growth function. As predicted by the Excess Central Gain  
104 model, neural activity grew significantly more steeply with increasing sound level in DH participants  
105 (**Figure 1C**).

106 Tinnitus and sound sensitivity are heterogenous co-morbid conditions. The cohort of DH  
107 participants presented with varying degrees of sound aversion, distress, anxiety and depression related  
108 to their disorder, as identified by standard clinical questionnaires for hyperacusis and tinnitus (HQ and  
109 THI, respectively, **Figure 1D**). This variability provided us with a valuable opportunity to study the  
110 relationship between excess central gain and psychological burden. Although central gain was  
111 significantly increased at a group level in DH participants (**Figure 1E**, top), it was not correlated with  
112 individual differences in hyperacusis or tinnitus severity (**Figures 1F and 1G**, respectively).

113 As illustrated in the cartoon model (**Figure 1A**), an extension of the Excess Central Gain model  
114 posits that hyperactive, hypersynchronized, and hyperresponsive projection neurons in the central  
115 auditory pathway drive abnormally strong functional connectivity and auditory recruitment in  
116 downstream limbic networks. Limbic hyperresponsivity, in turn, would elicit abnormal autonomic  
117 response for sounds that would not otherwise be encoded as unpleasant or highly arousing. In  
118 essence, a failure to homeostatically regulate neural activity in auditory brain networks disrupts  
119 allostatic processes that balance autonomic and behavioral responses to stressors. In this model,  
120 excess central gain is a distal, upstream precipitator of limbic-autonomic dysfunction that more directly  
121 determines whether an individual feels utterly debilitated versus slightly annoyed by their tinnitus. As  
122 such, central gain would not be expected to be highly correlated with the tinnitus or hyperacusis burden  
123 reported in surveys, but a more direct marker of limbic or autonomic dysfunction would.

## 124 125 **Pupil-indexed affective processing is correlated with tinnitus and sound sensitivity burden**

126 In constant light levels, pupil diameter provides an autonomic marker of brain-wide  
127 neuromodulator release<sup>55,56</sup> that, depending on task design, can index executive load<sup>57</sup>, or affective  
128 valence and arousal<sup>58</sup>. To determine whether autonomic and behavioral evaluation of sound affect was  
129 biased towards negative valence and hyper-arousal in DH subjects, we measured pupil diameter and  
130 skin conductance while subjects listened to 6s audio clips from an established database of emotionally  
131 evocative sounds (**Figure 2A**)<sup>59</sup>. These sounds spanned a wide valence range, including sounds rated  
132 as highly unpleasant (screaming) to pleasant (music) (**Figure 2B**). On average, selected sounds  
133 smoothly tiled the valence range (**Figure S2A**) but were idiosyncratic at the level of individual  
134 participants, presumably reflecting their individual hedonic sound associations (**Figure S2B**). When  
135 individually ordered by valence rating, we found that DH subjects rated sounds as less pleasant overall,  
136 particularly relatively pleasant or neutral sounds, suggesting a complementary metric to the generalized  
137 sound aversion captured by subjective self-report questionnaires<sup>60</sup> (**Figure 2C**).

138 We observed that emotionally evocative sounds elicited pupil dilations within approximately 0.5s  
139 followed by a slower increase in sound-evoked skin conductance (**Figure 2D**; **Figure S3**). Pupil dilation  
140 scaled with self-reported sound valence across all participants but was significantly greater overall in

141 DH subjects, indicating a hypersensitized autonomic response to both pleasant and unpleasant sounds  
142 (**Figure 2E**). Sound-evoked changes in skin conductance also scaled with self-reported valence but did  
143 not differ between groups (**Figure 2F**). Sound-evoked pupil dilation was significantly elevated in DH  
144 participants (**Figure 2G**) but, unlike central gain, was significantly correlated with individual differences  
145 in self-reported hyperacusis burden (**Figure 2H**) and tinnitus burden (**Figure 2I**). Average sound-  
146 evoked skin conductance did not differ between groups and was not correlated with tinnitus or  
147 hyperacusis severity (**Figure 2J-L**).

148

### 149 **Pupil hyper-responsivity is specific to affective processing**

150 These findings support our hypothesis that affective sound encoding is disrupted in persons with  
151 debilitating tinnitus and sound sensitivity, which can be measured through autonomic markers of  
152 affective arousal such as pupil dilation. Two negative control experiments support the assertion that  
153 pupil-indexed hyper-arousal was specific to affective processing. First, pupil dynamics in DH and NT  
154 participants were indistinguishable when entrained to periodic changes in light intensity (**Figure S4A-**  
155 **B**). Second, we measured pupil-indexed listening effort in a multi-talker speech intelligibility task  
156 (**Figure S4C**) and observed reduced behavioral accuracy and increased pupil diameter at a more  
157 challenging signal to noise ratio (**Figure S4D**). Importantly, behavioral accuracy and pupil-indexed  
158 listening effort were equivalent between NT and DH participants, confirming that DH subjects do not  
159 have widespread deficits in challenging listening tasks<sup>61</sup> or global autonomic regulation, but rather a  
160 more specific behavioral and autonomic aversion to the affective quality of sound (**Figure S4E-F**).

161

### 162 **Subtle facial movements identify auditory valence and hearing disorder severity**

163 To identify additional windows into auditory affective processing that might complement or  
164 extend upon pupil dynamics we turned our attention to subtle and rapid movements of the face. Facial  
165 movements have a long history in human emotion research, though these studies have almost  
166 exclusively relied on visual stimuli to convey affective cues<sup>62</sup>. To establish whether emotionally  
167 evocative sounds would also produce facial movements related to affective valence and arousal, we  
168 quantified high-resolution facial videography recordings that were performed in tandem with the pupil  
169 and electrodermal recordings (**Figure 3A**). We developed an analysis pipeline to localize changes in  
170 facial texture and observed that sounds do elicit subtle and rapid facial movements (**Figure 3B**). For  
171 example, in one instance an unpleasant “buzz” sound elicited a tightening of the muscles around the  
172 eyes and forehead (**Figure 3C**, left), whereas a more pleasant sound elicited a longer latency  
173 movement of the mouth and jaw (**Figure 3C**, right). Amongst this spatiotemporal complexity, we found  
174 stereotyped patterns that were associated with individual valence ratings. Pleasant sounds evoked  
175 increased movements in the area of the zygomaticus major, a muscle involved in shaping the corners  
176 of the lips (**Figure 3D**, left). Unpleasant sounds triggered increased movements globally but were  
177 particularly robust around the eyes and brows (**Figure 3D**, middle).

178

179 Like the pupil, we hypothesized that sound-evoked facial expressions would convey  
180 downstream limbic dysfunction in individuals with tinnitus and sound sensitivity. This prediction was  
181 upheld but, interestingly, in the opposite direction of changes in pupil dilation. Whereas facial  
182 movement amplitude scaled with valence in NT participants, DH participants exhibited a generally  
183 blunted affect that did not change across self-reported valence (**Figure 3E-G**). Importantly, reduced  
184 facial movements were significantly correlated with individual differences in sound sensitivity burden  
185 (**Figure 3H**) and tinnitus burden (**Figure 3I**). Together, these results show that the face encodes not  
186 only sound affect but can also provide a window into the intense aversion and lifestyle burden that can  
187 accompany tinnitus and sound sensitivity.

187

## 188 **Combined measures of sound affect best determine psychological burden**

189 Here, we have identified neural (**Figure 1C**), autonomic (**Figure 2E**), voluntary behavioral  
190 (**Figure 2C**), and involuntary behavioral (**Figure 3F**) measures that distinguish DH and NT subjects at a  
191 group level. A major goal for research on sensory disorders is to identify and refine a set of objective  
192 measurements – akin to what tumor imaging and biopsy data provide for oncologists or EEG measures  
193 of epileptiform activity provide to neurologists – that inform future care providers about the subtype and  
194 severity of the sensory disorder, the likelihood to benefit from a particular treatment, or whether they  
195 have demonstrated an improvement subsequent to treatment. While some measurements have been  
196 developed to identify whether an individual has tinnitus, they are insensitive to severity and lifestyle  
197 burden<sup>39,63,64</sup>. Here, we found that pupil dilation and facial reactions both demonstrated a correlation  
198 with symptom severity. As a next step, we determined whether these measures were redundant and  
199 how accurately they could predict an individual's self-reported symptom severity.

200 We incorporated all measures where DH and NT cohorts were significantly different at a group  
201 level (pupil diameter, facial movement, behavioral valence rating, central gain) as well as potential co-  
202 variates of lifestyle burden (age) in an elastic net regression analysis, developed to be robust to  
203 superfluous predictor variables (see Methods). For the severity of self-reported sound sensitivity, a  
204 cross-validated fitting procedure settled on an optimal model that combined measures of affective  
205 responses – pupil dilation, facial movement, and behavioral valence rating (**Figure 4B**). This model was  
206 significantly correlated with hyperacusis questionnaire scores and was moderately accurate in  
207 predicting the hyperacusis index score compiled across NH and DT participants ( $R = 0.6/R^2 = 0.36$ ,  
208 **Figure 4C**). When the same approach was applied to tinnitus, age, we noted that central gain, and  
209 behavioral valence rating were minimally weighted, a moderate weight was afforded to pupil dilation,  
210 but facial reactivity was heavily weighted (**Figure 4D-E**). This model was highly correlated with self-  
211 reported severity and exhibited fairly high accuracy in predicting individual tinnitus burden scores ( $R =$   
212  $0.78/R^2 = 0.61$ , **Figure 4D-F**). These findings demonstrate that pupil and facial reactivity to emotionally  
213 evocative sounds capture distinct features of generalized aversion, distress and anxiety that can  
214 accompany tinnitus and sound sensitivity. Although autonomic measures and affective processing have  
215 rarely been considered as biomarkers for these conditions, predictions of hyperacusis and tinnitus  
216 severity scores were significantly poorer when they were left out and the optimal model instead relied  
217 on neural and voluntary behavioral measures (likelihood ratio test,  $p < 0.001$ ).

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## 220 **Discussion**

### 221 **Extending upon the Excess Central Gain model of tinnitus and sound sensitivity**

222 Pioneering neuroimaging studies in human subjects with tinnitus and reduced sound level  
223 tolerance identified auditory hyper-responsivity in the inferior colliculus and auditory cortex as the  
224 proverbial “ghost in the machine”<sup>65</sup>, i.e., a biological substrate for these perceptual disorders<sup>42,66</sup>.  
225 Subsequent findings in human subjects and animal models highlighted the juxtaposition of normal or  
226 even hyper-responsive event-related potentials arising from later stages with reduced sound-evoked  
227 potentials arising from the auditory nerve<sup>12,15,67</sup>. Findings of this ilk laid the foundation for the Enhanced  
228 Central Gain theory for tinnitus and sound sensitivity, wherein central auditory circuits leverage  
229 disinhibition to compensate for reduced bottom-up input. In so doing, vulnerabilities for hyper-  
230 synchrony, hyperactivity, and abnormally steep sound intensity growth functions are introduced that  
231 generate phantom sounds and reduced tolerance of moderately intense sounds<sup>25,26</sup>. Here, we used  
232 40Hz amplitude modulation to enhance the relative contribution of the auditory cortex to the EFR<sup>68</sup> and  
233 derived the instantaneous amplitude as the sound level swept up and down across a 70 dB range to

234 provide a direct demonstration of enhanced central gain (i.e., increased neural output per unit step in  
235 sound input) in participants with tinnitus and reduced sound level tolerance.

236 Disinhibition and enhanced central gain at later stages of the auditory pathway may generate  
237 the sensory qualities of the phantom sound and disproportionate loudness but – in and of itself – is  
238 unlikely to account for the attentional and affective sequelae of tinnitus and sound sensitivity. Central  
239 gain does not account for why the phantom sound effortlessly recedes from conscious awareness when  
240 not attended to for some but is irrepressible for others. Likewise, central gain does not account for why  
241 internally and externally generated sounds a mild nuisance for some but are irritating, overwhelming,  
242 and anxiety-producing in others? That central gain does not account for these qualities does not mean  
243 that phenomenological models featuring auditory nerve degeneration and enhanced central gain are  
244 wrong, but rather that they are incomplete<sup>69</sup>.

245 Excitatory neurons from primary and higher-order auditory cortex project widely throughout  
246 prefrontal cortex executive control networks and limbic brain centers in neocortex and amygdala<sup>70–72</sup>.  
247 While relatively complex multi-regional feedback loops<sup>73</sup>, altered perceptual inference mechanisms<sup>74</sup>, or  
248 stochastic resonance<sup>75</sup> may account for the attentional and affective components of tinnitus and sound  
249 sensitivity disorder, a more parsimonious explanation that directly builds upon the Excess Central Gain  
250 model is simply that hyperactive auditory efferent projections into extra-auditory executive and limbic  
251 networks produce functional hyperconnectivity and knock-on dysregulation in these networks, and this  
252 dysregulation more directly accounts for the attentional and affective components of these disorders.  
253 Support for this model can be found in reports of enhanced auditory-limbic network connectivity in  
254 animals and humans<sup>33,35–37</sup>, though more detailed accounts of dysregulated spontaneous and sound-  
255 evoked processing in these regions are needed. Importantly, indirect but objective indices of affective  
256 and executive disruptions do not require specialized, costly, and low-throughput brain imaging systems.  
257 Pupil diameter, eye position, and involuntary facial reactivity have a well-established relationship with  
258 executive and affective processing and task designs to probe these relationships in neurotypical and  
259 neurodivergent populations have been the subject of study for many decades<sup>49,58,76</sup>. Here, we adapted  
260 pupil and facial assays of affective processing to the auditory modality and demonstrated their  
261 improved ability to account for the affective component of tinnitus and sound sensitivity disorder. While  
262 pupil and behavioral measurements reported here and elsewhere did not suggest deficits related to  
263 executive load or listening effort<sup>61</sup>, the attentional component of tinnitus disorder awaits more direct  
264 interrogation with paradigms that probe the persistence of attention to invariant sensory features with  
265 varying implicit significance.

266

### 267 **Limitations of the current study**

268 One general limitation of observational research on human sensory disorders relates to  
269 uncertainty about the underlying precipitators of tinnitus and sound sensitivity in our subjects. Hearing  
270 loss, age, and certain medications can directly impact central gain and tinnitus<sup>8-24</sup>, motivating us to  
271 strictly screen and match these variables in NT and DH cohorts to control for a confounding influence.  
272 Nevertheless, the underlying cause and duration of tinnitus and sound sensitivity in our DH cohort is  
273 unknown and may contribute to the heterogeneity reported here. Another limitation is that the EEG,  
274 pupil, and facial measures described here provide little insight into their underlying generators in the  
275 central and autonomic nervous systems. We leveraged the excellent temporal resolution of EEG to  
276 derive measures of central gain that would be impossible with measures like fMRI but acknowledge that  
277 non-invasive imaging approaches could significantly extend and enrich the observations reported here.  
278 Another consideration is that while optimized multi-variate models featuring these objective markers of  
279 affective processing captured a sizeable fraction of the variance in clinical outcome measures and  
280 clearly outstripped other predictors studied here, these linear models fall short of providing the

281 sensitivity and selectivity required of a diagnostic measure. One important point to consider here is that  
282 predictive accuracy cannot exceed the internal noise (e.g., test re-test reliability) and internal validity of  
283 the outcome measure. Whether because tinnitus and sound sensitivity are inherently dynamic disorders  
284 that ebb and flow over time or because the structure of the questionnaires elicit variable answers, the  
285 upper bound of the predictive accuracy reported here is capped by the reliability of the outcome  
286 measures themselves<sup>77</sup>. One of the underlying motivations for our study was to develop alternatives to  
287 self-report questionnaires, not only because of their implicit subjectivity but also because their validity  
288 as an instrument to probe the psychological burden arising from their tinnitus and hyperacusis  
289 independent of their broader mental state is not certain<sup>78,79</sup>. We propose that the predictive accuracy  
290 will be further improved by distilling the affective sound features used in the test battery, and combining  
291 these refined stimulus sets with ecological momentary assessment approaches that embrace the  
292 inherent dynamics of these disorders instead of reducing these subjects to a single measure of central  
293 tendency.

### 294 295 **Broader implications for clinical research on sensory disorders**

296 The affective biomarkers described here were non-invasive and could be measured without  
297 specialized equipment, suggesting a promising approach for complementing subjective self-report  
298 questionnaires in clinical settings. These measures could prove to be useful biomarkers for other  
299 neurological disorders where auditory aversion is a prominent clinical feature, particularly for  
300 neurodevelopmental disorders such as autism spectrum disorder, where participant age or language  
301 impairment may preclude objective assessments based on questionnaires<sup>80,81</sup>. Objective physiological  
302 or neuroimaging biomarkers have been essential for the development of effective treatments for  
303 epilepsy, stroke, and other neurological conditions. Better established objective biomarkers for  
304 symptom severity in heritable and acquired sensory disorders will accelerate the pace of identifying  
305 therapies for these conditions<sup>82</sup>.

306 **Supplemental Information**

307 A supplementary document consisting of four supplemental figures is available to download.

308

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313

314 **Author contributions**

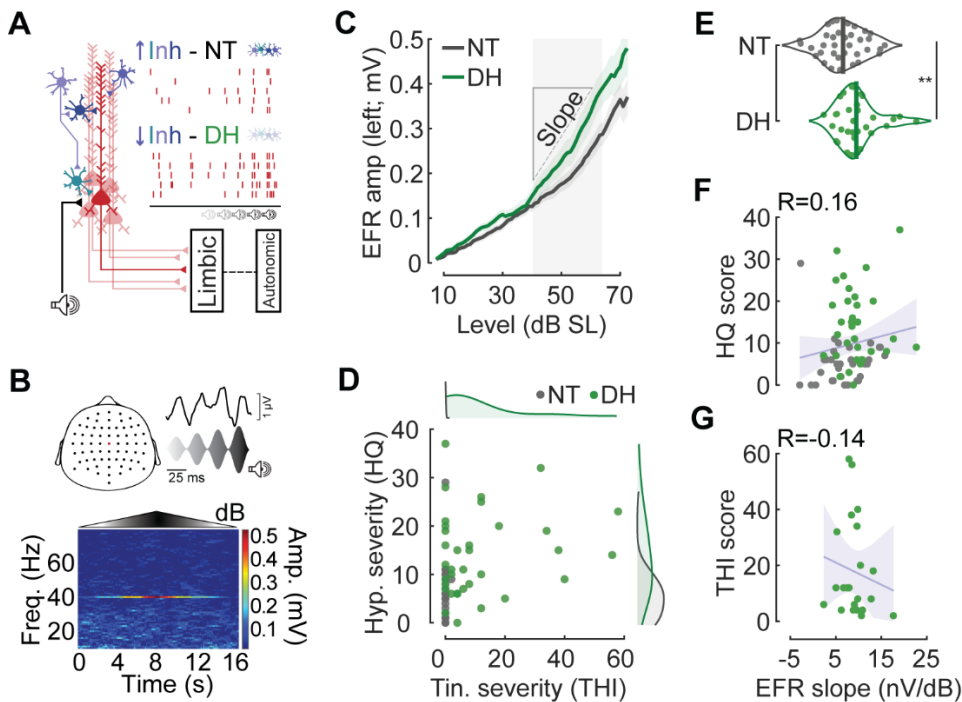
315 K.J. and D.P. conceived the project and designed the experiments. J.S. collected the data using  
316 software programmed by K.H and supported by K.J. and S.S. Data analysis was led by S.S. with  
317 contributions from K.J. Figure preparation and manuscript writing was performed by S.S. and D.P. with  
318 input from all authors.

319

320 **Declaration of Interests**

321 The authors declare no competing interests.





322

323

**Figure 1. Increased central gain is not correlated with tinnitus or sound sensitivity burden**

324

**A)** Cartoon denotes a stage of central auditory processing (e.g., the auditory cortex) with excitatory projection neurons (red) and inhibitory interneurons (cool colors). In this model, disinhibition of excitatory neurons promotes elevated, hypersynchronous firing in silence (the purported generator of the phantom sound) and a steeper growth in spiking with sounds of increasing intensity (i.e., excess central gain, the purported generator of loudness hyperacusis). Hyperactive auditory projection neurons feed into downstream centers of limbic processing and autonomic regulation but, as distal upstream precipitator, excess central gain is less predictive of individual differences in psychoaffective burden than autonomic affective markers.

332

**B) Top:** Cartoon denotes the 64-channel array of scalp EEG electrodes and activity from a central electrode corresponding to the increasing intensity of a 40Hz amplitude modulated tone. Note that EEG amplitude is synchronized to the amplitude modulation rate.

335

**Bottom:** Spectrogram plots the amplitude of synchronized EEG activity across frequencies and time as the amplitude modulated 2kHz tone slowly increases and decreases across a 70 dB range. Note the rise and fall of the 40Hz envelope following response (EFR) amplitude as a function of time/sound intensity.

339

**C)** EFR growth as a function of sound intensity relative to the 2kHz audibility threshold measured for each participant (i.e., the sensation level, SL). NT and DH are neurotypical and disordered hearing participants, respectively. Central gain was measured as the change in neural response over a 25 dB change in sound level.

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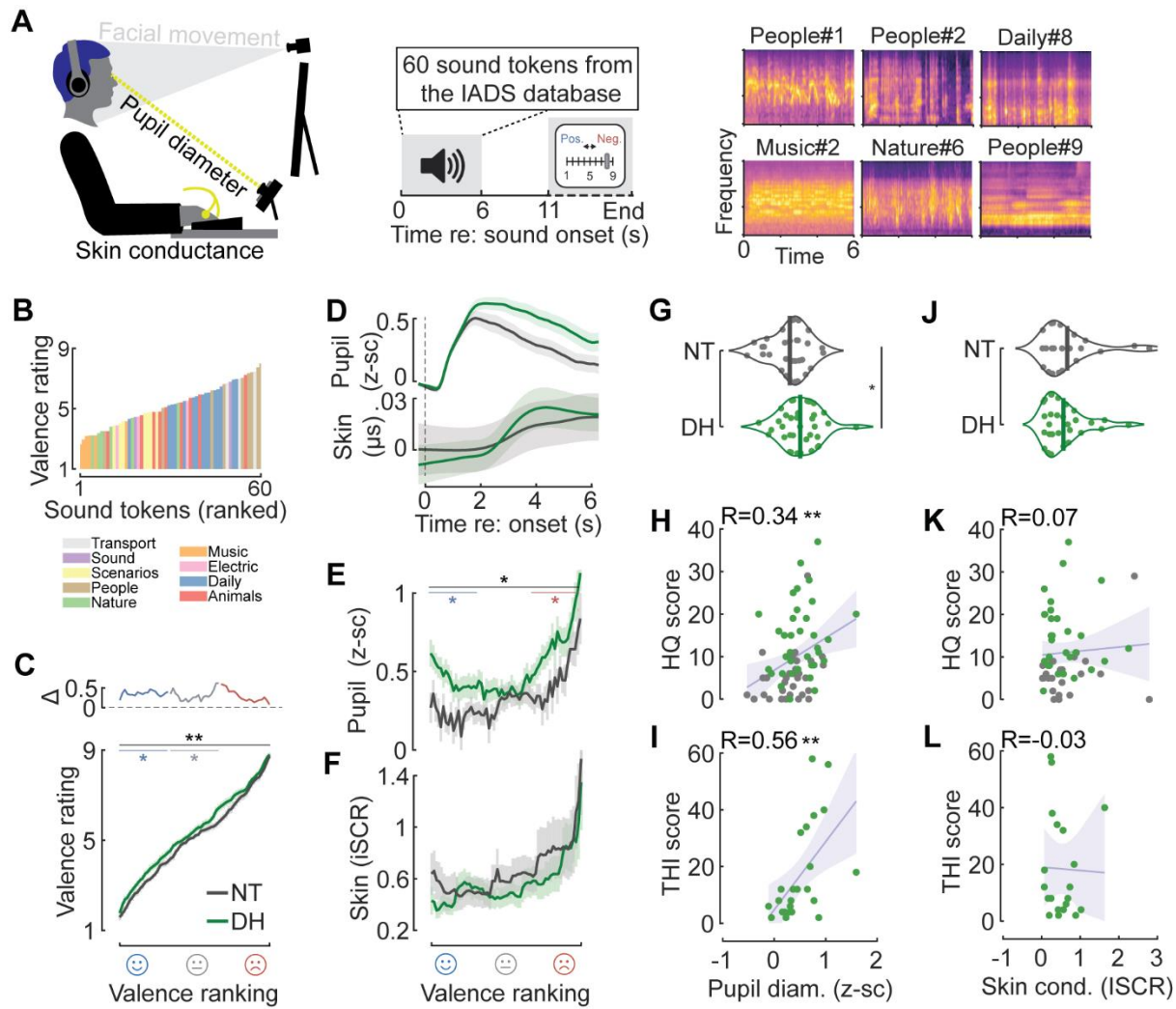
**D)** Hyperacusis and tinnitus severity for all participants based on Hyperacusis questionnaire (HQ) and Tinnitus Handicap Index (THI) scores, respectively (N = 35/35 NT/DH). Circles denote individual participants. Marginal distributions for each group are shown as normalized density functions. All participants can provide a meaningful HQ score but only participants with tinnitus can provide a meaningful THI value.

348

**E)** Central gain is significantly elevated in DH participants (two-sample t-test,  $p = 0.009$ ,  $N = 36/33$  NT/DH). Density functions display the central gain measure for each participant (individual circle) and sample mean (vertical lines).

350

351 **F)** Central gain is not correlated with hyperacusis severity (Pearson  $R = 0.16$ ,  $p = 0.19$ ,  $N = 68$ ).  
352 Shaded region denotes the 95% confidence interval. Solid line denotes linear fit. Circles denote  
353 individual participants.  
354 **G)** Central gain is not correlated with tinnitus severity (Pearson  $R = 0.13$ ,  $p = 0.52$ ,  $N = 22$ ). Plotting  
355 conventions as per e. Note that THI values are limited to participants with tinnitus.



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358

**Figure 2. Pupil-indexed affective processing is correlated with tinnitus and sound sensitivity burden**

359

**A)** Schematic of trial design and experimental setup for combined autonomic and behavioral evaluation of sound valence. Alongside are spectrograms of six representative sounds filtered with a gammatone filter bank.

360

**B)** Mean behavioral valence rating of 60 sounds drawn from the IADS affective sound library (low/high scores indicate pleasant/unpleasant). Sounds are shown rank ordered and color-coded by labeled category.

361

**C)** Mean individually rank-ordered valence ratings demonstrate a significant bias overall towards unpleasant ratings in DH participants (Wilcoxon rank sum,  $p = 0.005$ ,  $N = 36/35$  NT/DH). When discretized into pleasant, neutral, and unpleasant categories (blue/gray/red, respectively), valence ratings were significantly elevated for pleasant and neutral sounds (asterisks, Wilcoxon rank sum,  $p = 0.026$  and  $p = 0.048$ , respectively).

362

**D)** Mean  $\pm$  SEM pupil diameter and skin conductance for all sounds during the 6s stimulus period. Responses are grouped by NT and DH participants.

363

**E)** Sound-evoked pupil dilations were larger overall in DH participants (two-sample t-test,  $p = 0.03$ ,  $N=32/35$  NT/DH). Pupil dilations were significantly increased for pleasant and unpleasant sounds (two-sample t-tests,  $p = 0.01$  and  $0.03$ , respectively) in DH compared to NT subjects.

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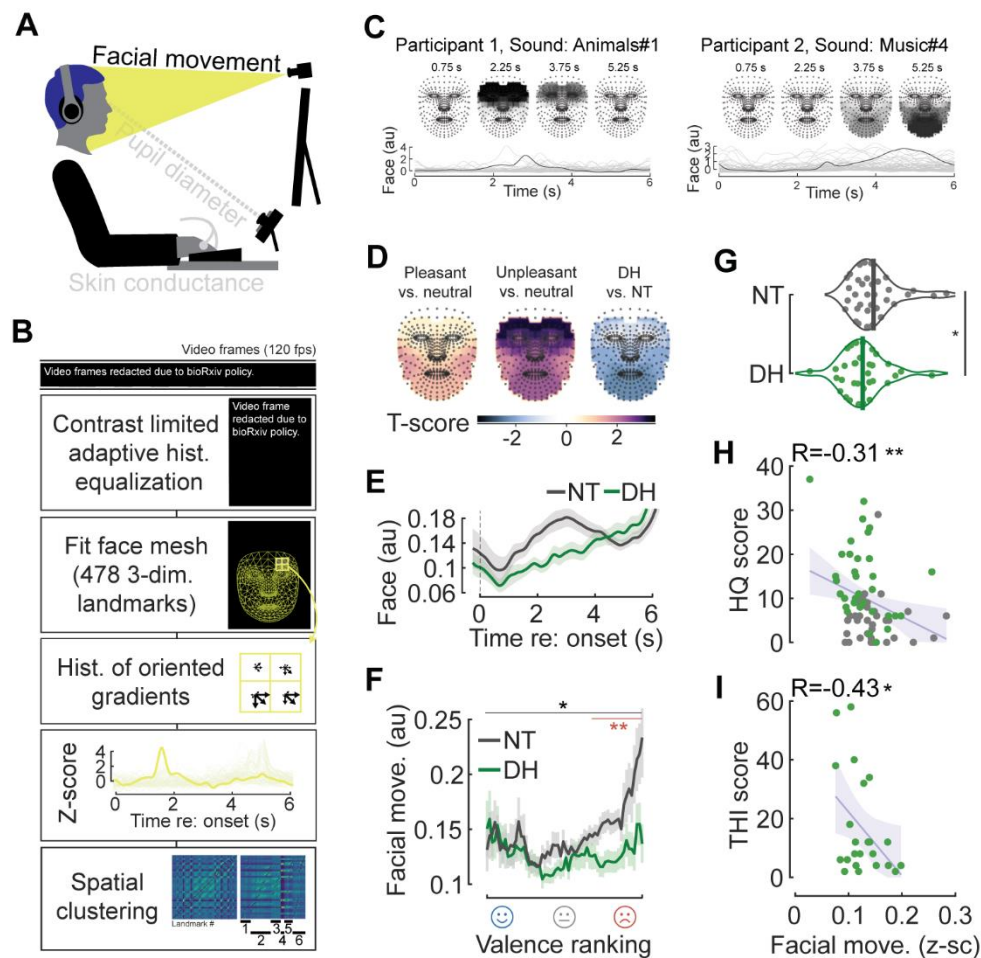
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- 375 **F)** Skin conductance did not differ overall (two-sample t-test,  $p = 0.59$ ,  $N = 24/30$  NT/DH) or as a  
376 function of valence (two-sample t-tests,  $p > 0.5$  for each valence category) in DH compared to NT  
377 subjects.
- 378 **G)** Density functions display the sound-evoked pupil response averaged for each participant (individual  
379 circle) and sample mean (vertical lines).
- 380 **H)** Pupil size is correlated with HQ score (Pearson  $R = 0.33$ ,  $p = 0.006$ ,  $N = 66$ ). Shaded region  
381 denotes the 95% confidence interval. Solid line denotes linear fit. Circles denote individual participants.
- 382 **I)** Pupil size is correlated with THI score (Pearson  $R = 0.56$ ,  $p = 0.005$ ,  $N = 24$ ).
- 383 **J)** Density functions display the skin conductance response averaged for each participant (individual  
384 circle) and sample mean (vertical lines).
- 385 **K)** Skin conductance is not significantly correlated with HQ score (Pearson  $R = 0.07$ ,  $p = 0.63$ ,  $N = 53$ ).  
386 Shaded region denotes the 95% confidence interval. Solid line denotes linear fit. Circles denote  
387 individual participants.
- 388 **L)** Skin conductance is not significantly correlated with THI score (Pearson  $R = -0.03$ ,  $p = 0.92$ ,  $N = 20$ ).



389

390

### Figure 3. Subtle facial movements identify auditory valence and hearing disorder severity

391

**A)** Facial videography experimental setup.

392

**B)** Videos were processed with a custom analysis pipeline incorporating a face-mesh mapping and subsequent pixel quantification (see Methods).

393

**C)** Single trial facial movement amplitudes in two participants illustrate differences in amplitude and time course for an unpleasant (*left*) and pleasant (*right*) sound.

394

**D)** T-score contrast maps of differences in facial movements for unpleasant vs neutral (*left*), pleasant vs. neutral (*middle*), and for NT vs. DT participants (*right*) during the 6s stimulus period.

395

**E)** Mean  $\pm$  SEM facial movement for all sounds during the 6s stimulus period. Responses are grouped into NT/DH.

396

**F)** Facial reactions were reduced overall in DH participants (two-sample t-test,  $p = 0.046$ ,  $N = 36/33$  NT/DH) and were significantly reduced for unpleasant sounds (two-sample t-test,  $p = 0.003$ ) in DH compared to NT subjects.

397

**G)** Density functions display sound-evoked facial movements averaged for each participant (individual circle) and sample mean (vertical lines).

398

**H)** Facial movement is negatively correlated with HQ score (Pearson  $R = -0.31$ ,  $p = 0.0096$ ,  $N = 68$ ). Shaded region denotes the 95% confidence interval. Solid line denotes linear fit. Circles denote individual participants.

399

**I)** Facial movement is negatively correlated with THI score (Pearson  $R = -0.42$ ,  $p = 0.042$ ,  $N = 23$ ).

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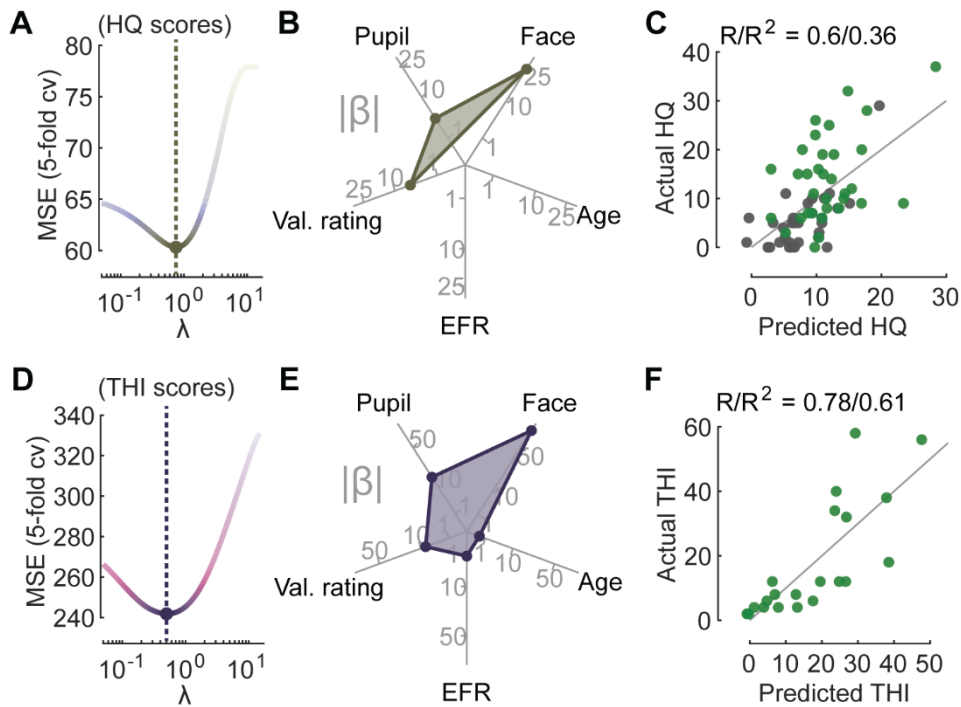
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**Figure 4. Combined measures of sound affect best determine psychological burden**

411

**A)** An elastic net regression model was fit to individual hyperacusis severity scores (HQ scores). A tuning parameter,  $\lambda$ , controls the extent to which the coefficients contributing least to predictive accuracy are suppressed.

414

**B)** A radar plot displays the coefficient weight (i.e.,  $|\beta|$ ) in the optimal model of HQ score (filled shape). The optimal model with minimal cross-validated error retained non-zero coefficients for pupil, facial movement, and valence ratings.

417

**C)** The HQ scores predicted via elastic-net regression versus participants' actual scores.

418

**D)** Plotting conventions as per A, for tinnitus burden (THI) scores.

419

**E)** Plotting conventions as per B, for THI scores. Predictors from the optimal elastic-net featured physiological measures of sound affect (face, pupil) as the highest weighted coefficients.

420

**F)** Plotting conventions as per C, for THI scores.

421

422

## Methods

423

### 424 **Experimental model and subject details.**

425 All procedures were approved by the Mass General Brigham Institutional Review Board.

426 **Participants.** Data are from 71 adults between 19 and 60 years of age (mean age = 33.9 years, 42  
427 females) that were fluent in English. Participants were recruited as part of a larger study through flyers,  
428 word of mouth, and by posting to the Mass General Brigham participant recruitment website. As  
429 detailed in **Figure S1A**, screening and grouping of the 196 potentially eligible participants were  
430 performed by licensed clinicians. Participants were required to have normal hearing (unremarkable  
431 otoscopic evaluation and air conduction thresholds for tones 0.25 to 8 kHz  $\leq$  25 dB HL, 75 participants  
432 excluded). Participants were required to have normal cognitive function (telephone Montreal Cognitive  
433 Assessment, t-MOCA  $\geq$ 18). We assessed mental health status and an ability to tolerate sound stimuli  
434 used in our experiments based on their response to question 24 in Beck's Depression Inventory,  
435 question 23 of the Tinnitus Reactivity Questionnaire, and question 23 of the Sound Reactivity  
436 Questionnaire (10 participants excluded). Of the remaining participants, 16 were lost to follow-up after  
437 the initial orientation and four were excluded for not completing the full course of testing.

438 Participants were assigned to neurotypical or disordered hearing groups by experienced  
439 clinicians based on their responses to an open-ended questionnaire and clinical evaluation. Participants  
440 were excluded if they had catastrophic tinnitus ( $> 77$  on Tinnitus Handicap Index, THI, 1 participant  
441 excluded), intermittent tinnitus (14 participants excluded), or inconsistently reported having tinnitus  
442 across questionnaires (4 participants excluded). Of the remaining participants, those who did not report  
443 sound sensitivity, nor intermittent or chronic tinnitus were classified as neurotypical (N=36, 25 females).  
444 The remaining subjects were assigned to the disordered hearing (DH) group (N=35, 17 females) based  
445 on their clinical evaluation of chronic tinnitus and/or abnormal sound sensitivity. Among these  
446 participants, we found that EEG data (N=2) and skin conductance recordings (N=17) were not usable  
447 on account of poor electrode contact. We excluded pupil data (N = 4) and facial movement (N = 2) due  
448 to inordinately high rates of blinking or failed tracking.

449

### 450 **Method details**

451 Participants performed psychophysical and questionnaire assessments remotely, between two in-lab  
452 sessions (approximately 3 hours each).

453 **Patient reported outcome measures.** The psychoaffective burden of tinnitus and hyperacusis  
454 symptoms was assessed with the Hyperacusis Questionnaire (HQ)<sup>83</sup> and the Tinnitus Handicap  
455 Inventory (THI)<sup>84</sup>. Both NT and DH participants can provide meaningful questionnaire responses to the  
456 HQ, which focuses on discomfort and aversion experienced with environmental sounds. By contrast,  
457 only participants who experience tinnitus can provide meaningful responses to the THI, which focuses  
458 on the lifestyle burden associated with phantom auditory percepts.

459 **Pure tone audiometry and uncomfortable loudness level testing.** Prior to EEG recordings, air  
460 conduction thresholds were measured for each ear with insert earphones (EarTone-3A) for pure tones  
461 ranging from 0.25 – 8 kHz in octave intervals using the modified Hughson-Westlake procedure.  
462 Uncomfortable loudness level (ULL) assessment was also performed for each ear just prior to the EEG  
463 session as well as during the remote tablet-based testing. Prior to the EEG session, ULL was  
464 determined with the Contour Test of Loudness Perception<sup>85</sup>, which presented three amplitude  
465 modulated 2kHz tones (200ms duration, 5ms raised cosine onset and offset ramps) beginning 5-dB  
466 below their 2 kHz hearing threshold and ascended in 5-dB steps until the participant rated the sound as

467 “Uncomfortably Loud”. Participants completed four runs and the median intensity level across the four  
468 runs determined the demarcation of all seven loudness categories. Tablet-based testing was performed  
469 with a calibrated tablet computer and circumaural headphones (Bose AE2). For tablet-based testing,  
470 participants dragged a virtual slider to adjust pure tone sound intensity to the point where sound was  
471 judged to be uncomfortably loud, as described previously<sup>77</sup>. The ULL was the average across three  
472 repetitions.

473 **Electroencephalography (EEG) measurements of central gain.** Participants were seated in a  
474 reclining chair within a sound-treated booth and watched a movie of their choice with the volume muted  
475 and subtitles on. Continuous audio and EEG monitoring ensured that participants remained in an  
476 awake, restful state for the duration of testing. EEG recordings were performed with a 64-channel array  
477 of scalp electrodes and insert earphones (EarTone 3A) connected to an electrically isolated digitizer  
478 and signal processor (BioSemi ActiveTwo, Cortech Solutions Inc.). Envelope following responses  
479 (EFRs) were measured in response to auditory stimuli delivered to the left ear via insert headphones  
480 (EarTone-3A). Stimuli were sinusoidal amplitude-modulated tones with a carrier frequency of 2 kHz, a  
481 modulation rate of 40-Hz, and 100% modulation depth. Stimulus delivery (sampling rate: 100 kHz) and  
482 data acquisition (sampling rate: 8192 Hz) were coordinated and aligned through custom LabVIEW  
483 applications. The stimulus was repeated 160 times with alternating polarity of the carrier signal.  
484 Stimulus intensity was continuously ramped up (8 seconds) and down (8 seconds) over a 70 dB range,  
485 corresponding to a rate of intensity change of 8.75 dB/second. The upper limit of the intensity range  
486 was initially set to the median sound rated 6, “Loud, but comfortable” with additional downward  
487 adjustments made upon subject request.

488 **Affective sound evaluations.** Participants listened to 60 emotionally evocative environmental sounds  
489 from the original International Affective Digitized Sounds (IADS) corpus and the extended IADS-E  
490 corpus<sup>59,86</sup>. The IADS corpus contains 167 naturally occurring sounds that have been extensively  
491 validated for quantifying differences in affective reactions. For the present study, a subset of sixty IADS  
492 stimuli were chosen to span previously established valence categories<sup>58,86,87</sup>. Stimuli were presented  
493 binaurally through calibrated circumaural headphones (Bose AE2) in random order at a root-mean-  
494 square level of 75 dB SPL. A single trial consisted of a 5-second pre-stimulus baseline period, a 6-  
495 second stimulus, a 5-second silent post-stimulus period, and 30 seconds for the participant to self-  
496 report their behavioral response to the stimulus and for the physiological responses to return to  
497 baseline. Behavioral evaluations asked participants to rate the valence, arousal, and loudness of the  
498 preceding sound with a nine-point Self-Assessment Manikin scale<sup>88</sup>. Participants’ heads were stabilized  
499 throughout the session with a padded head support frame with an adjustable chin and forehead rest  
500 (SR Research Ltd.).

501 **Pupil, skin conductance, and facial recordings.** Changes in pupil size, skin conductance, and facial  
502 expressions were recorded during each of the 60 trials of sound tokens selected from the IADS corpus.  
503 Participants sat in isoluminant conditions and fixated on a cross in the center of a front-facing monitor.  
504 Sound-evoked changes in pupil size were recorded using the EyeLink 1000 Plus (SR Research Ltd.) at  
505 a sampling rate of 1 kHz. Prior to testing, the participant’s pupil size dynamic range was characterized  
506 by presenting alternating bright and dark screens on the computer monitor. Skin conductance  
507 responses (SCRs) were recorded using the skin conductance module of the BioSemi ActiveTwo  
508 system (Cortech Limited Inc.) with two electrodes placed on the hand. Videos of the participant’s facial  
509 expressions were recorded at a sampling rate of 120 Hz with a Genie Nano-M2020 camera (Teledyne  
510 DALSA) fitted with a 16mm IP/CCTV lens (TAMRON).

511 **Multitalker speech intelligibility task.** The details of the task procedure are similar to previous  
512 work<sup>89</sup>. Briefly, participants were required to report four digits that were spoken by a male target



513 speaker ( $F_0=115$  Hz) masked by two additional speakers ( $F_0=90$  Hz,  $F_0=175$  Hz) who were also  
514 vocalizing digits. Digits (1-9, excluding the bisyllabic 'se-ven') were pseudorandomly selected for each  
515 speaker such that each speaker produced a distinct digit at any given time. Stimuli were presented  
516 diotically through calibrated circumaural headphones (Bose AE2). After familiarization with the task,  
517 participants performed randomly interleaved blocks where four blocks had a signal-to-noise ratio of 9  
518 dB SNR, and four blocks at 0 dB SNR. A block consisted of 10 trials (each a 4-digit sequence), where  
519 the first two trials were adaptive in difficulty, designed to re-familiarize the participant with the target,  
520 and were excluded from analyses. In each trial, digits were spaced with 0.68 s between onsets, and a  
521 virtual keypad appeared 1 s following the fourth digit to allow participants to report the target digits.  
522 Feedback was not provided during testing. Pupil size was simultaneously recorded throughout, as  
523 described above.

524

## 525 **Quantification and statistical analysis**

526 **Ranked valence rating.** Each participant's rank-ordered valence ratings were used to order their  
527 individual autonomic responses (e.g., in **Figure 2E**). As multiple ratings could have the same integer  
528 value, and hence their relative rank-order was arbitrary, all responses for a given integer valence rating  
529 were represented by their mean.

530 **Token spectrograms.** Sounds were filtered via a 64 channel gammatone filterbank with center  
531 frequencies spaced between .1 and 10 kHz on an ERB scale. Energy was calculated using 50 ms  
532 windows with 25 ms overlap. Values were converted to dB prior to display. Spectrogram plots omit  
533 sound frequencies and include additional modifications not present in the source material to honor the  
534 terms of use associated with the IADS and IADS-E stimulus batteries.

535 **EEG data analysis.** Analysis of EEG data was performed in MATLAB (MathWorks, Natick, MA) using  
536 FieldTrip software<sup>90</sup>. Data were down-sampled and filtered using zero-phase Butterworth bandpass  
537 filters. Eye movement artifacts were identified and removed using independent component analysis<sup>91,92</sup>.  
538 The 160 sweeps were averaged together and principal component analysis was used to identify the  
539 optimal subset of EEG channels across which to analyze the EFR response<sup>93-95</sup>. After pre-processing,  
540 amplitude-intensity functions were quantified using spectrograms, wherein multiple short-term Fourier  
541 transforms were computed on consecutive overlapping 1-second intervals using a rectangular  
542 window<sup>68</sup>. The second half of the sweep was time-reversed and vector-averaged with the first half of  
543 the sweep, combining data from the upward and downward sweeps into a single upward function. A  
544 first order polynomial was fit (least-squares) to each growth function between 40 and 65 dB SL. Central  
545 gain was quantified as the slope of this fit.

546 **Pupillometry data analysis.** Analysis of pupillometry data was performed in MATLAB (MathWorks,  
547 Natick, MA). To avoid including periods with blinks or missing data, a custom script thresholded  
548 absolute pupil size and pupil derivative, padding flagged periods with 100 samples (**Figure S3B**).  
549 Thresholding was verified by visual inspection. For each participant, z-score normalization was  
550 performed using the mean and standard deviation pooled from traces in the 3 seconds prior to all 60  
551 trials (**Figure S3C**). The covariate of baseline pupil-size was regressed out linearly  
552 (evoked= $0.58 \times \text{baseline} + 0.39$ ) (**Figure S3D**). Missing data resulting from blink extraction were replaced  
553 through linear interpolation. Trials missing more than 50% of data were excluded from analysis  
554 Otherwise, flagged missing data were linearly interpolated (**Figure S3E**). Evoked pupil responses were  
555 summarized as the mean response between 2 and 5 seconds re. stimulus onset. For the dynamic light  
556 stimulus and multi-talker speech intelligibility task, pupillometry analysis procedures matched those  
557 described for the responses to IADS stimuli. Trial responses in the multi-talker speech intelligibility task

558 were summarized as the mean pupil diameter between 0.5 and 3.5 second after the onset of the first  
559 digit.

560 **Skin conductance data analysis.** SCR data were pre-processed in MATLAB (MathWorks, Natick,  
561 MA) using the Ledalab Version 3.2.2 toolbox<sup>96,97</sup>. A non-negative deconvolution approach was used to  
562 separate the skin conductance data into continuous tonic signals (i.e., slow-varying skin conductance  
563 level) and phasic signals (i.e., fast-varying SCRs)<sup>96</sup>. For each stimulus trial, the integrated SCR (iSCR)  
564 was calculated by taking the time integral of the phasic signal during the eleven seconds following  
565 sound onset. The trial average iSCR was calculated for each participant for each sound token.

566 **Facial videography data analysis (Figure 3B).** We identified and mapped 478 3-dimensional facial  
567 landmarks using the Python MediaPipe toolbox at a downsampled rate of 20 Hz<sup>98</sup>. Face-mesh  
568 landmark positions were linearly interpolated across blinks. Landmark positions were temporally  
569 smoothed with a Gaussian kernel (sd of 5 samples). Contrast limited adaptive histogram equalization  
570 was applied to each video frame. Histogram of oriented gradients analyses (resolution of 8 orientations,  
571 local normalization, 2x2 blocks) were performed on each frame, on windows anchored to 77 uniformly  
572 spaced landmark. Windows were 20% the height and width of the fitted face-mesh. Euclidean distance  
573 relative to features in the preceding/proceeding second was derived and smoothed with a Gaussian  
574 kernel (sd of 10 samples). For each participant, Euclidean distances were numerically standardized  
575 (i.e., mode and sd calculated with kernel density estimates) across all 60 sound token responses. Trials  
576 that deviated by more than five times the average deviation were removed. Facial landmarks were  
577 clustered via kernel k-means<sup>99</sup>, where kernels were formed for each participant by calculating the  
578 Euclidian distance between facial region responses and applying a Gaussian kernel, before averaging  
579 the matrix across participants, and running k-means with 6 clusters (the maximum number of clusters  
580 that retained facial symmetry). Trial responses were summarized as the mean across all 77 facial  
581 regions between 0 and 6 seconds re. stimulus onset.

582 **Elastic net regression.** Elastic net regression<sup>100</sup> was used to investigate the relationship between  
583 predictor variables (pupil, face, valence rating, age, and EFR slope), and severity scores (THI, HQ).  
584 Predictor variables were first standardized such that fitted coefficients approximated relative predictor  
585 strength. Elastic net regression incorporates both regularization and feature selection. The predictive  
586 accuracy of the model is penalized for any non-zero coefficients within the model. To regulate  
587 correlated predictor variables, the coefficient penalty is a weighted sum of the L1 and L2 norms (here,  
588 equally weighted). The value  $\lambda$  scales the size of the coefficient penalty where for larger values of  $\lambda$  any  
589 coefficients that are not predictive of the outcome variable are suppressed (**Figure 4A,D**). Fivefold-  
590 validation, repeated for 500 random initializations, was used to derive  $\lambda$  that minimized out-of-sample  
591 mean square error (MSE). With the predictor variables selected via the elastic net, we refit a linear  
592 regression model on all available data (including individuals not in the original elastic net regression  
593 due to missing values when including other predictor variables) and contrasted against a linear  
594 regression model without the selected autonomic measures (pupil, face) with a likelihood ratio test.

595 **Statistical analysis.** Statistical analyses were performed with MATLAB (Mathworks, Natick, MA). Non-  
596 parametric tests were used when assumptions of parametric tests did not apply (i.e., for behavioral  
597 interval data). To assess statistical significance, we used a p-value criterion of  $p < 0.05$  (symbolized with  
598 an asterisk, when appropriate  $p < 0.01$  was also symbolized with two asterisks). Specific statistical  
599 details can be found in the corresponding figure legends.

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