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# Progress in Neurobiology

## Unilateral vestibular neurectomy induces a remodeling of somatosensory cortical maps

--Manuscript Draft--

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<b>Abstract:</b>	<p>Unilateral vestibular neurectomy (UVN) induces a postural syndrome whose compensation over time is underpinned by multimodal sensory substitution processes. However, at a chronic stage of compensation, UVN rats exhibit an enduring postural asymmetry expressed by an increase in the body weight on the ipsilesional paws. Given the anatomo-functional links between the vestibular nuclei and the primary somatosensory cortex (S1), we explored the interplay of vestibular and somatosensory cortical inputs following acute and chronic UVN. We determined whether the enduring imbalance in tactilo-plantar inputs impacts response properties of S1 cortical neurons and organizational features of somatotopic maps. We performed electrophysiological mapping of the hindpaw cutaneous representations in S1, immediately and 1 month after UVN. In parallel, we assessed the posturo-locomotor imbalance during the compensation process. UVN immediately induces an expansion of the cortical neuron cutaneous receptive fields (RFs) leading to a partial dedifferentiation of somatotopic maps. This effect was demonstrated for the ventral skin surface representations and was greater on the contralesional hindpaw for which the neuronal threshold to skin pressure strongly decreased. The RF enlargement was amplified for the representation of the ipsilesional hindpaw in relation to persistent postural asymmetries, but was transitory for the contralesional one. Our study shows, for the first time, that vestibular inputs exert a modulatory influence on S1 neuron's cutaneous responses. The lesion-induced cortical malleability highlights the influence of vestibular inputs on tactile processing related to postural control.</p>
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# 1 **Unilateral vestibular neurectomy induces a remodeling of** 2 **somatosensory cortical maps**

3  
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## 34 1. Introduction

35  
36 Unilateral vestibular loss produces a well-known vestibular syndrome in humans and animals  
37 that includes posturo-locomotor, oculomotor and cognitive disorders whose expression gradually  
38 decreases over time (Curthoys and Halmagyi, 1995; Darlington and Smith, 2000; Lacour and Tighilet,  
39 2010; Smith and Curthoys, 1989). To compensate for the loss of vestibular inputs, the central nervous  
40 system triggers multimodal sensory substitution and reweighting processes (Carriot et al., 2015;  
41 Jamali et al., 2014; Sadeghi et al., 2012, 2011, 2010; Xerri et al., 1983) that mainly take place within  
42 the vestibular nuclei, but also in other subcortical and cortical structures (Bense et al., 2004;  
43 Helmchen et al., 2009; Stiles and Smith, 2015; Zwergal et al., 2016). These processes that have  
44 remedial effects on the antigravity muscle asymmetries (Borel and Lacour, 1992; Lacour and Borel,  
45 1993; Luccarini et al., 1992; Zennou-Azogui et al., 1993) are often accompanied by spontaneous  
46 individual postural strategies (Horak et al., 1990; Shupert et al., 1994) which need to be supplemented  
47 by rehabilitative procedures to more efficiently restore posturo-locomotor balance (Horak, 2009;  
48 Tjernström et al., 2016).

49  
50 The typical temporal profile of posturo-locomotor deficits in rats subjected to unilateral  
51 vestibular neurectomy (UVN) is as follows: during the acute phase of the lesion (days 1 to 7) the  
52 animal's weight is consistently distributed on the contralesional paws to prevent disequilibrium and  
53 falling toward the lesion side. Then, the inverse pattern is observed and maintained from day 7 until  
54 at least one month postlesion, *i.e.* the body weight is shifted to the ipsilesional side (Marouane et al.,  
55 2020; Tighilet et al., 2017), and thus may reflect a long-term sensorimotor strategy in response to the  
56 posturo-locomotor instability induced by the vestibular lesion.

57  
58 It has long been recognized that vestibular, visual, somatosensory and auditory inputs together  
59 contribute to the regulation of posturo-locomotor activities. Challenging the traditional view that  
60 multimodal integration takes place in associative cortical areas, recent studies have provided  
61 convincing evidence that primary sensory cortices are anatomically and functionally interconnected  
62 (for review see: Teichert and Bolz, 2018; Xerri and Zennou-Azogui, 2021). Anatomical tracing  
63 studies in rodents have demonstrated extensive direct corticocortical projections from the primary  
64 auditory cortex (A1) and the primary somatosensory cortex (S1) to the primary visual cortex (V1),  
65 from V1 to S1 and from A1 to S1 (Charbonneau et al., 2012; Henschke et al., 2015; Massé et al.,  
66 2017). The vestibular cortex differs from other sensory cortices in that vestibular signals are  
67 distributed in an extensive network of cortical regions (Brandt and Dieterich, 2019; Lopez, 2016;

68 Lopez and Blanke, 2011). An investigation in rats using both electrophysiological methods and fMRI  
69 mapping described the cortical projections of vestibular inputs to functionally diverse cortical regions  
70 that included S1 (Rancz et al., 2015). In addition, a more recent investigation revealed that the  
71 optogenetic stimulation of the medial vestibular nucleus neurons elicited bilateral fMRI activations  
72 in the sensorimotor cortices and their thalamic nuclei (Leong et al., 2019). Nevertheless, which region  
73 of S1 receives vestibular inputs and how the bimodal interplay occurs has not yet been investigated.  
74 We reasoned that the vestibulo-somatosensory convergence in S1 could occur in the cortical zones  
75 of the paw representations that would be congruent with the functional role of these inputs in the  
76 posturo-locomotor regulation. Accordingly, we evaluated the effects of a complete and irreversible  
77 vestibular loss on the response properties of S1 neurons in the hindpaw cutaneous representations.  
78 The *first aim* of our study is to gain insight into this multisensory cortical integration process by  
79 assessing whether and how acute unilateral vestibular deprivation may reveal a modulatory effect of  
80 the vestibular inputs on the cutaneous response of S1 neurons. To the best of our knowledge, this is  
81 the first investigation of the impact of a permanent vestibular deafferentation on the somatosensory  
82 cortical representations.

83  
84 Furthermore, a wealth of studies on cortical plasticity have established that somatosensory  
85 cortical maps are not isomorphic representations of the body surfaces, but use-dependent,  
86 dynamically maintained representations which play a major role in the processing of behaviorally  
87 relevant sensory events underlying adaptive behavior (for review, see Xerri, 2008). Experience-  
88 dependent cortical map plasticity has been observed in all sensory systems during development and  
89 in mature brain, either after changes in sensory use (Jenkins et al., 1990; Xerri et al., 2005, 1999;  
90 Zennou-Azogui et al., 2016) or after an injury (somatosensory cortex: Merzenich et al., 1983; visual  
91 cortex: Hubel and Wiesel, 1964; auditory cortex: Robertson and Irvine, 1989; motor cortex: Sanes et  
92 al., 1990). Behaviorally relevant changes in somatosensory inputs leads to substantial alterations in  
93 the corresponding cortical representational area (Coq and Xerri, 1998; Polley et al., 2004; Rosselet et  
94 al., 2006; Xerri et al., 1996, 1994).

95  
96 The rationale of this study lies at the junction of two lines of research hitherto investigated  
97 separately: the vestibular compensation phenomenon and the experience-driven plasticity of  
98 somatosensory cortical maps. Our research also stems from the available evidence showing that the  
99 body weight distribution has a profound remodeling effect on the fore- or hindpaw maps in S1 (Canu  
100 et al., 2007; Coq and Xerri, 1999; Zennou-Azogui et al., 2016). We focused on the representational  
101 areas of the hindpaws which are crucially involved in postural and locomotor stabilization as

102 indicated by the predominant weight distribution (~75%) on the hindlimbs in rats (Tighilet et al.,  
103 2017). The *second aim* of our study is to determine whether a long-lasting imbalance in the flow of  
104 peripheral tactilo-plantar inputs, induced by an enduring postural asymmetry following the UVN  
105 (Marouane et al., 2020; Tighilet et al., 2017), impacts the response properties of S1 cortical neurons  
106 and thereby affects the organizational features of the hindpaws cutaneous maps.

107  
108 To achieve our aims, we performed cortical electrophysiological mapping of the hindpaws  
109 cutaneous representation in anesthetized rats, immediately and 1 month after the UVN. In parallel,  
110 we carried out a scoring procedure based on a qualitative behavioral assessment of the vestibular  
111 syndrome complemented with a quantitative automatized evaluation of the posturo-locomotor  
112 balance function during the course of the vestibular compensation.

113

## 114 **2. Methods**

115

### 116 **2.1 Animals and experimental protocols**

117

118 In this study, 33 male Long Evans rats weighing  $300 \pm 30$  g were used. All experiments were  
119 performed in accordance with the National Institutes of Health's Guide for Care and Use of  
120 Laboratory Animals (NIH Publication no. 80-23), revised in 1996 for the UK Animals (Scientific  
121 Procedures) Act of 1986 and associated guidelines and the Policy on Ethics approved by the Society  
122 for Neuroscience in November 1989 and amended in November 1993 and under veterinary and  
123 National Ethical Committee supervision (French Agriculture Ministry Authorization: B13-055-25).  
124 The present study was approved by Neurosciences Ethics Committee N°71 of the French National  
125 Committee of animal experimentation. Every attempt was made to minimize both the number and the  
126 suffering of animals used in this experiment. Animals were housed under standard laboratory  
127 environmental conditions in groups of three in plexiglas cages (26.5 cm wide  $\times$  42.5 cm deep  $\times$  18 cm  
128 high). Food and water were provided *ad libitum*.

129

130 We performed electrophysiological cortical mapping of the hindpaw cutaneous representation  
131 in the S1 cortex in intact rats (CTRL, n=7). Mapping of the ipsilesional or contralesional hindpaws  
132 was initiated 1 hour after left UVN in two groups of animals (1H<sub>ipsi</sub> n=7; 1H<sub>cont</sub> n=4) without waking  
133 up the animals, and 35 days after UVN in two other groups (D35<sub>ipsi</sub> n= 8; D35<sub>cont</sub> n=7). Among these  
134 postlesion groups, double cortical mapping was performed for the ipsilesional and contralesional  
135 hindpaws in the same rats at one hour (n=3) and 35 days (n=2) after UVN, starting with the

136 hemisphere either ipsilateral or contralateral to the lesion. We used the "resource equation" method  
137 developed by Mead (1988) to determine the total sample size. According to this method, if the error  
138 degrees of freedom (E) in an ANOVA is between about 10 and 20 or even more, then the experiment  
139 will be of an appropriate size (see also Festing and Altman 2002; Festing 2006). In a randomized  
140 design,  $E = (\text{total number of animals}) - (\text{number of treatment combinations})$  and  $10 < E < 20$ . In our  
141 experimental design,  $E = 33 - 5 = 28$ .

142  
143 Behavioral assessment of vestibular deficits and recovery was performed on days 1, 2, 3, 7,  
144 10, 14, 21 and 30 after UVN in the animals mapped at the 35<sup>th</sup> day postlesion (n=15). In these rats,  
145 we measured the body weight distribution on the hindpaws at 2 time points: one day before and 35  
146 days after UVN, prior to the electrophysiological recordings. Body weight distribution was also  
147 assessed in the CTRL rats, the day before the electrophysiological mapping of the S1 cortex (**Figure**  
148 **1A**).

149

## 150 **2.2 Surgical Procedures**

151

### 152 **2.2.1 Unilateral Vestibular Neurectomy**

153

154 Animals were anesthetized with intraperitoneal injection of ketamine 1000 (25mg/kg, Virbac,  
155 France) and medetomidine (0.25mg/kg, Domitor® OrionPharma, Finland), and were subjected to a  
156 unilateral vestibular nerve section (UVN) on the left side. UVN was performed under visual control  
157 through a dissecting microscope. The vestibular nerve was completely sectioned after the Scarpa's  
158 ganglion, as close to the brainstem as possible. The body temperature was monitored using a rectal  
159 thermistor probe and was maintained between 37 and 38 °C with a feedback-controlled homeothermic  
160 blanket system (Harvard Apparatus Ltd., Kent, United Kingdom). UVN animals in which cortical  
161 mapping was to be performed 35 days after the lesion received an anti-inflammatory and analgesic  
162 treatment (Tolfédine, Vétoquinol; 4 mg/kg, i.m.). In addition, a solution of Ringer Lactate (Virbac;  
163 10 ml/kg) was administered subcutaneously in order to alleviate the dehydration resulting from the  
164 inability of the animal to drink normally in the first days after the lesion. These animals were  
165 awakened by intraperitoneal injection of Antisedan® (Orion-Pharma; 1 mg/kg). The successful  
166 completion of the surgery was attested at the behavioral level by the presence of a characteristic  
167 vestibular syndrome (barrel rolling behavior, spontaneous nystagmus, etc.) and at the histological  
168 level by the observation under optical microscopy of the full section of the VIII<sup>th</sup> cranial nerve  
169 between the Scarpa's ganglion and the brainstem (see Péricat et al., 2017, for details).



170

## 171 **2.2.2 Preparation for cortical electrophysiological mapping**

172

173 In 1H<sub>ipsi</sub> and 1H<sub>cont</sub> rats, cortical mapping was started about an hour after the lesion. Level of  
174 anesthesia with ketamine and medetomidine was monitored by testing the hindpaw reflex and was  
175 maintained by injecting half of the induction dose throughout the recording sessions. Local anesthetic  
176 (Xylocaïne, Xylovet®) was applied on the scalp and to the external auditory meatus to minimize pain  
177 generated by the ear-bars. The core temperature was continuously monitored and maintained between  
178 37 and 38°C by a heating pad, as described above. The head of the animal was placed in a stereotaxic  
179 frame and a scalp incision was performed while attached muscles were retracted. Cerebrospinal fluid  
180 was drained through an opening in the dura covering the foramen magnum, after resection of posterior  
181 neck muscles, to prevent cerebral oedema. To expose the S1 cortex area to be mapped, a craniotomy  
182 (about 16 mm<sup>2</sup>) was made with bregma as reference point (posterior: 1-5 mm; lateral: 2-6 mm) and  
183 the dura protecting the exposed cortex was resected. A thin layer of warm silicone fluid was applied  
184 to the cortical surface to prevent drying. During the mapping session, repeated injections of a cocktail  
185 of saline and glucose solution every 3 hours allowed the animal to be kept in a stable physiological  
186 condition. At the completion of the mapping session, the animal received a lethal dose of  
187 embutramide (T61, Med'Vet).

188

## 189 **2.3 Cortical mapping procedure**

190

191 Conventional multiunit recording and receptive field mapping techniques were used to  
192 reconstruct the hindpaw representation in layer IV of S1. The mapping procedure used in the present  
193 study has been described in detail in previous papers (Xerri et al., 2005, 1999). We used a high-  
194 resolution camera mounted on an operating microscope to obtain magnified images of the cortical  
195 area to be mapped and the contralateral ventral and dorsal surfaces of the hindpaw. An enlarged image  
196 of the exposed cortex was used to guide and record the location of electrode penetrations relative to  
197 the vasculature of the cortical surface. Recordings were performed with parylene-coated tungsten  
198 microelectrodes (about 1 MΩ at 1 kHz; WPI, UK) introduced perpendicular to the cortical surface  
199 and moved in cartesian coordinates using a three-dimensional micromanipulator driven by stepping  
200 motors (Märzhauser, FST; Germany). Sites of electrode penetration were identified relative to the  
201 vasculature of the cortical surface. For all rats, the interelectrode penetration distance ranged from 50  
202 to 100 μm. The multi-unit signal was pre-amplified, filtered (bandwidth: 0.5–5 kHz), and displayed  
203 on an oscilloscope. This signal was also rectified and passed through a discriminator with an output

204 signal proportional to the part of the input signal which was higher than an adjustable threshold set  
205 just above the background noise. The output of the discriminator was then delivered to an  
206 audiomonitor. Using the recording artifact generated by the microelectrode contact with the cortex  
207 surface as a zero level, we advanced the electrode to a depth of about 650-700 microns to record  
208 responses from small clusters of neurons in layer IV (Waters et al., 1995; Welker et al., 1984). Under  
209 our recording conditions, the amplitude of the background noise usually ranged from 15 to 20  $\mu\text{V}$   
210 with a signal-to-noise ratio ranging from 4 to 6.

211  
212 At each recording site, evoked cortical responses detected by large bursts of activity enabled  
213 us to classify neuronal responses as cutaneous or non-cutaneous. Cutaneous RFs were defined as the  
214 skin area where just-visible skin indentation or hair deflection elicited reliable changes in multi-unit  
215 activity. This stimulation was produced with a fine-tipped wooden stick and monitored using  
216 magnifying glasses (x4). Non-cutaneous responses were identified by taps and pressure on tendons,  
217 intrinsic muscle or joint manipulations while no cutaneous response was found. Cortical sites with  
218 only spontaneous discharges were classified as unresponsive. Ridges of the glabrous skin of the digits  
219 and the foot sole (*i.e.* palm) were used as reliable landmarks to delineate RFs. The cutaneous RF areas  
220 were measured offline using custom-written software (MATLAB®, Mathworks, Inc.).

221  
222 The mechanical threshold of neuronal responses to skin stimulation recorded within the  
223 glabrous skin cortical sectors was determined using Von Frey monofilaments (Stoelting, Semmes-  
224 Weinstein aesthesiometer, Stoelting, Wood Dale, IL) that apply indenting stimuli at a relatively  
225 constant, predetermined force. The most commonly used filaments were 2.36 (bending force: 0.02 g;  
226 bending pressure: 4.39 g/mm<sup>2</sup>); 2.44 (0.04 g; 4.93 g/mm<sup>2</sup>); 2.83 (0.068 g; 5.37 g/mm<sup>2</sup>), 3.22 (0.166  
227 g; 9.15 g/mm<sup>2</sup>), 3.61 (0.407 g; 16.36 g/mm<sup>2</sup>), and 3.84 (0.692 g; 21.39 g/mm<sup>2</sup>). We used a stimulus  
228 series of increasing and decreasing strengths to determine the mechanical threshold eliciting  
229 noticeable changes in neuronal discharge. The stimulation consisted in pressing a filament gently  
230 against the ventral skin, perpendicular to its surface and at the center of the RF, until the filament  
231 began to bend. This procedure was done 5 to 10 times for each filament. **The mechanical threshold is**  
232 **conventionally used as a measure of neuronal response sensitivity.**

233  
234 After the recording session, we used Canvas software (ACD Systems) to make a cutaneous  
235 map of the hindpaw by drawing boundaries encompassing cortical sites whose RFs were restricted to  
236 a common hindpaw subdivision (*e.g.*, digit, palm, heel, etc.). When RFs were located on distinct and  
237 separate skin subdivisions, borders were drawn midway between adjacent recording sites. When a

238 single RF included different but adjoining skin subdivisions of the hindpaw, a boundary line was  
239 drawn that crossed cortical sites. Borders were drawn midway between responsive and unresponsive  
240 sites (**Figure 1B-C**). When RFs were located on two or more hindpaw skin subdivisions, we pooled  
241 together cortical sites in specific map sectors referred to as “*mixed*” areas. Cortical sectors defined as  
242 “*paw*” included recording sites in which RFs **included** the whole ventral or dorsal paw surface.

243

## 244 **2.4 Behavioral assessment of the vestibular syndrome**

245

246 The vestibular syndrome was scored after UVN based on 10 behavioral components following  
247 a procedure previously described (Rastoldo et al., 2020): tail hanging reflex, landing reflex, rearing,  
248 grooming, displacement, head-tilt, barrel rolling, retropulsion, circling and bobbing. Each session  
249 lasted about 15 min and was videotaped for off-line analysis.

250 - Tail hanging reflex: animals were picked up from the ground at the base of the tail and body rotation  
251 around z gravitational axis was scored from 0 (*no rotation*) to 3 points (*several rotations of 360°*).

252 - Landing reflex: after animals were picked up from the ground at the base of the tail, we scored the  
253 first 3 landings from 0 to 3 points (*presence or absence of landing reflex on the 3 landings,*  
254 *respectively*).

255 - Rearing: the ability of the rat to rear was scored from 0 point (*rearing is observed*) to 1 point (*rearing*  
256 *is absent*).

257 - Grooming: the ability of the rat to groom was scored as follows: 0 point (*correct grooming of full*  
258 *body*), 1 point (*grooming of the face, belly and flanks, but not the base of the tail*), 2 points (*grooming*  
259 *limited to the face and belly*), 3 points (*grooming of the face*), 4 points (*inability of the animal to*  
260 *groom itself*).

261 - Displacement: quality of the rat locomotion was scored from 0 (*displacement with no visible deficit*)  
262 to 3 points (*several deficits in the displacement, e.g., path deviation, falls, etc.*).

263 - Head tilt was scored by estimating the angle between the jaw plane and the horizontal with 0 points  
264 (*absence of a head-tilt*) to 3 points (*for a 90° angle*).

265 - Barrel rolling about the horizontal body axis was scored as follows: 0 points (*absence of barrel*  
266 *rolling*), 1 point (*barrel rolling triggered by an acceleration in the vertical axis of the rat in our*  
267 *hand*), 2 points (*spontaneous barrel rolling*).

268 - Retropulsion characterizes backward movements and was scored from 0 (*absence of retropulsion*)  
269 to 1 point (*presence of retropulsion*).

270 - Circling about the vertical axis was scored from 0 (*absence of circling behavior*) to 1 point (*presence*  
271 *of circling behavior*).

272 - Bobbing is assimilated to cephalic nystagmus and was scored from 0 (*absence of bobbing*) to 1 point  
273 (*presence of bobbing*).

274 A mean score was calculated by adding the points obtained for the different quantified components.  
275 For each rat, a mean score was collected the day before the lesion as a reference value, and at days 1,  
276 2, 3, 7, 10, 14, 21 and 30 postlesion.

277

## 278 **2.5 Support surface**

279

280 Static postural deficits and recovery were evaluated by measuring the support surface  
281 delimited by the four legs of the rat, after the tail hanging landing test. The support surface can be  
282 regarded as a good estimate of postural control because it reflects the rat's behavioral adaptation  
283 compensating for the static vestibulospinal deficits induced by the vestibular lesion. This test  
284 consisted in taking the animal by the tail and lifting it vertically over a height of about 50 cm (*lift*  
285 *duration 2 s; position holding at upper position: 1 s*). To quantify the support surface, rats were placed  
286 in a device with a graduated transparent floor that allowed them to be filmed from underneath. A  
287 scale drawn on the floor served to take measurements of the location of the four paws. When the  
288 animal landed on the ground, a picture was captured. The support surface was measured using a  
289 custom-written image analysis tool (MATLAB®, Mathworks, Inc.). At each testing session, twenty  
290 repeated measurements were taken, and an average value was calculated for each rat. Data were first  
291 acquired the day before the lesion, serving as a reference value, and then at days 1, 2, 3, 7, 10, 14, 21  
292 and 30 postlesion. For each rat, data recorded after UVN were compared to the reference value  
293 obtained in the same animal.

294

## 295 **2.6 Body weight distribution**

296

297 The body weight distribution of the animals was quantified with a DWB1 device (BIOSEB;  
298 France). This device consists of a plexiglas cage (25x25 cm) in which the animal is placed for 5 min  
299 recordings while moving freely. The floor of this cage is covered with a plate equipped with 2000  
300 force sensors. Sensors detect vertical pressure at a sample rate of 30 Hertz. They are connected to an  
301 electronic interface that converts the current flowing through it into a measure of weight, the whole  
302 being connected to a computer. The cage is closed by a lid on which a high definition camera  
303 connected to the computer through a USB cable is secured. We measured the weight distributed on  
304 the ipsi- and contralesional hindpaws before UVN and at 35 days postlesion (D35). In order to  
305 compensate for the weight variability of the rats, the weight distribution on the hindpaws was

306 expressed as a percentage of the animal body weight on the day of acquisition (before the lesion or  
307 D35 after UVN). In a previous work (Tighilet et al., 2017), we have shown that, before the lesion and  
308 30 days after the lesion, rats spent about 50% of the time in bipedal stance and 50% in quadrupedal  
309 stance. Therefore, body weight distribution on the hindpaws was analyzed separately for these two  
310 postural patterns.

311

## 312 **2.7 Experimental measurements**

313

314 Cutaneous glabrous and hairy RFs were measured in mm<sup>2</sup> and normalized relative to the total  
315 (ventral + dorsal) cutaneous surface of the hindpaw measured on the digitized images. The mean  
316 relative size of all recorded RFs was computed for each experimental group. The different cutaneous  
317 sectors of the hindpaw map (*simple* and *mixed* ventral or dorsal skin hindpaw territories) were  
318 measured in mm<sup>2</sup> and normalized relative to the whole map area. These normalized values were  
319 averaged for each experimental group. The mechanical thresholds of neuronal responses to  
320 stimulation of hindpaw ventral skin (*i.e.*, of ventral and ventral&dorsal RFs) obtained using the Von  
321 Frey filaments were processed to calculate an average pressure threshold (g/ mm<sup>2</sup>) for each group.

322

## 323 **2.8 Statistics**

324

325 Average percentage of the body mass applied on left and right hindpaw was calculated before  
326 UVN lesion (Pre-op) and at 35 days postlesion (D35) and compared (Left vs. Right hindpaw or  
327 Bipedal vs. Quadrupedal stance for the same animal) using a paired *t-test*. The statistical analyses of  
328 the support surface data were evaluated by ANOVA using Dunnett's *post-hoc* comparison test  
329 (GraphPad, Prism). Comparison of variances was performed using the Bartlett homogeneity of  
330 variance test.

331

332 As the RF sizes were not normally distributed, statistical analyses were carried out using non-  
333 parametric tests to make comparisons between all experimental groups. We first performed a Kruskal-  
334 Wallis H test to detect differences between the CTRL and the lesioned groups. Data in these lesioned  
335 groups have been treated using a design with two-level postlesion delay (1H and D35) and the two-  
336 level hindpaw side (ipsi- and contralesional) as crossed factors. Hence, we used a Scheirer-Ray-Hare  
337 test which is a multifactorial extension of the Kruskal-Wallis test (Scheirer et al., 1976) to reveal main  
338 effects of these two factors and their interaction. All these statistical analyses were supplemented with  
339 the *post-hoc* Dunn test. These analyses were also performed on absolute values of thresholds of

340 responses to cutaneous stimulation (pressure, g/mm<sup>2</sup>) for between-group comparisons of neuronal  
341 sensitivity. Moreover, we investigated whether RF size was associated with neuronal sensitivity in  
342 each experimental group. ANCOVA was carried out with neuronal threshold as dependent variate  
343 and RF size as a covariate of the group factor. This analysis allows testing regression slope  
344 homogeneity across experimental groups by detecting the interaction between group levels and the  
345 covariate.

346  
347 Statistical treatment of the normalized cortical areas was performed using ANOVA  
348 supplemented with multiple comparisons (contrast *post-hoc* test; JASP software, version 0.14.1).  
349 Repeated-measures ANOVA (1-between, 2-within) was used to compare ipsative data (*i.e.*, a set of  
350 responses that always sums to 100%; cf. Greer and Dunlap 1997) consisting of the proportions of  
351 cortical areas representing hindpaw skin sectors (ventral or/and dorsal) within the defined categories  
352 (*simple, mixed*) of the map regions. The between factor consisted in the 5 levels group, whereas the  
353 category and hindpaw skin sectors were considered as within factors.

354  
355 Mean ( $\pm$  SEM) values are used throughout the manuscript. Median values ( $\pm$  IQR) are also  
356 shown in some figures.

357

### 358 **3. Results**

359

#### 360 **3.1 Vestibular deficits induced by UVN**

361

362 A quantitative assessment of the vestibular syndrome allows a global evaluation of the  
363 vestibular compensation process. Immediately after the surgical unilateral vestibular neurectomy, rats  
364 displayed posturo-locomotor impairments characteristic of the vestibular syndrome. These deficits  
365 expressed by a ‘vestibular score’ based on 10 behavioral components were analyzed at different time  
366 points over the first four weeks following the vestibular lesion (**Figure 2A**). One day after the UVN,  
367 the mean vestibular score reached its maximum level ( $15.82 \pm 0.71$ ). Over the subsequent weeks, the  
368 behavioral deficits progressively diminished in two main phases. In the first phase, during the first 10  
369 days postlesion, we observed a progressive and linear decrease of the vestibular score that reached a  
370 value of  $9.25 \pm 1.15$  at D10. In the second phase, over the subsequent three weeks, the vestibular  
371 score reached a plateau. It is noticeable that the dispersion around the mean values gradually  
372 diminished during this period of time (D10 vs D30:  $p < 0.0001$ ), illustrating stronger similarities in  
373 the behavioral patterns across animals. At this stage, several residual deficits were found, such as

374 head tilt, tail-hanging reflex and locomotion impairment, whereas the barrel rolling, retropulsion and  
375 circling behaviors were no longer observed. The UVN also resulted in an increase in the support  
376 surface delimited by the animal's four paws. This parameter is commonly used to describe postural  
377 stability and restoration of balance (Dutheil et al., 2016; Liberge et al., 2010; Marouane et al., 2020;  
378 Tighilet et al., 2019, 2018). Our present results show that in UVN rats, the support surface area was  
379 significantly increased throughout the first 3 days postlesion (D1 to D3:  $p < 0.0001$ ) and gradually  
380 returned to pre-operative values from D7 to D30 ( $p$ : ns; **Figure 2B**).

381  
382 Then, we quantified the percentage of weight distribution along the lateral body axis, between  
383 the left and right hindpaws (**Figure 2C**). Before the lesion, freely moving rats distributed their weight  
384 equally between the left and right hindpaws ( $41.78 \pm 0.72$  % vs  $41.24 \pm 1.22$  %). These results are  
385 consistent with those previously described for the distribution of the body weight on the fore- and  
386 hindpaws (Marouane et al., 2020; Tighilet et al., 2017). At D35 after UVN, rats exhibited a significant  
387 increase of their weight on the left (ipsilesional) hindpaw ( $47.08 \pm 1.55$  %,  $p < 0.001$ ). We also  
388 separately evaluated the difference in percentage of body weight applied on the ipsilesional (left)  
389 hindpaw between bipedal and quadrupedal stance. The results are qualitatively similar for bipedal  
390 and quadrupedal stances. However, a statistically significant increase in the weight applied to the  
391 ipsilesional hindpaw was found in bipedal stance at D35 after UVN ( $58.83 \pm 2.01$  %,  $p < 0.001$ )  
392 whereas the increase in the quadrupedal stance was not found to be significant ( $49.60 \pm 0.93$  %,  $p =$   
393  $0.0598$ ) (**Figure 2D**). Since the hindpaws are more frequently in contact with the ground than the  
394 forepaws, and in view of the present behavioral findings, our electrophysiological recordings targeted  
395 the cortical zone of S1 serving the hindpaw representation.

396

## 397 **3.2 Remodeling of the hindpaw cutaneous representation following UVN**

398

### 399 **3.2.1 Changes in size and spatial distribution of cutaneous receptive fields**

400

401 Each individual cortical map was reconstructed on the basis of about 60 recording sites per  
402 animal. We recorded a total number of 786 cutaneous RFs in 33 rats. We first asked whether the  
403 vestibular deafferentation immediately impacts the S1 neurons response properties. We found that  
404 the spatial extent of the cutaneous RFs was significantly altered (**Figure 3A, B**). A significant increase  
405 in the mean RF size was indeed recorded during the first hours postlesion (CTRL:  $6.14 \pm 0.32$  %, 1H:  
406  $9.90 \pm 0.48$  %;  $p < 0.001$ ). A more detailed analysis revealed that these postlesion changes applied to  
407 both ipsilesional ( $1H_{\text{ipsi}}$ :  $8.74 \pm 0.48$  %;  $p < 0.0001$ ) and contralesional hindpaw RFs ( $1H_{\text{cont}}$ :  $12.37 \pm$

408 1.02 %;  $p < 0.00001$ ) (**Figure 3B**). Comparison between the ipsi- and contralesional RFs, however,  
409 showed a greater increase on the contralesional hindpaw ( $p < 0.02$ ). To gain further insight into the  
410 cortical impact of the vestibular deafferentation, we distinguished the ventral from dorsal skin RFs  
411 for both the contra- and the ipsilesional S1 cortex (**Figure 3C, D**). Hence, the RFs located on both  
412 ventral and dorsal skin surfaces (13.93 %) were discarded from analysis. First, considering the ventral  
413 skin RFs, we found that, compared to the intact rats, ventral skin RFs increased on both the  
414 ipsilesional (CTRL:  $5.77 \pm 0.33$  %,  $1H_{\text{ipsi}}$ :  $8.55 \pm 0.52$  %;  $p = 0.0001$ ) and contralesional ( $1H_{\text{cont}}$ :  
415  $11.97 \pm 0.97$  %;  $p = 0.00001$ ) hindpaws. However, the ventral RF expansion was greater on the  
416 contralesional than the ipsilesional hindpaw ( $p = 0.02$ ). Then, considering the dorsal skin RFs, the  
417 increase recorded during the first hours postlesion was not statistically significant (CTRL:  $7.87 \pm 0.97$   
418 %,  $1H_{\text{ipsi}}$ :  $10.20 \pm 1.04$  %,  $1H_{\text{cont}}$ :  $19.88 \pm 9.01$  %;  $p = 0.66$  and  $p = 0.68$  respectively). Overall, our  
419 data show that the main early effect of the UVN is a bilateral increase of the ventral skin RF size.  
420 However, this increase is more prominent on the contralesional hindpaw.

421  
422 Compared to the CTRL map, 35 days after the lesion, we observed a substantial enlargement  
423 of the RFs located on the ipsilesional hindpaw (CTRL:  $6.14 \pm 0.32$  %,  $D35_{\text{ipsi}}$ :  $16.98 \pm 0.88$  %;  $p <$   
424  $0.00001$  (**Figure 3B**). This increase was shown to be even greater than that recorded in the few hours  
425 after the lesion ( $1H_{\text{ipsi}}$  versus  $D35_{\text{ipsi}}$ :  $p < 0.001$ ). This ipsilesional expansion led to a striking  
426 difference with the contralesional hindpaw RFs ( $p < 0.00001$ ) for which no difference with respect to  
427 control values was found ( $D35_{\text{cont}}$ :  $7.62 \pm 0.71$  %;  $p = 1$ ). At D35 postlesion, we also compared  
428 separately the ventral and dorsal skin RFs after discarding from analysis the RFs located on both the  
429 ventral and dorsal skin surfaces (17.09 %) (**Figure 3C, D**). We reasoned that the postural imbalance  
430 increasing the body weight on the ventral surfaces of the ipsilateral hindpaw would selectively modify  
431 the ventral skin territories in the corresponding cortical map. Ventral skin RFs increased on the  
432 ipsilesional hindpaw as compared to CTRL (CTRL:  $5.77 \pm 0.33$  %,  $D35_{\text{ipsi}}$ :  $16.66 \pm 0.91$  %;  $p <$   
433  $0.00001$ ), and more prominently than during the first hours postlesion ( $1H_{\text{ipsi}}$  versus  $D35_{\text{ipsi}}$ :  $p <$   
434  $0.00001$ ). By contrast, a return to a normal size was found for the ventral RFs on the contralesional  
435 hindpaw ( $D35_{\text{cont}}$ :  $5.94 \pm 0.54$  %, CTRL versus  $D35_{\text{cont}}$ :  $p = 1$ ), indicating a strong asymmetrical  
436 alteration between ventral RFs on ipsi- and contralesional hindpaws at D35 ( $p < 0.00001$ ) (**Figure**  
437 **3C**). The dorsal skin RFs increased on the ipsilesional hindpaw as compared to CTRL (CTRL:  $7.87$   
438  $\pm 0.97$  %,  $D35_{\text{ipsi}}$ :  $19.37 \pm 3.13$  %;  $p < 0.001$ ), but not on the contralesional hindpaw ( $D35_{\text{cont}}$ :  $13.53$   
439  $\pm 2.30$  %, CTRL versus  $D35_{\text{cont}}$ :  $p = 1$ ). However, contrasting with the asymmetry of ventral RFs,  
440 dorsal RFs were not found to be significantly different between the two hindpaws ( $D35_{\text{ipsi}}$  versus  
441  $D35_{\text{cont}}$ :  $p = 0.15$ ) (**Figure 3D**).



442  
443 We assessed the mechanical threshold of the neuronal responses reflecting the minimum sensitivity  
444 to pressure exerted at the center of their RFs. Interestingly, a lesion-induced asymmetry was found  
445 **between the cortical areas representing the ipsi- and contralesional hindpaws**, depending on the  
446 postlesion time. During the first hours postlesion, **the neuronal sensitivity in the cortical area**  
447 **representing the contralesional hindpaw** was greater than that of the ipsilesional one, **as attested by**  
448 **smaller thresholds of response to the mechanical stimulation of ventral skin surfaces of the**  
449 **contralesional hindpaw** ( $1H_{\text{contra}}$ :  $7.55 \pm 0.53$  g/mm<sup>2</sup>,  $1H_{\text{ipsi}}$ :  $12.99 \pm 1.59$  g/mm<sup>2</sup>;  $p < 0.00001$ ). The  
450 reverse was observed at D35 ( $D35_{\text{contra}}$ :  $13.75 \pm 0.49$  g/mm<sup>2</sup>,  $D35_{\text{ipsi}}$ :  $11.01 \pm 0.43$  g/mm<sup>2</sup>;  $p < 0.0001$ )  
451 as the neuronal sensitivity within the area **of the contralesional hindpaw** strongly decreased ( $p <$   
452  $0.00001$ ) **(Figure 4A)**. We searched for a possible correlation between the neuronal RF size and  
453 sensitivity. When data were log-log plotted, the trends within each experimental group presented  
454 negative linear **relationships between threshold of response to skin pressure and RF size suggesting**  
455 **that the data follow a power law relationship under the form  $y \propto x^{-\beta}$ , between neuronal sensitivity (y)**  
456 **and RF size (x). (Figure 4B)**. Moreover, ANCOVA did not reveal statistically significant interaction  
457 between RF size and experimental group factor [ $F(4, 532) = 1.86$ ;  $p = 0.116$ ], indicating an acceptable  
458 hypothesis of identical slope coefficients for all the experimental groups [ $\beta = -0.155$ ;  $t(536) = -4.98$ ;  
459  $p < 0.001$ ]. **Therefore, in all groups, we found that the larger the RF size, the greater the sensitivity**  
460 **(i.e., the smaller the response threshold to skin pressure). It is noteworthy that in the cortical area of**  
461 **the hindpaw opposite to the lesion side**, a strong increase of neuronal sensitivity **was recorded** during  
462 the first hours postlesion, regardless the RF size [ $\Delta$  intercept =  $-0.103$ ,  $t(536) = -3.03$ ;  $p = 0.003$ ]  
463 **(Figure 4B)**.

464  
465 To ensure that postlesion alterations were not blurred by interindividual differences, we also  
466 performed mapping of both hemispheres in each postlesion group ( $1H$   $n = 3$ ,  $D35$   $n = 2$ , see  
467 **Supplementary Figure 1**. This double mapping corroborates both the bilateral expansion of ventral  
468 RFs at  $1H$  postlesion and only on the ventral ipsilesional hindpaw 35 days after the UVN, as well as  
469 the postlesion asymmetry in neuronal sensitivity. Therefore, in this respect, these animals can be seen  
470 as representative of their own experimental group. Such a conclusion cannot be drawn for the dorsal  
471 RFs, given the small size of the sample collected.

472

### 473 **3.2.2 Organization of hindpaw somatosensory maps**

474

475 The somatotopic organization of the hindpaw representation within the intact S1 cortex of rats  
476 displayed invariant organizational features despite inter-individual differences in representational  
477 details. The hindpaw cutaneous representation was consistently located medial and posterior to the  
478 forepaw map and in a medial-rostral location with respect to the tail and back representations. From  
479 rostral to caudal, the somatotopic organization was revealed by the progression of cortical sites from  
480 the toes, plantar pads of the sole to the heel. The cutaneous representation displayed a somatotopic  
481 order that clearly segregated individual digits and plantar pads, qualified as *simple* areas, that were  
482 ordered from the anterolateral to posteromedial cortical sector (**Figure 5A**). Additionally, control  
483 animals showed *mixed* areas corresponding to neurons with RFs localized on 2 or more skin territories  
484 of the paw.

485  
486 After the lesion, the overall map size was not affected either at one hour (CTRL:  $0.93 \pm 0.12$   
487  $\text{mm}^2$ ,  $1H_{\text{ipsi}}$ :  $0.78 \pm 0.08 \text{ mm}^2$ , p: n.s.;  $1H_{\text{cont}}$ :  $0.90 \pm 0.19 \text{ mm}^2$ , p: n.s.) or at 35 days postlesion ( $D35_{\text{ipsi}}$ :  
488  $0.86 \pm 0.13 \text{ mm}^2$ , p: n.s.;  $D35_{\text{cont}}$ :  $0.82 \pm 0.18 \text{ mm}^2$ , p: n.s.) (**Figure 5B**) for both hindpaw  
489 representations. However, the postlesion increase in RF size, described above, led to changes in the  
490 proportion of each representational area (*simple* and *mixed*) of the somatotopic map, *i.e.* a fusion of  
491 previously segregated areas.

492 Immediately after the lesion, we observed a significant bilateral diminution of the proportion  
493 of *simple* areas (CTRL:  $90.49 \pm 2.31 \%$ ,  $1H_{\text{ipsi}}$ :  $73.52 \pm 3.64 \%$ ,  $p < 0.0001$ ;  $1H_{\text{cont}}$ :  $71.02 \pm 5.03 \%$ ,  
494  $p < 0.0001$ ) related to an extension of *mixed* areas (CTRL:  $9.51 \pm 2.31 \%$ ;  $1H_{\text{ipsi}}$ :  $26.49 \pm 3.64 \%$ ,  $p <$   
495  $0.0001$ ;  $1H_{\text{cont}}$ :  $28.98 \pm 5.03 \%$ ,  $p < 0.0001$ ) in both the ipsilesional and contralesional hindpaw maps  
496 (**Figure 5C**). The expansion of the *mixed* areas reflects a partial dedifferentiation of the somatotopic  
497 maps. No differences between ipsi- and contralesional hindpaw maps were noticed (*simple* areas, p:  
498 n.s.; *mixed* areas, p: n.s.).

499 At 35 days postlesion, a drastic reduction of the relative extent of *simple* areas (CTRL:  $90.49$   
500  $\pm 2.31 \%$ ;  $D35_{\text{ipsi}}$ :  $36.22 \pm 5.28 \%$ ,  $p < 0.0001$ ) combined with an expansion of the *mixed* areas (CTRL:  
501  $9.51 \pm 2.31 \%$ ;  $D35_{\text{ipsi}}$ :  $63.78 \pm 5.28 \%$ ,  $p < 0.0001$ ) was found in the map representing the ipsilesional  
502 hindpaw. By contrast, a differentiation between cortical sectors of the contralesional hindpaw map  
503 was observed, approaching that found in prelesional maps (*simple* areas:  $D35_{\text{cont}}$ ,  $65.35 \pm 20.61 \%$ ,  $p$   
504  $< 0.05$ ; *mixed* areas:  $D35_{\text{cont}}$   $25.97 \pm 12.42 \%$ , p: n.s.) (**Figure 5C**). The somatotopic dedifferentiation  
505 resulting from the ipsilesional hindpaw map changes is mostly attributed to the substantial shrinkage  
506 of the *simple* ventral areas (CTRL:  $71.94 \pm 4.19 \%$ ;  $D35_{\text{ipsi}}$ :  $25.23 \pm 5.48 \%$ ,  $p < 0.0001$ ) and a  
507 prominent increase of the *mixed* ventral areas (CTRL:  $7.80 \pm 2.40 \%$ ;  $D35_{\text{ipsi}}$ :  $40.57 \pm 5.80 \%$ ,  $p <$

508 0.001) (**Figure 5D**). As for the contralesional hindpaw map, the data show no significant differences  
509 between control values and either ventral (*simple* areas: p: n.s.; *mixed* areas: p: n.s.) or dorsal (*simple*  
510 areas: p: n.s.; *mixed* areas: p: n.s.) skin areas (**Figure 5D, E**).

511

#### 512 **4. Discussion**

513

514 This study confirms previous findings on the time course of the postural strategy of rats  
515 subjected to a permanent unilateral loss of vestibular afferents, characterized by a support surface  
516 enlargement from day 1 to day 3 after the lesion and a predominant weight distribution on the  
517 ipsilesional hindlimb from day 7 that persisted at least until day 35. Based on electrophysiological  
518 recordings of small clusters of neurons in the primary somatosensory cortex, we demonstrate, for the  
519 first time, that the unilateral vestibular neurectomy (UVN) induces, over the first hours following the  
520 vestibular loss, a bilateral expansion of the cutaneous RF of the hindpaws. This expansion was  
521 **conclusively demonstrated for** the ventral skin surfaces and was greater on the contralesional  
522 hindpaw. **Neurons within the cortical area representing this contralesional hindpaw displayed a**  
523 **greater sensitivity to skin mechanical stimulation.** As a result of **RF enlargement**, a bilateral  
524 degradation of the spatial grain of representation of the cutaneous map of the hindpaws occurred. The  
525 overall surface area of the hindpaw cortical map was not modified immediately after UVN.

526

527 Thirty-five days after the lesion, the expansion of ventral cutaneous RFs on the ipsilesional  
528 hindpaw was even greater than early after the UVN, whereas the ventral RFs on the contralesional  
529 hindpaw returned to normal. **This latter effect was accompanied with a strong decrease in neuronal**  
530 **sensitivity to ventral skin stimulation.** The asymmetry between the sizes of ipsi and contralesional  
531 ventral RFs at 35 days was not observed for dorsal RFs. The ventral RF expansion was found as the  
532 animals displayed a predominant weight distribution on the ipsilesional hindlimb. The prominent RF  
533 enlargement led to a representational dedifferentiation of the cortical sectors of the map serving the  
534 ventral skin of the ipsilesional hindpaw. No such dedifferentiation was found for cortical areas  
535 representing dorsal skin territories. However, the total areal extent of the maps was not modified at  
536 this chronic stage of the lesion.

537

538 **Immediate expansion of the cutaneous RFs of S1 neurons following UVN reveals modulatory**  
539 **effects of vestibular inputs on the somatosensory neuron responses.**

540

541 Somatotopically organized responses to tactile stimulation are found in cells located  
542 throughout the ventral postero-medial (VPM, Diamond et al., 1992), ventral postero-lateral (VPL,  
543 Francis et al., 2008) nuclei and in S1, as has long been established. Interestingly, the vestibular nuclei  
544 complex also massively projects to the VPM and the VPL in rodents and humans (Nagata, 1986;  
545 Shiroyama et al., 1999; Lopez and Blanke, 2011 for review). Electrophysiological recordings have  
546 provided evidence that these thalamic nuclei respond not only to cutaneous or proprioceptive inputs,  
547 but also to vestibular stimulation (Deecke et al., 1977; Raymond et al., 1974; Sans et al., 1970;  
548 Wijesinghe et al., 2015). Furthermore, vestibular responses have also been recorded in the rodent  
549 somatosensory cortex (Leong et al., 2019; Rancz et al., 2015).

550  
551 Given the above-mentioned anatomical and functional connectivity between the vestibular  
552 nuclei and the primary somatosensory cortex, the impact of the vestibular neurectomy on the S1  
553 neuron activity was very likely to reveal crossmodal cortical interactions between somatosensory and  
554 vestibular inputs. Indeed, our electrophysiological mapping within the ipsi- and contralesional S1  
555 cortex during the first hours after the UVN did show immediate cortical effects of the vestibular loss.  
556 The early expansion and shift in location of RFs reported herein are consistent with those found in  
557 previous studies of cortical reorganization after peripheral nerve injury (Navarro et al., 2007),  
558 amputation (Calford and Tweedale, 1988; Turnbull and Rasmusson, 1990), local anesthesia (Rossini  
559 et al., 1994), or epidural block (Metzler and Marks, 1979), which all demonstrate immediate shifting  
560 of cutaneous RFs for neurons located in the deafferented cortical zone. In the present study, the early  
561 postlesion RF enlargement was recorded in both hemispheres **as early as the few hours after the lesion**  
562 **in the absence of behaviorally-induced changes, since the mapping procedure was initiated while the**  
563 **animal was still anesthetized.** Interestingly, this alteration was **mainly demonstrated for** the ventral  
564 skin of the hindpaw, suggesting that the influence of vestibular inputs on S1 neurons is primarily on  
565 those representing the foot sole which is strongly involved in antigravity stance and postural control.  
566 Postlesion increase in ventral RF size led to a substantial remodeling of the hindpaw cutaneous maps.  
567 The vestibulo-thalamic projections observed in humans (Magnin and Kennedy, 1979; for review see  
568 Lopez and Blanke, 2011) and cats (Condé and Condé, 1978; Kotchabhakdi et al., 1980) have been  
569 described as bilateral with a contralateral predominance. As mentioned earlier, vestibular responses  
570 have also been recorded in the rodent somatosensory cortex (Leong et al., 2019; Rancz et al., 2015).  
571 However, these studies showed no quantitative difference in the amplitude of bilaterally recorded  
572 responses. Nonetheless, we found a greater expansion of ventral RFs on the contralesional hindpaw.  
573 This effect is in accordance with a study showing a dominance of the vestibular processing in the left  
574 hemisphere (Best et al., 2014) in which the contralesional hindpaw is represented in our study. Hence,

575 our findings, based on vestibular deafferentation, corroborate and extend this previous study, and  
576 suggest that vestibular signals that influence S1 neurons receiving cutaneous inputs contribute to  
577 perceptually guided posturo-locomotor adjustments.

578  
579 **Neuroplasticity mechanisms underlying immediate RFs enlargement following vestibular**  
580 **deafferentation**

581  
582 It is well documented that cortical maps are dynamically reshaped through ongoing  
583 adjustments in the balance of excitatory and inhibitory influences on their constituent neurons. Drastic  
584 and immediate deafferentation-induced disruption in this balance alters the RF properties of cortical  
585 neurons through weakening/strengthening of already existing thalamocortical and intracortical  
586 synapses, and thus rapidly remodels the functional circuitry of cortical networks (Harding-Forrester  
587 and Feldman, 2018; Xerri, 2012). As the vestibular deafferentation induces an electrophysiological  
588 imbalance between the vestibular nuclei characterized by increased excitability within the intact  
589 medial vestibular nuclei (Curthoys and Halmagyi, 1995; Smith and Curthoys, 1988), and given  
590 predominant contralateral vestibulo-thalamic projections, one could postulate that the excitatory  
591 vestibular inputs to the ipsilesional somatosensory cortex are potentiated. The resulting  
592 hyperexcitability of S1 neurons may thus lead to cutaneous RF enlargement predominantly on the  
593 contralesional hindpaw. Our findings corroborate this hypothesis, as contralesional hindpaw RFs  
594 were more enlarged after the UVN than were the ipsilesional. In addition, we found a higher neuronal  
595 sensitivity to cutaneous stimulation in the cortical area of the contralesional hindpaw.

596  
597 Considering a non-exclusive alternative hypothesis, the postlesion RF enlargement might  
598 result from a rapid disinhibition process. Given the bilateral projections of vestibulo-thalamic inputs,  
599 the VN imbalance may be expected to result in decreased thalamo-cortical inputs on both S1 cortices,  
600 which would be consistent with the bilateral, however asymmetrical, effects of the UVN observed in  
601 our study. Therefore, we postulate that the immediate expansion of cutaneous RFs reveals a reduction  
602 of inhibition normally exerted by vestibular projections onto S1 layer IV neurons, possibly via  
603 thalamo-cortical inputs and/or cortico-cortical connections. Indeed, it has long been argued that  
604 intracortical inhibition plays a key role in controlling the spatial selectivity of cortical neurons through  
605 segregation of broad sets of converging thalamo-cortical synaptic inputs (see Calford, 2002; Jones,  
606 1993; Xerri, 2012). Consistently, cutaneous RFs of somatosensory cortical neurons were enlarged  
607 when GABA-mediated local inhibition was antagonized by intracortical bicuculine injection  
608 (Alloway et al., 1989; Dykes et al., 1984; Tremere et al., 2001) whereas injection of baclofen, a

609 selective agonist for the GABA<sub>A</sub> receptors, induced a shrinkage of S1 neurons' cutaneous RFs  
610 (Kyriazi et al., 1996). A release of afferent-driven intracortical tonic inhibition results in an enhanced  
611 effectiveness of convergent cutaneous inputs. Therefore, this could be a most likely mechanism for  
612 rapid unmasking of previously subthreshold afferent connections reflected by the rapid expansion of  
613 cutaneous RFs of S1 neurons following the loss of tonic modulatory vestibular inputs.

614  
615 To consider our data in the particular context of heteromodal sensory integration in primary  
616 cortical areas, it is worth mentioning that auditory inputs to V1 were found to decrease visually  
617 induced activity (Iurilli et al., 2012). Along the same lines, acute hearing loss was shown to release  
618 the inhibitory effects of A1 neurons on visually elicited responses in V1 and lead to a concomitant  
619 increase in V1 activation (Teichert and Bolz, 2017). However, the suppressive effect may be  
620 functionally adapted, as additional data showed that auditory stimulation sharpens the orientation  
621 selectivity of V1 neurons (Ibrahim et al., 2016). These data are in accordance with our findings on  
622 the vestibular deafferentation acute effects on cutaneous RFs of S1 neurons. Collectively, the  
623 available evidence supports the view that, in normal conditions, cross modal modulation may act to  
624 improve the tuning of neuronal response properties in primary sensory cortices.

625  
626 **The postural strategy leading to increased cutaneous feedback from the ipsilesional hindpaw**  
627 **remodels S1 cutaneous neurons' responses**

628  
629 One week after UVN, rats typically adopt a postural compensatory strategy to maintain their  
630 posturo-locomotor stability, *i.e.* by shifting their body weight toward the ipsilesional paws. This  
631 postural strategy has been reported in our previous studies (Marouane et al., 2020; Tighilet et al.,  
632 2017) highlighting that weight distribution is a sensitive parameter for the assessment of the postural  
633 syndrome in the UVN rodent model. The postural strategy which begins around day 7 and is  
634 consistently maintained beyond the first month after the lesion may reflect the need for the rat to  
635 better feel the ipsilesional limbs and increase tactilo-plantar feedback to achieve better antigravity  
636 stance and postural control. Such a strategy is very likely to accentuate the tactilo-plantar flow from  
637 the ipsilesional paws projecting to S1, and thus to create a functional asymmetry between the ipsi-  
638 and contralesional hindlimb cortical areas during posturo-locomotor activities. In line with our  
639 findings, stroke patients adopt a postural strategy by applying more weight on the non-impaired leg  
640 to achieve better postural stability (Aruin et al., 2000; Mizrahi et al., 1989; Sackley, 1991). Thus, the  
641 shift of body weight could represent a postural adaptive strategy following peripheral or central  
642 damage.

643  
644           Functional organization of somatotopic cortical areas is shaped by tactile experience (for  
645 reviews, Xerri 2008; Harding-Forrester and Feldman, 2018). Our data show a drastic remodeling of  
646 the ipsilesional hindpaw map due to a marked increase of the number of recording sites displaying  
647 enlarged ventral skin RFs (*mixed* areas) 35 days after UVN. This cortical remodeling disrupting the  
648 somatotopic arrangement of the cutaneous map led to a greater dedifferentiation of the hindlimb  
649 representation than that triggered in the few hours after the vestibular deafferentation. This finding is  
650 consistent with numerous studies showing a use-dependent recruitment of new cortical territories in  
651 S1, for more intensely or frequently stimulated skin surfaces, that is related to the translocation of the  
652 cutaneous RFs of constituent neurons over those skin territories. Furthermore, we reasoned that the  
653 asymmetrical tactilo-plantar stimulation of the hindpaws resulting from the shift in body weight  
654 would induce larger cutaneous surfaces temporally co-stimulated on the lesioned side. In line with  
655 this hypothesis, 35 days after the vestibular loss, we found a substantial expansion of cutaneous RFs  
656 covering the ventral skin surfaces of the ipsilesional hindpaw, whereas the RF size on the  
657 contralesional hindpaw were similar to those recorded prior to the lesion, thus leading to a strong  
658 interhemispheric asymmetry between ventral RFs. The neuronal sensitivity was also found to be  
659 asymmetric as the sensitivity in the ipsilesional hindpaw area tended to increase whereas that in the  
660 contralesional hindpaw area strongly decreased. These RF property changes are in accordance with  
661 the postural asymmetry.

662  
663           One can assume that the reduced weight on the contralesional paws at rest and during  
664 locomotion was sufficient to maintain the organizational features of the cortical map. By contrast, the  
665 experience-driven expansion of cutaneous RFs over the ipsilesional hindpaw is likely to result from  
666 amalgamation of normally distinct thalamic RFs, as neurons displayed extracellular responses to new  
667 sets of inputs. Because of the simultaneous stimulation of larger cutaneous territories during posturo-  
668 locomotor activities after UVN, one can hypothesize that the over-reliance on the ipsilesional  
669 hindpaw was likely to generate cutaneous inputs spatially less restricted on a particular region of the  
670 paw. This postural modification led to temporally more coherent inputs because of the simultaneous  
671 stimulation of larger cutaneous territories during posturo-locomotor activities. This interpretation is  
672 supported by earlier studies showing the critical role of input timing in determining cortical map  
673 topologies and spatial resolution. These studies have revealed that locally synchronous cutaneous  
674 stimulation leads to an enlargement of S1 neurons' cutaneous RFs over co-stimulated digits in primate  
675 (Byl et al., 1996; Clark et al., 1988; Wang et al., 1995) and Human (Godde et al., 2003; Schwenkreis  
676 et al., 2001; Stavrinou et al., 2007), and for co-stimulated whiskers in the barrel cortex (Diamond et

677 al., 1993). An increase in RF size was also observed in adult rats exposed to hypergravity (2G)  
678 generated by a centrifuge during development, altering both proprioceptive and cutaneous inputs  
679 (Zennou-Azogui et al., 2016) as well as in rats housed in impoverished environment that reduced  
680 their exploratory behavior (Coq and Xerri, 1999; Godde et al., 2002). Furthermore, somatotopic maps  
681 can be remodeled after a few days of salient tactile experience modifying the spatio-temporal  
682 dynamics of input to S1, such as nursing (Rosselet et al., 2006; Xerri et al., 1994), forced use of the  
683 non-restricted forelimb in postural balance after unilateral forelimb immobilization (Coq and Xerri,  
684 1999), or hypodynamia-hypokinesia (Canu et al., 2003; Dupont et al., 2003, 2001; Langlet et al.,  
685 1999).

686  
687 At 35 days postlesion, we also noticed an enlargement of the ipsilesional dorsal RFs, as  
688 compared to intact rats. However, this alteration did not lead to asymmetrical RF sizes between ipsi-  
689 and contralesional hindpaws, contrary to the ventral RFs. Moreover, the increase in dorsal RFs was  
690 not accompanied by a dedifferentiation of the dorsal sectors of the cortical maps. The differential  
691 effect of the UVN on the ipsi- and contralesional RFs leading to a ventral skin RF expansion restricted  
692 to the ipsilesional hindpaw confirms the view of a postural effect on somatosensory cortical maps  
693 *i.e.*, an asymmetry between ventral RF sizes.

694  
695 The ability to precisely localize tactile stimuli depends on the RF size of S1 neurons  
696 determining the grain of spatial representation and thus the representational differentiation of the  
697 body somatotopic maps. Accordingly, one can assume that the loss of vestibular inputs inducing an  
698 expansion and spatial shift of the cutaneous ventral RFs of S1 neurons has a strong impact on tactile  
699 discrimination abilities. In an attempt to reconcile our findings with those reported in the cited studies  
700 in healthy human participants, one can postulate that the loss of vestibular inputs strongly modulates  
701 the response characteristics of cortical somatosensory neurons, resulting in impaired spatial  
702 discrimination tactile abilities. Therefore, our findings indicate that crossmodal interplay between  
703 vestibular and cutaneous-plantar inputs within the primary somatosensory cortex contributes to  
704 modulate tactile discriminative abilities which may be crucial to optimally regulate posturo-  
705 locomotor activities. In line with this view, it has been shown that galvanic and caloric vestibular  
706 stimulation improves the ability to detect tactile stimuli applied on both hands of healthy participants  
707 (Ferrè et al., 2013, 2011a, 2011b).

708  
709 Numerous studies support the crucial contribution of plantar cutaneous sensation and pressure  
710 feedback in the control of human stance and locomotion (Inglis et al., 2002; Kavounoudias et al.,



711 1998; Magnusson et al., 1990; Strzalkowski et al., 2018). For instance, plantar anesthesia increases  
712 instability during standing and walking (Fiolkowski et al., 2002).-We hypothesized that the behavioral  
713 strategy consisting in body weight shift to ipsilesional side is aimed at reinforcing somatosensory  
714 plantar feed-back to improve postural control, although RF size enlargement is detrimental to fine  
715 spatial tactile discrimination. In normal conditions, vestibular inputs may improve the tactile acuity  
716 on the plantar skin by refining the RF size of S1 neurons, as indicated by the immediate RF  
717 enlargement induced by the UVN. Therefore, considering a potential clinical relevance of our  
718 findings, it is reasonable to assume that rehabilitative procedures (*e.g.* walking on a floor with  
719 different textures) aimed at enhancing spatial discrimination of plantar stimuli may improve posturo-  
720 locomotor adjustments in vestibulo-deficient patients.

721

## 722 **Conclusion**

723

724 The present study reveals for the first time that acute unilateral vestibular loss reshapes the  
725 cutaneous receptive fields of S1 neurons and, thereby, highlights the bilateral and asymmetrical  
726 modulatory influence of vestibular inputs on tactile processing related to posturo-locomotor balance  
727 control. The finding that the UVN induced an early expansion of the cortical cutaneous receptive  
728 fields reveals that vestibular influences contribute to maintaining a fine somatotopic organization of  
729 the foot sole cutaneous representation in S1. In addition, we suggest that the postural strategy  
730 consisting of a body shift to the lesioned side in order to improve posturo-locomotor balance in UVN  
731 rodents induces a use-dependent remodeling of the ipsilesional hindlimb cutaneous map at the chronic  
732 stage of the lesion (see **Figure 6** showing a schematic illustration of main effects of the UVN on S1  
733 cortex). Further studies should evaluate the relative contribution of corticocortical and  
734 thalamocortical inputs to the modulatory influence of vestibular inputs on S1 neurons.

735

## 736 **Declarations of interest**

737

738 The authors declare no competing financial interests.

739

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751

## 752 **Author Contributions**

753

754 Supervision: C.X., B.T., Y.Z.A.; conceptualization and writing-original draft: G.R., J.F., C.X., B.T.,  
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756 A.E.; writing – review & editing: G.R., J.F., C.X., B.T., Y.Z.A., A.E.

757

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1097 **Figure 1**  
1098 **Experimental protocol for evaluating postural deficits and remodeling of hindpaw cutaneous**  
1099 **cortical maps after unilateral vestibular neurectomy (UVN).**

1100 **A:** Vestibular score and support surface assessment were performed one day before unilateral  
1101 vestibular neurectomy (UVN) in the 1H and D35 groups and 1, 2, 3, 7, 10, 14, 21, 30 days after UVN  
1102 in the latter group. Body weight distribution was also assessed prior to UVN, and before cortical  
1103 mapping in all groups, including the controls (CTRL). Cortical mapping was initiated over the first  
1104 hours following the lesion in the 1H group, and 35 days later in the D35 group. **B-C:** Schematic  
1105 cortical mapping procedure. In each group, cortical recordings (about 60 sites per map; C1) were  
1106 performed in layer IV either in the ipsilesional (1H<sub>ipsi</sub>; D35<sub>ipsi</sub>) or contralesional (1H<sub>cont</sub>; D35<sub>cont</sub>)  
1107 hindpaw representational zone of S1 to determine the location and size of the neurons' cutaneous  
1108 receptive fields (RFs). The RF nomenclature indicate their location on the hindpaw skin surface (C2).  
1109 An example of a RF recorded in the *mixed* cortical area is represented by an orange circle including  
1110 digits 3 and 4 and part of the plantar skin. Collection of all RFs recorded in a mapping session (C3)  
1111 in order to generate a somatotopic cortical map (C4). **D:** Illustration of the device (DWB1®, Bioseb,  
1112 France) used for dynamic weight-bearing assessment. The animal was placed in a plexiglass chamber  
1113 (25 x 25 cm) and moved freely on a floor covered by a plate equipped with 2 000 force sensors. The  
1114 animal behavior was videotaped and the distribution of its body weight on each of the four limbs was  
1115 calculated offline (Marouane et al., 2020; Tighilet et al., 2017). **E:** The polygon in blue illustrates the  
1116 body support surface measured during static state.

1117  
1118 **Figure 2**  
1119 **Effect of the UVN on the body weight distribution on the hindpaws.**

1120 **A:** Vestibular score profile illustrating the time course of behavioral syndrome over postlesion days  
1121 (D). **B:** Time course of body support surface. **C:** Histograms illustrating the percentage of body mass  
1122 applied on the hindpaws (in red, ipsilesional *left hindpaw*; in green, contralesional *right hindpaw*)  
1123 before (Pre-op) and 35 days after UVN (D35). **D:** Histograms illustrating the percentage of body mass  
1124 applied on the ipsilesional hindpaw in bipedal (yellow) or quadrupedal (blue) stance before and 35  
1125 days after the lesion. \*\*: P < 0.01; \*\*\*: P < 0.001; \*\*\*\*: P < 0.0001, for comparisons with control  
1126 values. All data are expressed as means ± SEM.

1127  
1128 **Figure 3**  
1129 **Impact of the UVN on the size of hindpaw cutaneous receptive fields (RFs) of S1 neurons.**

1130 **A:** Typical RFs located on the hindpaw glabrous (top) and hairy (bottom) skin surfaces of an intact  
1131 rat (CTRL, left panel), and on the ipsilesional (Ipsi) and contralesional (Cont) hindpaws, recorded  
1132 one hour (1H, middle panel), and 35 days (D35, right panel) after the lesion, in two rats. **B:** Mean  
1133 relative size of all RFs (ventral, dorsal and ventral & dorsal) obtained in CTRL and UVN rats.  
1134 Boxplots represent the first and the third quartiles and medians, while black dots individual outlier  
1135 values. Red triangles show mean RF size. **C-D:** Relative size of ventral and dorsal skin RFs taken  
1136 from the data shown in B. Horizontally aligned \* and bars show statistical differences between the  
1137 experimental groups. Statistical analyses were performed using Kruskal Wallis and Scheirer-Ray-  
1138 Hare tests followed by Dunn *post-hoc* tests. \*: P < 0.05; \*\*: P < 0.01; \*\*\*: P < 0.001; \*\*\*\*: P <  
1139 0.0001.

1140  
1141 **Figure 4**  
1142 **Neuronal responsiveness to stimulation of the hindpaw ventral skin surfaces.**

1143 **A:** Mechanical thresholds of neuronal responses to stimulation of hindpaw ventral skin (*i.e.*, of ventral  
1144 and ventral & dorsal RFs) obtained using von Frey monofilaments (bending pressures, g/mm<sup>2</sup>), **taken**  
1145 **as measures of neuronal response sensitivity.** Red triangles represent the average threshold for each  
1146 experimental group, boxplots represent first and third quartiles and medians, while black dots show

1147 individual threshold outlier values. Horizontally aligned \* and bars show statistical differences  
1148 between the experimental groups. Statistical analyses were performed using Kruskal Wallis and  
1149 Scheirer-Ray-Hare tests followed by Dunn *post-hoc* tests. \*: P < 0.05; \*\*: P < 0.01; \*\*\*: P < 0.001;  
1150 \*\*\*\*: P < 0.0001. **B:** Correlation between RF size and neuronal sensitivity plotted with a log-log  
1151 scale (ANCOVA analysis, see Methods).

1152  
1153  
1154 **Figure 5**  
1155 **Remodeling of hindpaw cutaneous representational maps after UVN.**  
1156 **A:** Representative electrophysiological cortical maps recorded from an intact rat (CTRL: left panel)  
1157 and lesioned rats in which ipsilesional or contralesional hindpaw maps were obtained 1 hour (1H:  
1158 middle panels) and 35 days (D35: right panels) after UVN. Note the postlesion striking changes in  
1159 the proportion and topographic order of each representational zone, leading to a substantial  
1160 dedifferentiation of the somatotopic maps. This effect was found in both ipsi- and contralesional  
1161 hindpaw representations one hour after UVN, but only in ipsilesional hindpaw maps 35 days later. **B:**  
1162 Boxplot showing the mean total map size in each group (mm<sup>2</sup>). Boxplots illustrate the first and third  
1163 quartiles and the median values, while black dots individual map size outlier values. **C:** Stacked  
1164 histograms illustrating the relative mean areas of the different map regions, normalized with respect  
1165 to the total hindlimb cortical area. These relative areas are color-coded (green: *simple area in which*  
1166 *cutaneous RFs were confined on individual digits and plantar pads*; purple: *mixed area corresponding*  
1167 *to neurons with RFs localized on two or more hindpaw skin subdivisions*; yellow: *ventral paw area*  
1168 *in which RFs included the whole ventral or dorsal paw surface*). **D-E:** Separate distributions of ventral  
1169 and dorsal skin RFs in each size category. Mean values of normalized map sectors are illustrated  
1170 separately for ventral (D) and dorsal (E) skin surface representations. Statistical analysis was  
1171 performed using ANOVA supplemented with multiple comparisons (contrast *post-hoc* tests).  
1172 Horizontally aligned \* and bars show statistical differences between the experimental groups. P <  
1173 0.05; \*\*: P < 0.01; \*\*\*: P < 0.001; \*\*\*\*: P < 0.0001.

1174  
1175  
1176 **Figure 6**  
1177 **Schematically represented putative mechanisms illustrating the cortical effects of the unilateral**  
1178 **vestibular neurectomy (UVN).**  
1179 **Left panel:** *Main anatomical pathways conveying vestibular and somatosensory signals in intact*  
1180 *animals (CTRL).* Vestibular nerves project ipsilaterally onto the vestibular nuclei (VN) which  
1181 constitute the first relay of the vestibulo-spinal and vestibulo-thalamo-cortical pathways. Reciprocal  
1182 commissural inhibition between VN is represented (-). Peripheral somatosensory afferents from the  
1183 hindpaws that are conveyed via the lemniscal pathway form synapses in the gracile nucleus (GN).  
1184 Second-order neurons cross the midline and project onto the contralateral thalamic nuclei (Th)  
1185 in which the third-order neurons transmit somatosensory signals to the primary somatosensory cortex  
1186 (S1).  
1187 **Middle panel:** *Immediate consequences of the UVN assessed during the first postlesion hours.* The  
1188 vestibular deafferentation induces an imbalance between opposite VN, resulting from a  
1189 hyperexcitability of the contralesional VN and a reduced activity of the ipsilesional one. This  
1190 unilateral deafferentation leads to a syndrome characterized by vestibulo-ocular and postural  
1191 asymmetries (not observed under anesthesia). Given the bilateral projections of vestibulo-thalamic  
1192 inputs, with hypothetically dominant contralateral projections, presumably greater in the left  
1193 hemisphere, the VN imbalance is expected to result in a decrease, however asymmetrical, of thalamo-  
1194 cortical inputs in both S1 cortices. We postulate that the immediate expansion of cutaneous RFs  
1195 reveals a reduction of net tonic inhibition normally exerted by vestibular projections onto S1 layer IV  
1196 neurons, possibly via thalamo-cortical inputs and/or cortico-cortical connections. In normal

1197 conditions, ongoing vestibular inhibitory influence may thus contribute to refining the size of S1  
1198 neurons' cutaneous RFs, i.e, to maintaining a fine somatotopic order in the cutaneous cortical maps,  
1199 and consequently improve tactile spatial acuity on the foot sole during stance and locomotion, in  
1200 order to optimize postural adjustments and body balance.

1201 **Right panel:** *Consequences of the UVN at 35<sup>th</sup> days postlesion.* At this chronic stage of the vestibular  
1202 compensation, a symmetry of excitability between VN is restored to a large extent. By contrast, our  
1203 data indicate that the UVN rats displayed a strategy characterized by a shift of body weight  
1204 distribution toward the ipsilesional hindpaw, presumably to increase somatosensory feedback for  
1205 improving postural balance. We hypothesize that this increased body weight induced larger  
1206 temporally co-stimulated ventral skin surfaces during posture and locomotion and therefore increased  
1207 locally synchronized flow of tactilo-plantar inputs. Hence, consistently with the current knowledge  
1208 on cortical plasticity mechanisms, this postural strategy would induce an experience-driven expansion  
1209 of S1 neurons' cutaneous RFs located on the ipsilesional hindpaw.

1210 **S1:** Primary somatosensory cortex

1211 **Th:** Thalamus

1212 **GN:** Gracile Nucleus

1213 **VN:** Vestibular Nucleus

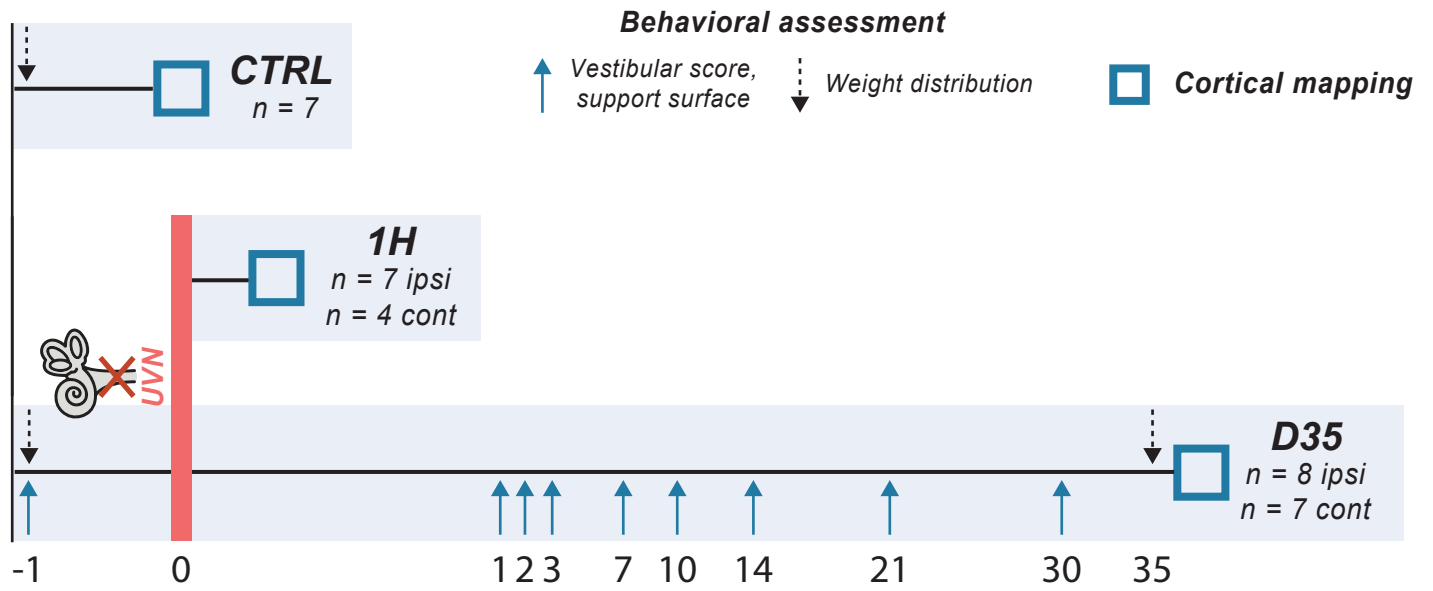
1214 **SC:** Spinal Cord

1215

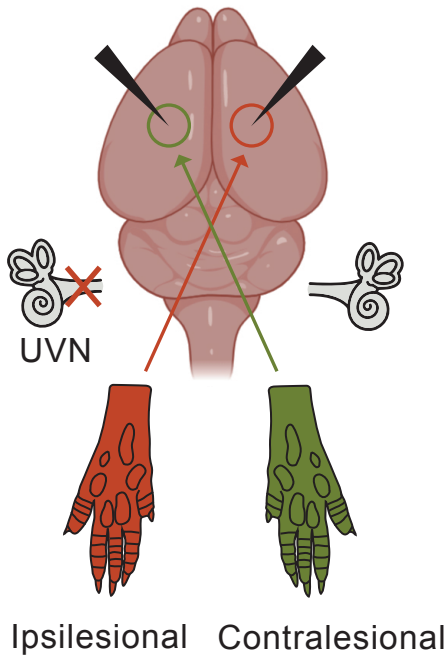
### 1216 **Supplementary Figure 1**

#### 1217 **Effects of UVN on the ipsi- and contralesional hindpaw cortical maps obtained after double** 1218 **mapping.**

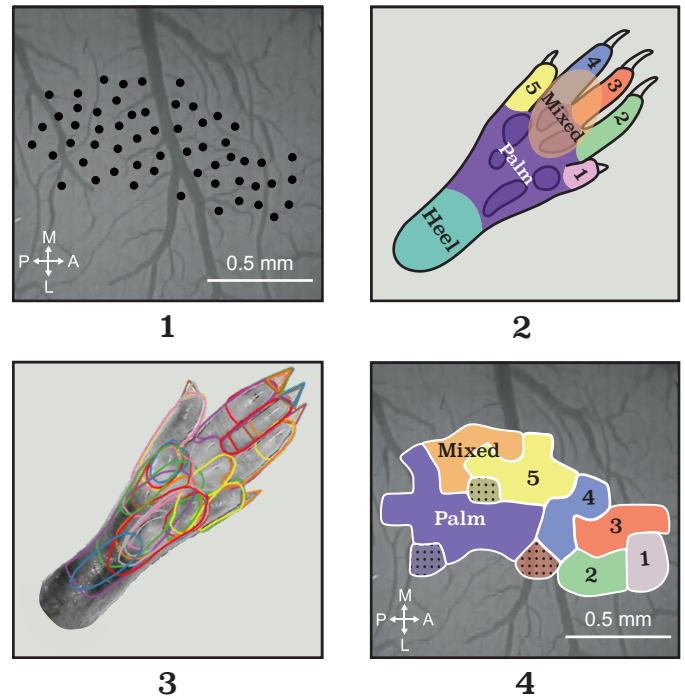
1219 Both ipsilesional and contralesional hindpaw representations were mapped in the same rat one hour  
1220 (n=3) and 35 days (n=2) after UVN, starting with the hemisphere either ipsilateral or contralateral to  
1221 the UVN. **A:** mean relative RF size (ventral, dorsal and ventral & dorsal) of intact (CTRL) and  
1222 lesioned rats. Black dots represent individual RF size outlier values and boxplots represent first and  
1223 third quartiles and medians. Red triangles show mean RF size. **B-C:** Separate mean relative RF size  
1224 of ventral and dorsal skin RFs taken from the data shown in A. **D:** Mean mechanical threshold of  
1225 neuronal responses obtained using Von Frey filaments (bending pressure). **E:** Mean size of hindpaw  
1226 map area. **F:** Stacked histogram illustrating relative mean areas of the different subregions of the  
1227 cortical maps normalized with respect to the hindlimb total surface area (green: *simple* regions;  
1228 purple: *mixed* regions). **G-H:** Separate relative mean areas of the ventral and dorsal skin map  
1229 territories taken from the data shown in F are also illustrated. Data of F to H are expressed as means  
1230  $\pm$  SEM.



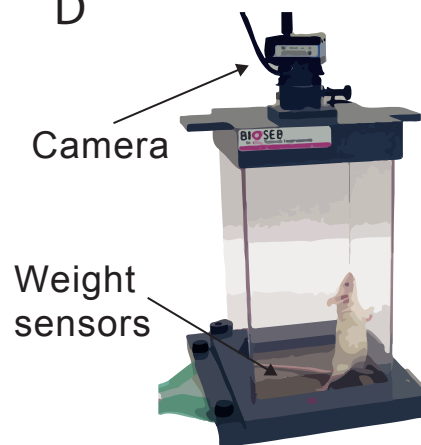
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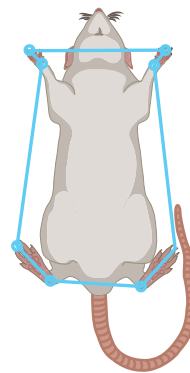
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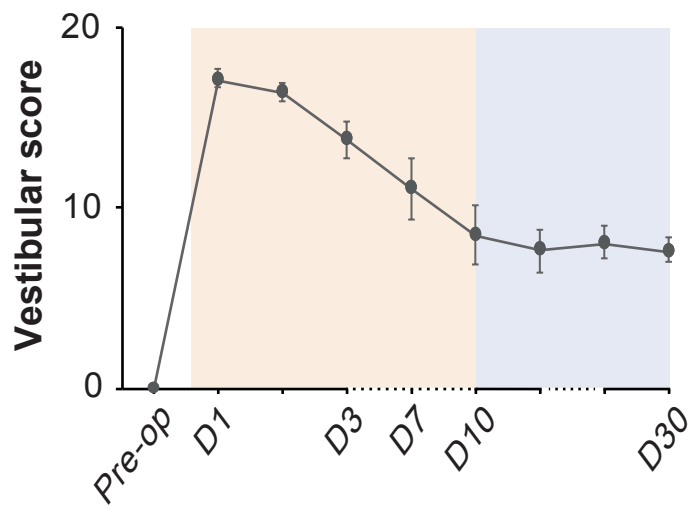
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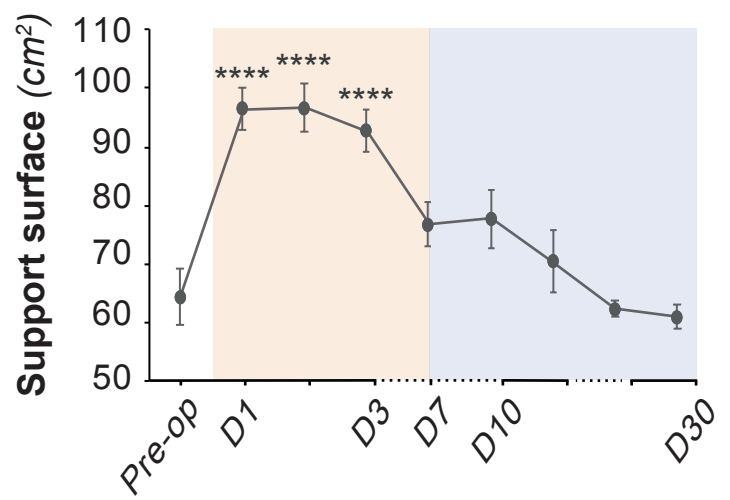
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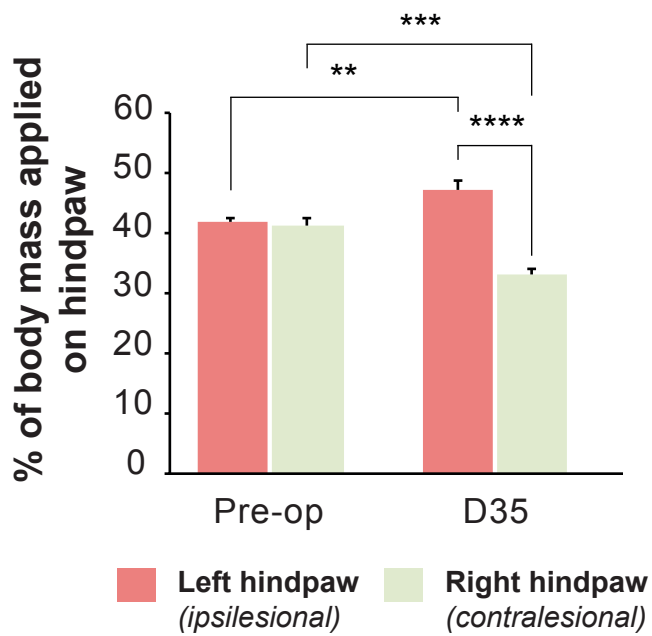
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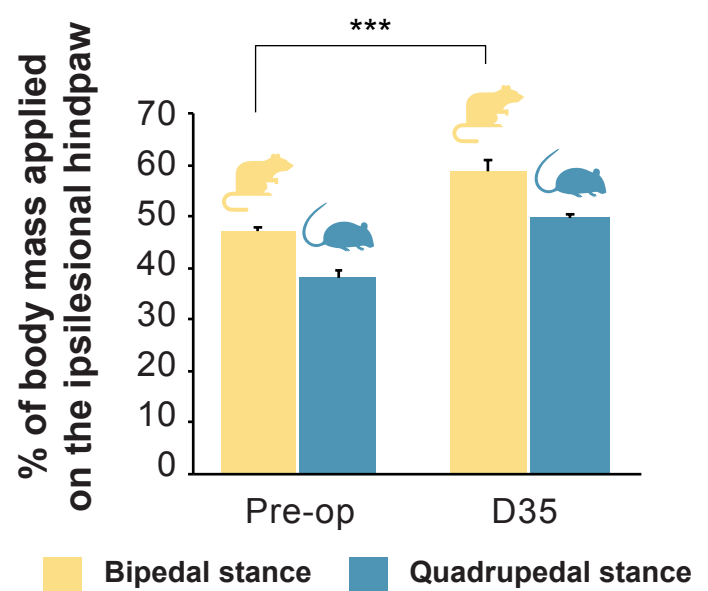
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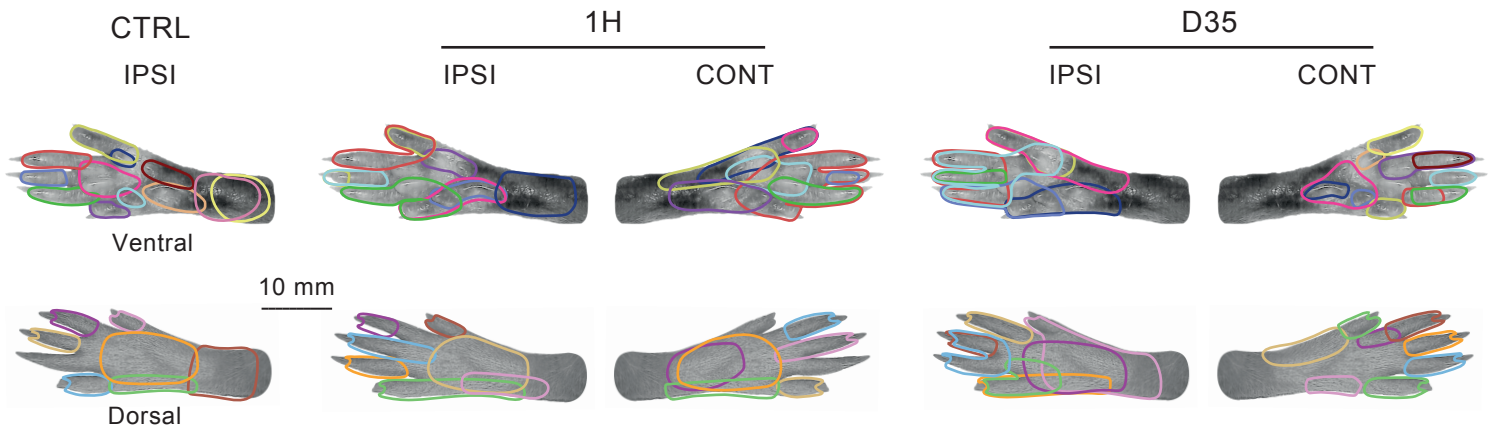
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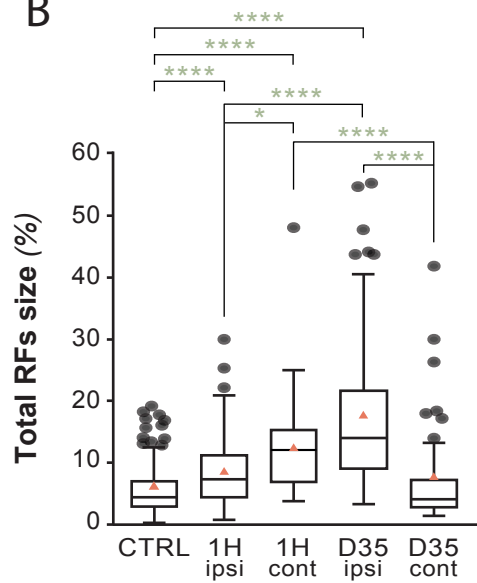
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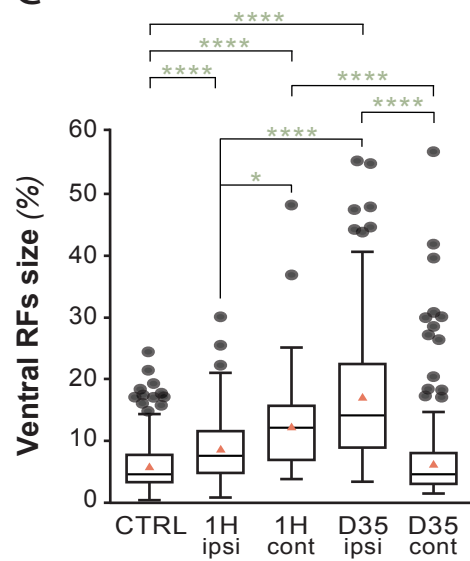
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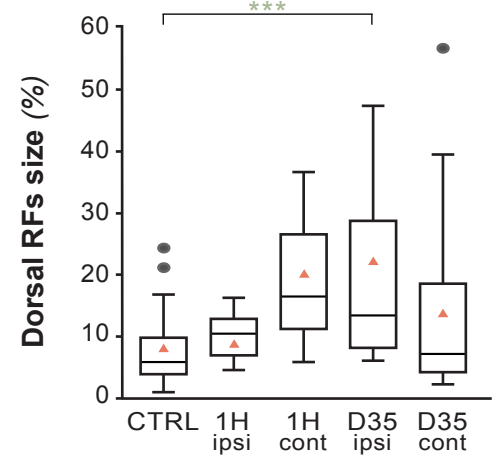
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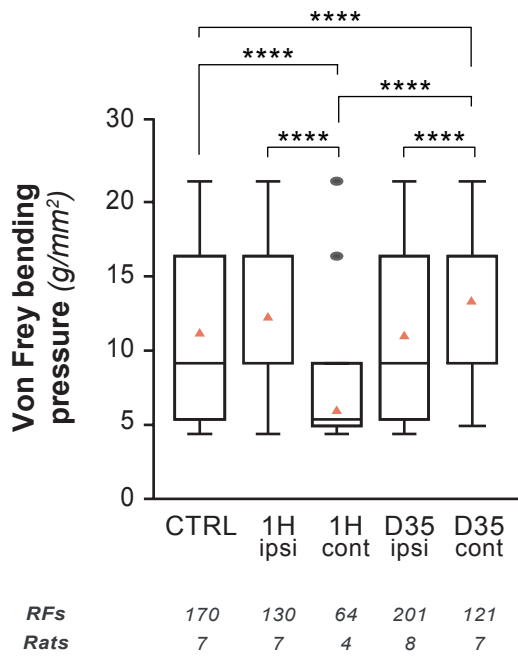
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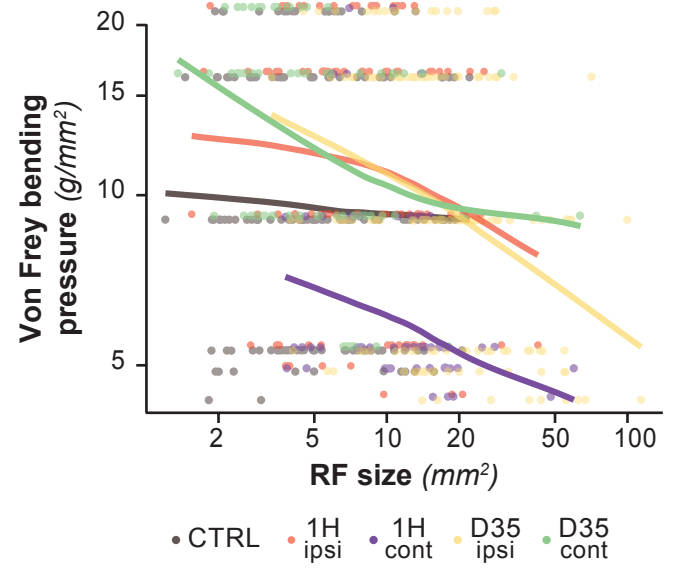
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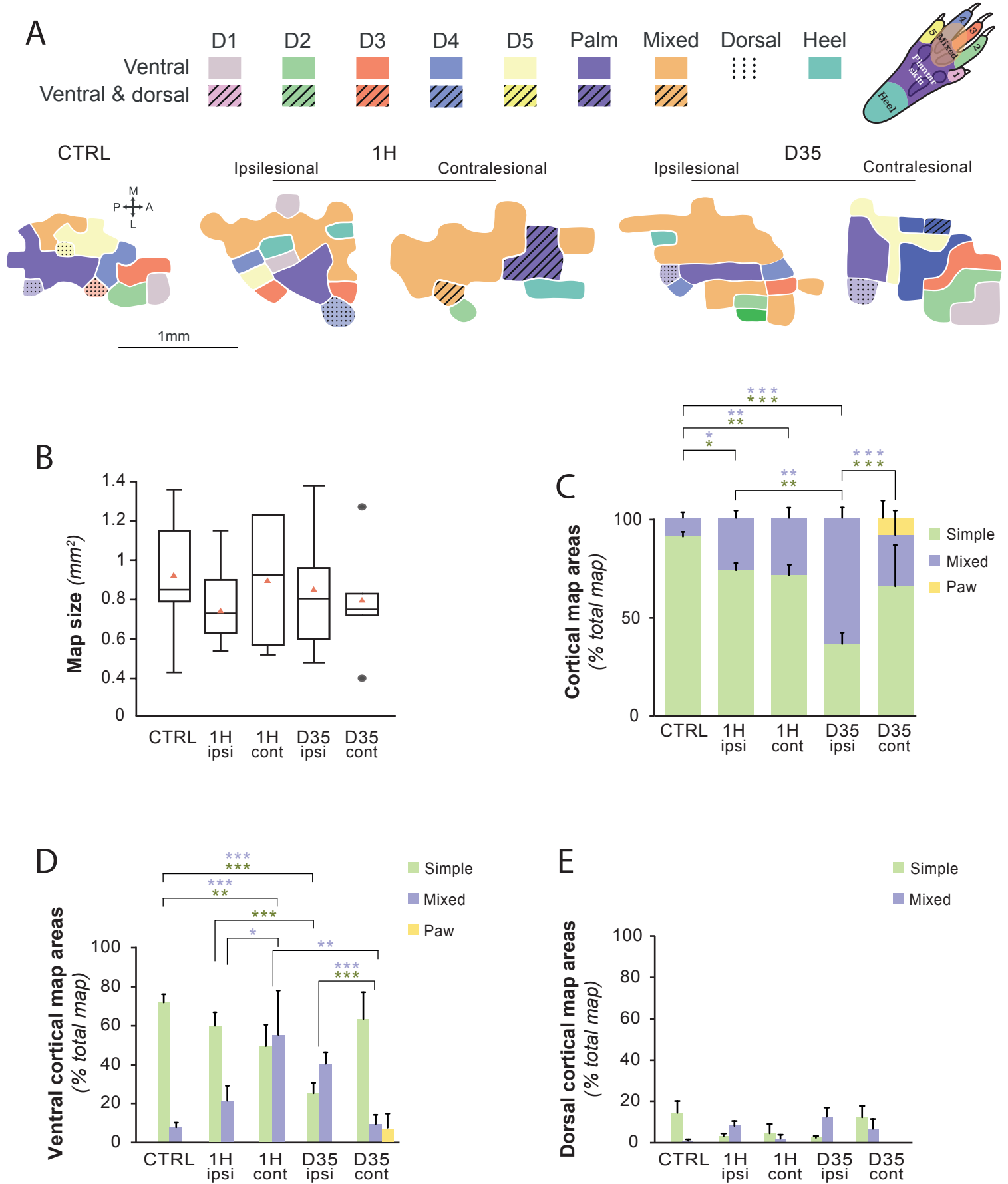
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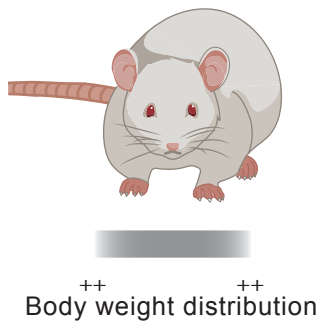
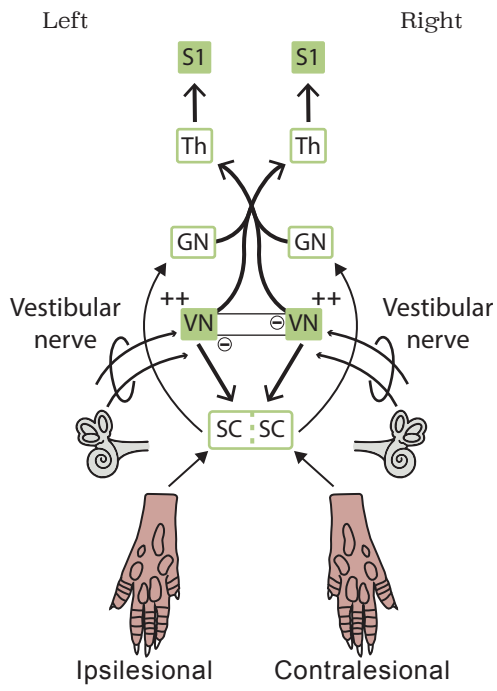
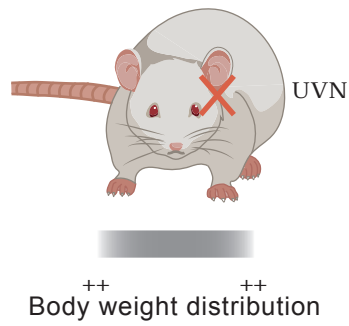
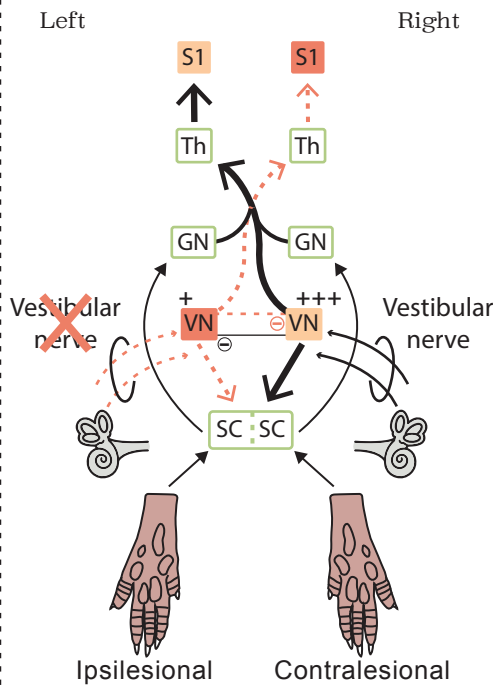
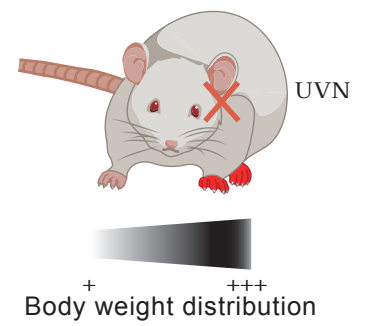
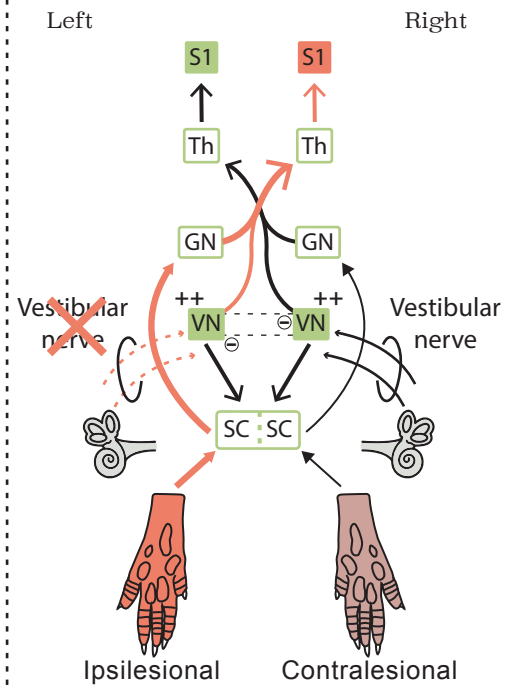


B







**CTRL****1H****D35**



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**Supplementary Material**  
Supplementary Figure 1.pdf

