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Title In vivo magnetic resonance imaging reveals the effect of gonadal hormones on morphological and functional brain sexual dimorphisms in adult sheep.

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Abstract

Sex differences in brain and behavior are produced by the perinatal action of testosterone, which is converted into oestradiol by the enzyme aromatase in the brain. Although magnetic resonance imaging (MRI) has been widely used in humans to study these differences, the use of animal models where hormonal status can be properly manipulated are necessary to explore the mechanisms involved. We used sheep, a recognized model in the field of neuroendocrinology, to assess brain morphological and functional sex differences and their regulation by adult gonadal hormones. To this end, we performed a voxel-based morphometry and a resting state functional MRI approach to assess sex differences in gonadally intact animals. We demonstrated significant sex differences in grey matter concentration (GMC) at the level of the gonadotropic axis; i.e. not only within the hypothalamus and pituitary, but also within the hippocampus and the amygdala of intact animals. We then performed the same analysis one month after gonadectomy and found that some of these differences were reduced following gonadectomy, especially in the hypothalamus and amygdala. By contrast, we found few differences in the organization of the functional connectome between males and females either before or after gonadectomy. As a whole, our study identifies brain regions that are sexually dimorphic in sheep brain at the resolution of MRI and highlights the role of gonadal hormones in the maintenance of these differences.

Keywords sex differences; sheep; voxel-based morphometry; resting state fMRI; gonadectomy.

Manuscript category Preclinical studies

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Highlights :

- Brain sex differences can be observed by using MRI in sheep, a well-recognized model in neuroendocrinology.
- Adult male and female brains show important sexual dimorphisms.
- Gonadectomy reduces these differences, showing their dependence on adult circulating hormone levels.

1 **In vivo magnetic resonance imaging reveals the effect of**
2 **gonadal hormones on morphological and functional brain**
3 **sexual dimorphisms in adult sheep.**

4

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17 **Abstract**

18 Sex differences in the brain and behavior are produced by the perinatal action of testosterone,
19 which is converted into estradiol by the enzyme aromatase in the brain. Although magnetic
20 resonance imaging (MRI) has been widely used in humans to study these differences, the use
21 of animal models, where hormonal status can be properly manipulated, is necessary to explore
22 the mechanisms involved. We used sheep, a recognized model in the field of
23 neuroendocrinology, to assess brain morphological and functional sex differences and their
24 regulation by adult gonadal hormones. To this end, we performed voxel-based morphometry
25 and a resting-state functional MRI approach to assess sex differences in gonadally intact
26 animals. We demonstrated significant sex differences in gray matter concentration (GMC) at
27 the level of the gonadotropic axis, *i.e.*, not only within the hypothalamus and pituitary but also
28 within the hippocampus and the amygdala of intact animals. We then performed the same
29 analysis one month after gonadectomy and found that some of these differences were reduced,
30 especially in the hypothalamus and amygdala. By contrast, we found few differences in the
31 organization of the functional connectome between males and females either before or after
32 gonadectomy. As a whole, our study identifies brain regions that are sexually dimorphic in the
33 sheep brain at the resolution of the MRI and highlights the role of gonadal hormones in the
34 maintenance of these differences.

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36 **Key words:** sex differences, sheep, voxel-based morphometry, resting state fMRI,
37 gonadectomy.

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39 **Highlights:**

40 - Brain sex differences can be observed by using MRI in sheep, a well-recognized model in
41 neuroendocrinology.

42 - Adult male and female brains show important sexual dimorphisms.

43 - Gonadectomy reduces these differences, showing their dependence on adult circulating
44 hormone levels.

45 **Introduction**

46 Males and females show various sexually dimorphic traits in adulthood at the behavioral level
47 that relate to the structure and function of the brain (McCarthy et al., 2015). Characterizing
48 these sexual differences is of importance not only to gain a global understanding of the normal
49 brain but also to gain insights into various brain disorders that are of differential prevalence and
50 progression between males and females (Miller et al., 2017). Sex differences related to
51 reproductive function are one of the most prominent types of sexual dimorphism, as both the
52 neuroanatomical and functional organization of the gonadotropic axis differ widely between
53 males and females.

54 In mammalian species, the classic view of sexual differentiation holds that these sex differences
55 develop under the perinatal influence of testosterone and/or estradiol derived from the neural
56 aromatization of testosterone (Alexander et al., 2011; Bakker and Baum, 2008). The brain
57 develops as male in the presence of these hormones, and testicular testosterone in male embryos
58 is necessary for the expression of male-typical hormonal and associated behavioral responses
59 later in life, a process known as masculinization. Testosterone exposure not only masculinizes
60 the brain but also actively defeminizes it so that males are unable to exhibit female-typical
61 behavioral or physiological responses. By contrast, the absence of hormonal exposure
62 predisposes animals to display female-typical adult sexual behaviors and hormone responses, a
63 process known as feminization. While the early actions of sex steroids are necessary for the
64 maturation and/or organization of several brain structures and neural circuits (Arnold, 2009),
65 the differentiated neural circuits in adults are then responsible for sex-typical responses when
66 sex steroids are synthesized by the mature gonad. Thus, the permanent developmental effects
67 of sex steroids are usually referred to as “organizational”, while the transient or reversible
68 effects observed during adulthood are referred to as “activational”.

69 While these effects have been studied mostly in rodents, similar mechanisms exist in many
70 other mammalian species. The sheep is an animal model that offers a unique opportunity to
71 study brain mechanisms underlying sexual differentiation for several reasons, including the
72 ability to perform long-term blood or cerebrospinal fluid sampling (Clarke and Cummins,
73 1982), the ability to manipulate the hormonal milieu in the fetus or adult (Clarke and Cummins,
74 1982; Perkins and Roselli, 2007) and the abundance of information that exists characterizing
75 reproductive physiology and behavior in this species (for review Roselli and Stormshak, 2010,
76 2009). Sexual differentiation of the sheep brain is dependent on testosterone and androgen
77 receptor signalling during gestation (Cheng et al., 2010; Foster et al., 2002; Robinson et al.,
78 1999; Roselli and Stormshak, 2010). While these studies, performed at the cellular or molecular
79 levels, are very informative, they only examined a limited number of hypothalamic nuclei.
80 Thus, information about other possible sexually dimorphic brain regions is lacking.

81 Magnetic resonance imaging (MRI) allows investigation at the level of the whole brain and has
82 been widely used in humans to study sex differences in the function and organization of the
83 brain (Burke et al., 2016, 2012). MRI is now a routine approach in neuroscience due to several
84 advantages, including its noninvasive nature and the ability to perform longitudinal studies that
85 allow changes within the same individuals to be tracked over time. However, due to ethical
86 considerations, it is not possible to experimentally manipulate the hormonal milieu in humans,
87 thus highlighting and reinforcing the usefulness of animal models such as sheep.

88 Some evidence suggests that gray and white matter content in sheep brain are sexually
89 dimorphic, but because of the suboptimal resolution of the images and the lack of the
90 appropriate neuroinformatic tools (namely, a brain template and atlas), the data could not be
91 analyzed properly (Nuruddin et al., 2013). We recently established the tools necessary for
92 conducting MRI experiments in sheep (Ella et al., 2017; Ella and Keller, 2015). In this study,
93 we employed these tools to map and compare sexually dimorphic brain structures and

94 connectivity in rams and ewes. This comparison was performed by using voxel-based
95 morphometry (VBM) to assess neuroanatomical differences in gray matter concentrations
96 (GMC) according to sex. We also validated resting-state functional MRI to assess basal
97 dynamic activity differences between sexes. Finally, we tested which sex differences are
98 programmed during sexual differentiation (organizational effect) or due to adult gonadal
99 hormones (activational effect) by analyzing the effect of gonadectomy.

100 **Materials and Methods**

101 **Animals.** Experiments were performed at the National Institute for Agronomic Research
102 (Institut national pour la recherche agronomique, INRA) in Nouzilly, France (latitude 47°, 32N
103 and longitude 0°, 46E) on adult Ile-de-France sheep (*Ovis aries*). A total of 24 animals (4 years
104 old) were used: 12 ewes (50.33 ± 0.71 kg) and 12 rams (70.91 ± 0.92 kg). Animals were
105 maintained indoors during the experiment and were fed daily with barley straw, Lucerne hay
106 and commercial concentrate and had access to water and mineral blocks *ad libitum*. All
107 procedures were performed in accordance with the European directive 2010/63/EU for animal
108 protection and welfare used for scientific purposes and approved by the local ethical committee
109 for animal experimentation (CEEA VdL, Tours, France, authorization N° 10465).

110

111 **Experimental protocol.** Animals were scanned twice in October and November 2017 at the
112 CIRE platform (INRA Nouzilly, France, <http://www.val-de-loire.inra.fr/cire>). One week before
113 the first scan, progesterone vaginal sponges (flugestone acetate, Chronogest CR 20 mg, MSD,
114 Beaucouze, France) were placed in ewes to induce and maintain a luteal-like phase until the
115 first day of the scan. On the day of the scan, sheep were weighed, and a blood sample was
116 collected by jugular venipuncture to check the hormonal status of the animal. After the first
117 scan, vaginal sponges were retrieved from the ewes, and both ewes and rams were
118 gonadectomized following established procedures. To this end, the sheep were fasted 24 h
119 before surgery. Following premedication with an i.v. injection of thiopental (14 mg/kg body
120 weight, BW; Nesdonal, Merial, Villeurbanne, France), the sheep were intubated and maintained
121 under anesthesia with a closed circuit of 3 to 4 % isoflurane (Vetflurane, Virbac, Carros, France)
122 and 100 % oxygen. Castration and ovariectomy were conducted under sterile surgical
123 conditions. Local anesthesia with lidocaine (4 %, Lurocaïne, Vétquinol, Luré, France) was
124 given prior to scrotal incision in males and laparotomy in females. Testicles or ovaries were

125 surgically extracted, and the tissues were sutured. The entire procedure was performed within
126 20 minutes. Postoperative ventilation with oxygen was maintained until the first signs of
127 awakening appeared. The sheep were then housed individually for 6 hours in a padded stall
128 before being put back with congeners. They received an anti-inflammatory drug for 2 days (2
129 mg/kg BW flunixin meglumine, Finadyne®, Intervet, Beaucouzé, France), an antiedema
130 medication: (1 mg/kg BW of furosemide, Dimazon®, Intervet, Beaucouzé, France) at the end
131 of surgery and 3 mg/kg BW hydrochlorothiazide with 0.03 mg/kg BW dexamethasone
132 (Diurizone®, Vétquinol, Luré, France) for 2 days. One month after the surgery, a second scan
133 session was performed; the sheep were again weighed, and blood samples were collected as
134 described above to assess the efficiency of the surgery (**Figure 1A and Figure S1**).

135

136 **Testosterone and progesterone assays.** Plasma was obtained from heparinized blood after 30
137 min of centrifugation at 3500 g. The concentration of testosterone was determined in duplicate
138 samples using a radioimmunoassay as previously described (Hochereau-de Reviers et al.,
139 1990). The sensitivity of this assay was 0.1 ng.mL⁻¹. The concentration of plasma progesterone
140 was determined in duplicate samples using an immunoenzymatic assay as previously described
141 (Chasles et al., 2016). The sensitivity of the progesterone assay was 0.25 ng.mL⁻¹ (**Figure 1A**).

142

143 **Anesthesia protocol.** Before scanning, the sheep were first anesthetized by an intrajugular
144 administration of a ketamine/xylazine mix (1 mg.mL⁻¹ ketamine/0.1 mg.mL⁻¹ xylazine, volume
145 of injection 6.5 mL). After induction, the animal was intubated (8.5 mm probe, SON612,
146 Centravet, France) and ventilated manually. The jugular vein was catheterized for a continuous
147 infusion of 0.1 mg.mL⁻¹ ketamine/xylazine mix (1.5 mL.min⁻¹), which permits preservation of
148 both pupillary and palpebral reflexes and of the regular spontaneous respiratory rate.

149 Since MRI investigation in animals requires that animals be sedated, we developed a specific
150 protocol of anesthesia for both functional and morphometric acquisition. Indeed, functional
151 connectivity is highly sensitive to the pharmacological class of anesthetics used, and numerous
152 studies have demonstrated that the widely used isoflurane gas obscures the naturally occurring
153 functional connectivity by inducing synchronous cortico-striatal fluctuations and silencing
154 subcortical activity (Kalthoff et al., 2013; Liu et al., 2013; Paasonen et al., 2018). For this
155 reason, we chose to use a low dose of ketamine/xylazine mix (Imalgene 500 mg/Rompun 2 %,
156 Centravet, France) for functional acquisitions and progressively replaced this with a standard
157 isoflurane anesthesia for morphological acquisitions to reduce motion artifacts during long
158 scanning.

159

160 **Scanning procedure.** Sheep were placed on the MRI-compatible mechanical bed of a 3 Tesla
161 VERIO Siemens system (Erlangen, Germany). They were gently restrained with a belt on the
162 mechanical bed while their head was placed within a circular rigid coil (¹H, 24 channels, phased
163 array, receiver only, 20/28 cm, P-H24LE-030, Siemens, Germany). During the functional
164 resting state scanning procedure, sheep were ventilated continuously using an anesthesia system
165 with an integrated ventilator (Aestiva MRI-compatible, GE Healthcare, Germany) delivering a
166 1:1 oxygen/air mix with a current volume of 500 mL for ewes and 650 mL for rams and the
167 frequency rate set at 16 bpm. Heart rate and O₂ saturation were monitored continuously using
168 an oximeter probe placed on the right hind paw (oxytip+ probe MRI-compatible, GE
169 Healthcare, Germany) and maintained at 87.21 ± 1.002 bpm and 89.83 ± 8.84 % for ewes and
170 78.19 ± 9.28 bpm and 87.63 ± 6.18 % for rams, respectively (for details see **Figure S1**). After
171 the functional resting state scanning procedure, the intravenous ketamine anesthesia regimen
172 was progressively replaced by gas anesthesia using isoflurane added to the air mix at a

173 concentration of 2.8 ± 0.14 % in ewes and 3.07 ± 0.01 % in rams using the same ventilatory
174 parameters (**Figure S1**).

175

176 **MRI data acquisition.**

177 Left-right orientation within the images was ensured by placing an α -tocopherol acetate capsule
178 (Toco 500 mg, α -tocopherol acetate, Alkopharm, France) on the right side of the sheep's head.

179 After positioning, a first localizer sequence was performed to align the brain on the anterior
180 commissure-posterior commissure (AC-PC) axis within the field of view (FOV). Then, two

181 successive gradient echoes (GRE) field maps were acquired using the same acquisition
182 parameters: repetition time (TR) = 500 ms, echo time (TE) = 4.92 ms and 7.38 ms, number of

183 excitations (NEX) = 1, flip angle (FA) = 55 degree, field of view = $166 \times 166 \times 166$ mm³ within
184 a $64 \times 64 \times 64$ matrix for a final voxel size = $2.6 \times 2.6 \times 2.6$ mm³. Both GRE field maps were

185 acquired within the axial acquisition plane, but a left-right encoding direction was used on the
186 first acquisition (LR-GRE); then, a right-left encoding direction was used on the second

187 acquisition (RL-GRE). Both LR- and RL-GRE images were acquired to calculate
188 inhomogeneity correction maps that were used within the functional analysis processing. Then,

189 a spin-echo echo-planar imaging (SE-EPI) sequence of 8.5 min was acquired in the axial plane
190 using the following parameters: TR=3260 ms, TE = 24 ms, NEX = 1, FOV = $170 \times 170 \times 45$ mm³

191 within a $110 \times 110 \times 90$ matrix for a final voxel size = $1.5 \times 1.5 \times 2$ mm³. This sequence generated
192 150 volumes that were used for resting-state fMRI analysis. Finally, a T1-weighted 3D

193 magnetization-prepared rapid acquisition of gradient echo (MPRAGE) sequence was acquired
194 using the following parameters: TR = 2500 ms, TE = 3.18 ms, FA =12 degrees, NEX = 2, FOV

195 = $190 \times 190 \times 190$ mm within a $384 \times 384 \times 384$ matrix for a final voxel size $0.5 \times 0.5 \times 0.5$ mm³. T1-
196 weighted images were used for voxel-based morphometry analysis. Four rams were excluded

197 from the analysis because of excessive motion during imaging acquisition, ($n_{\text{final}} = 8$ males

198 and 12 females). The final translations were less than 0.4 mm, and rotations did not exceed
199 0.006 radians (0.3 degrees) in our acquisitions (**Figure S2**).

200

201 **Functional MRI (fMRI) data preprocessing.** Resting-state fMRI data were preprocessed in
202 MATLAB (R2017b, MathWorks) with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) using the
203 SPMMouse Toolbox (Sawiak et al., 2014, 2009) and FSL5.1 (<https://fsl.fmrib.ox.ac.uk>). In the
204 first step of preprocessing, the EPI images were time corrected, realigned and resliced to the
205 first volume, corrected for inhomogeneity using the GRE field maps and coregistered with their
206 corresponding T1 anatomical images using SPM8. Thereafter, T1 anatomical images were
207 segmented using our previously published tissue priors (Ella et al., 2017), first to create specific
208 brain masks for each T1 image (gray matter (GM)+white matter (WM)+cerebrospinal fluid
209 (CSF) = Brain Mask) and second to normalize both T1 and EPI images onto our brain template
210 (Ella et al., 2017) using the affine matrix calculated by SPM8 during the segmentation step.
211 Finally, normalized images were masked to remove soft tissue using the brain masks generated
212 previously and spatially smoothed with a Gaussian kernel of 8 mm full-width at half-maximum
213 (FWHM). In the second step of preprocessing, EPI images were processed using FSL. The
214 effect of the six previously calculated motion parameters, including translations and rotations
215 and out brain signals, was removed from the data through linear regression using the FEAT
216 toolbox (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT>). Then, acquisition artifacts (ghosting)
217 were identified using the *melodic* function. Briefly, *melodic* decomposes the signal of the 4D
218 smoothed images into independent spatial components. These components were thresholded
219 ($p < 0.01$) and visually inspected for artifacts, which were removed using the *regfilt* function of
220 FSL (Kelly et al., 2010). Finally, a bandpass filtering (0.1 Hz-0.005 Hz) was applied to the time
221 series (**Figure 1B**).

222

223 **Construction of resting-state functional networks.** Pre- and post-gonadectomy, processed
224 functional images of each animal (40 data sets) were segmented into 86 anatomical regions of
225 interest (ROIs) (43 regions in each hemisphere) using the GM areas of our sheep atlas (Ella et
226 al., 2017) and the REX function of the CONN toolbox (<https://www.nitrc.org/projects/conn>;
227 **Figure 1B**). For each sheep, functional correlation coefficients (r values) were computed
228 between the time courses of each pair of ROIs and then transformed to z-scores using Fisher's
229 z transformation, resulting in an 86x86 matrix of normalized correlation coefficients for each
230 animal. Networks of altered connectivity were computed, extracted and plotted using Network-
231 Based Statistics (NBS, <http://brain-connectivity-toolbox.net/comparison/nbs>; Zalesky et al.,
232 2010), the Brain Connectivity Toolbox (<http://brain-connectivity-toolbox.net>; Rubinov and
233 Sporns, 2010), the BrainNet Viewer toolbox (<https://www.nitrc.org/projects/bnv/>; Xia et al.,
234 2013) and in-house developed MATLAB scripts. **As the sample size was unbalanced between**
235 **both sexes (8 males versus 12 females), we estimated the type 2 error (β value = 0.898) to assess**
236 **the number of permutations necessary to reach a β value = 0.95 ($n = 1500$).** Statistical
237 comparisons between groups were made at the global network level (*i.e.*, conjunction of all
238 ROIs). The NBS methodology works in two steps: first, the statistical hypothesis is tested at
239 each connection, and its statistical significance is determined; second, the connections are
240 thresholded by a user-defined significance ($p < 0.05$, < 0.01 and < 0.001); the subnetwork
241 components (groups of nodes and edges such that a path can be found between any pair of
242 network members) were found; and their size (number of surviving connections) was
243 determined. The component significance was determined through permutation testing ($n =$
244 **5000**), where the test subjects are randomly permuted between groups and the chance of
245 randomly finding networks of similar size determined, outputting a family-wise error rate-
246 corrected significance (α_{FWE} , 0.05). Differences between gonad-intact males and females and
247 the effect of gonadectomy on males and females were determined using analysis of variance

248 (ANOVA) with group or time as a factor. A p value < 0.05 after correction was considered
249 statistically significant. Considering the individual variability and as a control to test our
250 statistical power, we compared two random groups balanced for sex (4 males and 6 females in
251 each group; **Figure S3**). At the baseline, male and female z scores described a Gaussian
252 distribution ($K2_{(Males)} = 11.96$; $p = 0.0025$ and $K2_{(Females)} = 13.93$; $p = 0.0009$; D'Agostino &
253 Pearson normality test) that was significantly different ($p < 0.0001$; $t = 4.995$; $df = 354$, paired
254 t-test) with a shift of female values to the right. After gonadectomy, z scores also followed
255 Gaussian distributions ($K2_{(Males)} = 20.41$; $p < 0.0001$ and $K2_{(Females)} = 22.93$; $p < 0.0001$) and
256 were significantly different between the sexes ($p < 0.0001$; $t = 9.848$; $df = 354$), again with a
257 shift of the female values to the right. When baseline z scores for males and females were
258 mixed, the Gaussian distributions were conserved ($K2_{(Males)} = 14.77$; $p = 0.0006$ and $K2_{(Females)}$
259 $= 18.58$; $p < 0.0001$), but the curves were superimposed and not significantly different ($p =$
260 0.4382 ; $t = 0.7758$; $df = 708$). The same effect was observed after gonadectomy ($K2_{(Males)} =$
261 20.53 ; $p < 0.0001$ and $K2_{(Females)} = 21.5$; $p < 0.0001$; z score comparison: $p = 0.8802$, $t = 0.1507$;
262 $df = 708$).

263

264

265 **Voxel-Based Morphometry (VBM) data preprocessing.** VBM data were preprocessed with
266 SPM8 and SPMouse 1.1 Toolbox. First, each T1 anatomical image was aligned to the
267 stereotaxic space by registering each image to our anatomical template image (Ella et al., 2017)
268 using SPMouse. Then, each image was bias corrected and segmented into probability maps
269 of GM, WM, and CSF using the default settings in the SPM8 toolbox and our GM, WM, CSF
270 probability maps (Ella et al., 2017). The transformation matrices obtained were used to
271 normalize and resample ($0.5 \times 0.5 \times 0.5 \text{ mm}^3$) the GM, WM and CSF probability maps. To
272 produce a more accurate registration within each sheep as well as across all sheep, the

273 Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL)
274 algorithm, which is an automated, unbiased, and nonlinear template building program
275 (Ashburner, 2007), was applied using the strategy described by (Asami et al., 2012). First, a
276 subject-specific template was created by the DARTEL algorithm using the previous tissue class
277 images (GM, WM, and CSF maps) obtained from each sheep at both time points (before and
278 after gonadectomy). The DARTEL procedure releases individual-specific flow field maps,
279 permitting the application of diffeomorphic normalization on each tissue class of images to
280 spatially normalize each time point on a subject-specific template space. Each normalized tissue
281 class of images was modulated by the determinant of the Jacobian to account for the expansion
282 and/or contraction of brain regions over time. Then, a population-specific template was created
283 by the DARTEL algorithm using all of the subject-specific templates of the tissue class of
284 images. Here, the DARTEL procedure releases population-specific flow field maps, permitting
285 the application of diffeomorphic normalization from each animal onto each tissue class of
286 images. Finally, each tissue class image was modulated by the determinant of the Jacobian, and
287 the final modulated GM images were spatially smoothed by convolving with a 4 mm full-width
288 at half-maximum (FWHM) isotropic Gaussian kernel to create GMC maps (**Figure 1B**)
289 (Sumiyoshi et al., 2017).

290

291 **Voxel-Based Morphometry, statistics and analysis.** Statistical Parametric Mapping (SPM8)
292 was used to reveal the temporal and regional changes in gray matter occurring in GMC maps.
293 Second level analysis from SPM, a flexible factorial model that is equivalent to a 2×2 mixed-
294 model ANOVA, was used first to compare male *versus* female and then pregonadectomy *versus*
295 postgonadectomy groups. Brain volume was used as a covariate (**Figure S4A**) with between-
296 subject factor group and within-subject factor condition. The factors included in the analysis
297 were subjects, group (male, female), and time (pregonadectomy, postgonadectomy). A brain

298 mask was used to constrain the analysis. For each cluster, the significance of the peak voxel
299 was set as $p < 0.005$ (β value = 0.990, $t_{(35)} = 2.7238$), and the minimum cluster extent was set
300 to 300 voxels. The results are presented on an axial brain slice series generated by the xjView
301 plugin (<http://www.alivelearn.net/xjview/>) of SPM, and the corresponding surfacing results
302 were assembled with a BrainNet viewer, which allows the generation of both brain mesh and
303 brain plots for visualizing data. To assess the effect of individual variability and as a control
304 test for statistical power, we compared two random groups balanced for sex (4 males and 6
305 females in each group (**Figure S4**). At baseline, the comparison shows only a small significant
306 unilateral cluster on slices 14 and 12 corresponding to the left lateral *gyrus*, which was not
307 observed previously ($p = 0.005$, β value = 0.990, $t_{(35)} = 2.7238$, voxel threshold = 300), while the
308 comparison performed after the gonadectomy reveals no significant differences between the
309 groups.

310

311 **Postprocessing statistical analysis.** VBM cluster peaks revealed by flexible factorial analysis
312 data were identified using our atlas and a personal procedure developed in MATLAB. For each
313 comparison, ROI masks from Ella's atlas were used to extract GMC values of corresponding
314 regions within the GMC map using REX plugging. Endocrine, physiological, functional
315 connectivity and GMC data were compiled and analyzed using Prism 6.02 software GraphPad
316 Software, San Diego, CA) and were compared using two-way ANOVA with repeated measures
317 followed by the two-stage setup method of Benjamini, Krieger and Yekutieli as recommended
318 by the software. Statistical significance was defined as $p < 0.05$ for these analyses.

319 **Results**

320 **Morphological and functional sexual dimorphism in the adult sheep brain.**

321 VBM analysis

322 Using a voxel-based morphometry (VBM) approach, we found 37 brain regions that
323 were sexually dimorphic in intact sheep (see **Table S1 and S2** for detailed statistics).
324 Specifically, our VBM analysis found that the gray matter concentration (GMC) within the left
325 and right *gyrus ectolateralis*, left and right hippocampus, pituitary gland and right amygdala
326 were significantly higher in intact females than in intact males (red clusters, **Figure 2A**). In
327 contrast, GMC values in the hypothalamus and both posterior gyri sigmoideus were
328 significantly higher in intact males *versus* luteal phase females (blue clusters, **Figure 2A**).
329 Comparison between the same animals before and after gonadectomy reveals that only 22 brain
330 regions were still dimorphic. Among them, four bilateral cortical regions of the gyri
331 ectolateralis, both entolateral and lateral gyri, and the occipital lobe, still exhibited higher GMC
332 values in gonadectomized females than in gonadectomized males (red clusters, **Figure 2B**).
333 GMC values in the posterior gyri sigmoideus were still higher in gonadectomized males than
334 in gonadectomized females (blue, clusters, **Figure 2B**). The volumes of several dimorphic
335 subcortical structures, such as the right amygdala and the hypothalamus, decreased after
336 gonadectomy and were no longer different between males and females. Moreover, we observed
337 a large regression of the volume of the hippocampal cluster (120 mm³ within the intact
338 male/intact female comparison *versus* 15 mm³ within the gonadectomized
339 male/gonadectomized female comparison) and a large increase (10 times) of the volume of the
340 pituitary cluster (28 mm³ within the intact male/intact female comparison *versus* 280 mm³
341 within the gonadectomized male/gonadectomized female comparison).
342 Using our anatomical atlas (Ella et al., 2017), we collected GMC values within the bilateral
343 hippocampus, hypothalamus, pituitary gland and gyri ectolateralis to evaluate the effect of

344 gonadectomy on these structures. Within the hippocampus (**Figure 3A**), we observed a left-
345 right asymmetry in both males and females as previously reported (Sadeghi et al., 2017; Samara
346 et al., 2011), which was preserved after gonadectomy. In addition, we observed bilateral sexual
347 dimorphism in the hippocampus with higher GMC values in luteal phase females than in intact
348 males. This hippocampal sexual dimorphism was lost after gonadectomy. Within the
349 hypothalamus (**Figure 3B**), no left-right asymmetry was observed, but significantly higher
350 GMC values were found in intact males compared to luteal phase females. The sexual
351 dimorphism in the hypothalamus was also eliminated after gonadectomy. No side asymmetry
352 was observed within the pituitary gland (**Figure 3C**), but significantly higher GMC values were
353 observed in luteal phase females compared to intact males. GMC concentration in the pituitary
354 increased significantly in both sexes after gonadectomy, but sexual dimorphism was preserved.
355 Finally, analysis of GMC within the gyri ectolateralis (**Figure 3D**) revealed no left-right
356 asymmetry, but GMC values were significantly higher in luteal phase females when compared
357 to gonad-intact males.

358

359 Resting-state fMRI analysis

360 The analysis of the functional connectome between intact males and females revealed a
361 sexually dimorphic brain network composed of 332 functional connections shared between 77
362 functional nodes (**Figure 4A**, all statistics are available in **Table S3**). Intact luteal phase females
363 displayed higher functional connectivity than intact males (**Figure 4B**). Three internal
364 subnetworks involving the frontal region (red nodes), the occipitoparietal region (orange nodes)
365 and the diencephalic region (yellow nodes) compose this dimorphic network. When we focused
366 on the sexually dimorphic brain regions highlighted by our previous VBM analysis, we
367 observed that both the left and right hippocampus, hypothalamus pineal gland and gyrus
368 ectolateralis display higher functional connectivity in luteal phase females when compared to

369 intact males (**Table S3**). Notably, the hippocampus displayed stronger bilateral connections in
370 luteal phase females than in intact males within the geniculate nucleus, the parahippocampal
371 cortex, the periaqueductal gray substance (PAG), the suprasylvian *gyrus*, the cingulate cortex,
372 the pineal gland, the temporal lobe and the thalamus. The hypothalamus displayed stronger
373 bilateral connections in luteal phase females than in intact males within the lateral septal
374 nucleus, the preoptic hypothalamic area, the subfornical organ and the substantia nigra.
375 Importantly, the connectivity between the hypothalamus and the pituitary gland was also
376 significantly higher in luteal phase females than in intact males. Finally, the gyrus ectolateralis
377 displayed stronger bilateral connections in luteal phase females than in intact males within the
378 gyri entolateralis and the lateral gyri.

379 Surprisingly, the analysis of the functional connectome between gonadectomized males and
380 females revealed a similar brain network also composed of 332 functional connections shared
381 between 80 functional nodes (**Figure 4C**, all statistics are available in **Table S4**). This
382 functional network is characterized by higher functional connectivity in gonadectomized
383 females when compared to gonadectomized males (**Figure 4D**) and displayed the same internal
384 frontal, occipitoparietal and diencephalic subnetworks. Although it was statistically marginal,
385 some changes in resting-state functional connectivity were also detected within the
386 hippocampus, hypothalamus, and gyrus ectolateralis. Similar temporal correlations were
387 observed within the previously described structures. Additional bilateral connections were
388 observed within the gyrus ectolateralis, midbrain, left lateral *gyrus* and right nucleus of the
389 horizontal limb of the diagonal band (NHLDB) of gonadectomized females compared to
390 gonadectomized males. Within the hypothalamus, similar functional connectivity was observed
391 to that described in intact animals. Additional functional connectivity was observed with the
392 lateral septal nucleus bilaterally in gonadectomized females when compared to gonadectomized
393 males and with the right bed nucleus of the stria terminalis (BNST), the left globus pallidum

394 and the left NHLDB. Finally, the gyrus ectolateralis also displayed similar higher functional
395 connections with previously described structures and additional bilateral functional
396 connectivity with the cingulate cortex, the occipital lobe, the suprasylvian gyrus and the
397 hippocampus. Functional connections were also observed with the right parahippocampal
398 cortex, the right posterior sylvian *gyrus* and the right temporal lobe in gonadectomized females
399 when compared to gonadectomized males.

400

401 **Effect of gonadal secretion on brain morphology and functional connectivity in both male**
402 **and female adult sheep brains.**

403 VBM analysis

404 To evaluate the sex-specific effects of gonadectomy, we evaluated both brain
405 morphology and functional connectome modifications before and after gonadectomy in males
406 and females. In males, VBM analysis revealed 29 regions with significant GMC modifications
407 induced by gonadectomy (see **Table S5** for detailed statistics). We found significantly higher
408 GMC values within the bilateral amygdala and the pituitary gland after gonadectomy (red
409 clusters, **Figure 5A**). On the other hand, the GMC values were significantly decreased after
410 gonadectomy within the medial mamillary nucleus, the periaqueductal gray substance (PAG),
411 the pons and the medial preoptic hypothalamic area (blue clusters, **Figure 5A**). In females,
412 VBM analysis revealed 22 regions with significant GMC modifications induced by
413 gonadectomy (see **Table S6** for detailed statistics). We found significantly higher GMC values
414 only within the pituitary gland (red clusters, **Figure 5B**). By contrast, GMC values were
415 significantly decreased within the medial mamillary nucleus, *medulla oblongata* (MO), pons
416 and preoptic hypothalamic area (blue clusters, **Figure 5B**). Interestingly, after gonadectomy,
417 GMC values were also reduced within both gyri ectolateralis but only within the right
418 hemisphere (**Figure 5B**).

419 Using our anatomical atlas, we collected GMC values within the bilateral amygdala and PAG
420 in males and within the subfornical organ and NHLDB in females, which display sex-specific
421 modifications after gonadectomy. In males, GMC was significantly increased after
422 gonadectomy within the amygdala (**Figure 6A left panel**). On the other hand, the GMC values
423 within the PAG were significantly decreased after gonadectomy (**Figure 6A, right panel**). In
424 females, GMC values were significantly decreased after gonadectomy within the subfornical
425 organ (**Figure 6B left panel**). GMC values within the NHLDB were also significantly
426 decreased after gonadectomy (**Figure 6B, right panel**).

427

428 Resting-state fMRI analysis

429 The analysis of the functional connectome between intact and gonadectomized males
430 revealed a brain network sensitive to gonadal hormones composed of 66 functional connections
431 shared between 52 functional nodes (**Figure 7A**, all statistics are available in **Table S7**). This
432 functional network was significantly higher in gonadectomized males (**Figure 7A, Right**
433 **panel**) and was characterized by modifications of rostrocaudal functional connectivity and by
434 intense modifications of functional connectivity within the diencephalon. Importantly, the
435 pituitary gland, which is a critical structure in reproductive function and shows significant
436 variations of GMC after gonadectomy, displayed increased functional connectivity together
437 with the preoptic hypothalamic area, the BNST and the subfornical organ. By contrast, the
438 analysis of the functional connectome between intact and gonadectomized females revealed a
439 brain network sensitive to gonadal hormones composed of 94 functional connections shared
440 between 65 functional nodes (**Figure 7B**, all statistics are available in **Table S8**). This
441 functional network was also significantly higher in gonadectomized females (**Figure 7B, Right**
442 **panel**) and was characterized by an interhemispheric modification of functional connectivity
443 and, as previously described in males, by intense modifications of functional connectivity

444 within the diencephalon. As observed in males, the pituitary gland also displayed an increase
445 in GMC after gonadectomy in females along with an increase in the functional connectivity
446 within the medial septal nucleus, the BNST, the septum, the NHLBD, the preoptic
447 hypothalamic area and the subfornical organ.

448 **Discussion**

449

450 Our study is the first to report a detailed VBM analysis in sheep and to establish resting-state
451 fMRI in this species. Thanks to these methodological developments, we were able to highlight
452 brain sexually dimorphic territories and networks of functional connectivity differing between
453 males and females, mainly in the hypothalamus and pituitary. We also showed that these
454 differences are partly due to adult circulating levels of gonadal hormones, as some of these
455 differences vanished following gonadectomy, suggesting that the differences observed are due
456 to the activational effects of circulating gonadal hormones. These data add a high degree of
457 neuroanatomical precision compared to the previous MRI report of differences between the
458 sexes in sheep (Nuruddin et al., 2013) and were made possible through the construction of an
459 adapted brain template and atlas of the ovine brain (Ella et al., 2017; Ella and Keller, 2015).

460

461 **Sex differences in intact animals.**

462 VBM analysis

463 First, our VBM analysis revealed clear differences in GMC between intact males and females
464 in five main areas: the hippocampus, the hypothalamus—especially the arcuate region—the
465 pituitary, the amygdala and the gyrus ectolateralis. For all these regions, with the exception of
466 the hypothalamus, GMC was higher in males than in females. On the whole, the differences
467 measured in the hypothalamus and pituitary, which are key components of the gonadotropic
468 axis, are not very surprising because the axis is known to be highly sexually dimorphic. Indeed,
469 sexual differences have been previously reported in other species or by other approaches in
470 these areas. For example, similar to our results, MRI studies in humans have reported that the
471 volume of the hypothalamus is larger in men than women (Goldstein et al., 2001; Makris et al.,
472 2013). The hypothalamic cluster differing significantly between males and females appears to

473 include the region of the arcuate nucleus, a structure where the numbers of neurons expressing
474 kisspeptin, neurokinin B and dynorphin (KNDy neurons) as well as progesterone receptors are
475 higher in female than in male sheep (Cheng et al., 2010). This difference is linked to the fact
476 that KNDy neurons mediate the negative feedback of progesterone on GnRH secretion in
477 females. In the hypothalamic cluster, other regions, such as the ventromedial nucleus, are also
478 known to be sexually dimorphic, being larger in males than females (Flanagan-Cato, 2011).
479 Finally, it is important to note that a limitation of our study is the level of resolution that is
480 achievable using our MRI conditions (500 μm isovoxel resolution). This level of resolution
481 prevents visualization of very small neuron clusters, such as the sexually dimorphic nucleus of
482 the medial preoptic area, which has been consistently shown to be larger in males than females,
483 including in sheep (Roselli and Stormshak, 2010). In the pituitary, we found that females have
484 a higher concentration of gray matter than males. A recent human MRI study demonstrated that
485 the pituitary fossa, which grossly reflects the volume of the pituitary, is larger in women than
486 men (Pecina et al., 2017), thus corroborating our observations.

487 In the amygdala, we confirmed the sexual dimorphism previously reported in sheep (Nuruddin
488 et al., 2013) and recently in humans (Lotze et al., 2019). At the cellular level, it has been shown
489 that the size of neurons in the amygdala, as well as the content in estradiol receptors, is higher
490 in male than female sheep (Alexander et al., 2001; Perkins et al., 1995). In other animal models,
491 for example, in the rat, the volume of the medial amygdala is also higher in males than females
492 (Cooke et al., 1999). The hippocampus is another brain region that appears to be sexually
493 dimorphic in our study. As the hippocampus is a primary site for the regulation of cognitive
494 processes such as stress responses or spatial memory, which are also influenced by gonadal
495 hormones, such a difference is not surprising (Juraska, 1991; McCarthy and Konkle, 2005). In
496 addition, our results showing that part of the anterior hippocampus is larger in females than
497 males is congruent with a recent MRI study in mice (Meyer et al., 2017). Finally, the difference

498 measured in the gyrus ectolateralis is more surprising because it is not known as a traditional
499 region related to sex differences. Given the lack of anatomical and functional data regarding
500 this region in sheep, it is difficult to interpret this result. It has been shown that the gyrus
501 ectolateralis is part of the visual cortex (Clarke and Whitteridge, 1976), but further studies will
502 be needed to assess the nature and role of this dimorphism.

503 We performed the same VBM comparison one month following gonadectomy to assess whether
504 the differences observed are due to adult circulating levels of gonadal hormones. It is striking
505 to note that most of the observed differences diminished significantly after gonadectomy,
506 particularly in the hypothalamus and amygdala. Interestingly, adult castration of male rats
507 induces a reduction of the volume of the medial amygdala to a level comparable to that observed
508 in females, demonstrating that adult hormone manipulation can completely reverse the sexual
509 dimorphism observed in intact animals. Interestingly, this region is also rich in aromatase and
510 steroid receptors in adult sheep (Lehman et al., 1993; Roselli et al., 1998).

511

512 Resting-state fMRI

513 In addition to VBM analysis, our study is the first to report that the resting state connectome
514 differs between male and female sheep. This analysis revealed a sexually dimorphic brain
515 network composed of 332 functional connections shared between 77 functional nodes that
516 displays increased functional connectivity in intact luteal phase females when compared to
517 intact males. Three internal subnetworks involving the frontal region, the occipitoparietal
518 region and the diencephalic region compose this dimorphic network, with the diencephalic
519 region being by far the most sexually dimorphic. Interestingly, the functional connectivity
520 within the diencephalic region and especially in the hypothalamic regions showed the highest
521 degree of sexual dimorphism. Finally, these sexual differences were not significantly influenced

522 by adult circulating gonadal hormones, as the network differing between the sexes was not
523 influenced by gonadectomy.

524 **Sex differences in gonadectomized animals.**

525 VBM analysis

526 When considering the effect of gonadectomy within each sex in the VBM analysis, it is striking
527 to observe that gonadectomy induced very similar changes in GMC at the level of the
528 hypothalamus and pituitary in both males and females. The fact that gonadectomy abolishes
529 negative feedback (of testosterone for the males and progesterone for the females) is in line
530 with a similar response of the hypothalamic-pituitary axis in both sexes. However, it is notable
531 that in terms of GMC variations, the responses of the hypothalamus and pituitary were opposite.
532 While an increase of GMC was observed in the pituitary following gonadectomy, a clear
533 reduction was measured in the whole hypothalamus. The increase in GMC observed in the
534 pituitary is in line with previous data showing that ovariectomy induces a strong increase in the
535 number and size (2- to 3-fold hypertrophy) of the LH cell population in ewes (Polkowska et al.,
536 1980).

537 By contrast, the medial preoptic area of the hypothalamus is long known to be highly sexually
538 dimorphic in many species, including humans (Swaab et al., 1992). The size of the ovine
539 sexually dimorphic nucleus, measured either by Nissl staining or the expression of aromatase,
540 is significantly larger in adult rams than in ewes and is not affected by gonadectomy (Roselli et
541 al., 2004, 2000). In contrast, gonadectomy induced a significant reduction in GMC in the
542 hypothalamus in both sexes. This pattern of response remains to be explained in terms of
543 cellular mechanisms.

544

545 Resting-state fMRI

546 When analyzing the effect of gonadectomy within each sex for resting-state fMRI, it is striking
547 to first notice that within each sex, gonadectomy induced an increase in functional connectivity.
548 The pituitary gland, which displayed an increase in GMC after gonadectomy, also expressed an
549 increase in functional connectivity within the preoptic hypothalamic area and the BNST.
550 However, intense modifications of functional connectivity within the diencephalon diverged
551 according to sex. Indeed, while changes in males were characterized by rostrocaudal
552 modifications of functional connectivity, changes were mostly interhemispheric in females.
553 The meaning of such differences remains to be explored in the future.

554

555 **General considerations**

556 As already mentioned, differences between sexes or between intact and gonadectomized
557 animals are mainly located at the level of the hypothalamus and pituitary, reflecting differences
558 in the regulation of the gonadotropic axis. To fully validate the role of adult circulating sex
559 steroids, especially testosterone and progesterone, in the maintenance of these sexual
560 differences and determine which of these hormones is involved, it will be necessary in a future
561 study to supplement gonadectomized animals with adult levels of circulating steroids and see
562 whether we are able to restore the initial pattern of differences observed in intact animals.

563 Finally, it is important to consider several limitations that arise from the segmentation of our
564 brain atlas and the use of anesthetics in preclinical fMRI investigation. First, the current level
565 of anatomical/functional mapping of sheep brain neuroanatomy is far less precise than those in
566 other species such as rodents. Even if more than 80 brain structures have been segmented so
567 far, it should be remembered that MRI segmentation is dependent upon the contrasts on MRI
568 images that can differ from histological observations. Consequently, each label includes many
569 brain structures, and thus labeling would differ from the expectation of the reader. Second, in
570 our analysis, we failed to find any functional connectivity that was higher in males than in

571 females. Indeed, sex differences in ketamine sensitivity have been reported to affect the depth,
572 duration and efficacy of anesthesia (Molina et al., 2016). Thus, even though measures of heart
573 rate and O₂ saturation during functional acquisitions are similar between sexes (Figure S1), a
574 differential effect of ketamine on the resting-state network cannot be excluded. Moreover, the
575 greater sensitivity to ketamine displayed by males could obscure differences physiologically
576 present in males rather than in females, explaining the lack of higher functional connectivity in
577 males compared to females. Finally, our analysis was performed using Ella's Sheep brain
578 template and its associated probabilistic tissue maps, which were created from 18 ewes. Recent
579 studies have proposed using a more specific template to improve the segmentation step
580 (Fillmore et al., 2015; Huang et al., 2010). Hence, the development of a mixed brain template
581 (including males and females) with a higher number of animals (n = 100, sex ratio 1:1) will be
582 mandatory to improve the segmentation step and further develop future MRI studies using
583 sheep.

584 In conclusion, we demonstrated that MRI is a suitable method to study neuroendocrine
585 mechanisms that sustain sexual differences in the sheep brain and by inference in other large
586 animal models. In this context, sheep offer a unique mammalian model in which to study
587 neuroendocrine sexual differentiation and same-sex sexual partner preferences. Indeed, males
588 showing spontaneous preference for other rams (male-oriented) represent as many as 8 % of
589 the ram population (Roselli et al., 2011; Charles E. Roselli and Stormshak, 2009; Roselli and
590 Stormshak, 2010). The understanding of the biological determinants and underlying neural
591 networks mediating sexual attraction and mate selection are still quite incomplete in these
592 animals. Thus far, evidence supports the idea of an organization of neural substrates by
593 testosterone during prenatal development (C. E. Roselli and Stormshak, 2009). While much
594 attention has been given to the sexually dimorphic nucleus of the hypothalamus, a structure that

595 cannot be observed in MRI due to the limits of resolution, MRI could provide new insights on
596 whether the anatomy of other brain structures differ in male-oriented sheep.

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608

609

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755

756 **Figures**

757 **Fig 1.** Overview of the experiment. **A.** Experimental design and concentrations of testosterone
758 and progesterone before and after gonadectomy in both males and females. **B.** Processing
759 workflow for functional connectivity and voxel-based morphometry (VBM) analysis. Both
760 functional and anatomical images are coregistrated onto the Ella' sheep brain template and then
761 processed using a dedicated processing developed from SPM and FSL toolbox. **C.** 3D rendering
762 of the Ella' sheep brain template and atlas. Sheep brain atlas is composed by a mosaic of 86
763 anatomical region of interest (ROI) which were used to create the functional connectivity matrix
764 and functional networks analysis to identify brain territories revealed by the VBM analysis (for
765 further information, see Material & Method section).

766 Data are compared using a two-way ANOVA followed by Holm-Sidak multiple comparisons
767 test and expressed as mean \pm SEM; *** $p < 0.001$.

768 **Fig 2.** Morphological brain sexual dimorphisms in intact and gonadectomized animals. Male
769 *versus* female VBM comparison before and after the gonadectomy procedure. **A. left panel:**
770 brain plots representing the surface map of regional grey matter concentration (GMC)
771 differences between gonad-intact male *versus* luteal phase female sheep. **A. right panel:** brain
772 slices showing GMC differences between intact male *versus* intact female sheep. **B. left panel:**
773 brain plots representing the surface map of GMC differences between gonadectomized male
774 *versus* gonadectomized female sheep. **B. right panel:** brain slices showing GMC differences
775 between gonadectomized male *versus* gonadectomized female sheep.

776 Ecto = ectolateralis gyrus ; Hippo = hippocampus ; Pit = pituitary gland ; Hypo = hypothalamus.
777 Data are the results of interaction analysis (**A**) males versus females at the baseline (**B**) males
778 *versus* females after gonadectomy using a p value < 0.005 (β value = 0.990) corresponding to
779 $t_{(35)} = 2.7238$ and a cluster threshold set at 300 voxels. N = 20 animals (8 males and 12 females).

780 **Fig 3.** Effect of gonadectomy on sexually dimorphic structures. The mean values of Grey Matter
781 Concentration (GMC) were evaluated bilaterally in **A.** hippocampus, **B.** hypothalamus, **C.**
782 pituitary gland and **D.** ectolateralis gyrus for both male and female sheep before and after
783 gonadectomy.
784 Data were compared using a two-way ANOVA followed by Holm-Sidak multiple comparisons
785 test and expressed as mean \pm SEM; * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$. N = 20 animals
786 (8 males and 12 females).

787 **Fig 4.** Functional brain sexual dimorphisms in intact and gonadectomized sheep. **A.** Sagittal
788 and dorsal view of the sexually dimorphic brain functional network between entire males *versus*
789 entire females. **B.** Mean connectivity values within the previous network between entire males
790 and entire females. **C.** sagittal and dorsal view of the sexually dimorphic brain functional
791 network between gonadectomized males *versus* gonadectomized females. **D.** Mean
792 connectivity values within the previous network between gonadectomized males and
793 gonadectomized females.

794 The sexually dimorphic functional network are the results of interaction analysis between (A)
795 males *versus* females at the baseline and between (C) males *versus* females after gonadectomy
796 using network-based statistics (NBS; connection-level threshold p -uncorrected < 0.001 ,
797 networks were significant at $p < 0.05$ family-wise error (FWE) corrected), nodes and edges
798 colour coded according to statistical strength (t -value). Both comparison of the mean values of
799 the networks were evaluated using a two-tailed Student t-test and expressed as mean \pm SEM;
800 $*p < 0.05$. N = 20 animals (8 males and 12 females).

801 **Fig 5.** Effect of the gonadectomy procedure in both males and females on brain morphology.
802 **A. left panel:** brain plots representing the surface map of regional grey matter concentration
803 (GMC) differences between entire male *versus* gonadectomized male. **A. right panel:** brain
804 slices showing GMC differences between entire male *versus* gonadectomized male. **B. left**
805 **panel:** brain plots representing the surface map of GMC differences between entire female
806 *versus* gonadectomized female. **B. right panel:** brain slices showing GMC differences between
807 entire female *versus* gonadectomized female.

808 PAG : periaqueductal grey ; Amyg = amygdala ; Pit = pituitary gland ; Hypo = hypothalamus ;
809 MPOA = medial preoptic area. Data are the results of interaction analysis between (A) baseline
810 *versus* gonadectomy in males and between (B) baseline *versus* gonadectomy in female using
811 a p value < 0.005 (β value = 0.990) corresponding to $t_{(35)} = 2.7238$ and a cluster threshold set at
812 300 voxels. $N = 8$ in male group and $n = 12$ in female group.

813 **Fig 6.** Effect of the gonadectomy procedure on non-sexually dimorphic structures in both male
814 and female sheep. In males, the mean grey matter concentration (GMC) values were evaluated
815 bilaterally within **A.** the amygdala (Left), and the periaqueductal grey substance (PAG, Right).
816 In females, the mean GMC values were evaluated bilaterally within **B.** the subfornical organ
817 (Left), and the nucleus of the horizontal limb of the diagonal band (NHLDB, Right).
818 Data were compared using a two-way ANOVA followed by Holm-Sidak multiple comparisons
819 test and expressed as mean \pm SEM; * $p < 0.05$ and *** $p < 0.001$. N = 8 in male group and n =
820 12 in female group.

821 **Fig 7.** Effect of the gonadectomy procedure on brain functional connectivity in male and female
822 sheep. **A.** Sagittal and dorsal view of the altered functional network induced by gonadectomy
823 in males. **B.** Mean connectivity values within the previous network between entire *versus*
824 gonadectomized males. **C.** Sagittal and dorsal view of the altered functional network induced
825 by gonadectomy in females **D.** right panel: Mean connectivity values within the previous
826 network between gonad-intact or luteal phase females versus gonadectomized females.

827 The sexually dimorphic functional network are the results of interaction analysis between **(A)**
828 baseline *versus* gonadectomy in male group and between **(B)** Baseline versus gonadectomy in
829 female group using network-based statistics (NBS; connection-level threshold p -uncorrected $<$
830 0.05, networks were significant at $p < 0.05$ family-wise error (FWE) corrected), nodes and
831 edges colour coded according to statistical strength (t -value). Both comparison of the mean
832 values of the networks were evaluated using a two-tailed Student t-test and expressed as mean
833 \pm SEM; * $p < 0.05$ and ** $p < 0.01$. N = 8 in male group and n = 12 in female group.

834 **Supplementary Figures**

835 **Fig S1.** Physiological parameters recorded during the acquisition of functional scanning in
836 males and females, before and after the gonadectomy procedure. **(A)** animal weight, **(B)** Heart
837 rate, **(C)** O₂ saturation, **(D)** isoflurane concentration.

838 Data are compared using a two-way ANOVA followed by Holm-Sidak multiple comparisons
839 test and expressed as mean \pm SEM; *** $p < 0.001$.

840

841 **Fig S2.** Motions parameters recorded during the acquisitions. **(A)** Translations, **(B)** rotations,
842 **(C)** estimation of the breath during the acquisition, **(D)** a significant correlation is observed
843 between the Y-translation motion (Up-down motions) and breathing.

844 Data are expressed as mean \pm SD; Correlation was estimated using a two-tailed parametric
845 Pearson test ** $p < 0.001$.

846

847 **Fig S3.** Control testing of individual variability in functional data. Here, we compared two
848 group of sheep after randomly grouped (4 males and 6 females in each group) to insure our
849 statistical power. **(A)** Distribution of Z score in intact males (shaded blue) and intact females
850 (shaded red) is associated with a significant network in females. **(B)** Distribution of Z score in
851 mix 1 (shaded blue) and mix 2 (shaded red) is not associated with a significant network in intact
852 animals. **(C)** Distribution of Z score in gonadectomized males (shaded blue) and
853 gonadectomized females (shaded red) is associated with a significant network in females. **(B)**
854 Distribution of Z score in mix 1 (shaded blue) and mix 2 (shaded red) is not associated with a
855 significant network in gonadectomized animals. The sexually dimorphic functional network are
856 the results of interaction analysis entire male x luteal females at the baseline **(A)** and male x
857 females after gonadectomy using network-based statistics (NBS; connection-level threshold p -

858 uncorrected < 0.001 , networks were significant at $p < 0.005$ family-wise error (FWE)
859 corrected), nodes and edges colour coded according to statistical strength (t-value).

860

861 **Fig S4.** Control testing of individual variability in morphological data. Here, we compared two
862 group of sheep after randomly grouped (4 males and 6 females in each group) to insure our
863 statistical power. **(A)** Statistical analytical design showing the flexible factorial design used in
864 the study. The last column correspond to the brains volumes which are used as covariate. **(B)**
865 Comparisons of GMC between the mix 1 and the mix 2 at the baseline. A significant cluster
866 within the left lateral *gyrus* is observable. **(C)** Comparisons of GMC between the mix 1 and the
867 mix 2 after gonadectomy. No significant cluster observable.

868 Data are the results of interaction analysis Mix 1 x Mix 2 at baseline **(B)** and Mix 1 x Mix 2 at
869 gonadectomy **(C)** using a p value = 0.005 (β value = 0.990) corresponding to $t_{(35)} = 2.7238$ and
870 a cluster threshold set at 5 voxels.

871 **Supplementary Tables**

872 **Table S1.** Sexually dimorphic brain regions sensitive to the gonadectomy procedure. Data are
873 compared using a two-way ANOVA followed by Holm-Sidak multiple comparisons test and
874 expressed as mean \pm SEM; * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$.

875

876 **Table S2.** Sexually dimorphism brain region insensitive to the gonadectomy procedure. Data
877 are compared using a two-way ANOVA followed by Holm-Sidak multiple comparisons test
878 and expressed as mean \pm SEM; * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$.

879

880 **Table S3.** Sexually dimorphic brain functional connections. The sexually dimorphic functional
881 network between entire males *versus* entire females has been calculated in network-based
882 statistics (NBS; connection-level threshold p -uncorrected < 0.001 , networks were significant at
883 $p < 0.05$ family-wise error (FWE) corrected), nodes and edges colour coded according to
884 statistical strength (t -value).

885

886 **Table S4.** Sexually dimorphic brain functional connections. The sexually dimorphic functional
887 network between gonadectomized males *versus* gonadectomized females has been calculated
888 in network-based statistics (NBS; connection-level threshold p -uncorrected < 0.001 , networks
889 were significant at $p < 0.05$ family-wise error (FWE) corrected), nodes and edges colour coded
890 according to statistical strength (t -value).

891

892 **Table S5.** Effect of the gonadectomy procedure on brain morphology in males. Data are
893 compared using a two-way ANOVA followed by Holm-Sidak multiple comparisons test and
894 expressed as mean \pm SEM; * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$.

895 **Table S6.** Effect of the gonadectomy procedure on brain morphology in females. Data are
896 compared using a two-way ANOVA followed by Holm-Sidak multiple comparisons test and
897 expressed as mean \pm SEM; * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$.

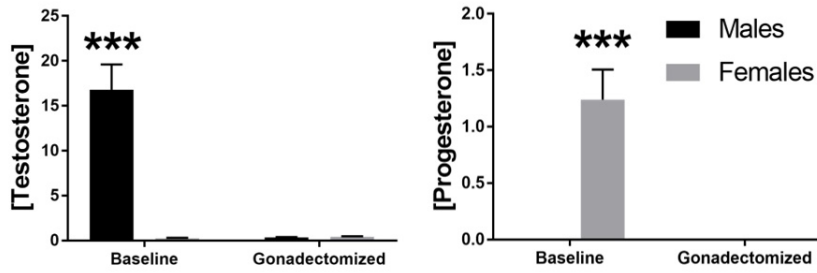
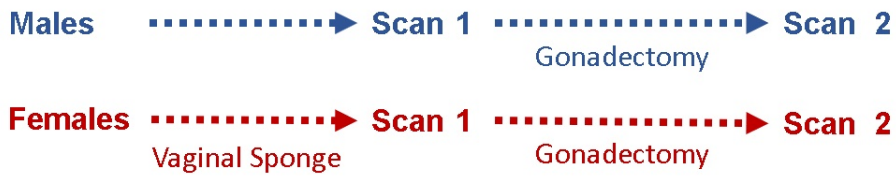
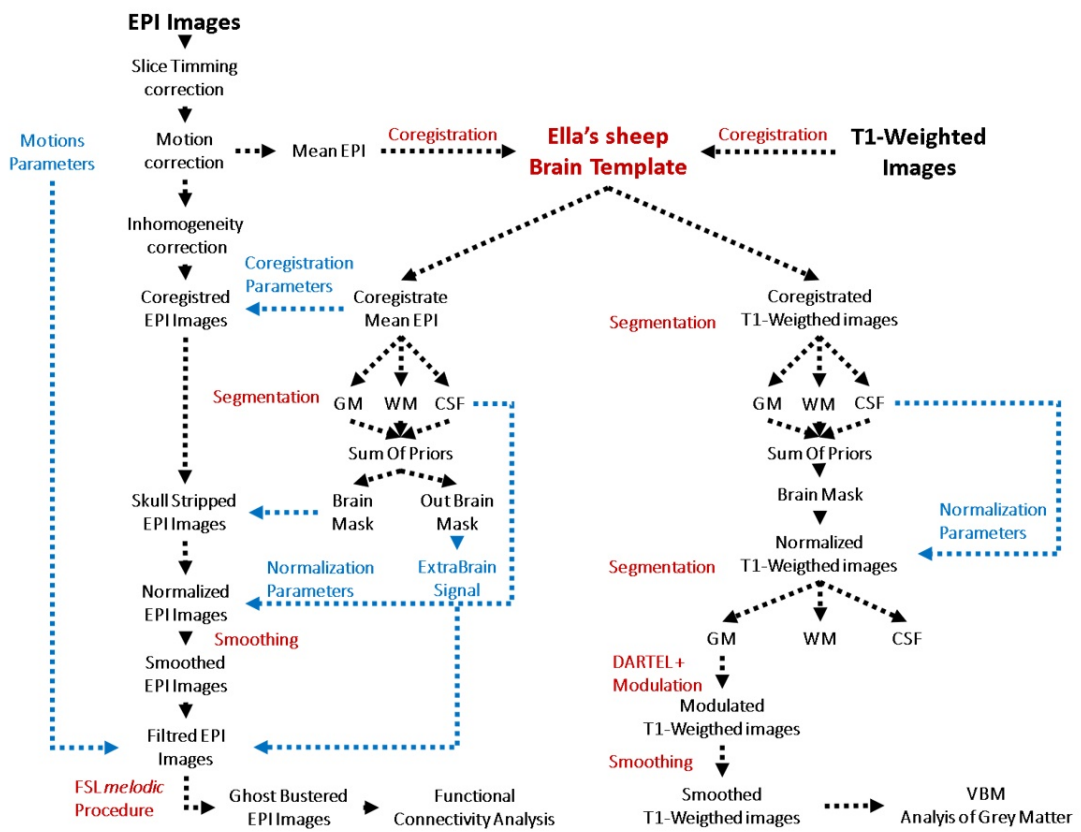
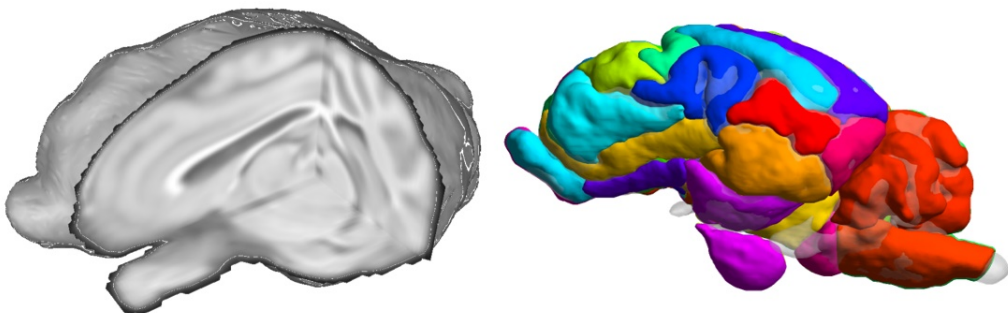
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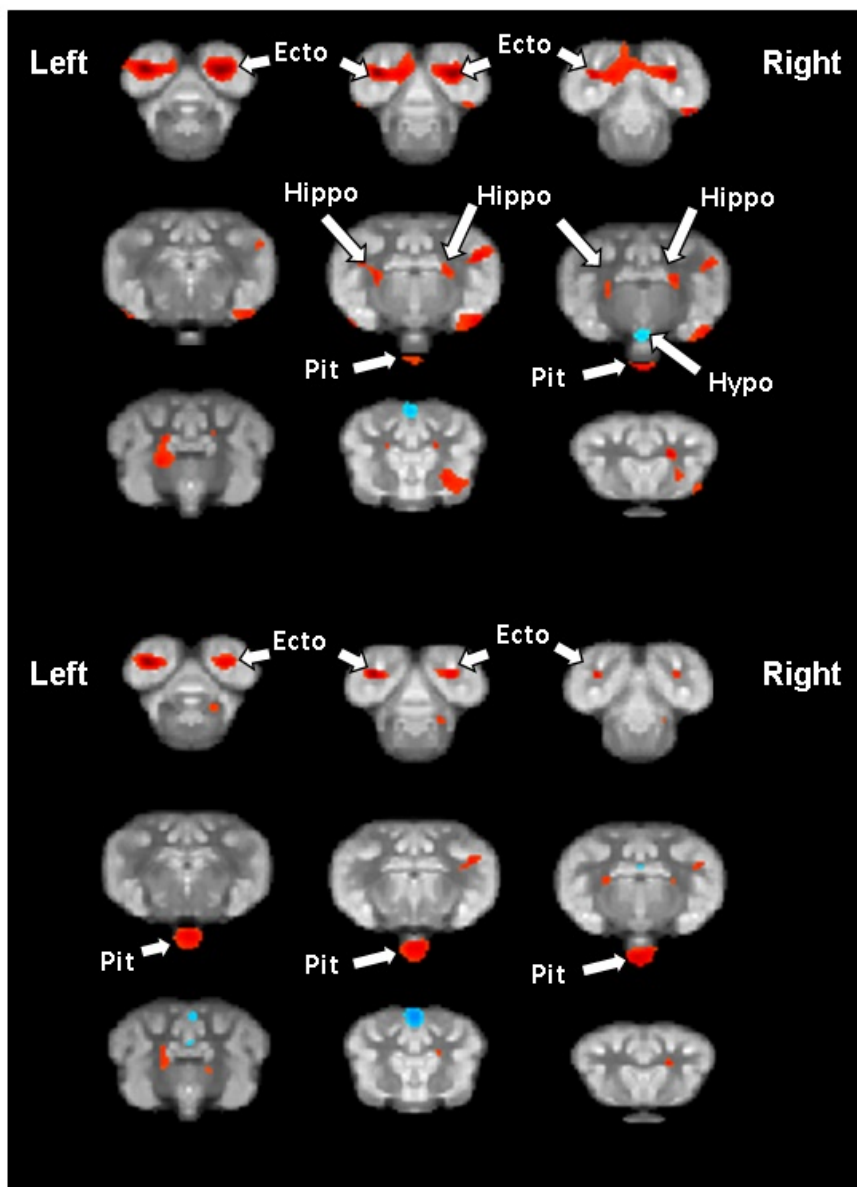
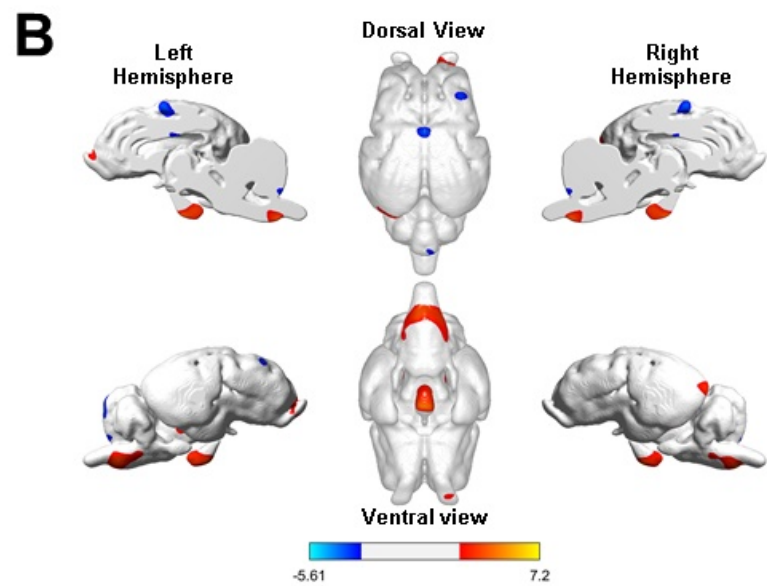
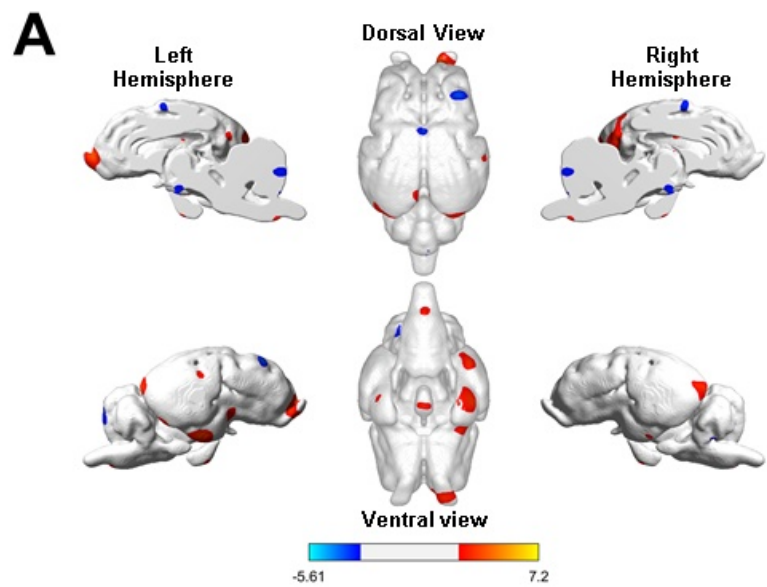
899 **Table S7.** Effect of the gonadectomy procedure on resting state functional connectivity in
900 males. The network has been calculated in network-based statistics (NBS; connection-level
901 threshold p -uncorrected < 0.05 , networks were significant at $p < 0.05$ family-wise error (FWE)
902 corrected), nodes and edges colour coded according to statistical strength (t -value).

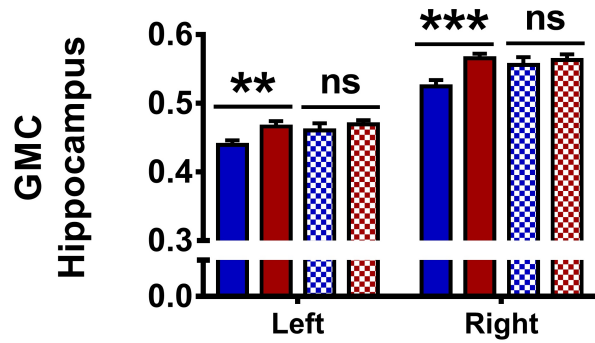
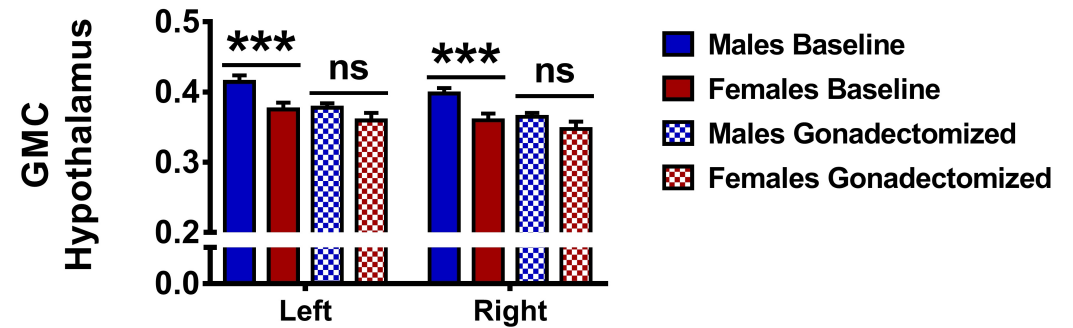
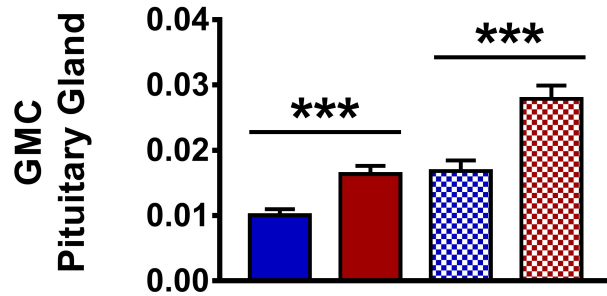
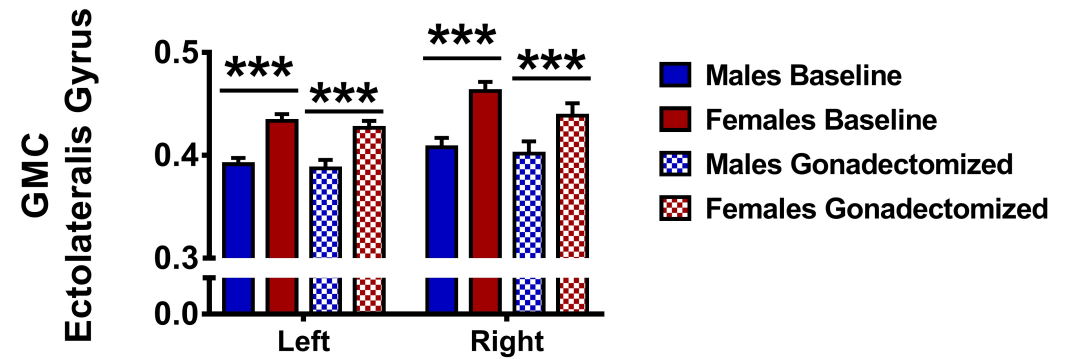
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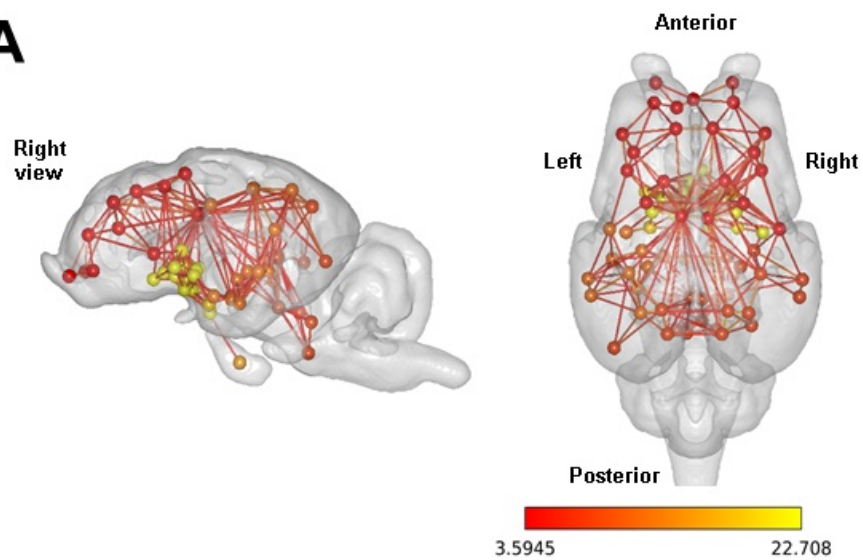
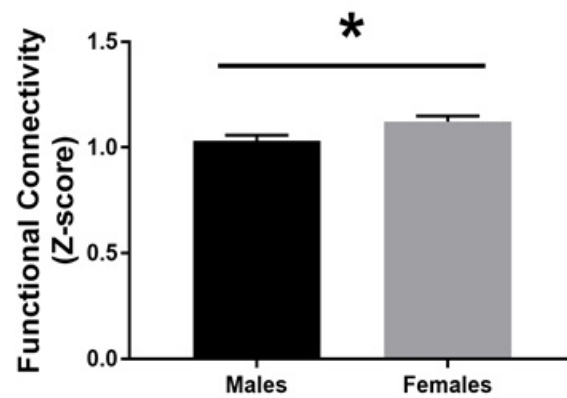
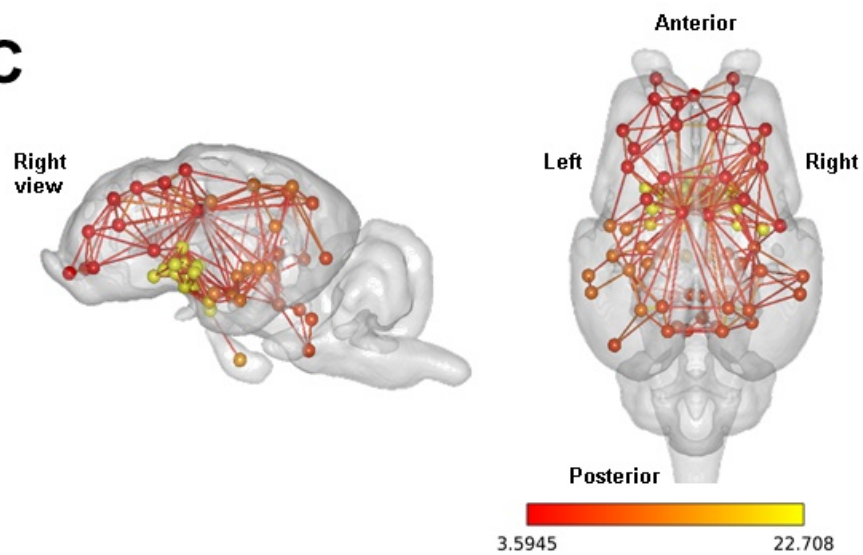
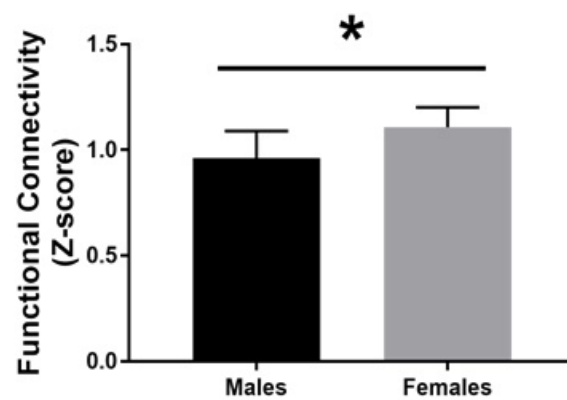
904 **Table S8.** Effect of the gonadectomy procedure on resting state functional connectivity in
905 females. The network has been calculated in network-based statistics (NBS; connection-level
906 threshold p -uncorrected < 0.05 , networks were significant at $p < 0.05$ family-wise error (FWE)
907 corrected), nodes and edges colour coded according to statistical strength (t -value).

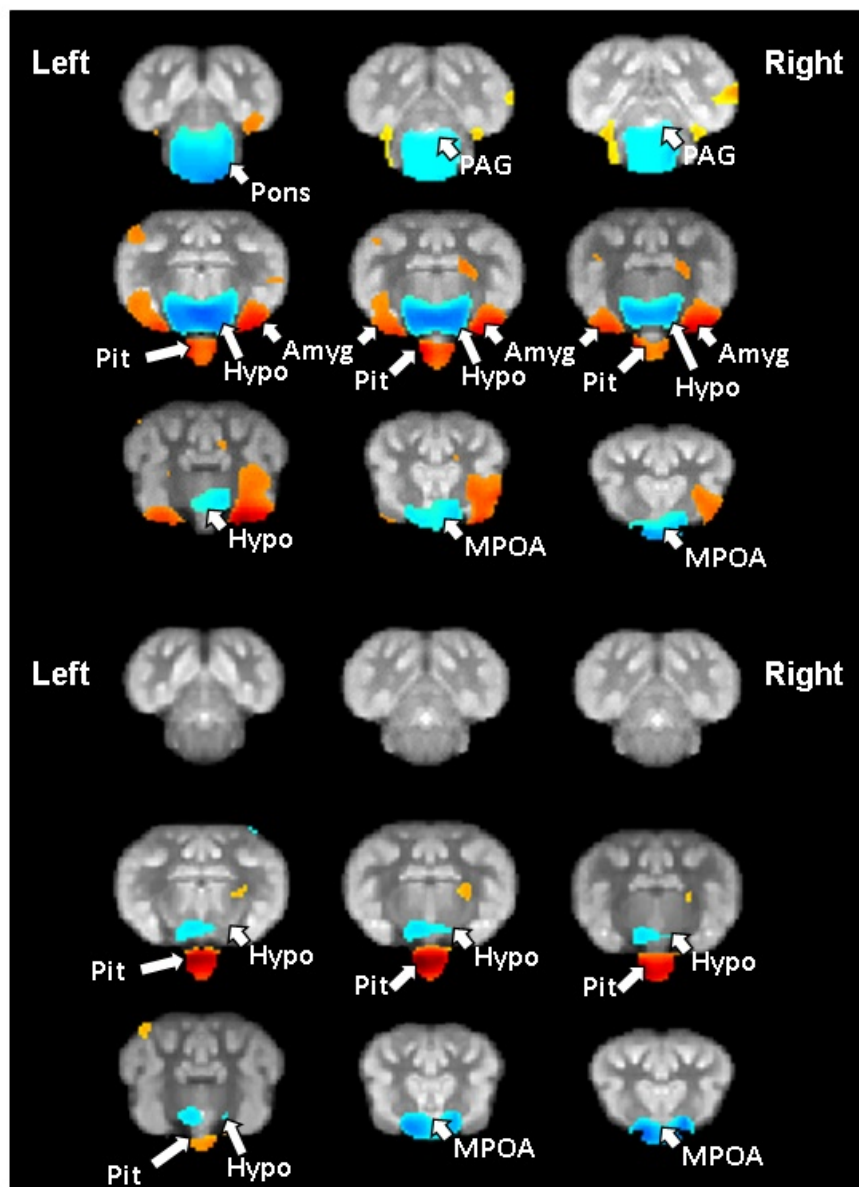
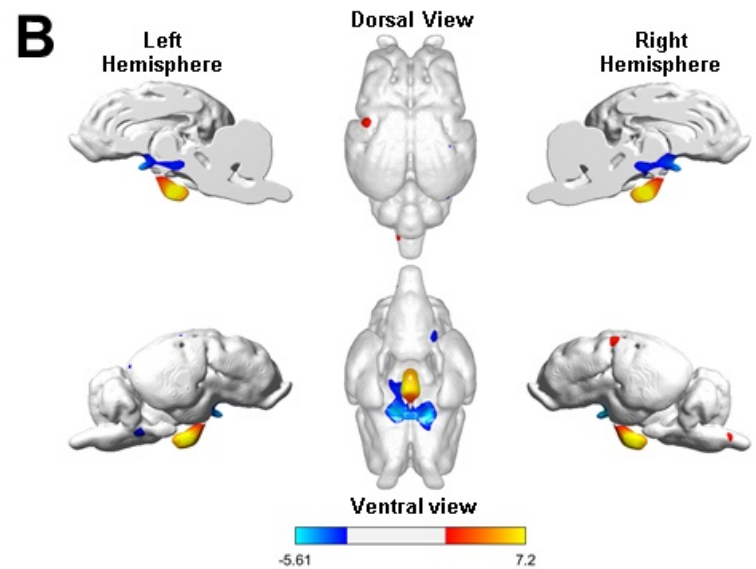
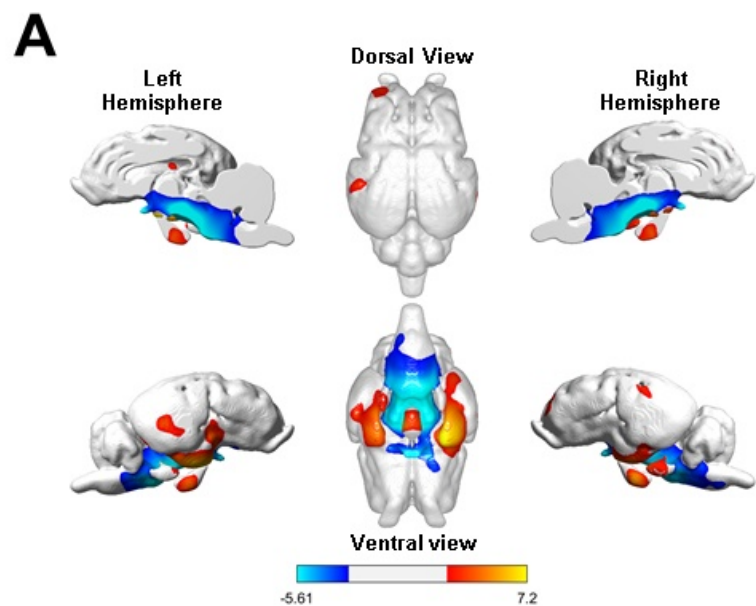
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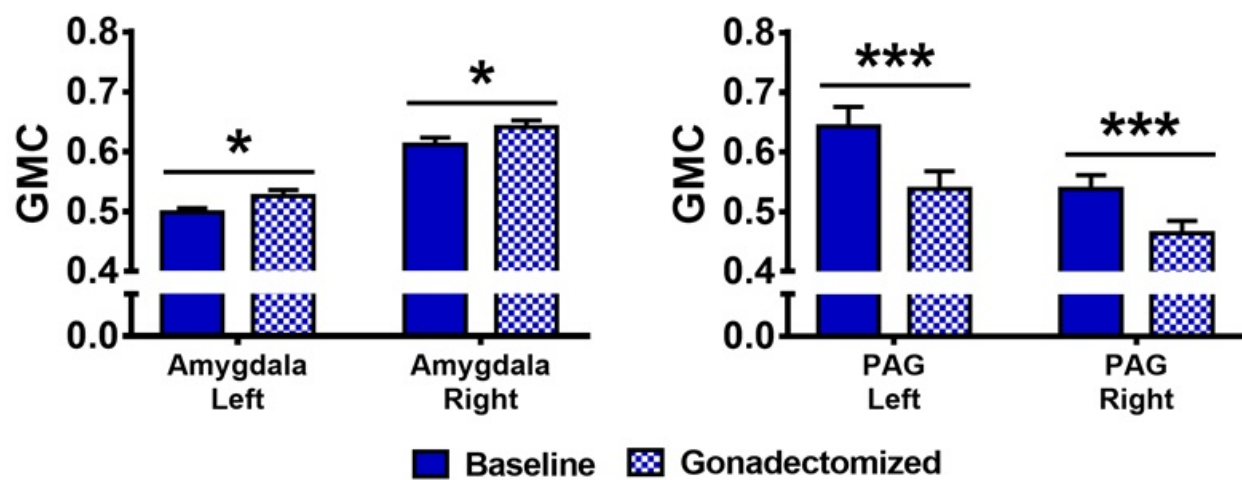
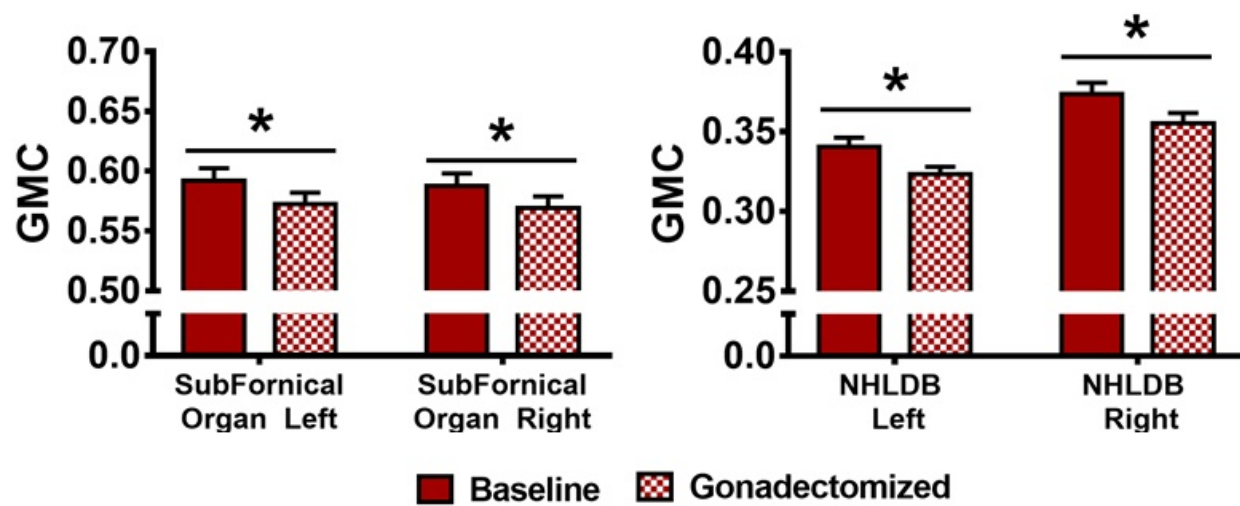
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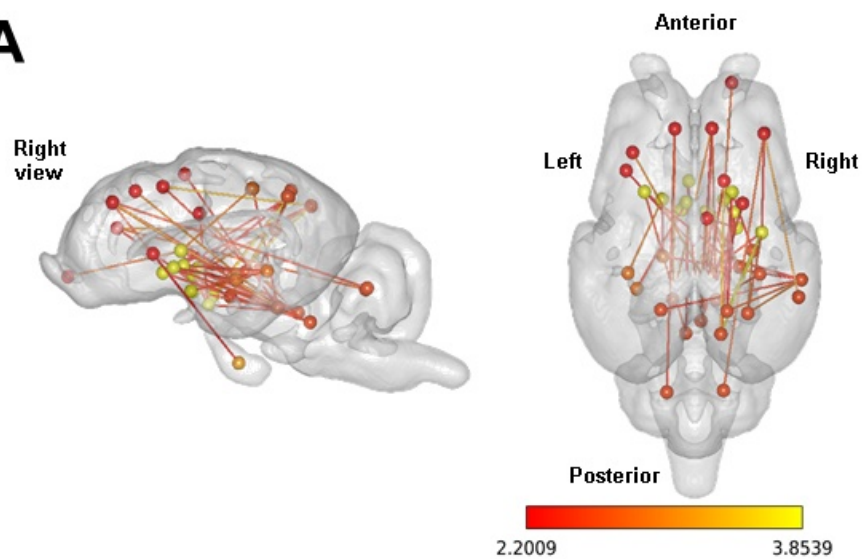
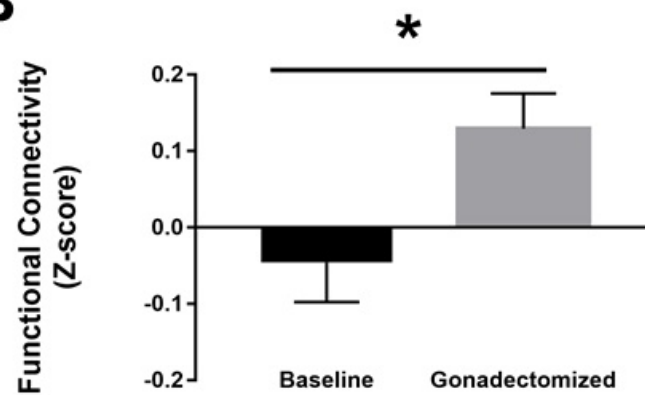
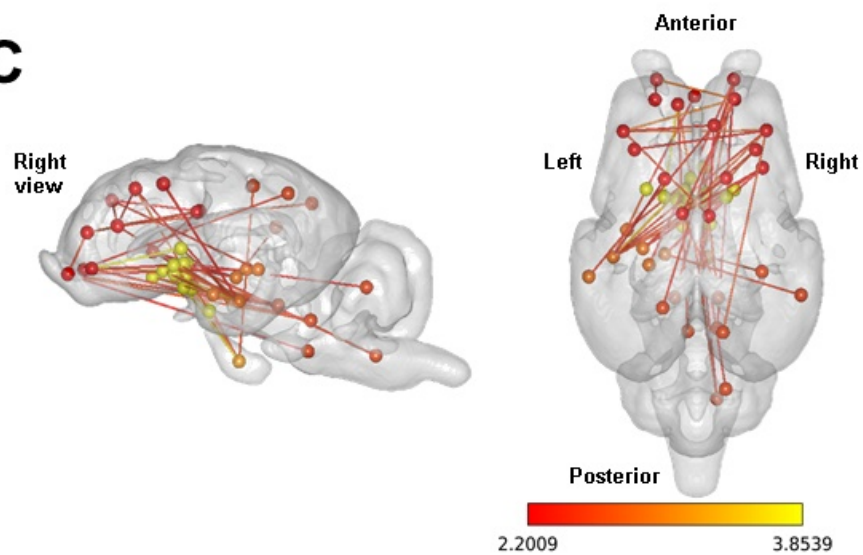
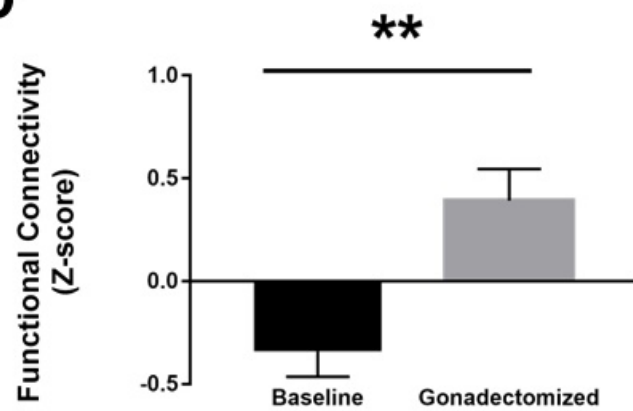


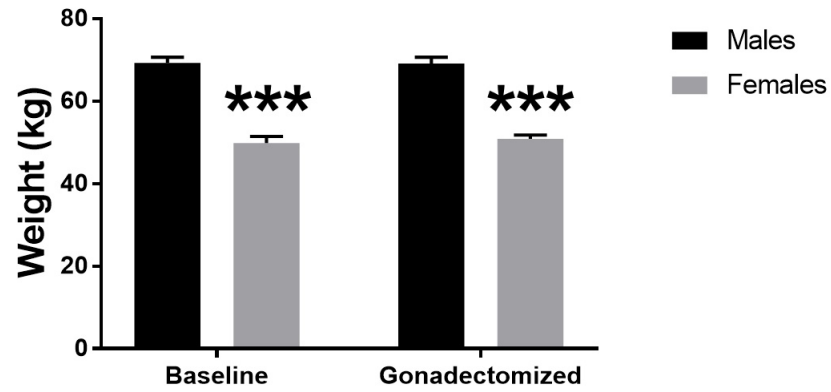
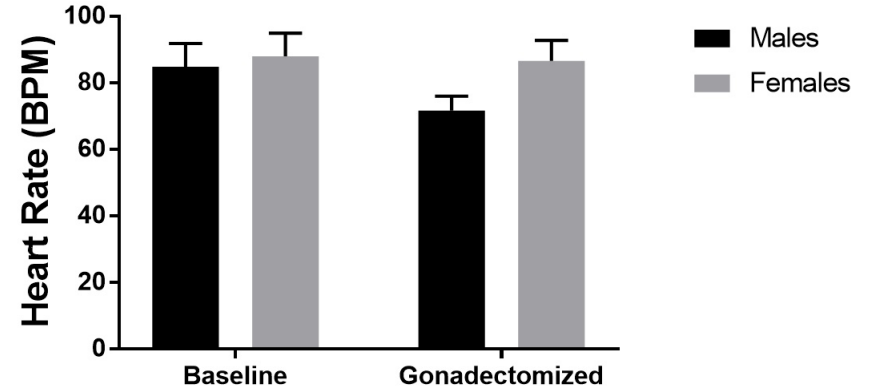
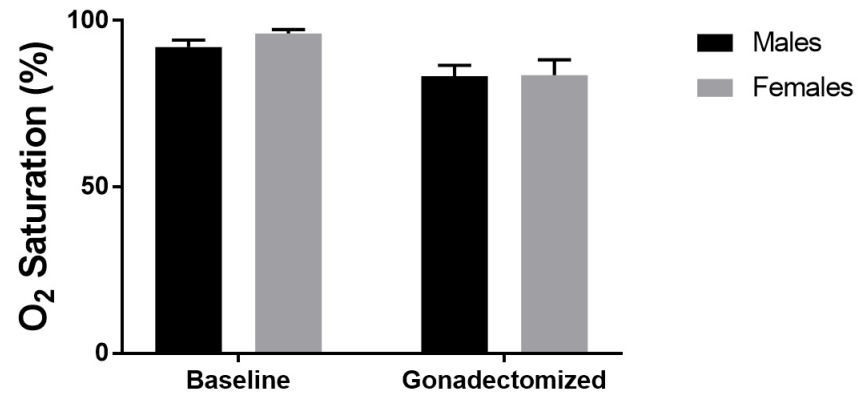
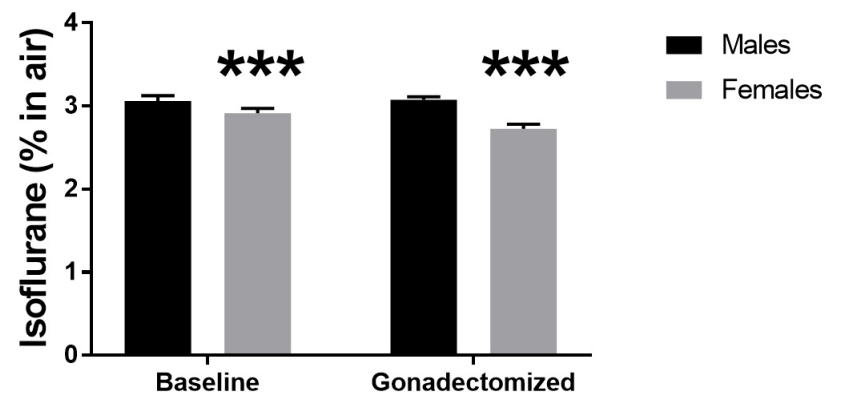
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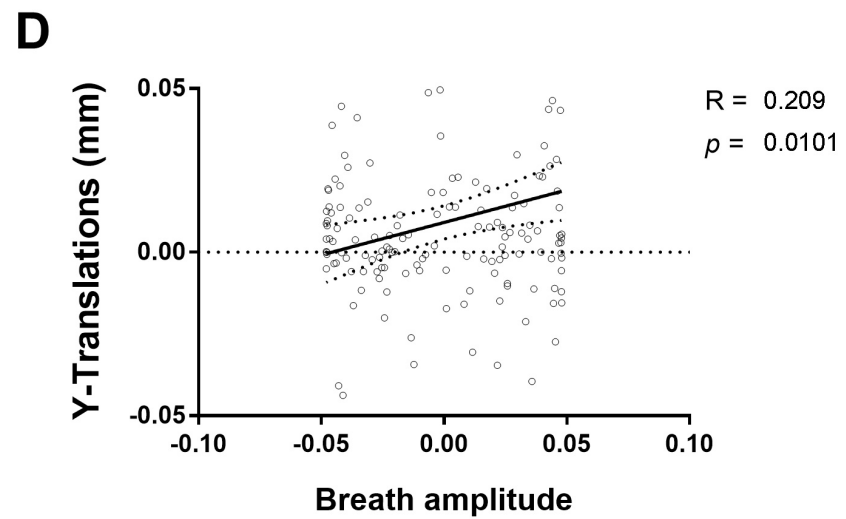
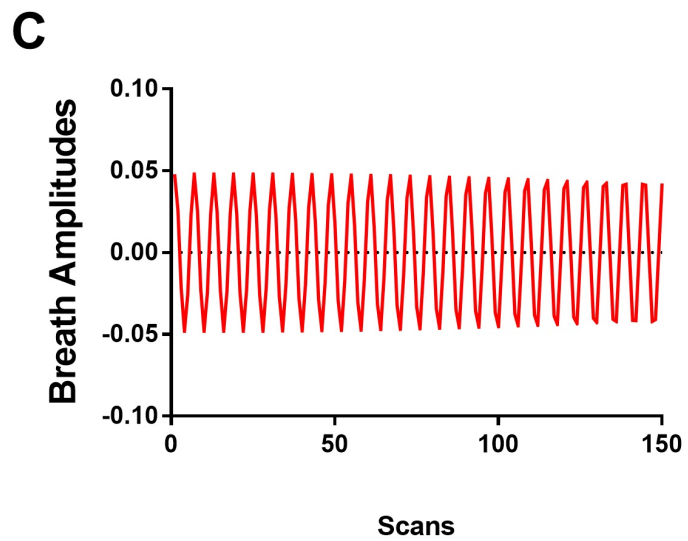
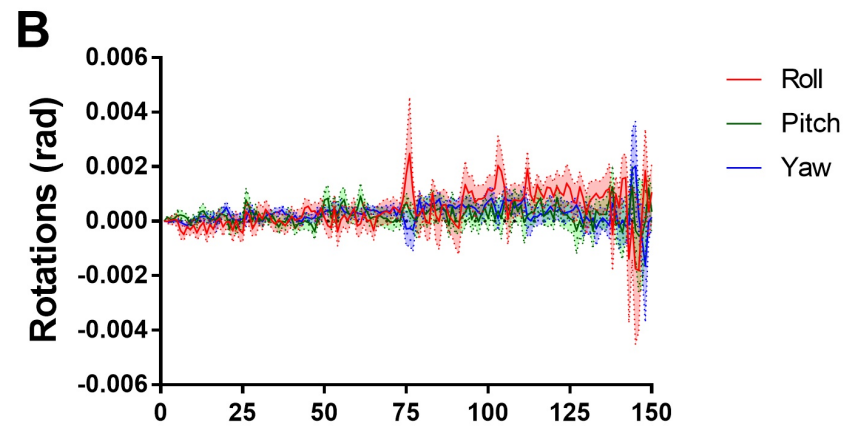
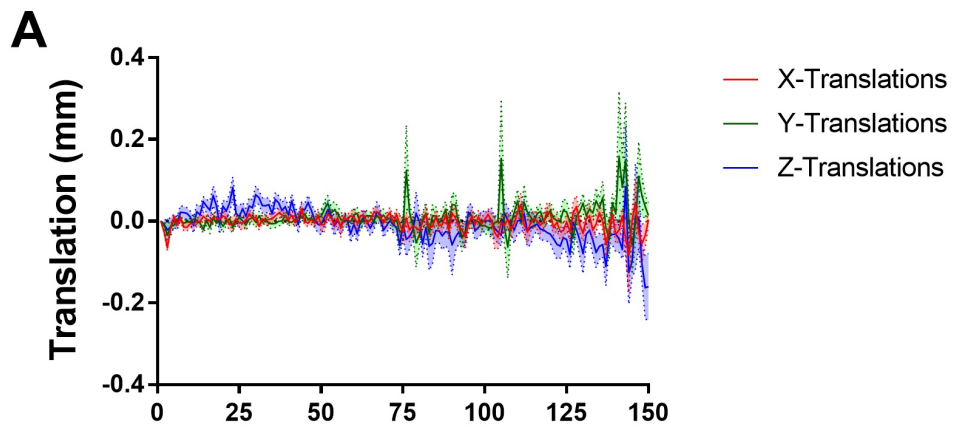
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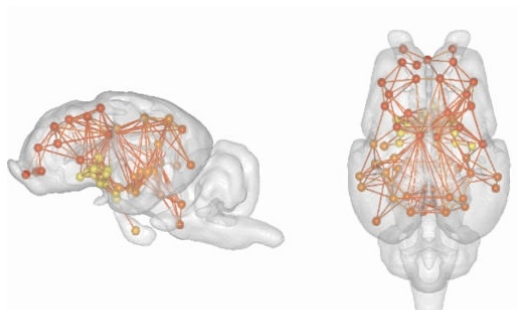
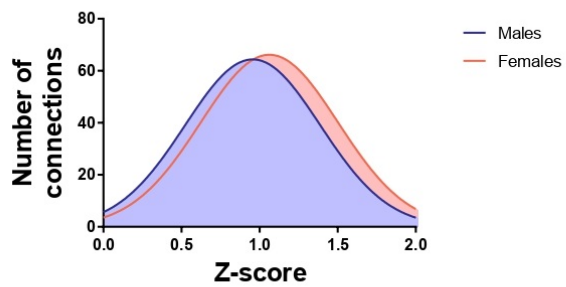
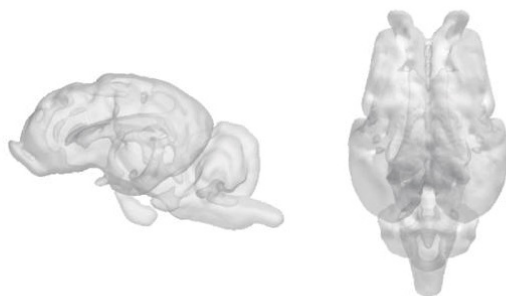
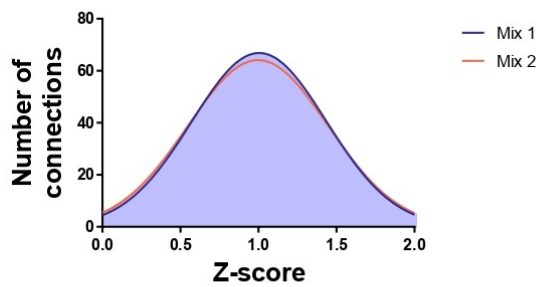
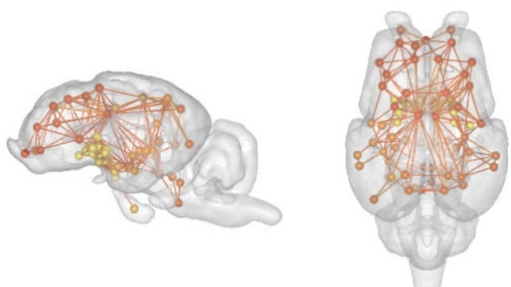
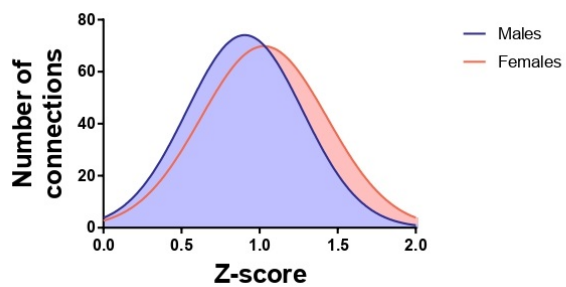
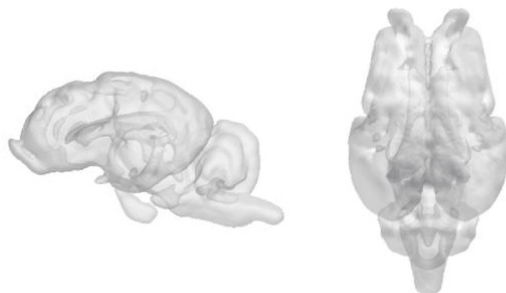
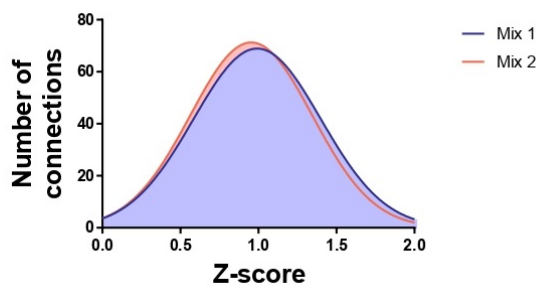


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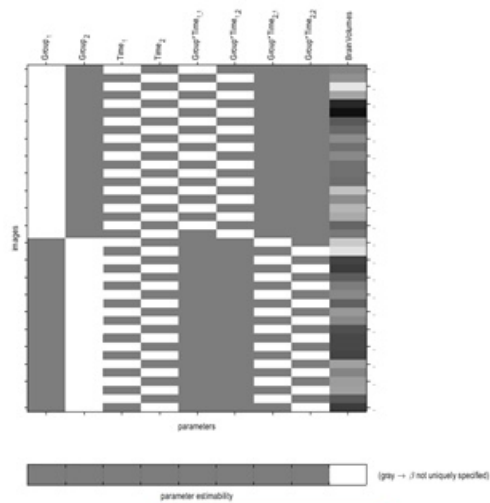
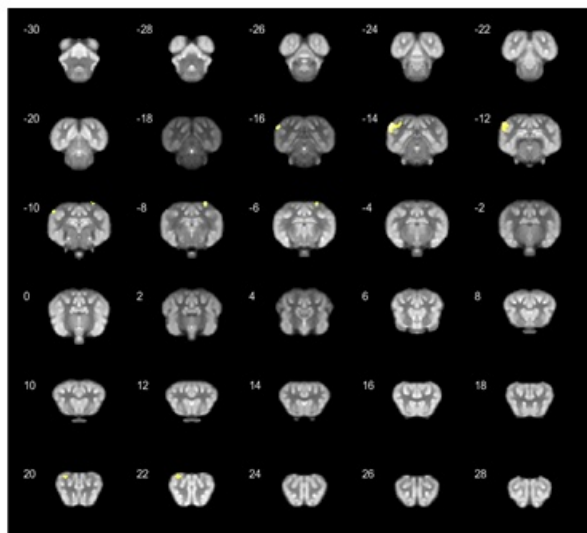
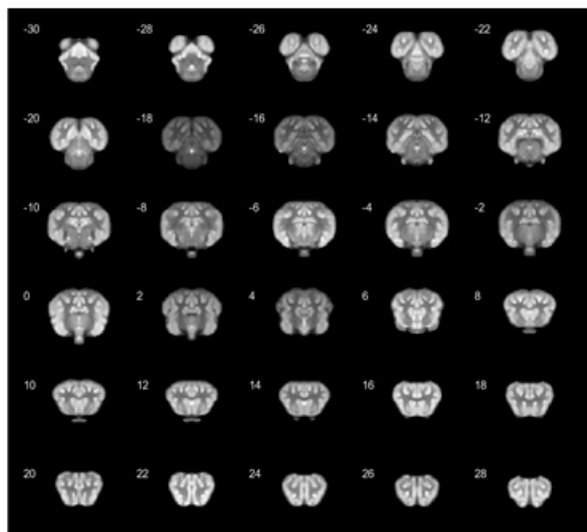
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A

Statistical analysis: Design

**B****C**

Comparison	Mean Males	Mean Females	Mean Diff	95,00% CI of diff	t	Individual P Value	Summary
Amygdala Right							
Males Baseline vs. Females Baseline	0,4821	0,5064	-0,02427	-0,04726 to -0,001285	2,071	0,0385	*
Males Gonadectomized vs. Females Gonadectomized	0,4952	0,501	-0,005836	-0,0279 to 0,01623	0,5188	0,6039	ns
Cingulate Cortex Left							
Males Baseline vs. Females Baseline	0,3795	0,4087	-0,02927	-0,05226 to -0,006284	2,497	0,0126	*
Males Gonadectomized vs. Females Gonadectomized	0,3748	0,394	-0,01917	-0,04124 to 0,002891	1,704	0,0885	ns
Hippocampus Left							
Males Baseline vs. Females Baseline	0,4393	0,4659	-0,02663	-0,04819 to -0,005069	2,422	0,0155	*
Males Gonadectomized vs. Females Gonadectomized	0,4602	0,4692	-0,008939	-0,0305 to 0,01262	0,813	0,4163	ns
Hippocampus Right							
Males Baseline vs. Females Baseline	0,5447	0,5915	-0,04677	-0,06976 to -0,02378	3,99	<0,0001	****
Males Gonadectomized vs. Females Gonadectomized	0,5856	0,588	-0,002384	-0,02445 to 0,01968	0,2119	0,8322	ns
Gyrus Rectus Right							
Males Baseline vs. Females Baseline	0,3713	0,3986	-0,0273	-0,05029 to -0,00431	2,329	0,02	*
Males Gonadectomized vs. Females Gonadectomized	0,3729	0,3903	-0,01737	-0,03944 to 0,004689	1,545	0,1226	ns
Medial Mamillary Nucleus Left							
Males Baseline vs. Females Baseline	0,4145	0,3754	0,03906	0,0175 to 0,06063	3,553	0,0004	***
Males Gonadectomized vs. Females Gonadectomized	0,3778	0,3596	0,0182	-0,003361 to 0,03976	1,655	0,098	ns
Medial Mamillary Nucleus Right							
Males Baseline vs. Females Baseline	0,3979	0,3599	0,03801	0,01644 to 0,05957	3,457	0,0006	***
Males Gonadectomized vs. Females Gonadectomized	0,3647	0,3474	0,01731	-0,004256 to 0,03887	1,574	0,1156	ns
Parahippocampal Cortex Left							
Males Baseline vs. Females Baseline	0,2995	0,3216	-0,02207	-0,04506 to 0,0009229	1,883	0,05	*
Males Gonadectomized vs. Females Gonadectomized	0,314	0,322	-0,008038	-0,0301 to 0,01403	0,7145	0,475	ns
Parahippocampal Cortex Right							
Males Baseline vs. Females Baseline	0,4254	0,4559	-0,03051	-0,0535 to -0,00752	2,603	0,0093	**
Males Gonadectomized vs. Females Gonadectomized	0,4503	0,4543	-0,004017	-0,02608 to 0,01805	0,3571	0,7211	ns
Pituitary Gland Left							
Males Baseline vs. Females Baseline	0,1744	0,1472	0,02718	0,005614 to 0,04874	2,657	0,015	*
Males Gonadectomized vs. Females Gonadectomized	0,1798	0,1653	0,01447	-0,007096 to 0,03603	1,236	0,1984	ns
Pituitary Gland Right							
Males Baseline vs. Females Baseline	0,1923	0,1631	0,02925	0,007684 to 0,05081	2,76	0,0069	**
Males Gonadectomized vs. Females Gonadectomized	0,1971	0,1832	0,0139	-0,007664 to 0,03546	1,64	0,1963	ns
Putamen Right							
Males Baseline vs. Females Baseline	0,3928	0,4173	-0,02443	-0,04741 to -0,001435	2,084	0,0373	*
Males Gonadectomized vs. Females Gonadectomized	0,4033	0,416	-0,01274	-0,0348 to 0,009325	1,132	0,2576	ns
Suprasylvian Gyrus Right							
Males Baseline vs. Females Baseline	0,415	0,4498	-0,03488	-0,05787 to -0,01189	2,976	0,003	**
Males Gonadectomized vs. Females Gonadectomized	0,4467	0,4477	-0,000936	-0,02306 to 0,02107	0,08833	0,9296	ns
Medial Mamillary Nucleus Left							
Males Baseline vs. Females Baseline	0,4145	0,3754	0,03906	0,0175 to 0,06063	3,553	0,0004	***
Males Gonadectomized vs. Females Gonadectomized	0,3778	0,3596	0,0182	-0,003361 to 0,03976	1,655	0,098	ns
Medial Mamillary Nucleus Right							
Males Baseline vs. Females Baseline	0,3979	0,3599	0,03801	0,01644 to 0,05957	3,457	0,0006	***
Males Gonadectomized vs. Females Gonadectomized	0,3647	0,3474	0,01731	-0,004256 to 0,03887	1,574	0,1156	ns

Comparison	Mean Males	Mean Females	Mean Diff	95,00% CI of diff	t	Individual P Value	Summary
AnteriorSigmoides Gyru Right							
Males Baseline vs. Females Baseline	0,2171	0,1821	0,03498	0,01199 to 0,05797	2,984	0,0029	**
Males Gonadectomized vs. Females Gonadectomized	0,2073	0,1791	0,02817	0,006102 to 0,05023	2,504	0,0124	*
Cerebellum Left							
Males Baseline vs. Females Baseline	0,5363	0,5033	0,03296	0,009972 to 0,05595	2,812	0,005	**
Males Gonadectomized vs. Females Gonadectomized	0,5331	0,4969	0,03621	0,01415 to 0,05827	3,219	0,0013	**
Cerebellum Right							
Males Baseline vs. Females Baseline	0,452	0,4275	0,0245	0,00151 to 0,04749	2,09	0,0368	*
Males Gonadectomized vs. Females Gonadectomized	0,4499	0,4211	0,0288	0,006735 to 0,05086	2,56	0,0106	*
Ectolateralis Gyru Left							
Males Baseline vs. Females Baseline	0,4044	0,4461	-0,04163	-0,06462 to -0,01864	3,552	0,0004	***
Males Gonadectomized vs. Females Gonadectomized	0,3992	0,4382	-0,03897	-0,06104 to -0,01691	3,465	0,0005	***
Ectolateralis Gyru Right							
Males Baseline vs. Females Baseline	0,4137	0,4663	-0,05258	-0,07557 to -0,02959	4,486	<0,0001	****
Males Gonadectomized vs. Females Gonadectomized	0,4047	0,4428	-0,03806	-0,06013 to -0,016	3,384	0,0007	***
Entolateral Gyru Left							
Males Baseline vs. Females Baseline	0,433	0,4709	-0,03788	-0,06087 to -0,01489	3,232	0,0013	**
Males Gonadectomized vs. Females Gonadectomized	0,4318	0,4572	-0,02542	-0,04748 to -0,003356	2,26	0,024	*
Entolateral Gyru Right							
Males Baseline vs. Females Baseline	0,4938	0,5382	-0,04439	-0,06738 to -0,0214	3,787	0,0002	***
Males Gonadectomized vs. Females Gonadectomized	0,4909	0,5205	-0,02962	-0,05169 to -0,007559	2,633	0,0085	**
Insula Right							
Males Baseline vs. Females Baseline	0,4799	0,5232	-0,04335	-0,06634 to -0,02036	3,698	0,0002	***
Males Gonadectomized vs. Females Gonadectomized	0,4853	0,5159	-0,03066	-0,05272 to -0,008596	2,725	0,0065	**
Lateral Gyru Left							
Males Baseline vs. Females Baseline	0,4826	0,5276	-0,045	-0,06799 to -0,02201	3,839	0,0001	***
Males Gonadectomized vs. Females Gonadectomized	0,4804	0,5171	-0,03669	-0,05876 to -0,01463	3,262	0,0011	**
Lateral Gyru Right							
Males Baseline vs. Females Baseline	0,4761	0,5282	-0,05214	-0,07513 to -0,02915	4,448	<0,0001	****
Males Gonadectomized vs. Females Gonadectomized	0,4725	0,5081	-0,03556	-0,05763 to -0,0135	3,162	0,0016	**
Medial Mamillary Nucleus Left							
Males Baseline vs. Females Baseline	0,3947	0,3483	0,04637	0,02338 to 0,06936	3,956	<0,0001	****
Males Gonadectomized vs. Females Gonadectomized	0,3615	0,3369	0,02457	0,002504 to 0,04663	2,184	0,0291	*
Medial Mamillary Nucleus Right							
Males Baseline vs. Females Baseline	0,3758	0,3316	0,04415	0,02116 to 0,06714	3,767	0,0002	***
Males Gonadectomized vs. Females Gonadectomized	0,346	0,3228	0,02318	0,001121 to 0,04525	2,061	0,0395	*
Medial Septal Nucleus Left							
Males Baseline vs. Females Baseline	0,3558	0,3852	-0,02944	-0,05243 to -0,006455	2,512	0,0121	*
Males Gonadectomized vs. Females Gonadectomized	0,3612	0,385	-0,02386	-0,04592 to -0,001795	2,121	0,0341	*
Occipital Lobe Left							
Males Baseline vs. Females Baseline	0,4001	0,443	-0,04296	-0,06595 to -0,01997	3,665	0,0003	***
Males Gonadectomized vs. Females Gonadectomized	0,3982	0,4349	-0,03663	-0,0587 to -0,01457	3,257	0,0011	**
Occipital Lobe Right							
Males Baseline vs. Females Baseline	0,4175	0,4589	-0,04142	-0,06441 to -0,01844	3,534	0,0004	***
Males Gonadectomized vs. Females Gonadectomized	0,4182	0,4438	-0,0256	-0,04766 to -0,003535	2,276	0,023	*
Olfactory Bulb Right							
Males Baseline vs. Females Baseline	0,2664	0,3154	-0,04899	-0,07198 to -0,026	4,18	<0,0001	****
Males Gonadectomized vs. Females Gonadectomized	0,2749	0,3135	-0,03868	-0,06074 to -0,01661	3,438	0,0006	***
Orbital Gyru Right							
Males Baseline vs. Females Baseline	0,4071	0,4407	-0,03356	-0,05655 to -0,01058	2,864	0,0042	**
Males Gonadectomized vs. Females Gonadectomized	0,4101	0,4337	-0,02368	-0,04574 to -0,001613	2,105	0,0355	*
PostCruciate Gyru Left							
Males Baseline vs. Females Baseline	0,4971	0,4549	0,04219	0,0192 to 0,06518	3,6	0,0003	***
Males Gonadectomized vs. Females Gonadectomized	0,4891	0,4472	0,04187	0,01981 to 0,06393	3,722	0,0002	***
Posterior Sygmoideus Gyru Left							
Males Baseline vs. Females Baseline	0,3077	0,2794	0,02831	0,005325 to 0,0513	2,416	0,0158	*
Males Gonadectomized vs. Females Gonadectomized	0,3027	0,274	0,02874	0,006673 to 0,0508	2,555	0,0107	*
Posterior Sygmoideus Gyru Right							
Males Baseline vs. Females Baseline	0,3678	0,337	0,03078	0,007788 to 0,05377	2,626	0,0087	**
Males Gonadectomized vs. Females Gonadectomized	0,363	0,3274	0,03554	0,01347 to 0,0576	3,159	0,0016	**
Posterior Sylvian Gyru Right							
Males Baseline vs. Females Baseline	0,4803	0,5318	-0,05155	-0,07454 to -0,02856	4,398	<0,0001	****
Males Gonadectomized vs. Females Gonadectomized	0,4782	0,515	-0,03686	-0,05892 to -0,0148	3,277	0,0011	**
Sylvian Gyru Right							
Males Baseline vs. Females Baseline	0,4623	0,5024	-0,0402	-0,06318 to -0,01721	3,429	0,0006	***
Males Gonadectomized vs. Females Gonadectomized	0,4597	0,4886	-0,02888	-0,05094 to -0,006813	2,567	0,0103	*

Brain Region 1	Brain Region 2	Mean functional connectivity Male baseline (Z score)	Mean functional connectivity Female baseline (Z score)
Amygdala Left	Substantia Nigra Left	1,311	3,452
Amygdala Left	Globus Pallidum Left	2,148	1,805
Amygdala Right	Parahippocampal Cortex Right	1,223	1,021
Amygdala Right	Substantia Nigra Right	0,845	1,507
Amygdala Right	Globus Pallidum Right	0,732	-0,067
AnteriorSigmoides Gyrus Left	Orbitofrontal Gyrus Left	1,446	1,935
AnteriorSigmoides Gyrus Left	PreCruciate Gyrus Left	0,622	1,501
AnteriorSigmoides Gyrus Left	PostCruciate Gyrus Left	0,887	1,685
AnteriorSigmoides Gyrus Left	Posterior Sygmoideus Gyrus Left	0,372	0,703
AnteriorSigmoides Gyrus Right	Cingulate Cortex Right	1,019	0,960
AnteriorSigmoides Gyrus Right	Orbital Gyrus Right	0,585	-0,354
AnteriorSigmoides Gyrus Right	Orbitofrontal Gyrus Right	1,163	1,868
AnteriorSigmoides Gyrus Right	Caudate Right	1,276	1,075
AnteriorSigmoides Gyrus Right	PreCruciate Gyrus Right	1,159	1,125
AnteriorSigmoides Gyrus Right	Putamen Right	1,245	0,960
AnteriorSigmoides Gyrus Right	Claustrocortex(Insula) Right	1,213	1,599
AnteriorSigmoides Gyrus Right	PostCruciate Gyrus Right	1,360	1,512
AnteriorSigmoides Gyrus Right	Posterior Sygmoideus Gyrus Right	1,141	0,650
AnteriorSigmoides Gyrus Right	Sylvian Gyrus Right	1,070	0,855
Bed Nucleus of Stria Terminalis Left	Lateral Septal Nucleus Left	1,017	1,913
Bed Nucleus of Stria Terminalis Left	Medial Septal Nucleus Left	1,292	1,638
Bed Nucleus of Stria Terminalis Left	Septum Left	1,054	1,776
Bed Nucleus of Stria Terminalis Left	Preoptic Hypothalamic Area Left	2,034	2,103
Bed Nucleus of Stria Terminalis Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1,773	2,092
Bed Nucleus of Stria Terminalis Left	Caudate Left	0,523	1,668
Bed Nucleus of Stria Terminalis Left	Globus Pallidum Left	1,194	0,931
Bed Nucleus of Stria Terminalis Left	Putamen Left	0,329	0,977
Bed Nucleus of Stria Terminalis Left	PostCruciate Gyrus Left	0,265	1,088
Bed Nucleus of Stria Terminalis Left	SubFornical Organ Right	1,246	1,844
Bed Nucleus of Stria Terminalis Left	Bed Nucleus of Stria Terminalis Right	1,285	1,735
Bed Nucleus of Stria Terminalis Left	Lateral Septal Nucleus Right	0,629	1,532
Bed Nucleus of Stria Terminalis Left	Septum Right	0,525	1,376
Bed Nucleus of Stria Terminalis Left	Preoptic Hypothalamic Area Right	1,542	1,735
Bed Nucleus of Stria Terminalis Right	Lateral Septal Nucleus Right	1,154	1,660
Bed Nucleus of Stria Terminalis Right	Medial Septal Nucleus Right	1,414	1,780
Bed Nucleus of Stria Terminalis Right	Septum Right	0,319	1,519
Bed Nucleus of Stria Terminalis Right	Preoptic Hypothalamic Area Right	1,955	1,896
Bed Nucleus of Stria Terminalis Right	Caudate Right	-0,261	1,093
Bed Nucleus of Stria Terminalis Right	Globus Pallidum Right	0,327	1,601
Bed Nucleus of Stria Terminalis Right	Putamen Right	-0,336	1,525
Caudate Left	Globus Pallidum Left	1,302	0,969
Caudate Left	Putamen Left	1,533	2,379
Caudate Left	Claustrocortex(Insula) Left	1,290	0,011
Caudate Left	PostCruciate Gyrus Left	0,753	0,528
Caudate Left	SubFornical Organ Right	-0,954	0,930
Caudate Left	Bed Nucleus of Stria Terminalis Right	-0,289	0,981
Caudate Left	Septum Right	1,279	0,922
Caudate Left	Preoptic Hypothalamic Area Right	0,543	1,115
Caudate Left	Caudate Right	1,047	0,867
Caudate Right	Globus Pallidum Right	0,759	1,362
Caudate Right	PreCruciate Gyrus Right	0,821	0,779
Caudate Right	Putamen Right	1,591	2,012
Caudate Right	Claustrocortex(Insula) Right	1,075	1,534
Caudate Right	PostCruciate Gyrus Right	1,159	1,515
Caudate Right	Posterior Sygmoideus Gyrus Right	0,868	1,505
Caudate Right	Suprasylvian Gyrus Right	0,306	0,854
Caudate Right	Sylvian Gyrus Right	0,759	1,408
Cingulate Cortex Left	Orbitofrontal Gyrus Left	1,292	0,549
Cingulate Cortex Left	Hippocampus Left	0,163	1,108
Cingulate Cortex Left	Caudate Left	1,008	1,235
Cingulate Cortex Left	PreCruciate Gyrus Left	1,605	2,187
Cingulate Cortex Left	Putamen Left	0,853	1,227
Cingulate Cortex Left	Thalamus Left	0,705	0,804
Cingulate Cortex Left	Lateral Gyrus Left	0,225	1,482
Cingulate Cortex Left	PostCruciate Gyrus Left	1,231	1,063
Cingulate Cortex Left	Posterior Sygmoideus Gyrus Left	0,594	0,885
Cingulate Cortex Left	Suprasylvian Gyrus Left	0,763	0,684
Cingulate Cortex Left	Ectolateralis Gyrus Left	-0,157	1,349
Cingulate Cortex Left	Entolateral Gyrus Left	1,118	0,943
Cingulate Cortex Left	Bed Nucleus of Stria Terminalis Right	-0,209	0,266
Cingulate Cortex Left	Medial Septal Nucleus Right	-0,468	-0,210
Cingulate Cortex Left	Pineal Gland Right	0,595	0,551
Cingulate Cortex Left	Septum Right	1,042	1,050
Cingulate Cortex Left	Preoptic Hypothalamic Area Right	0,636	0,395
Cingulate Cortex Left	AnteriorSigmoides Gyrus Right	1,054	0,830
Cingulate Cortex Left	Cingulate Cortex Right	1,249	2,113
Cingulate Cortex Left	Orbitofrontal Gyrus Right	1,107	1,375
Cingulate Cortex Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	0,845	0,728
Cingulate Cortex Left	Caudate Right	1,055	1,130
Cingulate Cortex Left	PreCruciate Gyrus Right	1,376	1,479
Cingulate Cortex Left	Putamen Right	0,917	0,268
Cingulate Cortex Left	Claustrocortex(Insula) Right	0,988	1,079
Cingulate Cortex Left	Lateral Gyrus Right	0,592	0,787
Cingulate Cortex Left	PostCruciate Gyrus Right	1,013	1,285
Cingulate Cortex Left	Suprasylvian Gyrus Right	0,754	0,628
Cingulate Cortex Right	Orbitofrontal Gyrus Right	1,230	1,517
Cingulate Cortex Right	Hippocampus Right	1,173	1,344
Cingulate Cortex Right	Caudate Right	1,049	1,066
Cingulate Cortex Right	PreCruciate Gyrus Right	1,385	1,673
Cingulate Cortex Right	Putamen Right	0,949	0,301
Cingulate Cortex Right	Thalamus Right	0,810	0,863
Cingulate Cortex Right	Claustrocortex(Insula) Right	1,150	1,390
Cingulate Cortex Right	Lateral Gyrus Right	0,955	1,556
Cingulate Cortex Right	PostCruciate Gyrus Right	1,244	1,282
Cingulate Cortex Right	Posterior Sygmoideus Gyrus Right	1,112	1,288
Cingulate Cortex Right	Suprasylvian Gyrus Right	1,048	1,272
Cingulate Cortex Right	Sylvian Gyrus Right	1,048	1,015
Cingulate Cortex Right	Ectolateralis Gyrus Right	0,939	1,796

Claustrocortex(Insula) Left	Sylvian Gyrus Left	0,944	0,346
Claustrocortex(Insula) Right	Sylvian Gyrus Right	1,381	1,561
Ectolateralis Gyrus Left	Entolateral Gyrus Left	-0,267	1,271
Ectolateralis Gyrus Left	Occipital Lobe Left	2,657	1,682
Ectolateralis Gyrus Left	Lateral Gyrus Right	-0,085	0,948
Geniculate Nucleus Left	Thalamus Left	1,797	2,872
Geniculate Nucleus Left	Midbrain Left	0,203	1,025
Geniculate Nucleus Right	Thalamus Right	1,801	0,225
Globus Pallidum Left	Putamen Left	0,621	1,291
Globus Pallidum Right	Putamen Right	0,485	1,770
Gyrus Rectus Left	Olfactory Bulb Left	2,989	2,483
Gyrus Rectus Left	Gyrus Rectus Right	2,883	2,094
Gyrus Rectus Right	Olfactory Bulb Right	2,231	2,710
Hippocampus Left	Parahippocampal Cortex Left	-0,225	1,241
Hippocampus Left	Geniculate Nucleus Left	1,009	2,304
Hippocampus Left	Thalamus Left	0,455	2,052
Hippocampus Left	Lateral Gyrus Left	0,524	1,795
Hippocampus Left	Suprasylvian Gyrus Left	0,572	2,436
Hippocampus Left	Ectolateralis Gyrus Left	0,528	1,865
Hippocampus Left	Midbrain Left	-0,702	1,017
Hippocampus Left	Pineal Gland Right	-0,915	0,854
Hippocampus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	0,175	1,284
Hippocampus Left	Periaqueductal Grey Substance Right	-1,578	-0,655
Hippocampus Right	Parahippocampal Cortex Right	0,858	1,224
Hippocampus Right	Geniculate Nucleus Right	1,061	0,727
Hippocampus Right	Periaqueductal Grey Substance Right	1,602	0,235
Hippocampus Right	Thalamus Right	0,940	0,796
Hippocampus Right	Suprasylvian Gyrus Right	1,143	1,893
Lateral Gyrus Left	Suprasylvian Gyrus Left	0,877	1,772
Lateral Gyrus Left	Ectolateralis Gyrus Left	2,332	2,461
Lateral Gyrus Left	Entolateral Gyrus Left	0,144	2,306
Lateral Gyrus Left	Occipital Lobe Left	2,382	1,454
Lateral Gyrus Left	Pineal Gland Right	1,109	0,802
Lateral Gyrus Left	Lateral Gyrus Right	0,158	0,756
Lateral Gyrus Right	Suprasylvian Gyrus Right	1,306	1,849
Lateral Septal Nucleus Left	Medial Septal Nucleus Left	1,060	2,146
Lateral Septal Nucleus Left	Septum Left	-0,136	0,654
Lateral Septal Nucleus Left	Preoptic Hypothalamic Area Left	1,236	1,554
Lateral Septal Nucleus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	2,579	2,331
Lateral Septal Nucleus Left	Substantia Nigra Left	1,295	0,142
Lateral Septal Nucleus Left	Globus Pallidum Left	-0,012	1,548
Lateral Septal Nucleus Left	Medial Mamillary Nucleus Right	1,400	0,503
Lateral Septal Nucleus Left	SubFornical Organ Right	2,200	1,703
Lateral Septal Nucleus Left	Bed Nucleus of Stria Terminalis Right	1,220	1,082
Lateral Septal Nucleus Left	Lateral Septal Nucleus Right	2,345	1,966
Lateral Septal Nucleus Left	Preoptic Hypothalamic Area Right	0,751	0,933
Lateral Septal Nucleus Right	Medial Septal Nucleus Right	1,650	1,786
Lateral Septal Nucleus Right	Preoptic Hypothalamic Area Right	0,654	1,188
Lateral Septal Nucleus Right	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	-0,590	-0,473
Lateral Septal Nucleus Right	Substantia Nigra Right	0,394	1,001
Lateral Septal Nucleus Right	Globus Pallidum Right	-0,520	0,729
Medial Mamillary Nucleus Left	Lateral Septal Nucleus Left	1,344	1,154
Medial Mamillary Nucleus Left	Medial Septal Nucleus Left	0,295	1,242
Medial Mamillary Nucleus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	0,756	0,803
Medial Mamillary Nucleus Left	Substantia Nigra Left	1,705	1,286
Medial Mamillary Nucleus Left	Medial Mamillary Nucleus Right	2,064	2,104
Medial Mamillary Nucleus Right	Lateral Septal Nucleus Right	1,502	1,414
Medial Mamillary Nucleus Right	Substantia Nigra Right	1,079	0,993
Medial Mamillary Nucleus Right	Pituitary Gland Right	1,235	1,002
Medial Septal Nucleus Left	Preoptic Hypothalamic Area Left	1,645	1,393
Medial Septal Nucleus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1,009	1,581
Medial Septal Nucleus Left	Substantia Nigra Left	0,551	1,268
Medial Septal Nucleus Left	Caudate Left	0,253	0,218
Medial Septal Nucleus Left	Globus Pallidum Left	1,230	2,072
Medial Septal Nucleus Left	SubFornical Organ Right	0,540	0,456
Medial Septal Nucleus Left	Lateral Septal Nucleus Right	0,646	0,673
Medial Septal Nucleus Left	Medial Septal Nucleus Right	-0,039	0,861
Medial Septal Nucleus Left	Preoptic Hypothalamic Area Right	-0,213	0,185
Medial Septal Nucleus Right	Preoptic Hypothalamic Area Right	0,210	1,479
Medial Septal Nucleus Right	Substantia Nigra Right	-0,246	-0,336
Medial Septal Nucleus Right	Caudate Right	-1,551	0,448
Medial Septal Nucleus Right	Globus Pallidum Right	-0,243	1,625
Medial Septal Nucleus Right	Putamen Right	-1,611	0,781
Midbrain Left	Pineal Gland Right	1,446	1,172
Midbrain Left	Pons Right	1,269	-0,536
Midbrain Left	Hippocampus Right	1,305	0,155
Midbrain Left	Periaqueductal Grey Substance Right	1,311	-1,194
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Globus Pallidum Left	0,679	1,534
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Putamen Left	-0,790	0,040
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	SubFornical Organ Right	1,741	1,597
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Bed Nucleus of Stria Terminalis Right	0,689	1,267
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Lateral Septal Nucleus Right	1,639	1,392
Olfactory Bulb Left	Gyrus Rectus Right	2,658	2,390
Orbital Gyrus Left	Orbitofrontal Gyrus Left	0,935	0,824
Orbital Gyrus Left	Precruciate Gyrus Left	0,657	-0,021
Orbital Gyrus Left	Gyrus Rectus Left	2,899	0,806
Orbital Gyrus Left	Claustrocortex(Insula) Left	0,824	2,944
Orbital Gyrus Right	Orbitofrontal Gyrus Right	0,362	-0,001
Orbital Gyrus Right	Precruciate Gyrus Right	1,012	1,563
Orbital Gyrus Right	Gyrus Rectus Right	0,967	1,447
Orbital Gyrus Right	Olfactory Bulb Right	0,333	0,547
Orbital Gyrus Right	Claustrocortex(Insula) Right	0,168	-0,086
Orbitofrontal Gyrus Left	Precruciate Gyrus Left	0,680	1,103
Orbitofrontal Gyrus Left	Claustrocortex(Insula) Left	1,596	2,134
Orbitofrontal Gyrus Right	Precruciate Gyrus Right	1,236	1,380
Orbitofrontal Gyrus Right	Claustrocortex(Insula) Right	1,170	0,891
Parahippocampal Cortex Left	Thalamus Left	0,160	1,725
Parahippocampal Cortex Left	Suprasylvian Gyrus Left	0,071	1,348
Parahippocampal Cortex Left	Sylvian Gyrus Left	1,144	1,953
Parahippocampal Cortex Left	Ectolateralis Gyrus Left	-1,481	1,166
Parahippocampal Cortex Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	1,831	2,215

Parahippocampal Cortex Right	Substantia Nigra Right	0,353	-0,863
Parahippocampal Cortex Right	Suprasylvian Gyrus Right	1,003	1,346
Parahippocampal Cortex Right	Sylvian Gyrus Right	1,128	1,667
Periaqueductal Grey Substance Left	Midbrain Left	0,484	-1,438
Periaqueductal Grey Substance Left	Pons Right	1,159	0,518
Periaqueductal Grey Substance Left	Periaqueductal Grey Substance Right	1,084	2,084
Pineal Gland Left	Pons Left	-0,010	0,497
Pineal Gland Left	Cingulate Cortex Left	-0,045	0,549
Pineal Gland Left	Hippocampus Left	-0,236	1,357
Pineal Gland Left	Geniculate Nucleus Left	0,412	1,156
Pineal Gland Left	Periaqueductal Grey Substance Left	0,092	-0,240
Pineal Gland Left	Thalamus Left	0,542	0,987
Pineal Gland Left	Lateral Gyrus Left	1,494	1,237
Pineal Gland Left	Entolateral Gyrus Left	-0,625	1,246
Pineal Gland Left	Midbrain Left	0,762	1,728
Pineal Gland Left	Pineal Gland Right	1,881	2,681
Pineal Gland Left	Hippocampus Right	0,905	0,545
Pineal Gland Left	Periaqueductal Grey Substance Right	1,296	-0,870
Pineal Gland Right	Hippocampus Right	1,176	0,669
Pineal Gland Right	Periaqueductal Grey Substance Right	1,504	-0,585
Pituitary Gland Left	Pituitary Gland Right	2,314	2,184
Pons Left	Periaqueductal Grey Substance Left	1,573	1,460
Pons Left	Midbrain Left	0,343	0,017
Pons Left	Pons Right	1,044	1,526
Pons Left	Periaqueductal Grey Substance Right	0,817	1,364
Pons Right	Periaqueductal Grey Substance Right	1,849	0,564
PostCruciate Gyrus Left	Posterior Sygmoideus Gyrus Left	1,150	1,807
PostCruciate Gyrus Left	Septum Right	0,993	0,885
PostCruciate Gyrus Left	Preoptic Hypothalamic Area Right	0,376	0,876
PostCruciate Gyrus Right	Posterior Sygmoideus Gyrus Right	1,255	1,142
PostCruciate Gyrus Right	Sylvian Gyrus Right	1,030	0,823
Posterior Sygmoideus Gyrus Left	Sylvian Gyrus Left	0,864	0,986
Posterior Sygmoideus Gyrus Left	Posterior Sygmoideus Gyrus Right	0,766	0,446
Posterior Sygmoideus Gyrus Right	Sylvian Gyrus Right	1,355	1,173
Posterior Sylvian Gyrus Left	Hippocampus Left	1,009	0,836
Posterior Sylvian Gyrus Left	Parahippocampal Cortex Left	-0,483	-0,249
Posterior Sylvian Gyrus Left	Suprasylvian Gyrus Left	0,798	1,657
Posterior Sylvian Gyrus Left	Ectolateralis Gyrus Left	0,437	0,279
Posterior Sylvian Gyrus Right	Temporal Lobe Right	1,423	2,239
Posterior Sylvian Gyrus Right	Suprasylvian Gyrus Right	1,078	1,773
Precruciate Gyrus Left	Claustrocortex(Insula) Left	0,981	0,668
Precruciate Gyrus Left	Precruciate Gyrus Right	1,373	1,764
Precruciate Gyrus Right	Gyrus Rectus Right	0,480	1,524
Precruciate Gyrus Right	Claustrocortex(Insula) Right	1,020	0,722
Precruciate Gyrus Right	PostCruciate Gyrus Right	1,044	0,376
Preoptic Hypothalamic Area Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1,691	1,901
Preoptic Hypothalamic Area Left	Caudate Left	0,298	1,499
Preoptic Hypothalamic Area Left	Globus Pallidum Left	0,627	1,494
Preoptic Hypothalamic Area Left	Putamen Left	-0,081	1,118
Preoptic Hypothalamic Area Left	PostCruciate Gyrus Left	0,141	0,619
Preoptic Hypothalamic Area Left	Medial Mamillary Nucleus Right	-0,011	0,471
Preoptic Hypothalamic Area Left	SubFornical Organ Right	1,523	1,668
Preoptic Hypothalamic Area Left	Bed Nucleus of Stria Terminalis Right	0,845	1,355
Preoptic Hypothalamic Area Left	Lateral Septal Nucleus Right	1,056	1,406
Preoptic Hypothalamic Area Left	Medial Septal Nucleus Right	0,426	1,718
Preoptic Hypothalamic Area Left	Septum Right	0,079	0,627
Preoptic Hypothalamic Area Left	Preoptic Hypothalamic Area Right	1,662	1,834
Preoptic Hypothalamic Area Left	Caudate Right	-0,121	0,465
Preoptic Hypothalamic Area Left	Globus Pallidum Right	0,046	0,830
Preoptic Hypothalamic Area Right	Cingulate Cortex Right	-0,149	0,599
Preoptic Hypothalamic Area Right	Substantia Nigra Right	-0,064	0,370
Preoptic Hypothalamic Area Right	Caudate Right	0,525	1,290
Preoptic Hypothalamic Area Right	Globus Pallidum Right	0,497	1,647
Preoptic Hypothalamic Area Right	Putamen Right	0,405	1,669
Preoptic Hypothalamic Area Right	PostCruciate Gyrus Right	0,035	1,466
Putamen Left	Claustrocortex(Insula) Left	1,313	1,129
Putamen Left	PostCruciate Gyrus Left	0,294	-0,109
Putamen Left	Bed Nucleus of Stria Terminalis Right	-0,539	0,429
Putamen Left	Septum Right	1,212	0,013
Putamen Right	Claustrocortex(Insula) Right	0,999	1,157
Putamen Right	PostCruciate Gyrus Right	1,025	0,706
Putamen Right	Sylvian Gyrus Right	0,692	0,431
Septum Left	Preoptic Hypothalamic Area Left	1,030	1,526
Septum Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	0,172	1,259
Septum Left	Caudate Left	1,230	1,777
Septum Left	Globus Pallidum Left	0,554	0,156
Septum Left	Putamen Left	1,126	1,397
Septum Left	PostCruciate Gyrus Left	0,750	1,134
Septum Left	SubFornical Organ Right	0,366	1,492
Septum Left	Bed Nucleus of Stria Terminalis Right	1,460	1,609
Septum Left	Lateral Septal Nucleus Right	-0,217	1,235
Septum Left	Medial Septal Nucleus Right	-0,383	0,888
Septum Left	Septum Right	1,631	2,003
Septum Left	Preoptic Hypothalamic Area Right	1,909	1,622
Septum Left	Caudate Right	1,054	1,662
Septum Left	Globus Pallidum Right	0,162	0,609
Septum Left	Putamen Right	0,953	1,309
Septum Right	Preoptic Hypothalamic Area Right	1,163	1,236
Septum Right	Caudate Right	1,320	1,918
Septum Right	Globus Pallidum Right	0,165	0,551
Septum Right	Putamen Right	1,248	1,385
SubFornical Organ Left	Bed Nucleus of Stria Terminalis Left	1,501	1,934
SubFornical Organ Left	Lateral Septal Nucleus Left	2,153	2,226
SubFornical Organ Left	Medial Septal Nucleus Left	1,178	1,707
SubFornical Organ Left	Septum Left	-0,013	1,324
SubFornical Organ Left	Preoptic Hypothalamic Area Left	1,836	2,001
SubFornical Organ Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	2,280	2,176
SubFornical Organ Left	Caudate Left	-0,668	1,164
SubFornical Organ Left	Globus Pallidum Left	0,049	1,127
SubFornical Organ Left	Medial Mamillary Nucleus Right	0,813	0,308
SubFornical Organ Left	SubFornical Organ Right	2,676	2,205

SubFornical Organ Left	Bed Nucleus of Stria Terminalis Right	1,896	1,799
SubFornical Organ Left	Lateral Septal Nucleus Right	2,306	1,928
SubFornical Organ Left	Medial Septal Nucleus Right	1,501	1,644
SubFornical Organ Left	Septum Right	-0,558	0,896
SubFornical Organ Left	Preoptic Hypothalamic Area Right	1,509	1,775
SubFornical Organ Left	Globus Pallidum Right	-0,005	0,713
SubFornical Organ Right	Bed Nucleus of Stria Terminalis Right	2,571	2,014
SubFornical Organ Right	Lateral Septal Nucleus Right	2,459	2,110
SubFornical Organ Right	Medial Septal Nucleus Right	1,842	1,882
SubFornical Organ Right	Septum Right	-0,581	1,120
SubFornical Organ Right	Preoptic Hypothalamic Area Right	1,568	1,854
SubFornical Organ Right	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	-0,588	-0,140
SubFornical Organ Right	Globus Pallidum Right	-0,135	1,102
Substantia Nigra Left	Globus Pallidum Left	0,643	1,423
Substantia Nigra Right	Globus Pallidum Right	0,262	-0,682
Suprasylvian Gyrus Left	Sylvian Gyrus Left	0,452	1,061
Suprasylvian Gyrus Left	Ectolateralis Gyrus Left	1,257	1,904
Suprasylvian Gyrus Left	Occipital Lobe Left	1,074	0,944
Suprasylvian Gyrus Right	Sylvian Gyrus Right	1,099	1,058
Temporal Lobe Left	Hippocampus Left	-0,132	1,036
Temporal Lobe Left	Parahippocampal Cortex Left	1,329	1,377
Temporal Lobe Left	Suprasylvian Gyrus Left	0,478	1,050
Temporal Lobe Left	Sylvian Gyrus Left	1,117	1,016
Temporal Lobe Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	1,324	1,307
Temporal Lobe Right	Hippocampus Right	0,866	1,823
Temporal Lobe Right	Parahippocampal Cortex Right	0,647	1,359
Temporal Lobe Right	Suprasylvian Gyrus Right	0,977	1,320
Temporal Lobe Right	Sylvian Gyrus Right	1,124	1,638
Thalamus Left	Midbrain Left	0,631	0,983
Thalamus Left	Pineal Gland Right	0,591	0,787
Thalamus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	0,632	1,585
Thalamus Left	Thalamus Right	1,512	-0,166

Brain Region 1	Brain Region 2	Mean functional connectivity Male castrated (Z score)	Mean functional connectivity Female castrated (Z score)
Amygdala Left	Parahippocampal Cortex Left	1.151	0.229
Amygdala Left	Substantia Nigra Left	1.986	1.828
Amygdala Left	Globus Pallidum Left	1.519	1.450
Amygdala Right	Parahippocampal Cortex Right	0.955	1.265
Amygdala Right	Substantia Nigra Right	2.025	0.577
Amygdala Right	Globus Pallidum Right	1.151	-0.136
AnteriorSigmoides Gyrus Left	Orbitofrontal Gyrus Left	0.899	2.907
AnteriorSigmoides Gyrus Left	Precruciate Gyrus Left	1.270	1.522
AnteriorSigmoides Gyrus Left	PostCruciate Gyrus Left	1.643	0.513
AnteriorSigmoides Gyrus Right	Cingulate Cortex Right	1.106	0.836
AnteriorSigmoides Gyrus Right	Orbital Gyrus Right	-0.446	0.401
AnteriorSigmoides Gyrus Right	Orbitofrontal Gyrus Right	1.382	1.759
AnteriorSigmoides Gyrus Right	Precruciate Gyrus Right	1.852	1.174
AnteriorSigmoides Gyrus Right	Putamen Right	0.011	0.213
AnteriorSigmoides Gyrus Right	Claustrocortex(Insula) Right	-0.775	1.323
AnteriorSigmoides Gyrus Right	PostCruciate Gyrus Right	1.712	1.891
AnteriorSigmoides Gyrus Right	Posterior Sigmoides Gyrus Right	1.060	1.902
AnteriorSigmoides Gyrus Right	Sylvian Gyrus Right	-0.290	0.801
Bed Nucleus of Stria Terminalis Left	Lateral Septal Nucleus Left	1.548	1.599
Bed Nucleus of Stria Terminalis Left	Medial Septal Nucleus Left	1.510	1.430
Bed Nucleus of Stria Terminalis Left	Septum Left	1.871	2.347
Bed Nucleus of Stria Terminalis Left	Preoptic Hypothalamic Area Left	1.725	2.130
Bed Nucleus of Stria Terminalis Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1.895	2.243
Bed Nucleus of Stria Terminalis Left	Caudate Left	1.023	1.906
Bed Nucleus of Stria Terminalis Left	Globus Pallidum Left	0.672	1.561
Bed Nucleus of Stria Terminalis Left	Putamen Left	0.628	1.166
Bed Nucleus of Stria Terminalis Left	SubFormical Organ Right	1.160	1.253
Bed Nucleus of Stria Terminalis Left	Bed Nucleus of Stria Terminalis Right	0.674	1.683
Bed Nucleus of Stria Terminalis Left	Lateral Septal Nucleus Right	0.815	0.452
Bed Nucleus of Stria Terminalis Left	Septum Right	0.829	1.310
Bed Nucleus of Stria Terminalis Left	Preoptic Hypothalamic Area Right	1.121	1.786
Bed Nucleus of Stria Terminalis Right	Lateral Septal Nucleus Right	1.851	1.622
Bed Nucleus of Stria Terminalis Right	Medial Septal Nucleus Right	1.735	2.407
Bed Nucleus of Stria Terminalis Right	Septum Right	0.480	1.670
Bed Nucleus of Stria Terminalis Right	Preoptic Hypothalamic Area Right	1.934	2.301
Bed Nucleus of Stria Terminalis Right	Caudate Right	0.604	0.704
Bed Nucleus of Stria Terminalis Right	Globus Pallidum Right	0.329	1.061
Bed Nucleus of Stria Terminalis Right	Putamen Right	-0.239	0.583
Caudate Left	Globus Pallidum Left	1.131	1.539
Caudate Left	Putamen Left	1.599	1.993
Caudate Left	Thalamus Left	0.212	0.142
Caudate Left	Claustrocortex(Insula) Left	1.502	0.480
Caudate Left	PostCruciate Gyrus Left	1.755	1.303
Caudate Left	Bed Nucleus of Stria Terminalis Right	1.222	0.843
Caudate Left	Septum Right	0.347	0.734
Caudate Left	Preoptic Hypothalamic Area Right	1.453	1.063
Caudate Left	Cingulate Cortex Right	0.640	0.188
Caudate Left	Caudate Right	1.026	0.352
Caudate Right	Globus Pallidum Right	1.365	2.068
Caudate Right	Putamen Right	2.242	2.444
Caudate Right	Claustrocortex(Insula) Right	0.457	2.147
Caudate Right	PostCruciate Gyrus Right	1.425	0.287
Caudate Right	Posterior Sigmoides Gyrus Right	0.992	1.625
Caudate Right	Sylvian Gyrus Right	1.023	0.390
Cingulate Cortex Left	Orbital Gyrus Left	1.032	-0.108
Cingulate Cortex Left	Orbitofrontal Gyrus Left	0.824	-0.392
Cingulate Cortex Left	Hippocampus Left	1.069	0.263
Cingulate Cortex Left	Caudate Left	0.565	0.581
Cingulate Cortex Left	Precruciate Gyrus Left	1.347	1.104
Cingulate Cortex Left	Putamen Left	0.556	0.203
Cingulate Cortex Left	Gyrus Rectus Left	0.756	1.257
Cingulate Cortex Left	Geniculate Nucleus Left	0.038	-1.093
Cingulate Cortex Left	Thalamus Left	0.154	-0.522
Cingulate Cortex Left	Claustrocortex(Insula) Left	0.779	0.414
Cingulate Cortex Left	Lateral Gyrus Left	0.749	-0.309
Cingulate Cortex Left	PostCruciate Gyrus Left	1.210	0.965
Cingulate Cortex Left	Posterior Sigmoides Gyrus Left	1.402	-0.454
Cingulate Cortex Left	Suprasylvian Gyrus Left	0.887	0.019
Cingulate Cortex Left	Sylvian Gyrus Left	0.037	-0.727
Cingulate Cortex Left	Ectolateralis Gyrus Left	0.750	-0.370
Cingulate Cortex Left	Entolateral Gyrus Left	1.809	0.731
Cingulate Cortex Left	Midbrain Left	0.413	0.200
Cingulate Cortex Left	Septum Right	0.624	0.682
Cingulate Cortex Left	AnteriorSigmoides Gyrus Right	-0.213	1.076
Cingulate Cortex Left	Cingulate Cortex Right	1.854	1.689
Cingulate Cortex Left	Orbital Gyrus Right	0.773	-0.117
Cingulate Cortex Left	Orbitofrontal Gyrus Right	1.258	1.006
Cingulate Cortex Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	0.648	0.057
Cingulate Cortex Left	Caudate Right	0.125	0.705
Cingulate Cortex Left	Precruciate Gyrus Right	0.107	1.094
Cingulate Cortex Left	Putamen Right	0.439	-0.015
Cingulate Cortex Left	Claustrocortex(Insula) Right	0.601	1.431
Cingulate Cortex Left	Lateral Gyrus Right	0.046	0.120
Cingulate Cortex Left	PostCruciate Gyrus Right	-0.408	1.267
Cingulate Cortex Left	Posterior Sigmoides Gyrus Right	-0.308	0.190
Cingulate Cortex Left	Sylvian Gyrus Right	0.523	0.414
Cingulate Cortex Left	Entolateral Gyrus Right	0.612	0.800
Cingulate Cortex Right	Orbital Gyrus Right	0.250	0.954
Cingulate Cortex Right	Orbitofrontal Gyrus Right	1.485	0.833
Cingulate Cortex Right	Hippocampus Right	0.643	0.991
Cingulate Cortex Right	Caudate Right	0.727	0.600
Cingulate Cortex Right	Precruciate Gyrus Right	1.329	1.380
Cingulate Cortex Right	Putamen Right	0.640	-0.206
Cingulate Cortex Right	Periaqueductal Grey Substance Right	0.440	0.908
Cingulate Cortex Right	Claustrocortex(Insula) Right	0.000	1.130
Cingulate Cortex Right	Lateral Gyrus Right	1.330	0.945
Cingulate Cortex Right	PostCruciate Gyrus Right	0.888	1.840
Cingulate Cortex Right	Posterior Sigmoides Gyrus Right	0.831	0.654
Cingulate Cortex Right	Suprasylvian Gyrus Right	1.086	0.628
Cingulate Cortex Right	Sylvian Gyrus Right	-0.079	1.163
Cingulate Cortex Right	Ectolateralis Gyrus Right	1.158	0.835
Cingulate Cortex Right	Entolateral Gyrus Right	1.442	1.453
Cingulate Cortex Right	Occipital Lobe Right	0.460	0.954
Claustrocortex(Insula) Left	Sylvian Gyrus Left	1.339	0.174
Claustrocortex(Insula) Left	Gyrus Rectus Right	0.306	-1.244
Claustrocortex(Insula) Right	PostCruciate Gyrus Right	-1.257	0.311
Claustrocortex(Insula) Right	Posterior Sigmoides Gyrus Right	-1.668	0.485
Claustrocortex(Insula) Right	Sylvian Gyrus Right	1.262	0.109
Ectolateralis Gyrus Left	Entolateral Gyrus Left	1.437	1.544
Ectolateralis Gyrus Left	Occipital Lobe Left	1.144	1.391
Ectolateralis Gyrus Right	Entolateral Gyrus Right	2.633	1.226
Ectolateralis Gyrus Right	Occipital Lobe Right	1.282	1.255
Entolateral Gyrus Left	Entolateral Gyrus Right	1.902	1.293
Entolateral Gyrus Right	Occipital Lobe Right	0.894	1.183

Geniculate Nucleus Left	Thalamus Left	1,841	2,128
Geniculate Nucleus Right	Thalamus Right	2,113	1,617
Globus Pallidum Left	Putamen Left	1,808	1,553
Globus Pallidum Right	Putamen Right	2,096	2,359
Gyrus Rectus Left	Olfactory Bulb Left	2,738	1,484
Gyrus Rectus Left	Gyrus Rectus Right	2,850	1,757
Gyrus Rectus Left	Olfactory Bulb Right	2,339	-0,370
Gyrus Rectus Right	Olfactory Bulb Right	2,348	1,383
Hippocampus Left	Parahippocampal Cortex Left	1,608	1,460
Hippocampus Left	Geniculate Nucleus Left	1,324	-0,135
Hippocampus Left	Lateral Gyrus Left	1,104	0,134
Hippocampus Left	Suprasylvian Gyrus Left	1,962	1,211
Hippocampus Left	Ectolateralis Gyrus Left	1,157	-0,940
Hippocampus Left	Midbrain Left	1,379	1,457
Hippocampus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	1,933	1,351
Hippocampus Right	Parahippocampal Cortex Right	1,447	1,140
Hippocampus Right	Geniculate Nucleus Right	0,029	0,707
Hippocampus Right	Periaqueductal Grey Substance Right	1,265	1,459
Hippocampus Right	Thalamus Right	0,760	1,004
Hippocampus Right	Suprasylvian Gyrus Right	0,516	0,699
Hippocampus Right	Ectolateralis Gyrus Right	0,131	1,343
Hippocampus Right	Midbrain Right	1,478	1,477
Lateral Gyrus Left	Suprasylvian Gyrus Left	1,506	0,293
Lateral Gyrus Left	Ectolateralis Gyrus Left	1,968	2,743
Lateral Gyrus Left	Entolateral Gyrus Left	1,976	1,816
Lateral Gyrus Left	Occipital Lobe Left	-0,025	1,326
Lateral Gyrus Left	Lateral Gyrus Right	1,392	0,817
Lateral Gyrus Right	Suprasylvian Gyrus Right	1,392	0,833
Lateral Gyrus Right	Ectolateralis Gyrus Right	2,711	1,810
Lateral Gyrus Right	Entolateral Gyrus Right	2,844	1,974
Lateral Gyrus Right	Occipital Lobe Right	1,443	1,373
Lateral Septal Nucleus Left	Medial Septal Nucleus Left	2,009	1,313
Lateral Septal Nucleus Left	Preoptic Hypothalamic Area Left	1,800	0,993
Lateral Septal Nucleus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	2,010	2,145
Lateral Septal Nucleus Left	Substantia Nigra Left	0,779	0,129
Lateral Septal Nucleus Left	Globus Pallidum Left	1,221	0,695
Lateral Septal Nucleus Left	Medial Mamillary Nucleus Right	-0,127	0,451
Lateral Septal Nucleus Left	SubFornical Organ Right	1,665	0,960
Lateral Septal Nucleus Left	Bed Nucleus of Stria Terminalis Right	0,944	0,544
Lateral Septal Nucleus Left	Lateral Septal Nucleus Right	1,643	1,132
Lateral Septal Nucleus Left	Preoptic Hypothalamic Area Right	1,539	0,595
Lateral Septal Nucleus Right	Medial Septal Nucleus Right	1,894	1,916
Lateral Septal Nucleus Right	Preoptic Hypothalamic Area Right	1,562	1,518
Lateral Septal Nucleus Right	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	-0,105	1,216
Lateral Septal Nucleus Right	Substantia Nigra Right	0,459	0,969
Lateral Septal Nucleus Right	Globus Pallidum Right	0,268	0,047
Medial Mamillary Nucleus Left	Lateral Septal Nucleus Left	1,162	1,682
Medial Mamillary Nucleus Left	Medial Septal Nucleus Left	1,166	-0,177
Medial Mamillary Nucleus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	0,951	1,205
Medial Mamillary Nucleus Left	Substantia Nigra Left	0,959	-0,462
Medial Mamillary Nucleus Left	Globus Pallidum Left	1,350	-0,582
Medial Mamillary Nucleus Left	Medial Mamillary Nucleus Right	0,390	1,526
Medial Mamillary Nucleus Left	Lateral Septal Nucleus Right	0,575	-0,159
Medial Mamillary Nucleus Right	SubFornical Organ Right	-0,957	0,043
Medial Mamillary Nucleus Right	Bed Nucleus of Stria Terminalis Right	-1,299	-0,255
Medial Mamillary Nucleus Right	Lateral Septal Nucleus Right	0,505	0,958
Medial Mamillary Nucleus Right	Medial Septal Nucleus Right	0,237	0,239
Medial Mamillary Nucleus Right	Preoptic Hypothalamic Area Right	-0,650	0,037
Medial Mamillary Nucleus Right	Substantia Nigra Right	1,888	1,594
Medial Mamillary Nucleus Right	Pituitary Gland Right	-1,985	1,360
Medial Septal Nucleus Left	Preoptic Hypothalamic Area Left	1,904	2,000
Medial Septal Nucleus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1,736	1,643
Medial Septal Nucleus Left	Substantia Nigra Left	0,458	0,773
Medial Septal Nucleus Left	Caudate Left	1,322	1,286
Medial Septal Nucleus Left	Globus Pallidum Left	1,012	2,008
Medial Septal Nucleus Left	SubFornical Organ Right	1,807	1,322
Medial Septal Nucleus Left	Lateral Septal Nucleus Right	1,689	0,803
Medial Septal Nucleus Left	Medial Septal Nucleus Right	1,337	0,950
Medial Septal Nucleus Left	Preoptic Hypothalamic Area Right	1,589	1,488
Medial Septal Nucleus Right	Preoptic Hypothalamic Area Right	1,638	1,900
Medial Septal Nucleus Right	Substantia Nigra Right	0,585	0,110
Medial Septal Nucleus Right	Caudate Right	0,752	0,683
Medial Septal Nucleus Right	Globus Pallidum Right	1,684	1,266
Medial Septal Nucleus Right	Putamen Right	0,551	0,493
Midbrain Left	Pineal Gland Right	1,109	1,480
Midbrain Left	Pons Right	1,073	1,393
Midbrain Left	Hippocampus Right	1,091	1,672
Midbrain Left	Periaqueductal Grey Substance Right	1,924	1,486
Midbrain Left	Midbrain Right	1,588	1,531
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Substantia Nigra Left	0,742	-0,476
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Globus Pallidum Left	1,362	1,675
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Putamen Left	0,961	0,896
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	SubFornical Organ Right	1,292	0,150
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Bed Nucleus of Stria Terminalis Right	0,659	0,536
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Lateral Septal Nucleus Right	0,870	-0,285
Olfactory Bulb Left	Gyrus Rectus Right	2,892	1,154
Orbital Gyrus Left	Orbitofrontal Gyrus Left	0,668	1,946
Orbital Gyrus Left	Precruciate Gyrus Left	1,728	1,149
Orbital Gyrus Left	Gyrus Rectus Left	1,681	0,430
Orbital Gyrus Left	Olfactory Bulb Left	1,911	0,784
Orbital Gyrus Left	Claustrocortex(Insula) Left	0,264	0,971
Orbital Gyrus Left	Gyrus Rectus Right	2,002	-1,310
Orbital Gyrus Right	Precruciate Gyrus Right	1,871	1,857
Orbital Gyrus Right	Gyrus Rectus Right	1,903	1,659
Orbital Gyrus Right	Olfactory Bulb Right	1,966	0,857
Orbitofrontal Gyrus Left	Precruciate Gyrus Left	0,777	1,469
Orbitofrontal Gyrus Left	Claustrocortex(Insula) Left	0,715	2,133
Orbitofrontal Gyrus Right	Precruciate Gyrus Right	-0,246	0,911
Orbitofrontal Gyrus Right	Claustrocortex(Insula) Right	0,262	1,429
Parahippocampal Cortex Left	Substantia Nigra Left	0,741	0,925
Parahippocampal Cortex Left	Thalamus Left	1,694	0,645
Parahippocampal Cortex Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	2,155	1,731
Parahippocampal Cortex Right	Substantia Nigra Right	0,152	0,735
Parahippocampal Cortex Right	Caudate Right	1,449	0,617
Parahippocampal Cortex Right	Globus Pallidum Right	1,004	0,143
Parahippocampal Cortex Right	Putamen Right	1,655	0,314
Parahippocampal Cortex Right	Geniculate Nucleus Right	-1,083	-0,004
Parahippocampal Cortex Right	Thalamus Right	-0,905	0,264
Parahippocampal Cortex Right	Claustrocortex(Insula) Right	0,857	0,701
Parahippocampal Cortex Right	Lateral Gyrus Right	-0,545	0,222
Parahippocampal Cortex Right	Suprasylvian Gyrus Right	0,139	0,319
Parahippocampal Cortex Right	Sylvian Gyrus Right	1,414	0,160
Parahippocampal Cortex Right	Ectolateralis Gyrus Right	0,184	0,083
Parahippocampal Cortex Right	Occipital Lobe Right	-0,517	0,851
Parahippocampal Cortex Right	Midbrain Right	0,294	0,401
Periaqueductal Grey Substance Left	Pons Right	1,505	1,333
Periaqueductal Grey Substance Left	Periaqueductal Grey Substance Right	1,880	1,523

Periaqueductal Grey Substance Right	Midbrain Right	1.079	1.524
Pineal Gland Left	Hippocampus Left	1.684	0.835
Pineal Gland Left	Geniculate Nucleus Left	0.690	-0.182
Pineal Gland Left	Midbrain Left	0.925	0.887
Pineal Gland Left	Pineal Gland Right	3.477	1.567
Pineal Gland Left	Hippocampus Right	0.454	0.825
Pineal Gland Left	Midbrain Right	0.995	0.818
Pineal Gland Right	Hippocampus Right	0.355	1.276
Pineal Gland Right	Midbrain Right	0.368	1.304
Pituitary Gland Left	Pituitary Gland Right	2.126	2.046
Pons Left	Periaqueductal Grey Substance Left	2.554	1.781
Pons Left	Pons Right	2.007	1.691
Pons Right	Periaqueductal Grey Substance Right	0.937	1.584
PostCruciate Gyrus Left	Posterior Sylvian Gyrus Left	1.857	2.180
PostCruciate Gyrus Left	Anterior Sylvian Gyrus Right	-0.997	0.319
PostCruciate Gyrus Left	PostCruciate Gyrus Right	-0.363	-0.292
PostCruciate Gyrus Right	Posterior Sylvian Gyrus Right	1.940	2.105
PostCruciate Gyrus Right	Sylvian Gyrus Right	-0.016	1.122
Posterior Sylvian Gyrus Left	Suprasylvian Gyrus Left	-0.390	0.036
Posterior Sylvian Gyrus Left	Sylvian Gyrus Left	-0.417	0.330
Posterior Sylvian Gyrus Right	Sylvian Gyrus Right	-0.678	0.431
Posterior Sylvian Gyrus Left	Suprasylvian Gyrus Left	1.820	1.751
Posterior Sylvian Gyrus Right	Temporal Lobe Right	0.396	2.102
Posterior Sylvian Gyrus Right	Suprasylvian Gyrus Right	-0.996	1.365
Posterior Sylvian Gyrus Right	Ectolateralis Gyrus Right	-0.217	0.092
PreCruciate Gyrus Left	Gyrus Rectus Left	1.076	-0.913
PreCruciate Gyrus Left	Claustrocortex(Insula) Left	0.376	0.824
PreCruciate Gyrus Left	Orbital Gyrus Right	1.376	-1.059
PreCruciate Gyrus Left	PreCruciate Gyrus Right	1.178	1.971
PreCruciate Gyrus Right	Gyrus Rectus Right	0.470	1.239
PreCruciate Gyrus Right	PostCruciate Gyrus Right	0.636	0.427
Preoptic Hypothalamic Area Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1.740	1.492
Preoptic Hypothalamic Area Left	Caudate Left	1.567	1.548
Preoptic Hypothalamic Area Left	Globus Pallidum Left	0.799	1.436
Preoptic Hypothalamic Area Left	Putamen Left	0.611	0.540
Preoptic Hypothalamic Area Left	Medial Mamilary Nucleus Right	0.247	0.099
Preoptic Hypothalamic Area Left	SubFornical Organ Right	1.803	1.576
Preoptic Hypothalamic Area Left	Bed Nucleus of Stria Terminalis Right	1.232	1.713
Preoptic Hypothalamic Area Left	Lateral Septal Nucleus Right	1.634	0.889
Preoptic Hypothalamic Area Left	Medial Septal Nucleus Right	1.461	1.548
Preoptic Hypothalamic Area Left	Septum Right	-0.370	0.527
Preoptic Hypothalamic Area Left	Preoptic Hypothalamic Area Right	1.908	2.433
Preoptic Hypothalamic Area Left	Substantia Nigra Right	-0.096	0.179
Preoptic Hypothalamic Area Left	Globus Pallidum Right	0.220	-0.248
Preoptic Hypothalamic Area Right	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	-0.255	-0.039
Preoptic Hypothalamic Area Right	Substantia Nigra Right	-0.515	0.212
Preoptic Hypothalamic Area Right	Caudate Right	1.008	0.298
Preoptic Hypothalamic Area Right	Globus Pallidum Right	0.415	0.407
Preoptic Hypothalamic Area Right	Putamen Right	0.126	0.004
Putamen Left	Claustrocortex(Insula) Left	2.184	1.342
Putamen Left	Septum Right	0.609	0.087
Putamen Right	Claustrocortex(Insula) Right	1.379	1.469
Putamen Right	PostCruciate Gyrus Right	0.225	-0.985
Putamen Right	Posterior Sylvian Gyrus Right	-0.233	0.931
Putamen Right	Sylvian Gyrus Right	1.181	-0.288
Septum Left	Preoptic Hypothalamic Area Left	1.812	1.756
Septum Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1.454	1.625
Septum Left	Caudate Left	1.547	1.722
Septum Left	Putamen Left	0.836	0.694
Septum Left	SubFornical Organ Right	1.337	0.742
Septum Left	Bed Nucleus of Stria Terminalis Right	1.341	1.578
Septum Left	Lateral Septal Nucleus Right	1.088	0.253
Septum Left	Septum Right	1.552	2.189
Septum Left	Preoptic Hypothalamic Area Right	1.723	1.874
Septum Left	Caudate Right	1.341	1.210
Septum Right	Preoptic Hypothalamic Area Right	-0.187	0.828
Septum Right	Caudate Right	0.789	1.924
Septum Right	Putamen Right	0.851	1.655
SubFornical Organ Left	Bed Nucleus of Stria Terminalis Left	1.664	1.836
SubFornical Organ Left	Lateral Septal Nucleus Left	1.810	1.982
SubFornical Organ Left	Medial Septal Nucleus Left	1.964	1.961
SubFornical Organ Left	Septum Left	1.523	1.189
SubFornical Organ Left	Preoptic Hypothalamic Area Left	1.864	2.070
SubFornical Organ Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1.686	1.380
SubFornical Organ Left	Globus Pallidum Left	0.879	1.288
SubFornical Organ Left	Medial Mamilary Nucleus Right	-0.222	0.274
SubFornical Organ Left	SubFornical Organ Right	2.332	2.206
SubFornical Organ Left	Bed Nucleus of Stria Terminalis Right	1.645	1.905
SubFornical Organ Left	Lateral Septal Nucleus Right	1.989	1.794
SubFornical Organ Left	Medial Septal Nucleus Right	1.567	1.492
SubFornical Organ Left	Septum Right	-0.738	0.263
SubFornical Organ Left	Preoptic Hypothalamic Area Right	1.888	1.968
SubFornical Organ Right	Bed Nucleus of Stria Terminalis Right	2.019	2.354
SubFornical Organ Right	Lateral Septal Nucleus Right	2.304	2.120
SubFornical Organ Right	Medial Septal Nucleus Right	1.709	1.936
SubFornical Organ Right	Septum Right	-0.960	0.561
SubFornical Organ Right	Preoptic Hypothalamic Area Right	1.936	2.157
SubFornical Organ Right	Globus Pallidum Right	-0.253	-0.148
Substantia Nigra Left	Globus Pallidum Left	1.557	0.780
Substantia Nigra Right	Globus Pallidum Right	0.908	-0.197
Suprasylvian Gyrus Left	Sylvian Gyrus Left	0.557	1.659
Suprasylvian Gyrus Left	Ectolateralis Gyrus Left	1.921	-0.031
Suprasylvian Gyrus Right	Ectolateralis Gyrus Right	2.095	1.129
Temporal Lobe Left	Parahippocampal Cortex Left	1.797	1.003
Temporal Lobe Right	Hippocampus Right	0.226	-0.041
Temporal Lobe Right	Parahippocampal Cortex Right	1.336	0.436
Temporal Lobe Right	Suprasylvian Gyrus Right	-0.979	0.279
Temporal Lobe Right	Ectolateralis Gyrus Right	-0.816	-0.081
Thalamus Left	Midbrain Left	1.757	-0.094
Thalamus Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	1.872	0.223
Thalamus Right	Midbrain Right	0.886	0.803

Regions Of Interest	Baseline	Gonadectomized	Mean Diff,	95,00% CI of diff	t	Individual P Value	Summary
Amygdala Left	0,5747	0,5947	-0,02003	-0,0394 to -0,0006694	2,033	0,0426	*
Amygdala Right	0,6125	0,6351	-0,02259	-0,04195 to -0,003222	2,293	0,0224	*
Cerebellum Left	0,4168	0,3852	0,03157	0,0122 to 0,05093	3,204	0,0015	**
Clastrum Left	0,4534	0,3776	0,07577	0,05641 to 0,09514	7,692	<0,0001	****
Clastrum Right	0,4363	0,3628	0,07348	0,05412 to 0,09284	7,459	<0,0001	****
Ectolateralis Gyrus Left	0,6395	0,4975	0,1421	0,1227 to 0,1614	14,42	<0,0001	****
Ectolateralis Gyrus Right	0,6409	0,5043	0,1366	0,1173 to 0,156	13,87	<0,0001	****
Fornix Left	0,4503	0,4237	0,02661	0,007247 to 0,04597	2,701	0,0072	**
Fornix Right	0,4793	0,4462	0,03301	0,01365 to 0,05237	3,351	0,0009	***
Geniculate Nucleus Left	0,179	0,1576	0,02133	0,001967 to 0,04069	2,165	0,0309	*
Hippocampus Left	0,5206	0,5416	-0,02107	-0,04043 to -0,001703	2,138	0,033	*
Medial Mamillary Nucleus Left	0,3783	0,3503	0,02796	0,008596 to 0,04732	2,838	0,0048	**
Medial Mamillary Nucleus Right	0,3745	0,3433	0,03117	0,01181 to 0,05053	3,164	0,0017	**
Medial Septal Nucleus Right	0,4452	0,4234	0,02187	0,002503 to 0,04123	2,22	0,027	*
Medulla Oblongata Left	0,2755	0,211	0,06453	0,04516 to 0,08389	6,55	<0,0001	****
Medulla Oblongata Right	0,3083	0,2387	0,06954	0,05017 to 0,0889	7,059	<0,0001	****
Midbrain Left	0,234	0,1787	0,05531	0,03594 to 0,07467	5,614	<0,0001	****
Midbrain Right	0,2313	0,1792	0,05206	0,0327 to 0,07143	5,285	<0,0001	****
Orbital Gyrus Left	0,468	0,492	-0,024	-0,04337 to -0,004639	2,436	0,0152	*
Periaqueductal Grey Substance Left	0,6429	0,538	0,1049	0,08554 to 0,1243	10,65	<0,0001	****
Periaqueductal Grey Substance Right	0,5522	0,4744	0,07781	0,05845 to 0,09717	7,898	<0,0001	****
Pons Left	0,4104	0,2825	0,1279	0,1086 to 0,1473	12,98	<0,0001	****
Pons Right	0,3971	0,2762	0,1209	0,1015 to 0,1402	12,27	<0,0001	****
Preoptic Hypothalamic Area Left	0,442	0,4189	0,02306	0,003696 to 0,04242	2,341	0,0197	*
Preoptic Hypothalamic Area Right	0,4748	0,4432	0,03164	0,01228 to 0,051	3,212	0,0014	**
SubFornical Organ Right	0,5848	0,559	0,02578	0,006419 to 0,04515	2,617	0,0092	**
Suprasylvian Gyrus Right	0,3862	0,4068	-0,02064	-0,04 to -0,001274	2,095	0,0368	*
Thalamus Left	0,3032	0,2707	0,03245	0,01309 to 0,05182	3,294	0,0011	**
Thalamus Right	0,3102	0,2793	0,03091	0,01155 to 0,05028	3,138	0,0018	**

Regions Of Interest	Baseline	Gonadectomized	Mean Diff,	95,00% CI of diff	t	Individual P Value	Summary
Clastrum Left	0,4085	0,3737	0,03473	0,02561 to 0,04385	7,489	<0,0001	****
Clastrum Right	0,4046	0,3703	0,03427	0,02515 to 0,0434	7,391	<0,0001	****
Ectolateralis Gyrus Right	0,4411	0,4165	0,02462	0,0155 to 0,03374	5,31	<0,0001	****
Subformical Organ Left	0,4372	0,4115	0,0257	0,01658 to 0,03482	5,541	<0,0001	****
Subformical Organ Right	0,4431	0,4166	0,02647	0,01734 to 0,03559	5,707	<0,0001	****
Globus Pallidum Left	0,2584	0,2484	0,01006	0,0009362 to 0,01918	2,169	0,0308	*
Globus Pallidum Right	0,2473	0,2372	0,01018	0,001057 to 0,0193	2,195	0,0289	*
Medial Mamillary Nucleus Left	0,3348	0,3135	0,02131	0,01219 to 0,03043	4,595	<0,0001	****
Medial Mamillary Nucleus Right	0,3335	0,3116	0,02195	0,01283 to 0,03107	4,733	<0,0001	****
Medulla Oblongata Right	0,1898	0,1649	0,02496	0,01584 to 0,03409	5,383	<0,0001	****
Midbrain Left	0,2078	0,1805	0,02727	0,01815 to 0,03639	5,881	<0,0001	****
Midbrain Right	0,2595	0,2321	0,02736	0,01824 to 0,03648	5,9	<0,0001	****
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	0,2834	0,2678	0,01566	0,006534 to 0,02478	3,376	0,0008	***
Nucleus Of The Horizontal Limb Of The Diagonal Band Right	0,3093	0,2903	0,01902	0,009901 to 0,02814	4,102	<0,0001	****
Parahippocampal Cortex Right	0,3541	0,323	0,03116	0,02204 to 0,04028	6,719	<0,0001	****
Pituitary Gland Left	0,04898	0,06561	-0,01663	-0,02575 to -0,007506	3,586	0,0004	***
Pituitary Gland Right	0,05069	0,06808	-0,01739	-0,02651 to -0,008265	3,749	0,0002	***
Preoptic Hypothalamic Area Left	0,4288	0,4038	0,02504	0,01592 to 0,03416	5,4	<0,0001	****
Preoptic Hypothalamic Area Right	0,4189	0,394	0,02485	0,01573 to 0,03397	5,358	<0,0001	****
Putamen Right	0,328	0,3159	0,01215	0,003031 to 0,02127	2,621	0,0092	**
Substantia Nigra Right	0,1451	0,1353	0,009719	0,0005973 to 0,01884	2,096	0,0368	*
Thalamus Left	0,3341	0,3113	0,0228	0,01368 to 0,03192	4,916	<0,0001	****

Brain Region 1	Brain Region 2	Mean functional connectivity Male baseline (Z score)	Mean functional connectivity Male castrated (Z score)
AnteriorSigmoideus Gyrus Left	Caudate Left	0,022	0,900
AnteriorSigmoideus Gyrus Left	Gyrus Rectus Left	0,879	0,181
AnteriorSigmoideus Gyrus Left	Gyrus Rectus Right	0,391	0,293
Bed Nucleus of Stria Terminalis Left	Orbital Gyrus Right	0,105	-0,923
Bed Nucleus of Stria Terminalis Left	Orbitofrontal Gyrus Right	0,211	-0,207
Bed Nucleus of Stria Terminalis Right	AnteriorSigmoideus Gyrus Right	0,727	-0,791
Bed Nucleus of Stria Terminalis Right	Orbital Gyrus Right	-0,741	-2,185
Bed Nucleus of Stria Terminalis Right	Orbitofrontal Gyrus Right	0,729	-1,148
Bed Nucleus of Stria Terminalis Right	Precruciate Gyrus Right	-0,134	-1,563
Caudate Left	Occipital Lobe Left	0,488	-1,465
Cingulate Cortex Left	Bed Nucleus of Stria Terminalis Right	0,542	-0,209
Gyrus Rectus Left	Entolateral Gyrus Left	-1,063	-1,000
Gyrus Rectus Left	Lateral Septal Nucleus Right	-0,430	-1,212
Gyrus Rectus Left	Pineal Gland Right	-0,554	-2,254
Gyrus Rectus Left	Periaqueductal Grey Substance Right	-0,088	-2,178
Hippocampus Left	Lateral Gyrus Left	1,104	0,524
Hippocampus Left	Thalamus Right	0,935	-0,579
Lateral Gyrus Left	Suprasylvian Gyrus Left	1,506	0,877
Medial Septal Nucleus Left	PostCruciate Gyrus Left	1,009	-0,131
Medial Septal Nucleus Left	PostCruciate Gyrus Right	0,287	-0,464
Medial Septal Nucleus Right	Orbital Gyrus Right	0,223	-0,890
Occipital Lobe Left	Thalamus Right	-0,014	-1,364
Orbital Gyrus Right	Globus Pallidum Right	0,936	-0,657
Parahippocampal Cortex Left	Periaqueductal Grey Substance Left	0,484	-0,113
Parahippocampal Cortex Left	Cerebellum Left	-0,686	-0,987
Parahippocampal Cortex Left	Lateral Gyrus Left	1,258	-1,429
Parahippocampal Cortex Left	Pons Right	0,886	-0,569
Parahippocampal Cortex Left	Geniculate Nucleus Right	1,582	-0,500
Parahippocampal Cortex Left	Lateral Gyrus Right	1,138	0,177
Parahippocampal Cortex Left	Suprasylvian Gyrus Right	0,970	0,286
Parahippocampal Cortex Left	Ectolateralis Gyrus Right	0,668	0,493
Periaqueductal Grey Substance Left	Periaqueductal Grey Substance Right	1,880	1,084
Periaqueductal Grey Substance Right	Midbrain Right	1,079	1,294
Pituitary Gland Left	Thalamus Left	-0,054	-0,006
Pituitary Gland Left	Entolateral Gyrus Left	0,330	-0,179
Pituitary Gland Left	Septum Right	0,031	-0,589
Pituitary Gland Left	Putamen Right	0,614	-0,440
Pituitary Gland Left	Claustrocortex(Insula) Right	0,073	-0,661
Pituitary Gland Left	Lateral Gyrus Right	-0,111	-0,555
Pituitary Gland Left	Ectolateralis Gyrus Right	0,326	-0,731
Pituitary Gland Left	Medulla Oblongata Right	0,428	0,144
Pons Left	Pons Right	2,007	1,044
PostCruciate Gyrus Left	Medulla Oblongata Left	0,198	-0,112
PostCruciate Gyrus Left	Medulla Oblongata Right	0,007	0,141
Posterior Sygmoideus Gyrus Left	Medulla Oblongata Right	0,362	1,138
Posterior Sylvian Gyrus Left	Substantia Nigra Left	0,153	-2,259
Posterior Sylvian Gyrus Left	Septum Right	0,323	-1,120
Posterior Sylvian Gyrus Left	Orbitofrontal Gyrus Right	0,341	-0,673
Posterior Sylvian Gyrus Left	Ectolateralis Gyrus Right	-0,392	-0,094
Preoptic Hypothalamic Area Right	Orbital Gyrus Right	-0,522	-0,748
Preoptic Hypothalamic Area Right	Orbitofrontal Gyrus Right	0,517	-0,010
Septum Left	Nucleus Of The Horizontal Limb Of The Diagonal Band Left	1,454	0,172
Septum Left	PostCruciate Gyrus Left	1,290	0,750
Septum Left	Orbital Gyrus Right	0,147	-0,865
Septum Left	Orbitofrontal Gyrus Right	0,713	0,414
Septum Right	AnteriorSigmoideus Gyrus Right	0,605	0,763
Septum Right	Orbital Gyrus Right	0,195	-1,094
SubFornical Organ Left	Orbital Gyrus Right	-0,705	-0,449
SubFornical Organ Left	Orbitofrontal Gyrus Right	0,576	-0,881
SubFornical Organ Right	Orbital Gyrus Right	-0,825	-0,944
SubFornical Organ Right	Orbitofrontal Gyrus Right	0,744	-1,245
Substantia Nigra Left	Posterior Sylvian Gyrus Right	1,244	-1,712
Temporal Lobe Left	Periaqueductal Grey Substance Left	0,725	0,428
Temporal Lobe Left	Pons Right	1,263	0,006
Temporal Lobe Left	Gyrus Rectus Right	-0,660	-0,144
Temporal Lobe Left	Periaqueductal Grey Substance Right	0,429	-0,023

Brain Region 1	Brain Region 2	Mean functional connectivity Female baseline (Z score)	Mean functional connectivity Female castrated (Z score)
Amygdala Left	Globus Pallidum Left	1,450	1,805
AnteriorSigmoides Gyrus Left	Gyrus Rectus Left	-1,753	0,239
AnteriorSigmoides Gyrus Left	Orbitofrontal Gyrus Right	-0,017	0,569
AnteriorSigmoides Gyrus Right	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	0,258	0,273
Bed Nucleus of Stria Terminalis Left	Lateral Septal Nucleus Left	1,599	1,913
Bed Nucleus of Stria Terminalis Left	Pituitary Gland Left	-1,046	-0,106
Bed Nucleus of Stria Terminalis Left	Medial Mamillary Nucleus Right	-0,408	0,313
Bed Nucleus of Stria Terminalis Left	Pituitary Gland Right	-1,004	-0,466
Bed Nucleus of Stria Terminalis Left	Midbrain Right	-0,529	-0,096
Bed Nucleus of Stria Terminalis Right	Pituitary Gland Right	-0,560	0,057
Caudate Left	Gyrus Rectus Left	0,147	-0,087
Cingulate Cortex Left	Orbital Gyrus Right	-0,117	0,374
Cingulate Cortex Left	Orbitofrontal Gyrus Right	1,006	1,375
Cingulate Cortex Left	Claustrocortex(Insula) Right	1,431	1,079
Cingulate Cortex Left	Sylvian Gyrus Right	0,414	1,002
Cingulate Cortex Right	Orbital Gyrus Right	0,954	1,582
Cingulate Cortex Right	Orbitofrontal Gyrus Right	0,833	1,517
Cingulate Cortex Right	Precruciate Gyrus Right	1,380	1,673
Claustrocortex(Insula) Left	Pineal Gland Right	-1,819	-0,527
Ectolateralis Gyrus Left	Suprasylvian Gyrus Right	-0,335	0,272
Geniculate Nucleus Left	Olfactory Bulb Right	-0,632	0,543
Gyrus Rectus Left	Olfactory Bulb Left	1,484	2,483
Gyrus Rectus Left	Periaqueductal Grey Substance Left	-0,037	0,782
Gyrus Rectus Left	PostCruciate Gyrus Left	0,173	-1,528
Gyrus Rectus Left	Orbital Gyrus Right	0,604	1,130
Gyrus Rectus Left	Precruciate Gyrus Right	0,657	0,784
Lateral Gyrus Left	Olfactory Bulb Right	-0,732	-0,374
Lateral Septal Nucleus Left	SubFornical Organ Right	0,960	1,703
Medial Mamillary Nucleus Left	AnteriorSigmoides Gyrus Right	-0,397	-0,404
Medial Septal Nucleus Left	Medulla Oblongata Right	-0,925	-0,949
Medial Septal Nucleus Right	Pituitary Gland Right	0,346	-0,483
Medulla Oblongata Left	Pineal Gland Right	0,849	0,099
Midbrain Left	Olfactory Bulb Right	-0,560	-0,482
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Midbrain Left	-1,287	-0,321
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Pituitary Gland Right	-1,293	-0,716
Nucleus Of The Horizontal Limb Of The Diagonal Band Left	Midbrain Right	-1,303	0,564
Nucleus Of The Horizontal Limb Of The Diagonal Band Right	Claustrocortex(Insula) Right	-0,644	0,332
Olfactory Bulb Left	Periaqueductal Grey Substance Left	-1,022	0,373
Olfactory Bulb Left	Orbital Gyrus Right	-1,102	1,148
Orbital Gyrus Left	Olfactory Bulb Left	0,784	0,780
Orbitofrontal Gyrus Left	Suprasylvian Gyrus Left	-1,883	-0,474
Orbitofrontal Gyrus Left	Cingulate Cortex Right	-2,575	-0,288
Orbitofrontal Gyrus Left	Orbital Gyrus Right	-1,481	1,601
Orbitofrontal Gyrus Left	Orbitofrontal Gyrus Right	-0,935	0,861
Orbitofrontal Gyrus Left	Precruciate Gyrus Right	-0,624	1,118
Orbitofrontal Gyrus Right	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	-1,614	0,049
Orbitofrontal Gyrus Right	Entolateral Gyrus Right	-0,748	0,735
Parahippocampal Cortex Left	Putamen Left	-0,318	-0,225
Parahippocampal Cortex Left	Claustrocortex(Insula) Left	-0,677	1,192
Parahippocampal Cortex Left	PostCruciate Gyrus Left	-1,375	0,197
Parahippocampal Cortex Left	Posterior Sygmoideus Gyrus Left	-0,916	1,433
Parahippocampal Cortex Left	Bed Nucleus of Stria Terminalis Right	-0,574	-0,465
Parahippocampal Cortex Left	Septum Right	-1,430	-0,317
Parahippocampal Cortex Left	AnteriorSigmoides Gyrus Right	0,556	-0,735
Parahippocampal Cortex Left	Orbitofrontal Gyrus Right	-1,258	0,102
Parahippocampal Cortex Left	Caudate Right	-1,275	0,276
Parahippocampal Cortex Left	Claustrocortex(Insula) Right	-0,818	-0,413
Parahippocampal Cortex Left	PostCruciate Gyrus Right	0,632	-0,639
Parahippocampal Cortex Left	Posterior Sygmoideus Gyrus Right	-0,588	0,989
Periaqueductal Grey Substance Left	Olfactory Bulb Right	-0,388	0,598
Pineal Gland Left	Pineal Gland Right	1,567	2,681
Pituitary Gland Left	Posterior Sylvian Gyrus Right	-1,618	0,084
Pituitary Gland Left	Medial Septal Nucleus Right	-0,724	-1,003
Pituitary Gland Left	Sylvian Gyrus Right	-0,107	-0,194
Pituitary Gland Right	Suprasylvian Gyrus Right	-1,205	0,823
Pons Right	Gyrus Rectus Right	0,227	0,592
Pons Right	Olfactory Bulb Right	-0,091	1,389
Posterior Sygmoideus Gyrus Left	Thalamus Right	-1,079	0,282
Precruciate Gyrus Left	Olfactory Bulb Left	1,339	1,082
Preoptic Hypothalamic Area Left	Gyrus Rectus Left	-0,201	-0,290
Preoptic Hypothalamic Area Left	Medulla Oblongata Left	-0,600	-0,107
Preoptic Hypothalamic Area Left	Medulla Oblongata Right	-1,066	0,564
Preoptic Hypothalamic Area Right	Pituitary Gland Right	-0,026	0,041
Preoptic Hypothalamic Area Right	Cerebellum Right	-0,957	1,223
Preoptic Hypothalamic Area Right	Medulla Oblongata Right	-1,287	1,184
Putamen Left	Gyrus Rectus Left	-0,020	-0,348
Putamen Left	Substantia Nigra Right	-1,607	1,091
Putamen Left	Gyrus Rectus Right	-0,218	-0,535
Septum Left	Amygdala Left	-0,073	-0,751
Septum Left	Parahippocampal Cortex Left	-1,055	-0,384
Septum Left	Gyrus Rectus Left	-0,005	-0,062
Septum Left	Pituitary Gland Left	-1,204	0,739
Septum Left	Pituitary Gland Right	-0,880	0,087
Septum Left	Midbrain Right	-0,887	-0,194
Septum Right	Nucleus Of The Horizontal Limb Of The Diagonal Band Right	-1,401	0,646
Septum Right	Periaqueductal Grey Substance Right	-1,765	0,544
Septum Right	Midbrain Right	-1,555	-0,130
SubFornical Organ Left	Pituitary Gland Right	-0,240	-0,374
SubFornical Organ Right	Pituitary Gland Right	-0,102	-0,056
Temporal Lobe Left	Septum Right	-1,371	-0,233
Temporal Lobe Left	Precruciate Gyrus Right	-1,495	-0,235
Thalamus Left	Posterior Sylvian Gyrus Right	-1,023	-0,824
Thalamus Left	Putamen Right	-0,639	0,336
Thalamus Left	Claustrocortex(Insula) Right	-1,006	-0,675

Conflict of interest :

The authors state that they have no conflict of interest.

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