

# <sup>1</sup> Whole-brain comparison of rodent and human brains <sup>2</sup> using spatial transcriptomics

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<sup>4</sup> Antoine Beauchamp<sup>1,2,3,\*</sup>, Yohan Yee<sup>1,2,3</sup>, Ben C. Darwin<sup>1,2</sup>, Armin Raznahan<sup>4</sup>, Rogier B.  
<sup>5</sup> Mars<sup>5,6,†</sup>, Jason P. Lerch<sup>1,2,3,5,\*†</sup>

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<sup>7</sup> <sup>1</sup>Mouse Imaging Centre, Toronto, Ontario, Canada.

<sup>8</sup> <sup>2</sup>The Hospital for Sick Children, Toronto, Ontario, Canada.

<sup>9</sup> <sup>3</sup>Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada.

<sup>10</sup> <sup>4</sup>Section on Developmental Neurogenomics, Human Genetics Branch, National Institute of Mental Health Intramural  
<sup>11</sup> Research Program, Bethesda, MD, U.S.A.

<sup>12</sup> <sup>5</sup>Wellcome Centre for Integrative Neuroimaging, Centre for Functional MRI of the Brain (FMRIB), Nuffield Depart-  
<sup>13</sup> ment of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom.

<sup>14</sup> <sup>6</sup>Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, Netherlands.

<sup>15</sup> <sup>†</sup>These authors contributed equally to this work.

<sup>16</sup> \*Corresponding author. Email: antoine.beauchamp@sickkids.ca (A.B.); jason.lerch@ndcn.ox.ac.uk (J.P.L)

## <sup>17</sup> Abstract

<sup>18</sup> The ever-increasing use of mouse models in preclinical neuroscience research calls for an improvement in the  
<sup>19</sup> methods used to translate findings between mouse and human brains. Using openly accessible brain-wide  
<sup>20</sup> transcriptomic data sets, we evaluated the similarity of mouse and human brain regions on the basis of ho-  
<sup>21</sup> mologous gene expression. Our results suggest that mouse-human homologous genes capture broad patterns  
<sup>22</sup> of neuroanatomical organization, but that the resolution of cross-species correspondences can be improved  
<sup>23</sup> using a novel supervised machine learning approach. Using this method, we demonstrate that sensorimotor  
<sup>24</sup> subdivisions of the neocortex exhibit greater similarity between species, compared with supramodal sub-  
<sup>25</sup> divisions, and that mouse isocortical regions separate into sensorimotor and supramodal clusters based on  
<sup>26</sup> their similarity to human cortical regions. We also find that mouse and human striatal regions are strongly  
<sup>27</sup> conserved, with the mouse caudoputamen exhibiting an equal degree of similarity to both the human caudate  
<sup>28</sup> and putamen.

## <sup>29</sup> Introduction

<sup>30</sup> Animal models play an indispensable role in neuroscience research, not only for understanding disease and  
<sup>31</sup> developing treatments, but also for obtaining data that cannot be obtained in the human. While numerous  
<sup>32</sup> species have been used to model the human brain, the mouse has emerged as the most prominent of these,  
<sup>33</sup> due to its rapid life cycle, straightforward husbandry, and amenability to genetic engineering (Dietrich et  
<sup>34</sup> al., 2014; Ellenbroek and Youn, 2016; Hedrich et al., 2004; Houdebine, 2004). Mouse models have proven  
<sup>35</sup> to be extremely useful for understanding diverse features of the brain, from its molecular neurobiological  
<sup>36</sup> properties to its large-scale network properties (Hodge et al., 2019; Oh et al., 2014; Yao et al., 2021).  
<sup>37</sup> However, translating findings from the mouse to the human has not been straightforward. This is especially

38 evident in the context of neuropsychopharmacology, where promising neuropsychiatric drugs have one of the  
39 highest failures rates in Phase III clinical trials (Hay et al., 2014).

40 Successful translation requires an understanding of how effects on the brain of the model species are likely to  
41 manifest in the brain of the actual species of interest. This is not trivial in the case of the mouse and human,  
42 as the two species diverged from a common ancestor about 80 million years ago (Kaas, 2012). Although  
43 common themes are apparent in the brains of all mammalian species studied to date (Krubitzer, 2007), there  
44 remain substantial differences between the mouse and human brain. Beyond the obvious differences in size,  
45 large parts of the human cortex potentially have no corresponding homologues in the mouse (Preuss, 1995).  
46 Direct comparisons across the brains of different species are further complicated by the fact that researchers  
47 from different traditions use inconsistent nomenclature to refer to similar neuroanatomical areas (Heukelum  
48 et al., 2020; Laubach et al., 2018).

49 Over the course of the last decade, we have developed novel approaches to explicitly evaluate similarities  
50 and differences between the brains of related species. These approaches describe brains using common data  
51 spaces that are directly comparable between species, making it possible to evaluate the similarity of different  
52 regions in a quantitative fashion (Mars et al., 2021). This way, potential homologues can be formally tested  
53 and regions of the brain that do not allow for straightforward translation can be identified (Rogier B. Mars  
54 et al., 2018b). Establishing such a formal translation between the mouse and the human brain would allow  
55 scientists involved in translational research to explicitly test hypotheses about conservation of brain regions,  
56 identify regions that are well suited to translational paradigms, and directly transform quantitative maps  
57 from the brain of one species to the other.

58 One approach towards building these common spaces has been to exploit connectivity. The connections of  
59 a brain region tend to be unique and can therefore be seen as a diagnostic of an area (Rogier B. Mars et  
60 al., 2018a; Passingham et al., 2002). The common connectivity space approach relies on defining agreed  
61 upon neuroanatomical homologues *a priori* and then expressing the connectivity fingerprint of regions under  
62 investigation with those established homologues in the two brains (Mars et al., 2016b). The connections  
63 of any given region to the established homologues thus form a common space, which links the two brains.  
64 In a series of early studies, we compared the connectivity of the macaque and human brain, identifying  
65 homologies as well as specializations across association cortex (Mars et al., 2013; Neubert et al., 2014; Sallet  
66 et al., 2013). The same approach has recently been applied to mouse-human comparisons for the first time,  
67 demonstrating conserved organization between the mouse and human striatum, but some specialization in  
68 the human caudate related to connectivity with the prefrontal cortex (Balsters et al., 2020). A similar study  
69 recently compared connectivity of the medial frontal cortex across rats, marmosets, and humans (Schaeffer et  
70 al., 2020). However, the lack of established neuroanatomical homologues in mice, particularly in the cortex,  
71 limits the use of connectivity to compare these species.

72 A more promising approach to mouse-human comparisons could be to exploit the spatial patterns of gene  
73 expression. Advances in transcriptomic mapping can be used to characterise the differential expression of  
74 many thousands of genes across the brain and compare the pattern between regions (Ortiz et al., 2020).  
75 Moreover, the availability of whole-brain spatial transcriptomic data sets for multiple species provides an  
76 opportunity to run novel analyses at low cost (Hawrylycz et al., 2012; Lein et al., 2007). Such maps for the  
77 human cortex show topographic patterns that mimic those observed in other modalities, such as a gradient  
78 between primary and heteromodal areas of the neocortex (Burt et al., 2018). Importantly, these patterns  
79 appear to be conserved across mammalian species (Fulcher et al., 2019), which opens up the possibility

80 of using the expression of homologous genes as a common space across species. In fact, a recent study  
81 demonstrated how the expression of homologous genes can be used to directly register mouse and vole brains  
82 into a common reference frame, which allows for direct point-by-point comparisons of brain maps (Englund  
83 et al., 2021). However, this specific approach is only feasible because of the large degree of morphological  
84 similarity between mouse and vole brains. In the case of mouse-human comparisons, we almost certainly  
85 cannot directly register mouse and human brains into a common coordinate frame using methods for image  
86 registration. Hence we need to be more creative in our approach.

87 Here we examine the patterns of similarity between the mouse and human brain using a common space  
88 constructed from spatial gene expression data sets. We begin with an initial set of 2624 homologous genes.  
89 Subsequently, we present and evaluate a novel method for improving the resolution of mouse-human neu-  
90 roanatomical correspondences using a supervised machine learning approach. Using the novel representation  
91 of the gene expression common space, i.e. a latent gene expression space, we analyse the similarity of mouse  
92 and human isocortical subdivisions and demonstrate that sensorimotor regions exhibit a higher degree of sim-  
93 ilarity than supramodal regions. Finally, we examine the patterns of transcriptomic similarity at a voxel-wise  
94 level in the mouse and human striatum.

## 95 Results

### 96 Homologous genes capture broad similarities in the mouse and human brains

97 We first examined the pattern of similarities that emerged when comparing mouse and human brain regions  
98 on the basis of their gene expression profiles. We constructed a gene expression common space using widely  
99 available data sets from the Allen Institute for Brain Science: the Allen Mouse Brain Atlas (AMBA) and  
100 the Allen Human Brain Atlas (AHBA) (Hawrylycz et al., 2012; Lein et al., 2007). These data sets provide  
101 whole-brain coverage of expression intensity for thousands of genes in the mouse and human genomes.  
102 For our purposes we filtered these gene sets to retain only mouse-human homologous genes using a list  
103 of orthologues obtained from the NCBI HomoloGene system (NCBI 2018). Prior to analysis, both data  
104 sets were pre-processed using a pipeline that included quality control checks, normalization procedures, and  
105 aggregation of the expression values under a set of atlas labels. The result was a gene-by-region matrix in  
106 either species, describing the normalized expression of 2624 homologous genes across 67 mouse regions and  
107 88 human regions (see Materials and methods). We quantified the degree of similarity between all pairs of  
108 mouse and human regions using the Pearson correlation coefficient, resulting in a mouse-human similarity  
109 matrix (Fig. 1A).

110 We find that the similarity matrix exhibits broad patterns of positive correlation between the mouse and  
111 human brains. These clusters of similarity correspond to coarse neuroanatomical regions that are generally  
112 well-defined in both species. For instance, we observe that, overall, the mouse isocortex is similar to the  
113 human cerebral cortex, with the exception of the hippocampal formation, which forms a unique cluster.  
114 Similarly the mouse and human cerebellar hemispheres cluster together, while the cerebellar nuclei show  
115 relatively high correlation to each other ( $r = 0.404$ ) as well as to brain stem structures like the pons ( $r = 0.359$   
116 and  $r = 0.371$  for the mouse and human nuclei respectively) and myelencephalon ( $r = 0.318$  and  $r = 0.374$ ).  
117 The associations between broad regions such as these are self-evident in the correlation matrix.

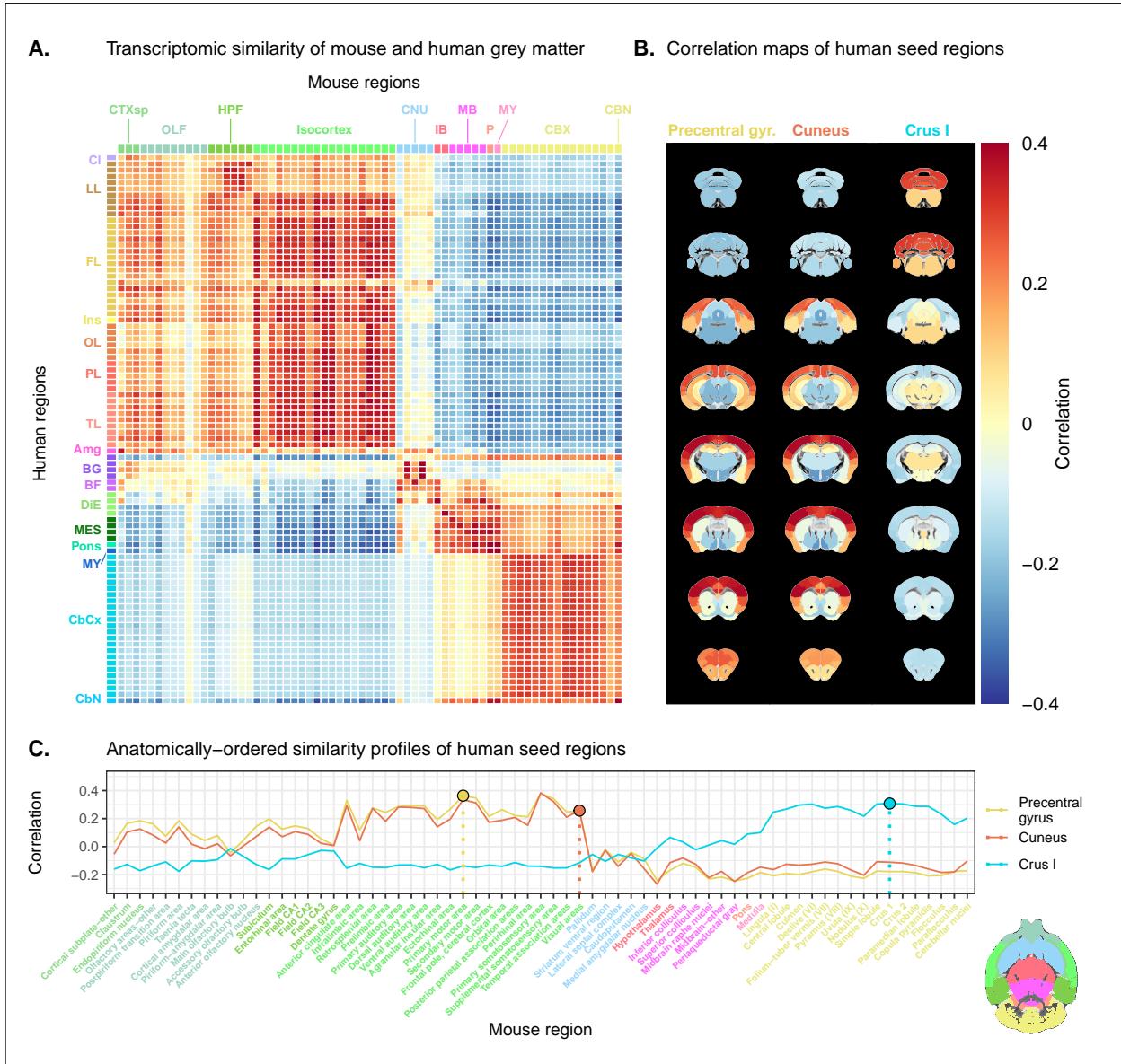
118 Our ability to resolve regional matches on a finer scale is limited when using all homologous genes in this way.  
119 This is especially true for regions within the cerebral and cerebellar cortices, which exhibit a high degree  
120 of internal homogeneity. This is apparent in the similarity profiles, defined here as the set of correlation  
121 values between a given seed region and all target regions in the other species. For example, the human  
122 precentral gyrus and cuneus are most strongly correlated to many regions of the mouse isocortex. While  
123 the brain maps feature a rostral-caudal gradient (Fig. 1B), the profiles of the two seeds are highly similar  
124 despite the regions having very different functions (Fig. 1C). Indeed, the correlation between the similarity  
125 profiles of the precentral gyrus and cuneus is  $r = 0.980$ . The similarity profile of human cerebellar crus 1  
126 highlights another example of this homogeneity. The profile of crus 1 is similar to that of all regions of the  
127 mouse cerebellum, with an average correlation of  $r = 0.269$  and a standard deviation of  $\sigma = 0.041$ . Across  
128 all regions, the variance of the correlations across cortical regions is  $\sigma^2 = 0.0052$  while that across cerebellar  
129 hemispheric regions is  $\sigma^2 = 0.0017$ , compared with a total variation of  $\sigma^2 = 0.0416$  across all entries in the  
130 matrix.

131 So, although there is some distinguishing power in the profiles of regions at a finer scale, this is much smaller  
132 than between coarse anatomical regions. This is also true for parts of the broad anatomical systems that are  
133 part of the same functional system. This suggests that the regional expression patterns of mouse-human  
134 homologous genes can be used to identify general similarities between the brains of the two species even  
135 using a simple correlation measure, but the ability to identify finer scale matches might require a more  
136 subtle approach.

### 137 **A latent gene expression space improves the resolution of mouse-human associations**

139 In the previous analyses, we showed that the expression profiles of homologous genes capture broad simi-  
140 larities across the mouse and the human for the major subdivisions of the brain. Some information at a  
141 finer resolution (e.g. within the isocortex) was also evident, but much less distinctive. Our next goal was  
142 to investigate whether it is possible to leverage the gene expression data sets to relate mouse and human  
143 brains to one another at a finer regional level. In order to do so, we sought to maximise the informational  
144 value in the set of 2624 homologous genes by creating a new latent common space that exploits the regional  
145 distinctiveness of the expression profiles.

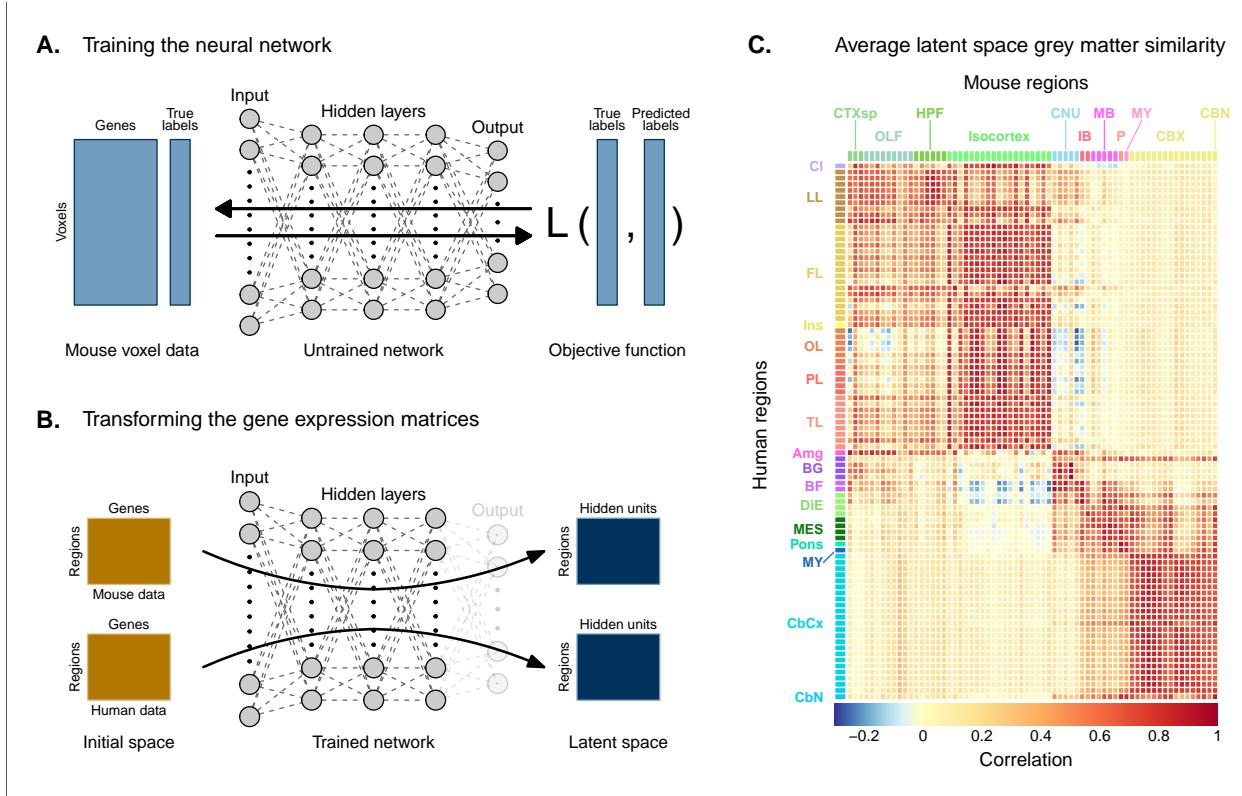
146 The approach used in the previous analysis relied on using homologous genes as a common space between  
147 the mouse and human brain. This approach effectively assigns equal value to each gene, whereas a more  
148 powerful approach would be to weight genes by their ability to distinguish between different brain regions.  
149 We investigated whether we could accomplish this by constructing a new set of variables from combinations  
150 of the homologous genes. Our primary goal here was to transform the initial gene space into a new common  
151 space that would improve the locality of the matches. However while we sought a transformation that would  
152 allow us to recapitulate known mouse-human neuroanatomical homologues, we also wanted to avoid directly  
153 encoding such correspondences in the transformation. Using this information as part of the optimization  
154 process for the transformation would run the risk of driving the transformation towards mouse-human pairs  
155 that are already known. While we are interested in being able to recover such matches, we are equally  
156 interested in identifying novel and unexpected associations between neuroanatomical regions in the mouse  
157 and human brains (e.g. one-to-many correspondences). Given these criteria, our approach to identifying an



**Fig. 1. Transcriptomic similarity in the mouse and human brains.** (A) Similarity matrix displaying the correlation between 67 mouse regions and 88 human regions based on the expression of 2624 homologous genes. Columns are annotated with 11 broad mouse regions: Cortical subplate (CTXsp), olfactory areas (OLF), hippocampal formation (HPF), isocortex, cerebral nuclei (CNU), interbrain (IB), midbrain (MB), pons (P), medulla (MY), cerebellar cortex (CBX), cerebellar nuclei (CBN). Rows are annotated with 16 broad human regions: Claustrum (Cl), limbic lobe (LL), frontal lobe (FL), insula (Ins), occipital lobe (OL), parietal lobe (PL), temporal lobe (TL), amygdala (Amg), basal ganglia (BG), basal forebrain (BF), diencephalon (DIE), mesencephalon (MES), pons, myelencephalon (MY), cerebellar cortex (CbCx), cerebellar nuclei (CbN). Broad patterns of similarity are evident between coarsely defined brain regions, while correlation patterns are mostly homogeneous within these regions. (B) Mouse brain coronal slices showing similarity profiles for the human precentral gyrus, cuneus and crus I. Correlation patterns for the precentral gyrus and cuneus are highly similar to one another and broadly similar to most isocortical regions. The crus I is homogeneously similar to the mouse cerebellum. (C) Anatomically-ordered line charts displaying the similarity profiles for the seed regions in (B). Dashed vertical lines indicate the canonical mouse homologue for each human region. Annotation colours correspond to atlas colours from the AMBA and AHBA for mouse and human respectively.

appropriate transformation was to train a multi-layer perceptron classifier on the data from the AMBA. The classifier was tasked with predicting the 67 labels in our mouse atlas from the voxel-wise expression of the homologous genes (Fig. 2A).

While the model could have been trained using the data from either species, we chose to use the mouse data because it provides continuous coverage of the entire brain and is thus better suited to this purpose. In training the model to perform this classification task, we effectively optimize the network architecture to identify a transformation from the input gene space to a space that encodes information about the delineation between mouse brain regions. To extract this transformation, we removed the output layer from the trained neural network. The resulting architecture defines a transformation from the input space to a lower-dimensional gene expression latent space. We then applied this transformation to the mouse and human gene-by-region expression matrices to obtain representations of the data in the latent common space (Fig. 2B). Finally, we used these gene expression latent common space matrices to compute the new similarity matrix (Fig. 2C). Since the optimization algorithm used to train the perceptron features an inherent degree of stochasticity, we repeated this training and transformation process 500 times to generate a distribution of latent spaces and similarity matrices over training runs.



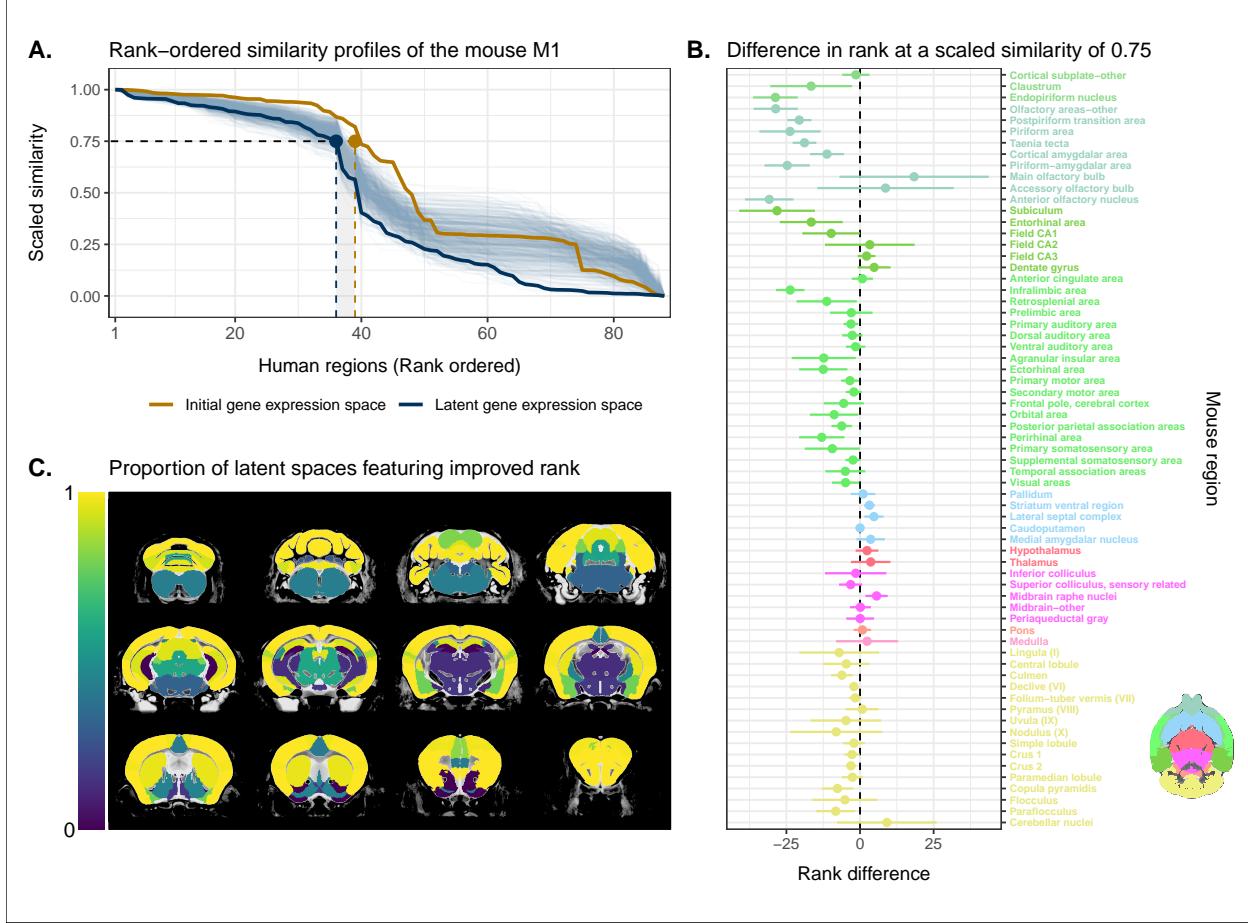
**Fig. 2. Creating a new common space.** (A) Voxel-wise expression maps from 2624 homologous genes in the AMBA were used to train the neural network to classify each mouse voxel into one of 67 atlas regions. (B) Once the network is trained, the output layer is removed. The mouse and human regional gene expression matrices are passed through the network, resulting in lower-dimensional latent space representations of the data. The training and transformation process was repeated 500 times. (C) A similarity matrix displaying the gene expression latent space correlation between mouse and human regions, averaged over 500 neural network training runs. Similar brain regions exhibit very high correlation values. Column and row annotations as described in Figure 1.

To assess whether the latent space representations of the data improved the resolution of the mouse-human matches, we considered two criteria. The first was whether the similarity profiles of the mouse atlas regions were more localized within the corresponding broad regions of interest (e.g. primary motor area within

176 isocortex), compared with their similarity profiles in the original gene space. We term this the locality  
177 criterion. The second criterion was whether the degree of similarity between canonical neuroanatomical  
178 homologues improved in this new latent common space. We term this the homology criterion. The locality  
179 criterion tells us about our ability to extract finer-scale signal in these profiles, while the homology criterion  
180 informs us about our ability to recover expected matches in this finer-scale signal. To evaluate these criteria,  
181 we computed ranked similarity profiles for every region in the mouse brain, ordered such that a rank of 1  
182 indicates the most similar human region. In addition, given the difference in absolute value between the  
183 input gene space and gene expression latent space correlations, we scaled the similarity profiles to the interval  
184 [0, 1] in order to make comparisons between the spaces.

185 We evaluated the locality criterion by examining the decay rate of the top of the similarity profiles. We  
186 reasoned that the plateau of similarity to a broad brain region, as seen in the anatomically-ordered similarity  
187 matrices and profiles (Fig. 1, A and C; Fig. 2C), would correspond to a similar plateau at the head of the  
188 rank-ordered profiles. Moreover, the emergence of local signal would manifest as an increase in the range  
189 between the peaks and troughs within the broad region. In the rank-ordered profiles, this would correspond  
190 to a faster rate of decay at the head of the profile. In order to quantify this decay, we computed the rank  
191 at which each region's similarity profile decreased to a scaled value of 0.75. This was calculated for every  
192 mouse region in the initial gene space, as well as in each of the 500 gene expression latent spaces. As a  
193 measurement of performance between the two representations of the data, we then took the difference in  
194 this rank between each of the latent spaces and the original gene space (Fig. 3A). A negative rank difference  
195 indicates an improvement in the latent space.

196 Examining the structure-wise distributions of these rank differences, we found that for the majority of regions  
197 in our mouse atlas, the classification approach resulted in either an improvement in the amount of locality  
198 within a broad region, or no difference from the original gene space (Fig. 3, B and C). Specifically, 47 regions  
199 (70.1%) had a mean rank difference less than or equal to zero. Additionally, the same number of regions  
200 returned non-positive rank differences in at least 80% of latent spaces. A few regions performed considerably  
201 worse in the latent spaces, notably the main olfactory bulb ( $\mu = 18.4$ ;  $\sigma = 12.7$ ), the accessory olfactory  
202 bulb ( $\mu = 8.7$ ;  $\sigma = 11.6$ ), and the cerebellar nuclei ( $\mu = 9.1$ ;  $\sigma = 8.5$ ). In particular, the main olfactory  
203 bulb performed worse in 96.6% of latent spaces. Regions within the cortical subplate and olfactory areas  
204 (e.g. endopiriform nucleus, postpiriform transition area) benefited the most from the classification approach,  
205 with many regions showing improvements in all latent spaces. While the effects are smaller, the similarity  
206 profiles of regions belonging to the isocortex and cerebellar cortex also saw an improvement in locality. In  
207 the isocortex, 16 out of 19 regions (84.2%) improved in at least 96% of latent spaces. In the cerebellar  
208 cortex, 73.3% of regions saw a similar improvement. In contrast, regions belonging to the cerebral nuclei,  
209 the diencephalon, midbrain and hindbrain did not see much improvement in this new common space. For  
210 instance, only 13.2% of latent spaces returned a non-positive rank difference in the thalamus. For many  
211 such regions the degree of locality appears to be worse in this space, though only by a small number of  
212 ranks (e.g. striatum ventral region, thalamus, midbrain raphe nuclei). Indeed, the mean rank difference  
213 and standard deviation over these regions and all latent spaces are  $\mu = 1.4$  and  $\sigma = 3.6$ . These results  
214 demonstrate that the supervised learning approach used here can improve the resolution of neuroanatomical  
215 correspondences between the mouse and human brains, though the amount of improvement varies over the  
216 brain. Regions that were already well-characterized using the initial set of homologous genes (e.g. subcortical  
217 regions) did not benefit tremendously, but numerous regions in the cortical plate and subplate, as well as  
218 the cerebellum, saw an improvement in locality in this new common space.



**Fig. 3. Quantifying improvement in locality in gene expression latent space.** (A) The amount of local signal within a broadly similar region of the brain for a finer seed region's (e.g. primary motor area) similarity profile can be quantified by the decay rate of the head of the rank-ordered profile. Decay rate was quantified by computing the rank at a similarity of 0.75. This metric was compared between the initial gene expression space (orange line) and every gene expression latent space resulting from repeated training of the neural network (every blue line is a training outcome, heavy blue line serves as an example). A negative difference between these rank metrics indicates an improvement in locality in the latent space. (B) Structure-wise distributions of differences in rank at a similarity of 0.75 between the initial gene expression space and the gene expression latent spaces. Points and error bars represent mean and 95% confidence interval. Dashed black line at 0 indicates the threshold for improvement in one space over the other. Colours correspond to AMBA annotations as in Figures 1 and 2. (C) Proportion of perceptron training runs resulting in an improvement or null difference in the gene expression latent space compared with the initial space. Cortical and cerebellar regions exhibit high proportions of improvement, while subcortical regions are less likely to be improved by the classification process.

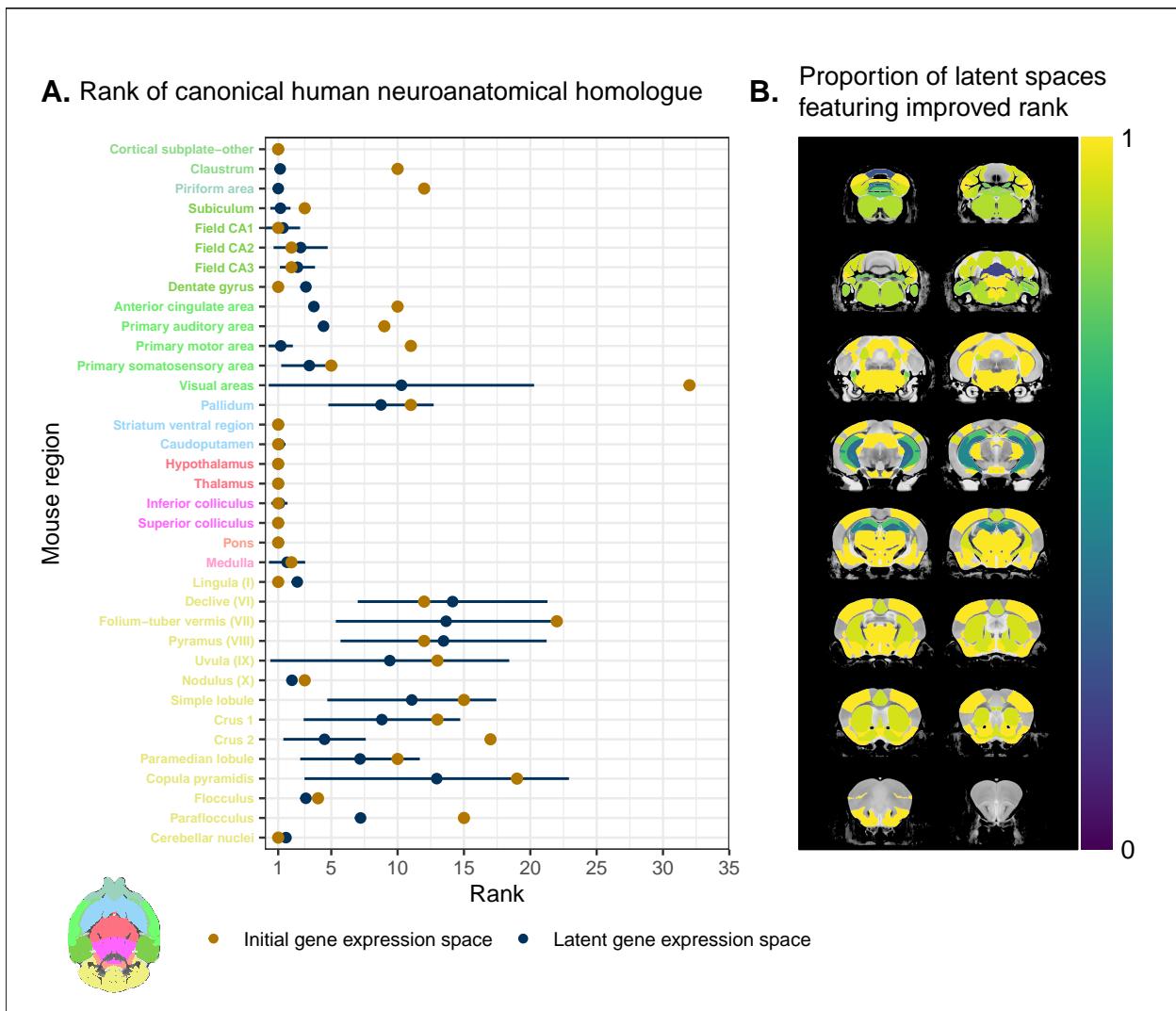
219 While the supervised learning approach improved our ability to identify matches on a finer scale for a number  
220 of brain regions, this does not necessarily mean that those improved matches are biologically meaningful. The  
221 second criterion for evaluating the performance of the neural network addresses whether this improvement  
222 in locality captures what we would expect in terms of known mouse-human homologies. To this end, we  
223 examined the degree of similarity between established mouse-human neuroanatomical pairs, both in the  
224 initial gene expression space and in the set of latent spaces. We began by establishing a list of 36 canonical  
225 mouse-human homologous pairs on the basis of common neuroanatomical labels in our atlases. For each of  
226 these regions in the mouse brain, we compared the rank of the canonical human match in the rank-ordered  
227 similarity profiles between the latent spaces and the original gene expression space (Fig. 4A). The lower the  
228 rank, the more similar the canonical pair, with a rank of 1 indicating maximal similarity. We additionally  
229 calculated the proportion of latent spaces in which each mouse region was more similar or as similar to its  
230 canonical human match compared with the initial gene space (Fig. 4B).

231 We find that for most regions in this subset, the classification approach either improves the correspondence or  
232 performs as well as the full set of homologous genes. For example, 73% of regions exhibit improved similarity  
233 in at least 80% of latent spaces. The improvement is most pronounced for regions in the cortical subplate and  
234 isocortex. In particular, the visual areas improve from a rank of 32 to an average of 10, though the variance  
235 is much higher in this case. Many regions in the sub-cortex do not benefit from the gene expression latent  
236 spaces since the initial gene set was already recapitulating the appropriate match with maximal similarity.  
237 Apart from the pallidum and the medulla, each of these regions is maximally similar to its canonical match  
238 in at least 90% of latent spaces. In such cases, the classification approach performs as well as the original  
239 approach. Finally, although many regions in the cerebellum feature some improvement in the latent spaces,  
240 the variation in the rank of the standard human pair is often quite large, indicating some instability in the  
241 neural network's ability to recover these matches. However, while the rank of the canonical pair varies in  
242 different instances of the latent space, the top matches for any given cerebellar region are always cerebellar  
243 regions. For instance, when the mouse crus 1 is used as the seed region, the human crus 1 is most often  
244 assigned a rank between 6 and 9. However, similar proportions in that range occur for the crus 2 and lobules  
245 V, VI and VIIIB, indicating that these cerebellar regions are swapping ranks in the different latent spaces.  
246 Thus while cerebellar regions are reliably associated with other cerebellar regions in the gene expression  
247 latent spaces, these associations are not stable over multiple training runs.

248 Together, these results demonstrate that the multi-layer perceptron classification approach improves our abil-  
249 ity to resolve finer scale mouse-human neuroanatomical matches within the broadly similar regions obtained  
250 using the initial gene expression space. By training a classifier to predict the atlas labels in one species, we  
251 were able to generate a new common space that amplified the amount of local signal within broadly similar  
252 regions while also improving our ability to recover known mouse-human neuroanatomical pairs.

253 **Cortical areas involved in sensorimotor processing show greater transcriptomic  
254 similarity than supramodal areas**

255 It is well established that the brains of most, if not all, extant mammalian species follow a common organi-  
256 zational blueprint inherited from an early mammalian ancestor (Kaas, 2011a). A number of cortical subdivi-  
257 sions have consistently been identified in members of many distantly related mammalian species (Krubitzer,  
258 2007) and hypothesized to have been present in the common ancestor of all mammals (Kaas, 2011a). While



**Fig. 4. Recovering canonical neuroanatomical pairs in gene expression space.** (A) Comparison between the ranks of canonical human matches for mouse seed regions between the initial gene expression space and gene expression latent spaces. Points and error bars represent mean and 95% confidence interval. Mouse region names are coloured according to the AMBA palette. (B) Proportion of latent spaces resulting in an improvement or null difference compared with the initial gene space. Uncoloured voxels correspond to regions with no established canonical human match.

259 it is clear that basic sensorimotor cortical regions are found in the majority of mammals, including mice and  
260 humans, there is much debate about the extent to which cortical areas involved in supramodal processing  
261 are conserved across mammalian taxa. Although some supramodal regions were likely present in the earliest  
262 mammals, including some cingulate regions and an orbitofrontal cortex (Kaas, 2011a), since the divergence  
263 of mouse and human lineages some 80 million years ago, the primate neocortex has undergone substantial  
264 expansion and re-organization (Kaas, 2012). Indeed, when comparing the human neocortex even to primate  
265 model species, this is the likely locus of areas that cannot be easily translated between species (Rogier B.  
266 Mars et al., 2018b). As a result, it is important to investigate whether our between-species mapping is more  
267 successful in somatosensory areas than supramodal areas.

268 We assessed the similarity between mouse and human isocortical areas using the pairwise correlations in each  
269 of the gene expression latent spaces returned from the multi-layer perceptron. For every region in the mouse  
270 isocortex, we evaluated the distribution of maximal correlation values over latent spaces (Fig. 5A). While  
271 the region-wise variance for each isocortical area was large, we found that, on average, sensorimotor regions  
272 exhibited higher maximal correlation values than supramodal regions. The mouse primary somatosensory  
273 and motor areas have the highest average maximal correlation values, with  $r = 0.94 \pm 0.04$  and  $r = 0.93 \pm 0.04$   
274 respectively. We additionally examined the distributions of maximal correlation, grouped by cortex type (Fig.  
275 5B). To generate these distributions, we computed average maximal correlation values by cortex type in each  
276 of the latent spaces. Here too we find that sensorimotor regions are associated with higher maximal  
277 correlation values on average ( $r = 0.89 \pm 0.04$ ), compared with supramodal areas ( $r = 0.85 \pm 0.03$ ). These  
278 distributions demonstrate that sensorimotor isocortical regions exhibit more similarity overall on the basis  
279 of homologous gene expression than do supramodal regions.

280 While we found that sensorimotor isocortical areas in the mouse brain were more similar to human brain  
281 regions than supramodal areas, the distributions of maximal correlation do not speak to the neuroanatomical  
282 patterns of organization for these matches. To understand how the similarity patterns of mouse and human  
283 cortical subdivisions were organized, we used hierarchical clustering to cluster mouse and human isocortical  
284 regions on the basis of their similarity profiles in the average gene expression latent space (Fig. 5C). This  
285 allows us to examine the similarity of regions to one another within and across brains at multiple levels  
286 simultaneously.

287 At a high level, we find a striking segregation of the mouse isocortex into one main cluster that corresponds  
288 to regions that are primarily engaged in sensorimotor processing and separate clusters of regions that are  
289 supramodal. All of the sensorimotor areas cluster together, but three supramodal areas also form part of this  
290 cluster: the retrosplenial area, the posterior parietal association areas, and the anterior cingulate cortex. Of  
291 these, the retrosplenial area is the most different, being the first to separate out from the other regions. In  
292 fact, the retrosplenial area is the mouse isocortical region with the smallest correlation values (Fig. 5A). The  
293 mouse sensorimotor cluster is characterized by high correlation values to human sensorimotor regions like  
294 the precentral gyrus, the cuneus, and the postcentral gyrus, as well as low correlation values to the piriform  
295 cortex and paraterminal gyrus.

296 At this level of clustering, the remaining mouse supramodal subdivisions form two clusters. These both  
297 exhibit low similarity to the human somatosensory and visual areas, but the cluster containing the infral-  
298 imbic and perirhinal areas additionally exhibits low correlation values with the precentral gyrus, anterior  
299 paracentral lobule, and transverse gyri. The human cortical regions do not segregate as cleanly into senso-  
300 rimotor and supramodal clusters. Under a similar level of description of four clusters of areas, the majority

301 of areas belong to a large cluster that includes a mix of cortical types. However, at a lower level of the  
302 hierarchy, if the number of clusters is increased to five, this large cluster breaks up into two smaller clusters  
303 that feature some delineation between supramodal and sensorimotor areas, which are primarily motor and  
304 auditory in nature (e.g. precentral gyrus, Heschl's gyrus). Interestingly, the postcentral gyrus, i.e. primary  
305 somatosensory area, forms a separate cluster with a set of visual areas such as the cuneus and lingual gyrus.  
306 These regions exhibit very similar correlation profiles to the mouse isocortical regions, including maximal  
307 correlation to the mouse primary somatosensory area, with an average of  $r = 0.92$ . The cluster is character-  
308 ized by high correlations to the mouse sensorimotor cluster and low correlations to the mouse supramodal  
309 clusters. Overall the human sensorimotor isocortical regions are loosely organized in clusters that contain  
310 sensory-visual areas and auditory-motor areas.

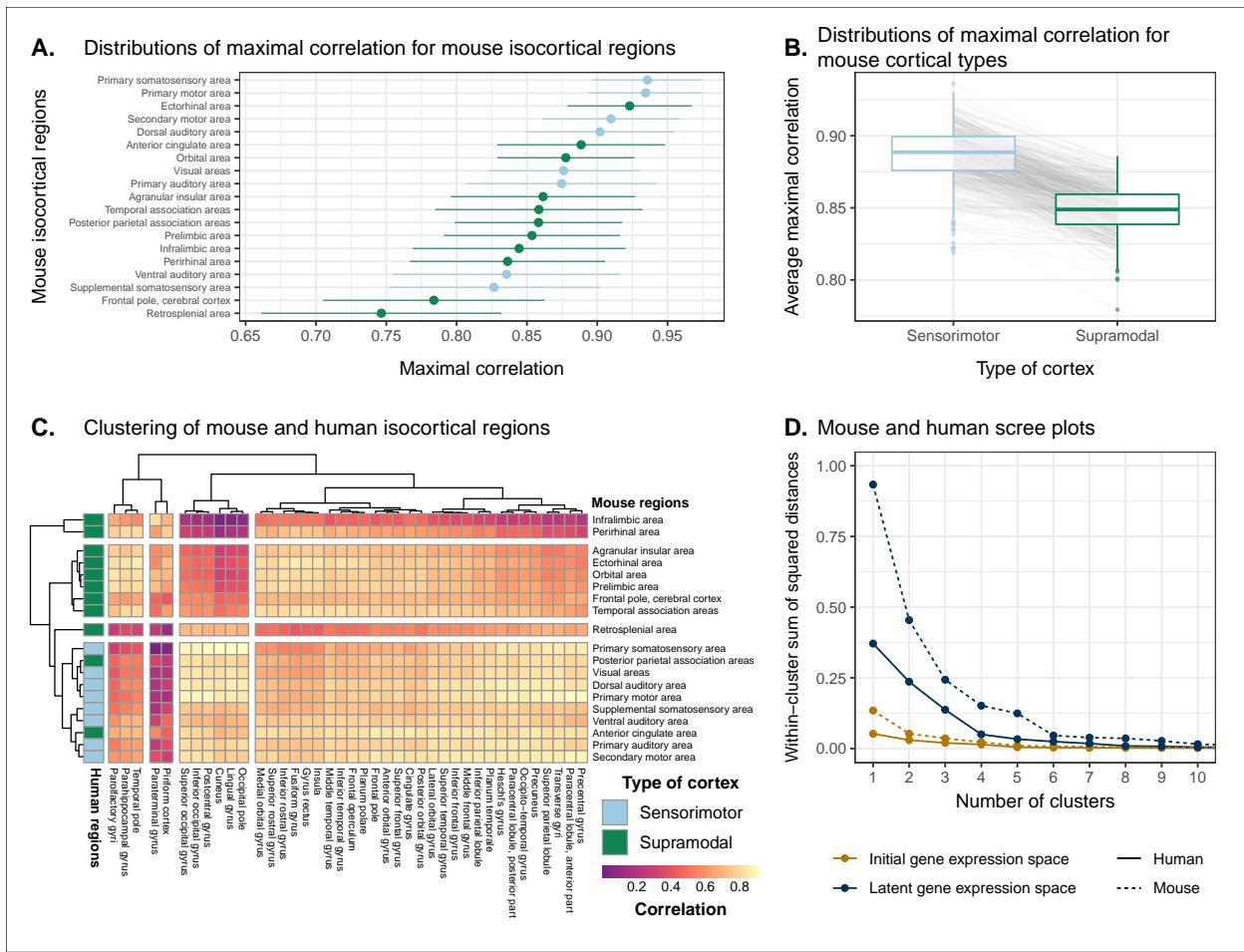
311 We additionally ran hierarchical clustering on the isocortical similarity matrix in the original homologous  
312 gene space. While the cluster annotations were not substantially different in this space, we observed that  
313 the Euclidean distances within and between clusters were smaller compared with the latent space clustering,  
314 further confirming that the perceptron classification approach improves the segregation of brain regions in  
315 the gene expression common space (Fig. 5D).

316 Overall, we observe a greater degree of similarity between mouse and human cortical regions involved in  
317 basic sensorimotor processing compared with supramodal or association areas. This is in line with the large  
318 body of existing research that suggests that sensory and motor areas of the cortex are conserved across the  
319 brains of mammals. While sensorimotor areas exhibit a greater degree of similarity than supramodal areas,  
320 the neuroanatomical pattern of correspondences obtained using mouse-human homologous genes is not at  
321 the level of individual cortical areas. Still, using a clustering approach we identified clear distinctions in  
322 the patterns of similarity between sensorimotor and supramodal areas, especially for regions in the mouse  
323 isocortex.

### 324 Transcriptomic comparison of the mouse and human striatum

325 We have focused here on comparing mouse and human brain organization using transcriptomic data, with  
326 a latent space based on homologous genes as the common space between the two species. To date, common  
327 space comparisons between the mouse and human brain have only been performed using functional con-  
328 nectivity (Balsters et al., 2020; Schaeffer et al., 2020). As a case in point, Balsters et al. (2020) compared  
329 mouse and human striatal organization using this measure. They found that the nucleus accumbens was  
330 highly conserved between mice and humans, and that voxels in the posterior part of the human putamen  
331 were significantly similar to the lateral portion of their mouse caudoputamen parcellation. Additionally,  
332 they report that 85% of voxels in the human striatum were not significantly similar to any of their mouse  
333 striatal seeds, and that 25% of human striatal voxels were significantly dissimilar compared with the mouse.  
334 These differences were understandable, as they involved parts of the human striatum that connected to parts  
335 of prefrontal cortex that have no known homolog in the mouse (Neubert et al., 2014). However, it is not  
336 necessarily the case that between-species differences in connectivity are associated with distinct architectonic  
337 or molecular signatures. Therefore, we investigated the patterns of similarity between the mouse and human  
338 striata on the basis of gene expression using the neural network latent space representations.

339 We first identified the striatal regions present in the Allen human dataset: the caudate, the putamen, and the  
340 nucleus accumbens. We evaluated the correlation between the microarray samples in these regions and every



**Fig. 5. Similarity of mouse-human isocortical regions.** (A) Maximal correlation distributions of mouse isocortical regions. Points and error bars represent mean and 95% confidence interval over latent space samples. (B) Distributions of average maximal correlation for sensorimotor and supramodal isocortical areas in each gene expression latent space. Grey lines correspond to individual latent spaces. (C) Hierarchical clustering of mouse and human isocortical regions based on average latent space correlation values. Mouse regions are annotated as sensorimotor or supramodal. Four clusters were chosen for visualization using the elbow method. (D) Within-cluster sum of squared distances for different numbers of mouse and human isocortical clusters in the average latent space and initial homologous gene space.

region in the mouse atlas. Based on these correlation values, we focused our analysis on the four mouse regions that were consistently the most similar across all latent spaces: the caudoputamen, the nucleus accumbens, the fundus of striatum, and the olfactory tubercle. For each of the human striatal regions, we then calculated the average correlation over the samples to each of the mouse targets. We examined the distribution of these average correlation values over the latent spaces (Fig. 6A). We find that the human caudate and putamen consistently exhibit the strongest degree of similarity to the mouse caudoputamen. The median of the distribution for the caudate-caudoputamen pairs is 0.95 and 0.97 for the putamen-caudoputamen pairs, with modal values of 0.94 and 0.97, respectively. All latent spaces return correlations greater than 0.9 for caudate-caudoputamen and putamen-caudoputamen pairs. Beyond this expected top match, the caudate and putamen both exhibit high similarity to the nucleus accumbens and the fundus of striatum, with mean correlation values of about 0.80. Neither of these target regions is consistently more similar to the mouse caudoputamen over all latent spaces.

While the similarity of the caudate and the putamen to the caudoputamen is unsurprising, the story is not as clear for the human nucleus accumbens. We find that the variance in correlation calculated over all mouse targets is much lower ( $\sigma = 0.04$ ) compared with the equivalent variances for the caudate ( $\sigma = 0.09$ ) and putamen ( $\sigma = 0.10$ ), indicating less specificity to any one mouse striatal target. In particular, the human nucleus accumbens isn't as specifically similar to the mouse nucleus accumbens in the way that the caudate and putamen are similar to the caudoputamen. The mouse target distributions are right-shifted compared with those for the caudate and putamen, with mean values of 0.90, 0.89, and 0.89 for the mouse nucleus accumbens, caudoputamen, and fundus of striatum, respectively. The human accumbens also exhibits a high degree of similarity to the mouse olfactory tubercle, the distribution of which is also right-shifted compared with the caudate and putamen.

Given the high correlation of the human caudate and putamen to the mouse caudoputamen, as well as the finding reported by Balsters et al. about the similarity of the lateral caudoputamen to the putamen, we were curious as to whether we could identify sub-regional patterns of similarity in the caudoputamen and other striatal regions using these gene expression data. To probe this question, we first examined the average latent space correlation between each voxel in the mouse striatum and every region in the human atlas. We created brain maps for the human regions that exhibited the highest mean correlation values, averaged over mouse striatal voxels: the caudate, the putamen, the nucleus accumbens, and the septal nuclei (Fig. 6B). We find that voxels in the caudoputamen exhibit a homogeneous pattern of similarity to both the caudate and the putamen. On average, voxels in the caudoputamen have a correlation of 0.95 to the caudate and 0.94 to the putamen, with standard deviations of 0.04 and 0.05 respectively. The caudate and putamen are associated with correlations of at least 0.90 in 88% and 84% of caudoputamen voxels. A number of voxels are also highly similar to the human nucleus accumbens, with an average correlation value of 0.90 and 55% of voxels returning a correlation of at least 0.9. The caudoputamen voxels most similar to the nucleus accumbens lie in the ventral-rostral part of the region. Of course, voxels in the mouse nucleus accumbens are also highly similar to the human nucleus accumbens, with an average of 0.90 and standard deviation of 0.06. While the human nucleus accumbens is the most strongly correlated region, a number of voxels also exhibit reasonably strong correlations to the substantia innominata, the septal nuclei, and the amygdala. Indeed, 91% of voxels in the accumbens are correlated at a value of 0.7 or higher to the substantia innominata. The equivalent percentages for the septal nuclei and amygdala are 78% and 74% respectively.

We additionally examined the proportion of latent spaces in which each voxel in the mouse striatum was

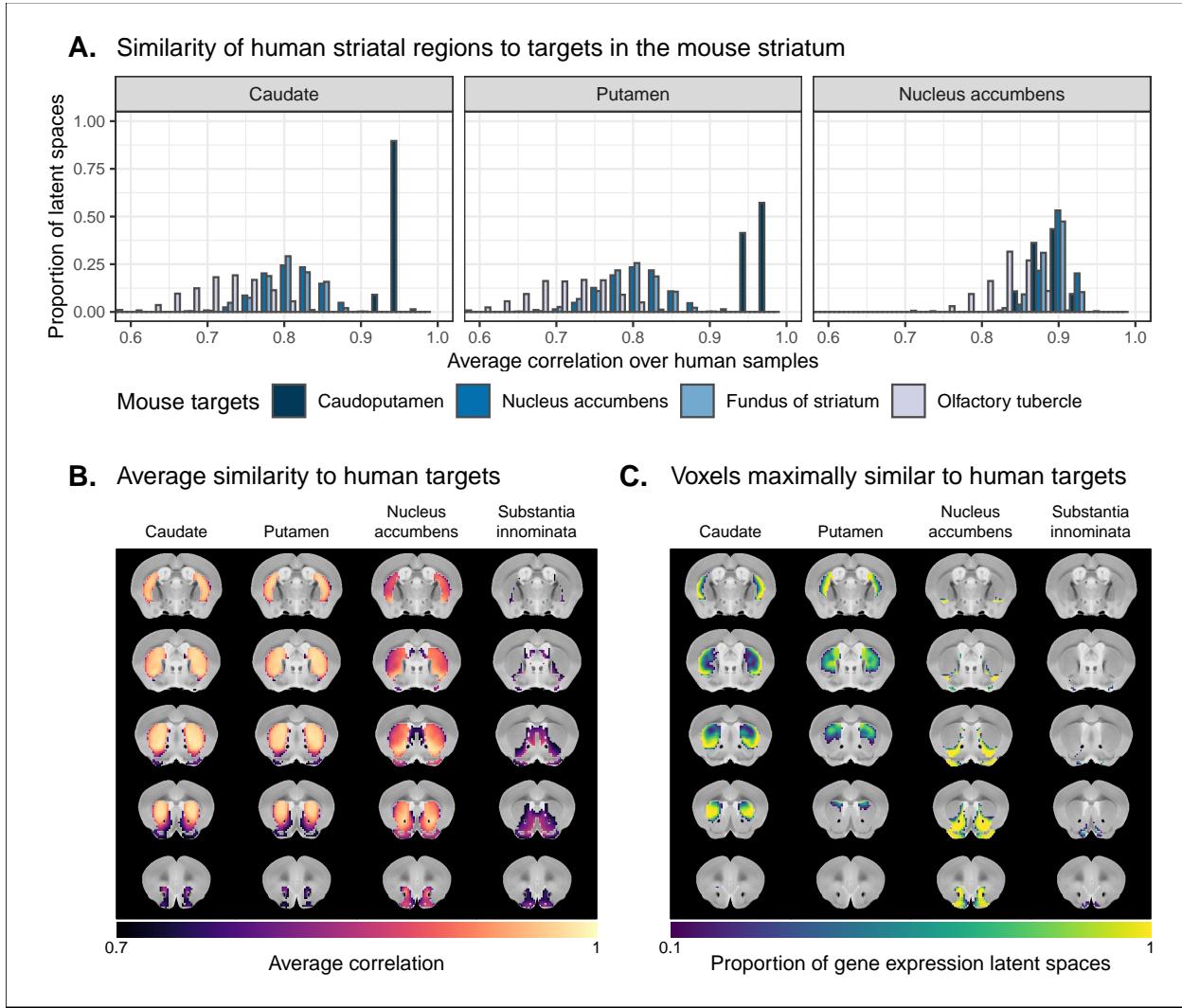
383 maximally similar to the human target regions (Fig. 6C). As expected, we find that voxels in the caudop-  
384 utamen are most often maximally similar to the human caudate and putamen, with 75% of voxels in the  
385 caudoputamen being maximally similar to the caudate or putamen in at least 95% of latent spaces, and  
386 62% of voxels being maximally similar to one of those targets in all latent spaces. Interestingly, we observe  
387 the emergence of a continuous bilateral pattern of specificity to the caudate and putamen, with voxels in  
388 the rostral and lateral-caudal parts of the caudoputamen being more specific to the caudate, and voxels in  
389 the medial-rostral part being more specific to the putamen. This map highlights subtle differences in the  
390 similarity between caudoputamen voxels and the caudate or putamen. While this pattern distinguishes the  
391 two regions on the basis of which is the top match, individual voxels have very similar correlation values to  
392 the targets (Fig. 6B), with a mean difference in correlation of only 0.006. Beyond the caudoputamen, we  
393 find that the accumbens and olfactory tubercle in the mouse are consistently similar to the human nucleus  
394 accumbens, with 80% of mouse accumbens voxels and 65% of olfactory tubercle voxels having the human  
395 accumbens as their top match in at least 80% of latent spaces. For those voxels below this threshold, the  
396 human regions that are most often the top match are once again the amygdala, the septal nuclei, and the  
397 substantia innominata.

398 Overall, we observe a strong association between the mouse caudoputamen and both the human caudate and  
399 putamen. While we find a subtle pattern of specificity to either region among voxels in the caudoputamen on  
400 the basis of maximal similarity, the high degree of similarity in the correlation values to each region suggests  
401 that the majority of voxels in the caudoputamen are equally similar to the caudate and the putamen on the  
402 basis of the expression of mouse-human homologous genes. We also find that the nucleus accumbens is well  
403 conserved across species. However the region also exhibits patterns of similarity that go beyond the simple  
404 one-to-one match. The human accumbens features similar correlation values to the mouse caudoputamen  
405 and fundus of striatum, in addition to the accumbens proper, with no sharp distinction between these regions.  
406 It also exhibits a larger degree of similarity to the mouse olfactory tubercle. This is also seen in the mouse  
407 striatum, where voxels in the accumbens and the olfactory tubercle map onto the human accumbens.

## 408 Discussion

409 We have demonstrated how spatial transcriptomic patterns of homologous genes can be used to make quan-  
410 titative comparisons between the mouse and human brain. We showed that using homologous genes as a  
411 common space allows one to easily identify coarse similarities in brain structures across species, but that  
412 more fine-scaled parcellations, such as at the level of cortical areas, are more complex. Despite this limi-  
413 tation, the approach still allows for a formal assessment of different patterns of between-species similarity  
414 in primary compared to supramodal regions, identifications of distinct clusters of cortical territories across  
415 species, and comparison of between-species similarities at the transcriptomic level to those observed using  
416 other modalities. We will discuss our observations in the context of the importance of the mouse as a model  
417 for human neuroscience below.

418 The abundance of neuroscience research performed using mice has resulted in a wealth of knowledge about the  
419 mouse brain. In the preclinical setting, mouse models are utilized with the intention of better understanding  
420 human neuropathology. For instance, in the context of autism spectrum disorders, a plethora of studies  
421 using mouse models have reported on the neurobiological and neuroanatomical phenotypes that arise from  
422 mutations at specific genetic loci (Gompers et al., 2017; Horev et al., 2011; Pagani et al., 2021). It is common



**Fig. 6. Similarity among mouse and human striatal regions.** (A) Distributions over gene expression latent spaces of region-wise average correlation values for mouse and human striatal pairs. Human regions were chosen based on the AHBA ontology. Mouse target regions were chosen to be those with the highest average correlation values. (B) Latent space averaged correlations between voxels in the mouse striatum and human target regions. Target regions were selected based on the highest mean correlation across all striatal voxels. (C) Proportions of latent spaces in which mouse striatal voxels are maximally similar to human target regions.

423 for researchers involved in translational neuroscience to rely on findings of this kind to make inferences about  
424 the human disorder. The typical approach, which is to identify rough post-hoc correspondences between  
425 neuroanatomical ontologies, is not particularly comprehensive and is subject to confirmation bias. While it  
426 may be a reasonable starting point for comparison, the true correspondence between the mouse and human  
427 brain is likely more complicated given the evolutionary distance between the two species. Although overall  
428 patterns of brain organization, including the general pattern of neocortical organization, are similar across  
429 all mammals, substantial differences are evident (Ventura-Antunes et al., 2013). To make matters worse,  
430 researchers from the different neuroscientific traditions often use distinct terminology, further complicating  
431 detailed information exchange. To address these problems, we sought to establish a first quantitative whole-  
432 brain comparison between the two species.

433 The expression of homologous genes provides an elegant way to define a common space for quantitative cross-  
434 species comparisons since it relies on homology at a deep molecular biological level. The approach is not  
435 without limitations however. First, the acquisition of whole-brain transcriptomic data is labour-intensive,  
436 time consuming, and invasive. These data sets cannot be generated easily, especially in the human, in which  
437 the process depends on the availability of post-mortem samples. As a result, the effective sample sizes are  
438 extremely limited in this domain. For instance, in the Allen mouse coronal in-situ hybridization data set  
439 used here, the brain-wide expression of each gene is sampled only once (barring a few exceptions). This  
440 constrains the types of analyses that are possible (e.g. null hypothesis significance testing) and largely limits  
441 the availability of replication data sets. That being said, new technologies, such as spatial transcriptomics,  
442 are gradually making it easier to acquire brain-wide gene expression data in less time and at lower cost (Ortiz  
443 et al., 2020; Stahl et al., 2016; Vickovic et al., 2019). Second, the approach of relying on all available genes  
444 is subject to noise. To address this issue, Myers (2017) (Myers, 2017) used a method of gene set selection  
445 to attempt to improve the correspondence between established mouse-human homologies. While this lead  
446 to improvement, it was only at the level of coarsely defined regions (e.g. cortex-cortex). Our approach,  
447 therefore, was to use supervised machine learning to create a latent common space based on combinations  
448 of homologous genes that can delineate areas within a single species.

449 This latent common space approach led to a substantial improvement in specificity of between-species com-  
450 parisons. Nevertheless, it is evident that the first major distinction in gene expression patterns within a  
451 species, and the easiest identification of similarity across species, is at the coarse anatomical level of the  
452 major subdivisions of the vertebrate brain, such as the isocortex, cerebellar hemispheres and nuclei, and  
453 brain stem. All of these territories were present in the ancestral vertebrate brain (Striedter and Northcutt,  
454 2020) and the ability to detect conserved transcriptomic signatures at this level is not surprising. Within  
455 such structures, such as the isocortex, our ability to make simple one-to-one correspondences decreased. This  
456 is partly because areas within a coarse structure have more similar transcriptomic profiles, but also likely  
457 due to the fact that a single area in one brain does not have a single correspondent in another, larger brain.  
458 In other words, regions in the brains of related species may exhibit one-to-many or many-to-many mappings.  
459 In our study, we found greater cross-species similarity between cortical areas associated with sensorimotor  
460 processing than areas in supramodal cortex. Primary areas, including the sensorimotor areas, are present  
461 in all mammals studied to date and likely part of the common ancestors of all mammals (Kaas, 2011a;  
462 Krubitzer, 2007). Although this common ancestor likely also had non-primary areas, it cannot be denied  
463 that association cortex expanded dramatically in primates and especially so in the human brain (Chaplin et  
464 al., 2013; Mars et al., 2016a). Again, the pattern found here of greater similarity in more conserved areas  
465 might reflect this evolutionary history. In that context it is interesting to note that some non-primary areas

466 thought to be present in the common mammalian ancestor, such as cingulate and orbitofrontal cortex (Kaas,  
467 2011a) showed relatively high correlation to human areas.

468 An advantage of the approach presented here is that it can, in principle, be applied to any aspect of brain  
469 organization. Beyond simply establishing whether areas are similar across species in a particular common  
470 space, comparing the results across common spaces established using different types of neuronal data can  
471 inform on which larger principles of organization are similar across brains (Eichert et al., 2020). This is  
472 illustrated here by the results of our striatal analysis. We found high similarity between the human caudate  
473 and putamen and mouse caudoputamen, with little differentiation within these regions in a single species.  
474 In contrast, Balsters et al. (2020) demonstrated that human caudoputamen contains a distinct pattern of  
475 connectivity. At first sight, one could argue the results are in contrast. However, evolutionarily speaking, it  
476 is quite probable that an overall similar transcriptomic signature of the striatum can be accompanied by a  
477 distinct connectivity pattern to areas of the cortex present in only one of the two species. Indeed, this speaks  
478 to the different types of similarity that can be studied, depending on which aspect of brain organization one  
479 is interested in. Although the human brain is much larger than the mouse brain and contains a number  
480 of cortical territories that have no homologue in the mouse brain (Kaas, 2011b; Rudebeck and Izquierdo,  
481 2022), the similarity in transcriptomic signature mean that translations between the species is valid in many  
482 contexts.

483 The power of a formal understanding of similarities and differences between brains at different levels of  
484 organization is evident. In fundamental neuroscience, it will help translate results from data types that  
485 cannot be obtained in humans to the human brain (Barron et al., 2021). In translational neuroscience, it  
486 will, in a negative sense, help establish the limits of the translational paradigm by showing which aspects  
487 of the human brain cannot be understood using the model species (Liu et al., 2021). In a positive sense,  
488 it will also help by establishing and improving our understanding of the many aspects in which the model  
489 and human brain do concur (Mandino et al., 2021). More ambitious still, it can provide a way in which  
490 highly diverse manifestations of certain disease syndromes (e.g. autism spectrum disorder) (Grzadzinski et  
491 al., 2013; Simonoff et al., 2008) and the availability of many distinct model strains (Ellegood et al., 2015),  
492 each hypothesized to capture a distinct aspect of a multi-dimensional clinical syndrome, can be related to  
493 one another. Ultimately, we believe that using the mapping of homologous gene expression between species  
494 can be an important part of building a transform that maps information obtained using mice to humans and  
495 vice versa.

## 496 Materials and methods

### 497 Mouse gene expression data

498 We used the adult mouse whole-brain in-situ hybridization data sets from the Allen Mouse Brain Atlas  
499 (Lein et al., 2007). Specifically, we used 3D expression grid data, i.e. expression data aligned to the Allen  
500 Mouse Brain Common Coordinate Framework (CCFv3)(Wang et al., 2020) and summarized under a grid  
501 at a resolution of 200 $\mu$ m. We downloaded the gene expression “energy” volumes from both the coronal  
502 and sagittal in-situ hybridization experiments as a sequence of 32-bit float values using the Allen Institute’s  
503 API (<http://help.brain-map.org/display/api/Downloading+3-D+Expression+Grid+Data>). These volumes  
504 were subsequently reshaped into 3D images in the MINC format. Origin, extents, and spacing were defined

505 such that the image was RAS-oriented, with the origin at the point where the anterior commissure crosses  
506 the midline. The MINC images from the coronal and sagittal data sets were then processed separately  
507 using the Python programming language. The sagittal data set was first filtered to keep only those genes  
508 that were also present in the coronal set. Images were imported using the `pyminc` package, masked and  
509 reshaped to form an experiment-by-voxel expression matrix. We pre-processed this data by first applying a  
510 `log2` transformation for consistency with the human data set. For those genes associated with more than  
511 one in-situ hybridization experiment, we averaged the expression of each voxel across the experiments. We  
512 subsequently filtered out genes for which more than 20% of voxels contained missing values. Finally, we  
513 applied a K-nearest neighbours algorithm to impute the remaining missing values. The result of this pre-  
514 processing pipeline was a gene-by-voxel expression matrix with 3958 genes and 61315 voxels for the coronal  
515 data set and a matrix with 3619 genes and 26317 voxels for the sagittal data set.

## 516 Human gene expression data

517 Human gene expression data was obtained from the Allen Human Brain Atlas (Hawrylycz et al., 2012). The  
518 data were downloaded from the Allen Institute’s API (<http://api.brain-map.org>) using the `abagen` package  
519 in Python (<https://abagen.readthedocs.io/en/stable/>) (Markello et al., 2021). We used the microarray data  
520 from the brains of all six donors, each of which contains `log2` expression values for 58692 gene probes  
521 across numerous tissue samples. The data were pre-processed using a custom pipeline built following the  
522 recommendations from Arnatkeviciūtė et al. (Arnatkeviciūtė et al., 2019). The pipeline was implemented  
523 using the R programming language. Specifically, once imported, we passed the data from individual donors  
524 through a set of filters. The first filter removed gene probes that were not associated with an existing Entrez  
525 gene ID. The second filtering step used the probe intensity filter provided by the AHBA. For each donor,  
526 we only retained the probes for which more than 50% of samples passed the intensity filter. After filtering,  
527 we aggregated the expression values for probes that corresponded to the same gene. To do so, we computed  
528 the average expression per sample for probes corresponding to a given gene. This was done separately for  
529 each donor, and the averages were computed in linear space rather than `log2` space. Once the average gene  
530 expression values were obtained, we transformed the data back to `log2` space. Finally, we combined the  
531 gene-by-sample expression matrices across the different donors. In doing so, we retained only those genes  
532 present in the data sets from all six donors. The result was a gene-by-sample expression matrix with 15125  
533 genes and 3702 samples.

## 534 Mouse atlases

535 We used a version of the DSURQE atlas from the Mouse Imaging Centre (Dorr et al., 2008; Qiu et al., 2018;  
536 Richards et al., 2011; Steadman et al., 2014; Ullmann et al., 2013), modified using the AMBA hierarchical  
537 ontology, which was downloaded from the Allen Institute’s API. The labels of the DSURQE atlas correspond  
538 to the leaf node regions in the AMBA ontology, which allowed us to use the hierarchical neuroanatomical  
539 tree to aggregate and prune the atlas labels to the desired level of granularity. For the purposes of our  
540 analyses, we removed white matter and ventricular regions entirely. The remaining grey matter regions were  
541 aggregated up the hierarchy so that the majority of resulting labels contained enough voxels to be classified  
542 appropriately by the multi-layer perceptron. In doing so, we maintained approximately the same level of  
543 tree depth within a broad region (e.g. cerebellar regions were chosen at the same level of granularity). This

544 resulted in a mouse atlas with 67 grey matter regions. We additionally generated an atlas with 11 broader  
545 regions for visualization and annotation purposes.

546 **Human atlases**

547 We used the hierarchical ontology from the AHBA, which we obtained using the Allen Institute’s API.  
548 We aggregated and pruned the neuroanatomical hierarchy to correspond roughly to the level of granularity  
549 obtained in our mouse atlas, resulting in 88 human brain regions. We additionally generated a set of 16  
550 broad regions for visualization and annotation. White matter and ventricular regions were omitted entirely.

551 **Regional expression and similarity matrices**

552 We created the mouse and human gene-by-region expression matrices from the mouse gene-by-voxel and  
553 human gene-by-sample expression matrices. First, we intersected the gene sets in these matrices with a  
554 list of 3331 homologous genes obtained from the NCBI HomoloGene database (NCBI, 2018), resulting in  
555 2624 homologous genes present in both the mouse and human expression matrices. We then annotated  
556 each of the human samples with one of the 88 human atlas regions, and each of the mouse voxels with  
557 one of the 67 mouse atlas regions, discarding white matter and ventricular entries in the process. These  
558 labelled expression matrices were subsequently normalized as follows: For each matrix, we first standardized  
559 every gene across all voxels/samples using a z-scoring procedure. We then centered every voxel/sample  
560 by subtracting the average expression over all homologous genes. Finally, we generated the gene-by-region  
561 expression matrices by averaging the expression of every gene over the voxels/samples corresponding to  
562 each atlas region. Using these expression matrices, we generated the mouse-human similarity matrix by  
563 computing the Pearson correlation coefficient between all pairs of mouse and human regions.

564 **Multi-layer perceptron classification and latent space**

565 To improve the resolution of mouse-human neuroanatomical matches, we performed a supervised learning  
566 approach, wherein we trained a multi-layer perceptron neural network to classify 67 mouse atlas regions  
567 from the expression values of 2624 homologous genes. We chose a model architecture in which each layer  
568 of the network was fully connected to previous and subsequent layers. To optimize the hyperparameters,  
569 we implemented an ad hoc cross-validation procedure that took into account the fact that the majority of  
570 genes in the coronal AMBA data set are sampled only once over the entire mouse brain. The procedure  
571 involved a combination of the coronal data set and the sagittal in-situ hybridization data sets. For the  
572 sagittal data set, we used the expression matrix described above. However, we used a modified version  
573 of the coronal expression matrix. This matrix was generated using the pipeline described above with the  
574 following modifications: 1. We applied a *unilateral* brain mask to the coronal images since the sagittal data  
575 is unilateral by construction, and 2. we did not aggregate the expression of multiple in-situ hybridization  
576 experiments for those genes in the coronal set pertaining to more than one experiment. We then filtered  
577 these experiment-by-voxel expression matrices according to the list of mouse-human homologous genes, as  
578 well as the human sample expression matrix. We also annotated the voxels in each of the expression matrices  
579 with one of the 67 regions in the mouse atlas. Our validation procedure then involved iterative construction

580 of training and validation sets by sampling gene experiments from either the coronal or sagittal matrices: For  
581 every gene in the homologous set, we first determined whether that gene was associated with more than one  
582 experiment in the coronal matrix. If this was the case, we randomly sampled one of those experiments for the  
583 training set and one of the remaining experiments for the validation set. If the gene was associated with only  
584 one experiment in the coronal set, we randomly sampled either the coronal or sagittal experiment for the  
585 training set and the other for the validation set. Once the training and validation sets were generated, they  
586 were normalized using the procedure described above. We then trained the neural network using the training  
587 set and evaluated its performance on the validation set. Given that the construction of the training and  
588 validation sets involved some stochasticity, we repeated this construction, training, and validation procedure  
589 10 times for every combination of hyperparameters.

590 The hyperparameters that we optimized using this method were the number of hidden layers in the network,  
591 the number of hidden units (i.e. neurons) per hidden layer, the dropout rate, and the amount weight decay.  
592 The values we optimized over were as follows. We varied the number of hidden layers between 3 and 5. We  
593 varied the number of hidden units between 100 and 1000 in increments of 100. For the dropout rate, we  
594 examined values of 0, 0.25 and 0.50. For the amount of weight decay, we examined values of  $10^{-6}$  and  $10^{-5}$ .  
595 We found that the best-performing model had 3 hidden layers, 200 neurons per layer, a dropout rate of 0,  
596 and a weight decay value of  $10^{-6}$ . This model returned an average classification accuracy of 0.926 on the  
597 training sets and of 0.526 on the validation sets. Following validation, we used the optimal hyperparameters  
598 to train the network on the full bilateral coronal voxel-wise expression matrix.

599 These models were implemented in Python using PyTorch via the `skorch` library (<https://skorch.readthedocs.io/en/stable/>). For both validation and training, the models were trained over 200 epochs  
600 using a maximum learning rate of  $10^{-5}$ . We used the `AdamW` optimization algorithm (Loshchilov and Hutter,  
601 2019) and `OneCycleLR` learning rate scheduler policy. The activation function used in the forward pass  
602 was the rectified linear unit (ReLU) and the loss function was the negative log-likelihood loss, which is the  
603 default for the `NeuralNetClassifier` class in `skorch`.

604 We used the trained perceptron to generate the latent gene expression space. To extract the appropriate  
605 transformation, we removed the predictive output layer and soft-max transformation from the network  
606 architecture. The resulting architecture returns the 200 hidden units in the third hidden layer as the output  
607 of the network. To create the latent space data representations, we applied this network to the mouse  
608 and human gene-by-region expression matrices, transposed so that the genes were the input variables. The  
609 resulting matrices have 200 columns corresponding to the hidden units and 67 (88) rows corresponding to  
610 the mouse (human) regions. They describe each brain region's weight over the hidden units. To create the  
611 similarity matrix, we calculated the Pearson correlation coefficient between all pairs of mouse and human  
612 regions.

613 Given the stochasticity inherent in training the network (e.g. random weight initialization and stochastic  
614 optimization), we repeated the training and transformation process 500 times using the same network  
615 architecture and input data.

## 617 Data and code availability

618 This manuscript, including all figures, was generated programmatically using R Markdown (<https://rmarkdown.rstudio.com>) and L<sup>A</sup>T<sub>E</sub>X(<https://www.latex-project.org>). The Allen Mouse Brain At-

620 las and Allen Human Brain Atlas data sets are openly accessible and can be downloaded from the  
621 Allen Institute's API (<http://api.brain-map.org>). All of the code and additional data needed to gen-  
622 erate this analysis, including figures and manuscript, is accessible at <https://github.com/abeaucha/MouseHumanTranscriptomicSimilarity/>.  
623

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## 629 Competing interests

630 The authors declare that they have no competing interests.

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