

# Generation of Infant-dedicated Fine-grained Functional Parcellation Maps of Cerebral Cortex

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## Abstract

Infancy is a dynamic and immensely important period in human brain development. Studies of infant functional development using resting-state fMRI rely on precisely defined cortical parcellation maps. However, available adult-based functional parcellation maps are not applicable for infants due to their substantial differences in functional organizations. Fine-grained infant-dedicated cortical parcellation maps are highly desired but remain scarce, due to difficulties ranging from acquiring to processing of infant brain MRIs. In this study, leveraging 1,064 high-resolution longitudinal rs-fMRIs from 197 infants from birth to 24 months and advanced infant-dedicated processing tools, we create the first set of infant-specific, fine-grained cortical functional parcellation maps. Besides the conventional folding-based cortical registration, we specifically establish the functional correspondences across individuals using functional gradient densities and generate both age-specific and age-common fine-grained parcellation maps. The first set of comprehensive brain functional developmental maps are accordingly derived, and reveals a complex, hitherto unseen multi-peak fluctuation development pattern in temporal variations of gradient density, network sizes, and local efficiency, with more dynamic changes during the first 9 months than other ages. Our proposed method is applicable in generating fine-grained parcellations for the whole lifespan, and our parcellation maps will be available online to advance the neuroimaging field.

**Keywords:** infant brain, functional parcellation, functional connectivity.

1    **1. Introduction**

2    The dynamic brain functional development during the first two postnatal years is important for  
3    establishing cognitive abilities and behaviors that could last a lifetime (1-3). As a prerequisite for  
4    understanding how the brain works and develops, cortical parcellation maps provide a repository  
5    that helps cortical area localization, network node definition, inter-subject comparison, inter-study  
6    communication, and comparison, as well as reducing data complexity while improving statistical  
7    sensitivity and power (4). In the functional aspect, researchers used to reveal and understand the  
8    cortical network topography by clustering cortical vertices into parcels that are different from each  
9    other in functional architecture using adult resting-state fMRI (rs-fMRI) data (5, 6). Although these  
10   clustering-based methods can produce convincing results given a limited number of clusters, they  
11   are not suitable for fine-grained parcellations (e.g.,  $\gg 100$  parcels), as they usually result in  
12   considerable disjointed fragments that are hardly explainable. To this point, recent adult  
13   parcellations (7-10) started to use gradient-based methods, i.e., the functional gradient density, to  
14   delineate sharp changes of resting-state functional connectivity (RSFC) patterns to promote the  
15   meaningfulness and accuracy of parcel boundaries.

16    All the abovementioned studies derived functional parcellation maps using adult data, which  
17   are not suitable for infant studies featuring dynamic brain structural and functional development,  
18   due to enormous differences in brain functional organization between infants and adults (11, 12).  
19   Therefore, infant-specific cortical functional parcellation maps are highly desired, but remain  
20   scarce, due to difficulties in both acquiring high-resolution infant brain multi-modal MR images  
21   and challenges in processing infant MR images that typically have prominently dynamic imaging  
22   appearance and extremely poor tissue contrast (1, 2, 13). Of note, another critical issue of using the  
23   abovementioned methods for generating infant functional parcellations is that these methods  
24   typically computed the functional gradient density map for a cohort directly based on cortical  
25   folding-based registration and extensive spatial smoothing of functional connectivity, which,

26 however, cannot lead to accurate functional alignment across individuals, due to large variation  
27 between folding and functional areas. Thus many vital details of the functional architecture are  
28 blurred and inherently missed in the resulting functional parcellation maps.

29 In this paper, we aim to generate the first set of infant-specific, high-resolution, fine-grained  
30 functional parcellation maps on the cortical surface to significantly accelerate early brain  
31 development studies. To this end, this study leverages a large high-resolution dataset with 1,064 rs-  
32 fMRI scans and 394 T1-weighted and T2-weighted structural MRI scans from birth to 2 years of  
33 age, as part of the UNC/UMN Baby Connectome Project (14). To ensure accuracy, all MR images  
34 are processed using an extensively validated, advanced infant-dedicated cortical surface-based  
35 pipeline (15). To establish accurate cortical functional alignment across individuals, we propose a  
36 novel method to first compute the functional gradient density map of each infant scan, rather than  
37 for the whole cohort in the traditional way, to capture fine-grained functional patterns, and then co-  
38 register all functional gradient density maps across individuals based on both cortical folding and  
39 functional gradient information. Following steps detailed in Fig. 1, our derived group-average  
40 functional gradient density maps capture much more details of cortical functional architecture than  
41 the conventional method, thus enabling us to generate fine-grained age-specific cortical parcellation  
42 maps of infants at multiple ages, i.e., 3, 6, 9, 12, 18, and 24 months of age. To facilitate infant  
43 studies requiring parcel-to-parcel correspondences across ages, we also generate age-common  
44 parcellation maps that are suitable for all ages during the first two years. Our infant functional  
45 parcellation maps will soon be released to the public to greatly contribute to the pediatric  
46 neuroimaging research community.

47 2. Results

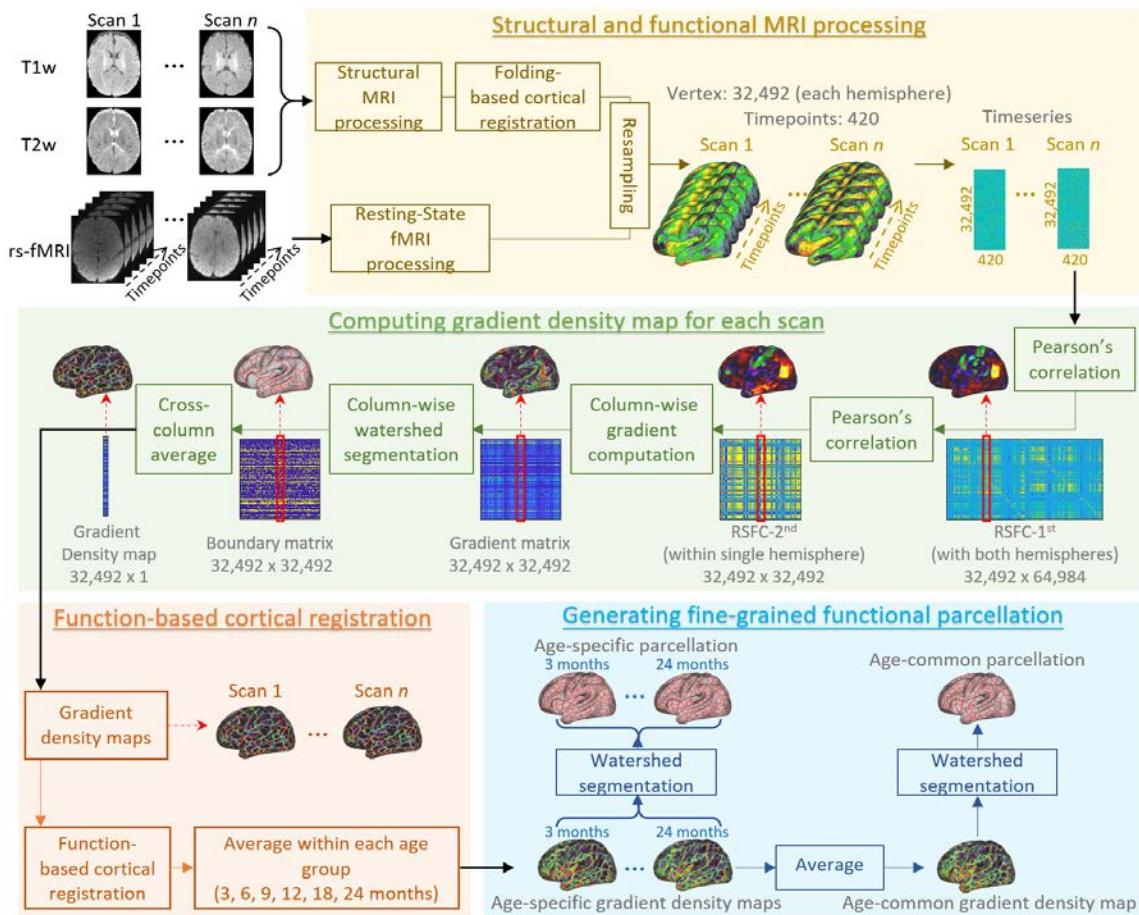


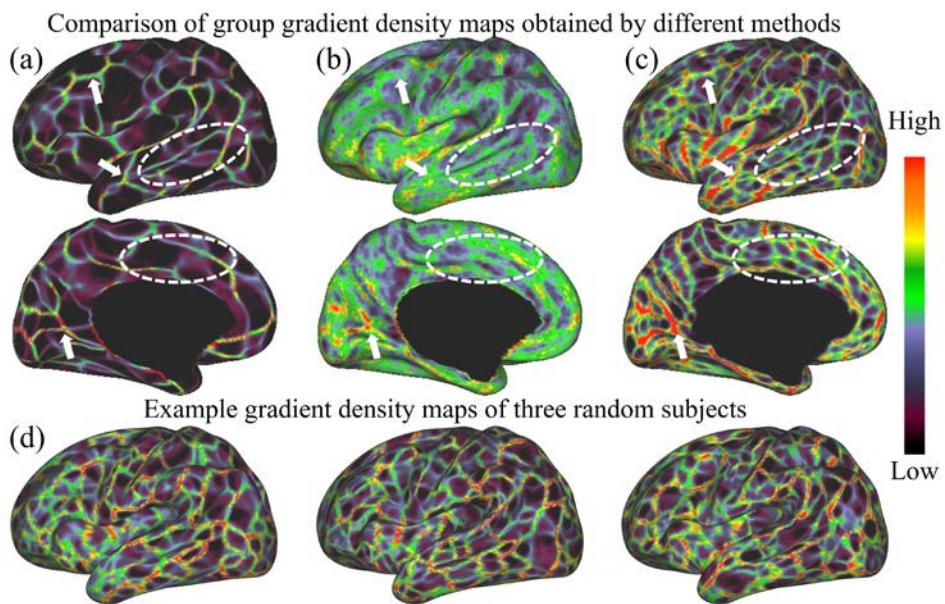
Fig. 1. The procedure of infant parcellation using functional gradient density. Our major steps include structural and functional MRI processing, computing gradient density map for each scan, function-based cortical registration, and generating fine-grained functional parcellation.

48

49 We unprecedently investigated the fine-grained cortical surface-based functional parcellation  
 50 maps of the infant cerebral cortex using  $1,064$  high-resolution ( $2 \times 2 \times 2 \text{ mm}^3$ ) resting-state fMRI  
 51 scans from  $197$  healthy infants, with subject demographics shown in Table 1 and Fig. 8. To capture  
 52 detailed patterns of sharp transition between cortical areas, after the conventional cortical folding-  
 53 based inter-individual cortical registration, the gradient density map of cortical functional  
 54 connectivity was computed on each scan of each individual and further used as a reliable functional

55 feature for function-based registration for establishing functionally more meaningful cortical  
56 correspondences across individuals. This resulted in considerably detailed visualization of  
57 functional boundaries on the cerebral cortex, which was used to create the infant-dedicated fine-  
58 grained cortical functional parcellation maps. Detailed steps of the proposed method are illustrated  
59 in Fig. 1.

60 **2.1 Advantage of the Proposed Method**



**Fig. 2.** Comparison of the group-average functional gradient density maps on the 3-month age group generated by different methods. (a) The gradient density map computed directly on the population-average connectivity matrix. (b) The gradient density map computed on each individual and then averaged across individuals. (c) The gradient density map generated by our method, which computes the average of individual gradient density maps after co-registration of them based on both cortical folding and functional gradient density. White arrows point out consistent gradient density patterns using different methods, and white dashed circles show some more detailed and fine-grained patterns revealed by our method. (d) Example gradient density maps of three random subjects. This figure demonstrates that some detailed

gradient patterns in the individual cortex are usually missed by other methods, and can be well captured by our method.

61

62 The functional gradient density maps of 3-month infant scans generated by different methods are  
63 compared in Fig. 2, which demonstrates the advantage of our proposed method. Specifically, Fig.  
64 2 (a) shows the group-average gradient density map directly computed using the group-average  
65 RSFC-2<sup>nd</sup> as in (7, 9). Fig. 2 (b) shows the group-average gradient density map based on individual  
66 gradient density maps, in which we first computed a gradient density map on the RSFC-2<sup>nd</sup> of each  
67 individual and then averaged them across individuals. Fig. 2 (c) shows the group-average gradient  
68 density map generated by the proposed method, where all individual gradient density maps are co-  
69 registered using the gradient density as a functional feature and then further averaged across  
70 individuals. It can be observed that major patterns of the functional gradient density in Fig. 2 (a)  
71 are well preserved in Fig. 2 (c) (with some examples pointed out with white arrows), which implies  
72 the meaningfulness of the functional gradient density patterns in Fig. 2 (c). Most importantly, Fig.  
73 2 (c) exhibits much more detailed and clear patterns of the functional gradient density, compared  
74 to Fig. 2 (a) and (b), especially in the temporo-occipital, parietal, and lateral prefrontal areas,  
75 indicating the advantage of performing the 2<sup>nd</sup> round of co-registration based on functional gradient  
76 density. Consequently, the functional gradient density maps generated by the proposed method are  
77 able to capture fine-scaled architectures of infant functional connectivity while maintaining the  
78 major functional patterns, thus leading to more meaningful fine-grained functional parcellation  
79 maps. We also show the gradient density maps of three random subjects in Fig. 2 (d), which further  
80 demonstrates that our method can well capture these important and detailed functional gradient  
81 patterns, which are usually missed by the compared methods.

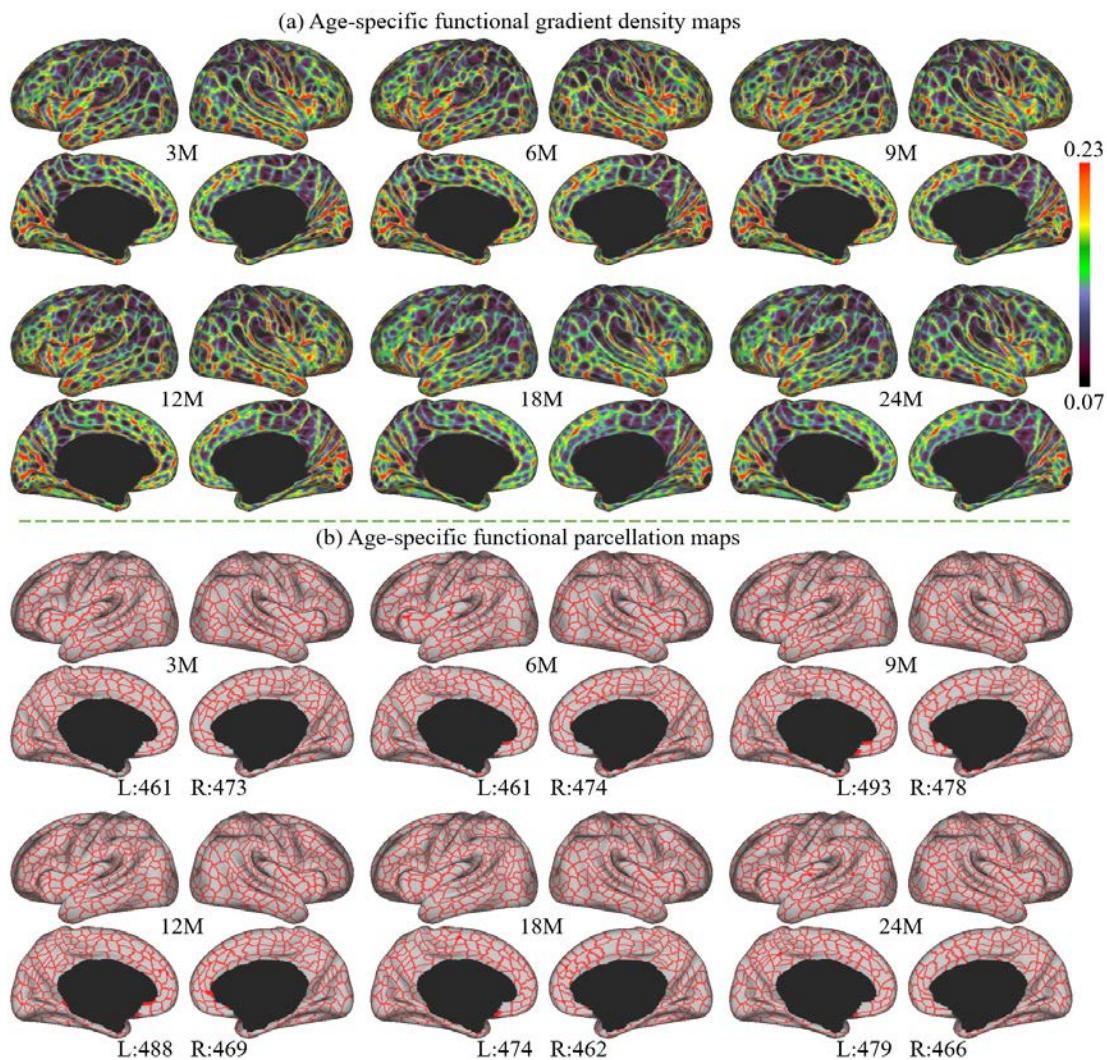
82 To test whether the gradient density maps are reproducible, we randomly divided subjects into  
83 two non-overlapping parts and computed the dice ratio between two gradient maps after

84 thresholding. A higher dice ratio indicates higher reproducibility. By repeating this experiment  
85 1,000 times, the overall dice ratio reaches  $0.9295 \pm 0.0021$ , indicating the high reproducibility of  
86 our results.

87 **2.2 Age-specific Functional Gradient Density and Parcellation Maps**

88 The age-specific functional gradient density maps are computed by averaging gradient density  
89 maps of subjects in corresponding age groups and results at 3, 6, 9, 12, 18, and 24 months are shown  
90 in Fig. 3 (a). As can be observed, the major gradient patterns are distributed bilaterally  
91 symmetrically on the cortex, like the central sulcus, superior temporal gyrus, middle temporal gyrus,  
92 parieto-occipital fissure, and calcarine fissure. Nevertheless, certain gradient patterns exhibit  
93 hemispheric differences. For example, the precentral gyrus in the right hemisphere has a higher  
94 gradient density than that in the left hemisphere. All these spatial distributions of functional  
95 gradient density remain largely consistent across ages.

96 Age-specific cortical parcellation maps derived from these functional gradient density maps are  
97 presented in Fig. 3 (b). These maps were obtained using a watershed algorithm without thresholding  
98 or any manual editing. It can be observed that major gradient density patterns are well reflected as  
99 parcellation boundaries. Due to some slight differences in age-specific gradient density maps, the  
100 resulting age-specific parcellation maps show different parcel numbers. However, all parcel  
101 numbers fall between 461 to 493 parcels per hemisphere, and parcel numbers show slight changes  
102 that follow a multi-peak fluctuation, with inflection ages of 9 and 18 months of age.

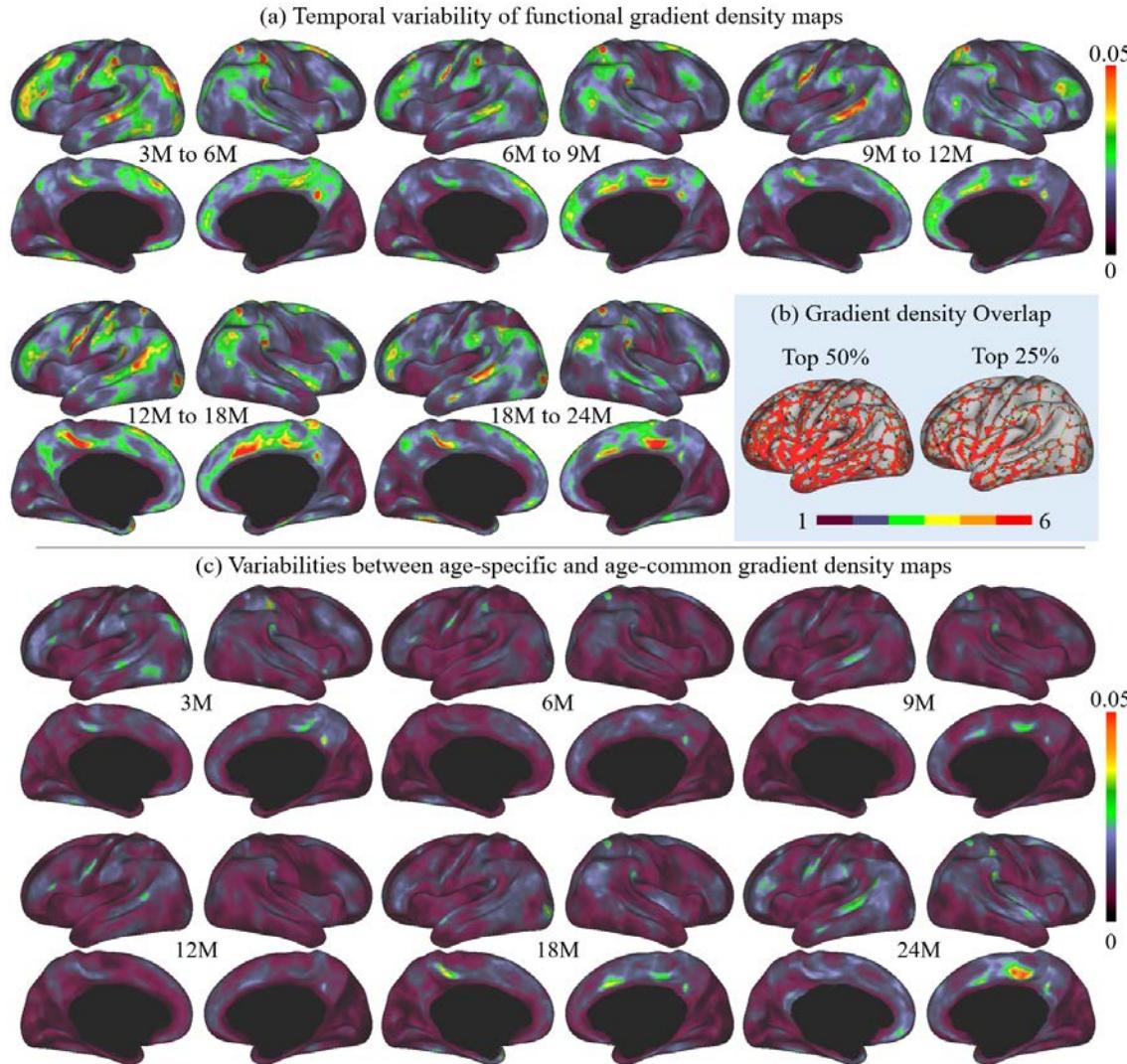


**Fig. 3.** (a) Age-specific functional gradient density maps. (b) Age-specific fine-grained functional parcellation maps, with parcel numbers noted for each age.

103

104 To evaluate the consistency of gradient density across different age groups, we thresholded and  
105 binarized the age-specific functional gradient density maps to their top 50% and 25% gradient  
106 density. These binary maps were summed up, resulting in a gradient density overlap map indicating  
107 its age consistency shown in Fig. 4 (b). In these maps, “one” stands for high gradient densities that  
108 appeared in only one age group, and “six” represents high gradient densities that appeared in all six

109 age groups. It is worth noting that most high gradient densities are repeatedly detected in all six age  
110 groups, suggesting the high consistency of majorities of high gradient densities in all age groups.



**Fig. 4.** (a) Temporal variabilities of functional gradient density maps between every two consecutive ages.  
(b) Consistency of high gradient density across ages. (c) Variabilities between each age-specific functional gradient density map and that of the age-common map.

111 Further, to better illustrate the functional architecture development, we computed the temporal  
112 variability of gradient density maps between neighboring age groups, as shown in Fig. 4 (a). In  
113 general, the temporal variabilities of functional gradient density are at a relatively low level ( $\leq 0.05$ )  
114 at all age intervals. Across all ages, high temporal variabilities are mainly presented in high-order

115 association areas, including the left middle and inferior frontal, middle temporal, right superior  
116 frontal, precuneus medial prefrontal, and bilateral supramarginal, posterior superior temporal, and  
117 medial frontal areas. Other regions mostly exhibit low temporal variabilities, especially in the  
118 sensorimotor and medial occipital regions. Keeping this spatial distribution, the temporal variability  
119 shows a multi-peak fluctuation, where the gradient density decreases from 3-6 to 6-9 months,  
120 followed by an increase during 9-12 and 12-18 months, and drops again during 18-24 months.

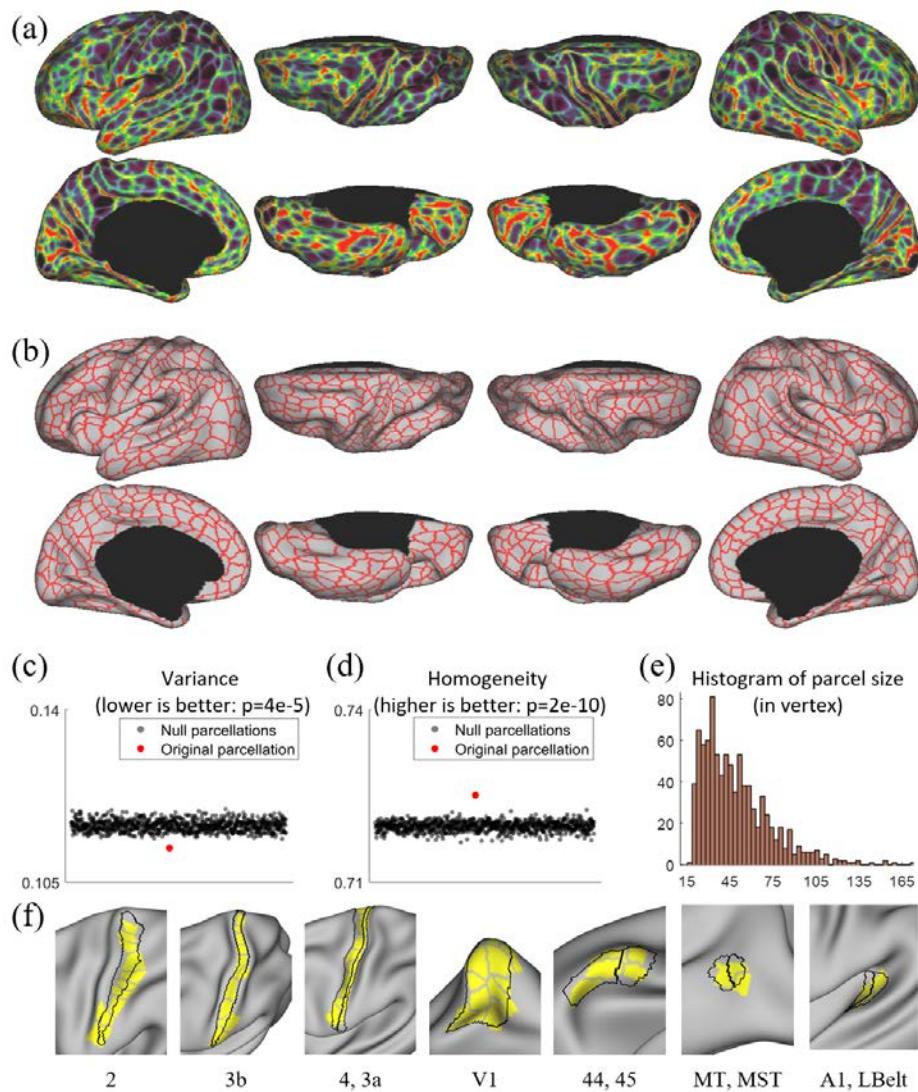
121

122 **2.3 Age-common Functional Gradient Density and Parcellation Maps**

123 Since infant functional MRI studies typically involve multiple age groups, it is highly desired to  
124 have an age-common functional parcellation map that features parcel-to-parcel correspondences  
125 across ages, so that it can be conveniently employed for all ages during infancy. Therefore, we also  
126 computed the age-common gradient density map (Fig. 5 (a)) as the average of the functional  
127 gradient density maps of all six age groups. The variabilities between the age-common gradient  
128 density map and each age-specific gradient density map are illustrated in Fig. 4 (c). Compared to  
129 the temporal variability between neighboring age groups (Fig. 4 (a)), the age-common gradient  
130 density map shows small variability to all age-specific maps. The spatial distributions of high and  
131 low variabilities remain mostly similar to that of the temporal variabilities between neighboring  
132 age groups, with high variability presented in some high-order association cortices and low  
133 variability in unimodal cortices. Consequently, it can be speculated that the age-common gradient  
134 density map can be used to generate an age-common parcellation map that is suitable for all subjects  
135 from birth to 2 years of age.

136

137 The resulted age-common functional parcellation map based on the age-common gradient



**Fig. 5.** (a) Age-common gradient density map. (b) Age-common parcellation map (864 parcels, L: 432, R: 432). (c) Our age-common parcellation shows significantly lower variance compared to the null parcellations. (d) Our age-common parcellation shows significantly higher homogeneity compared to null parcellations. (e) The histogram of parcel size, where parcel sizes are counted in vertices. (f) Some parcels correspond to known cortical areas defined by multi-modal features in adults (4).

138 density map is shown in Fig. 5 (b), which has 864 parcels in total (L: 432, R: 432) excluding the  
139 medial wall. It should be noted that we manually removed some apparently over-segmented regions

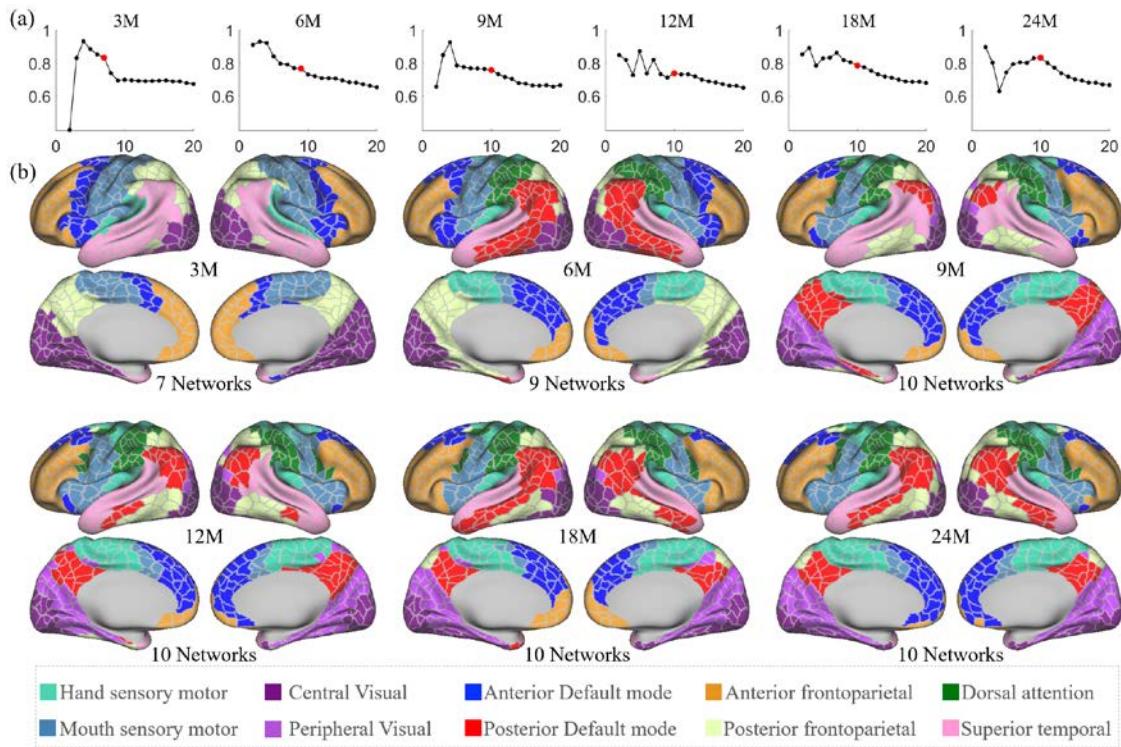
140 after using the watershed algorithm, and prior to that, we had 903 parcels in total (L: 448, R: 455).  
141 The parcel boundaries of the age-common parcellation map are well aligned with high gradient  
142 density regions and show largely bilaterally symmetric patterns of the areal organization. In the  
143 following development-related analyses in this study, we mainly employed the age-common  
144 parcellation map to facilitate comparisons of infants across ages.

145 Compared to existing fine-grained parcellation maps, such as the multi-modal adult parcellation  
146 (4), the age-common infant parcellation map has comparatively smaller and more evenly  
147 distributed parcel sizes and shapes. Also, as shown in Fig. 5 (f), some areas of our parcels show  
148 substantial overlap with the known cortical areas of adults, such as the visual areas V1, MT, MST,  
149 sensorimotor areas 2, 3, 4, auditory areas A1, LBelt, and language areas 44, 45. To further examine  
150 the validity of our parcellation map, we compared it with 1,000 null parcellation maps in terms of  
151 variance and homogeneity, with the results shown in Fig. 5 (c) and (d). It can be observed that our  
152 parcellation map shows significantly higher homogeneity ( $p=2e-10$ ) and lower variance ( $p=4e-05$ ),  
153 indicating the meaningfulness of the resulting parcellation map.

154 **2.4 Network Organization and Development**

155 We performed network clustering of the generated parcels in each age group to reveal the early  
156 development of functional network organization. The number of networks for each age group is  
157 determined separately according to the random split-half stability analysis. Empirically, the  
158 network number is set as 2 to 30, and the stability plots are shown in Fig. 6 (a). Higher stability  
159 suggests a better clustering result, hence a more meaningful network organization. Overall, when  
160 the network number surpasses 15, the stability does not show a substantial raise or decrease,  
161 indicating the network numbers likely hold less than 15. Hence, we look for the cluster number on  
162 a ‘peak’ or prior to a ‘descending cliff’, which guarantees high stability or more significant network  
163 numbers. As a result, we find that the most suitable cluster numbers for different age groups are 7  
164 networks for 3 months, 9 networks for 6 months, 10 networks for 9, 12, 18, and 24 months. Of note,

165 we choose 10 networks for 18 months so as to be consistent during development, even though it is  
166 neither a peak nor a cliff.



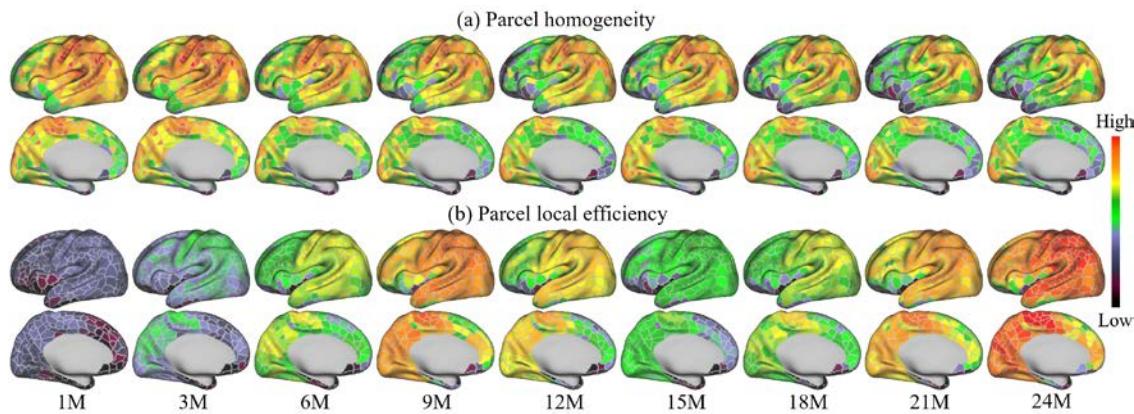
**Fig. 6.** (a) Stabilities of different network numbers of different age groups computed by repeating 200 times random split-half test. The selected numbers are highlighted in solid red dots. (b) Discovered functional network organization of parcels during infantile brain development, color-coded by corresponding networks denoted below.

167 The spatiotemporal patterns of the discovered functional network organization are shown in Fig.  
168 6 (b). Overall, changes in network structure from 3 to 9 months are more extensive than those from  
169 9 to 24 months. Specifically, the sensorimotor network splits into two subnetworks from 3 to 6  
170 months, and the boundary between them moved toward the ventral direction from 6 to 9 months.  
171 The hand sensorimotor expands, while the mouth sensorimotor shrinks and both stabilize after 9  
172 months. The auditory network is distinguished at 3 months and merges into the hand sensorimotor  
173 at 6 months. The visual network splits into peripheral and central visual subnetworks from 6 to 9  
174 months and remains stable until a slight shrinkage at 24 months.

175 Other networks exhibit more complex development with multi-peak fluctuation of the size in  
176 certain networks. Specifically, the anterior default mode network expands from 3 to 6 months, and  
177 shrinks from 6 to 9 months and from 12 to 18 months, and expands thereafter. The lateral posterior  
178 default mode network that emerged at 6 months shrinks from 6 to 9 months and then expands from  
179 9 to 18 months; while the medial posterior default mode network emerged at 9 months only lightly  
180 shrinks thereafter. The anterior and posterior default mode networks develop to the adult-like  
181 pattern at 18 months, while till 24 months, they are still detected as two separate networks. The  
182 superior temporal network shrinks from 3 to 6 months, expands from 6 to 9 months, and then  
183 shrinks again from 9 to 24 months. The anterior frontoparietal network gradually shrinks from 3 to  
184 24 months, except for an expansion from 12 to 18 months. On the medial surface, the posterior  
185 frontoparietal network expands to include the parahippocampal gyrus from 3 to 6 months and then  
186 disappears by 9 months. On the lateral surface, the posterior frontoparietal network expands from  
187 3 to 9 months to include the inferior temporal part and becomes stable thereafter. The dorsal  
188 attention network is seen at 6 months and evolves to the adult-like pattern at 9 months and keeps  
189 stable thereafter.

190 **2.5 Parcel-wise Development**

191 Homogeneity of functional connectivity can be used as a criterion for characterizing functional  
192 development. Fig. 7 (a) shows the parcel-wise homogeneity development during infancy. Our  
193 results suggest that the overall parcel-wise homogeneity shows a monotonic decrease trend during  
194 the first two years by maintaining similar relative spatial distribution. Higher homogeneities are  
195 located in the sensorimotor, paracentral, posterior insula, inferior parietal, posterior superior  
196 temporal, lateral occipital, and occipital pole. Low homogeneities are presented in lateral prefrontal,  
197 medial frontal, anterior insula, inferior temporal, and temporal pole.



**Fig. 7.** Development of parcel homogeneity and local efficiency during infancy.

198 Fig. 7 (b) shows the development of the local efficiency of each parcel. Overall, the local  
199 efficiency also exhibits a strong multi-peak fluctuation, with inflection ages observed at 9 and 15  
200 months. Parcels with low efficiency are located in the lateral superior frontal, medial superior  
201 frontal, orbitofrontal, ventral insula, and anterior inferior temporal cortices. Parcels with high local  
202 efficiency are mainly observed in sensorimotor, paracentral, parietal, and precuneus regions.

203 **3. Discussion**

204 In this study, we created the first set of both age-specific and age-common, infant-dedicated, fine-  
205 grained, and cortical surface-based functional parcellation maps using functional gradient density  
206 maps. We analyzed the spatiotemporal patterns of age-specific functional gradient density maps  
207 and found that age-common functional gradient density maps are suitable for creating fine-grained  
208 functional parcellation maps for all ages in the infant cohort. We validated the meaningfulness of  
209 the parcellation and showed that its boundaries substantially reproduced known areal boundaries,  
210 and its parcels featured high homogeneity and low variance. Finally, we illustrated the infantile  
211 development in network structure, parcel homogeneity, and parcel local efficiency.

212 This study used the functional gradient density as a feature for improving functional alignment  
213 across individuals, in addition to the conventional cortical folding features used by previous adult  
214 functional parcellations (7, 9). As a result, our method not only captured important coarse gradient

215 patterns discovered by previous methods, but also revealed much more detailed areal boundaries at  
216 a remarkable resolution, as compared in Fig. 2. The main reason is that previous studies solely  
217 relied on cortical folding-based registration, thus inevitably suffered from significant inter-subject  
218 variability in the relation between cortical folding and functional areas, leading to less accurate  
219 inter-subject functional correspondences. For infant-dedicated functional parcellations, the only  
220 one available is the volumetric-based parcellation based on image registration and clustering  
221 generated by Shi et al. (16), without any advanced surface-based processing and registration. In  
222 contrast, our parcellation maps are generated based on the cortical surface, which well respects the  
223 topology of the convoluted cerebral cortex, and avoids mixing signals from opposite sulcal banks  
224 and different tissues, leading to more accurate functional signals resampling, smoothing,  
225 computation and registration. Moreover, our parcellations leveraged high-quality 2 mm isotropic  
226 fMRI data that densely covers the first two years, instead of data with a coarse resolution of 4 mm  
227 isotropic centering at birth, 1 and 2 years of age (16).

228 Standing upon the detailed gradient density patterns by the proposed method, we generated age-  
229 specific fine-grained parcellation maps for 3, 6, 9, 12, 18, and 24 months of age. We found that the  
230 temporal variability (temporal changes) of the functional gradient density generally decreases  
231 during most age intervals, except for a slight increase from 9 to 12 months. This may suggest that  
232 the development of functional architecture gradually slows down during the first two years. We  
233 also found that high temporal variabilities mostly presented in high-order association cortices,  
234 implying that they are developing at a more considerable pace compared to unimodal cortices.  
235 Besides the age-specific parcellations, we also generated an age-common parcellation that suites  
236 infants at all ages to help brain development-related studies under two considerations. First, infant  
237 studies typically involve subjects of different ages, and it is not convenient to use different  
238 parcellations for comparison between different ages. Second, our age-common gradient density  
239 map shows low variability to all age-specific gradient density maps and therefore can generate the

240 representative fine-grained functional parcellation map that is suitable for all ages during infancy.  
241 However, we will make both the age-specific and age-common functional parcellation maps  
242 accessible to the public in the case that some researchers may still prefer age-specific parcellation  
243 maps.

244 This study successfully augmented the resolution of the existing cortical parcellations from ~300  
245 to ~900 areas, which represents a finer architecture of brain functional organizations compared to  
246 previous ones. This fine-grained cortical organization is also in line with Eickhoff et al. (17), where  
247 they believe that 200-300 areas are not the ultimate resolution for cortical parcellations due to the  
248 multi-hierarchical formation of the brain. Glasser et al. (4) also consider 360 as a lower bound for  
249 cortical parcellations since each parcel can be represented as a combination of several smaller  
250 regions. Consequently, our fine-grained infant cortical parcellation maps provide a great platform  
251 for analyzing pediatric neuroimaging data with a greatly boosted resolution, thus leading to more  
252 meaningful discoveries on the fine-scaled functional architecture of infant brains.

253 Besides, it is worth noting that our parcellation increased the resolution in a meaningful way.  
254 First, our functional gradient density maps are highly reproducible. By separating subjects into non-  
255 overlapping parts, their gradient density patterns are repeated with a dice ratio of ~0.93. Second,  
256 our age-common infant parcellation shows high accordance in some specific cortical areas defined  
257 by Glasser et al. (4), which is recognized as the state-of-the-art adult parcellation map. As illustrated  
258 in Fig. 5 (d), our gradient density map-derived parcellation contains parcels that have substantial  
259 overlap with the known adult area V1 defined by Glasser et al. (4). Other known cortical areas of  
260 adults, such as sensorimotor areas 2, 3, and 4, were also overlapped with a combination of several  
261 parcels in our parcellation. These observations that parcel borders conform to some adult cortical  
262 areas lend substantial visual validity to the parcellation.

263 When applying parcellation as a tool to explore infant brain functional development, our results  
264 reveal complex multi-peak fluctuations in several aspects, including parcel number, temporal

265 variation of gradient density, network organization, and local efficiency. To the best of our  
266 knowledge, this complex fluctuation development trend is not reported in previous literature and  
267 should fill an important knowledge gap for infantile brain functional development. These functional  
268 developmental patterns are very different from early brain structure development, where the  
269 cortical thickness follows an inverted-“U” shaped trajectory, while the surface area and cortical  
270 volume monotonically increase following a logistic curve. The multi-peak fluctuations potentially  
271 mirror different milestones of behavioral/cognitive abilities, which likely emerge at different ages  
272 during infancy (30). However, the underlying mechanisms of such developmental patterns remain  
273 to be further investigated.

274 For network organization (Fig. 6 (b)), at 3 months, networks likely groups vertices with close  
275 spatial locations, resulting in networks being more dependent on the local anatomy. After 9 months,  
276 the primary functional systems reach steady and present adult-like patterns, while high-order  
277 functional networks still show substantial differences compared to the adult-like pattern. Our results  
278 suggest that a primitive form of brain functional networks is present at 3 months, which is largely  
279 consistent with recent studies suggesting that most resting-state networks are already in place at  
280 term birth (18-20). Besides, our results also suggest that, compared to high-order functional  
281 networks, the primary functional system is more developed in infants. This confirms previous  
282 findings in infant cortical thickness development (21), suggesting that the primary functional  
283 systems develop earlier than high-order systems.

284 At the network level, the sensorimotor system splits into two sub-networks, i.e., the mouth- and  
285 hand-sensorimotor at 6 months, which were also observed in infants and toddlers (22). The visual  
286 network is split into central (primary) visual and peripheral (high-order) visual cortices at 9 months  
287 and well maintains this pattern until 24 months. This subdivision of mouth- and hand-sensorimotor  
288 networks is also found in adults (5). The high-order functional systems, including the default mode,  
289 frontoparietal, and dorsal attention network, exhibit considerable development during 3 to 9 months,

290 followed by some minor adjustments from 12 to 24 months. A previous infant study (19) also  
291 demonstrated that functional network development shows more considerable change in the first  
292 year compared to the second year. At 24 months, both default mode and frontoparietal networks  
293 show a lack of strong cross-lobe connections. Though several studies identified some prototypes of  
294 cross-lobe connection (19, 23), their links seem not as strong as to be stably distinguished (24-26).  
295 Our results suggest that the high-order functional networks are far more from established at 24  
296 months of age. It is worth noting that, the size changes of networks can be quite subtle between a  
297 short time interval, which emphasizes the importance of using a fine-grained parcellation map.

298 The parcel homogeneity measures the development within parcels. Our result shows (Fig. 7 (a))  
299 that unimodal cortices, including the sensorimotor, auditory, and visual areas, show high  
300 homogeneity, which is largely consistent with adults (7). However, the inferior parietal and  
301 posterior superior temporal cortices, which show high homogeneity in infants, are observed low  
302 homogeneity in adults (7). Besides, the prefrontal area, which shows relatively low homogeneity  
303 in infants, seems to develop to a medium-to-high homogeneity in adults. Almost all parcels are  
304 observed decreased homogeneity with age. This is likely related to the development of brain  
305 function, especially in high-order cortices, which show increased heterogeneity, and consequently  
306 decreased homogeneity. Among the high-order association cortices, the prefrontal area has the  
307 lowest homogeneity, followed by temporal and then parietal regions, suggesting different levels of  
308 functional development.

309 Local efficiency measures a different developmental aspect – it represents the connection of  
310 parcels to neighbors. Higher local efficiency is usually related to higher functional segregation (11).  
311 Our results (Fig. 7 (b)) suggest that local efficiency shares certain similar spatial distribution with  
312 homogeneity – they both increase in anterior to posterior and ventral to dorsal directions. During  
313 development, the local efficiency shows a complex developmental trend: although 24 months  
314 shows a strong increase compared to 1 month, there is a dip from 12 to 21 months that should be

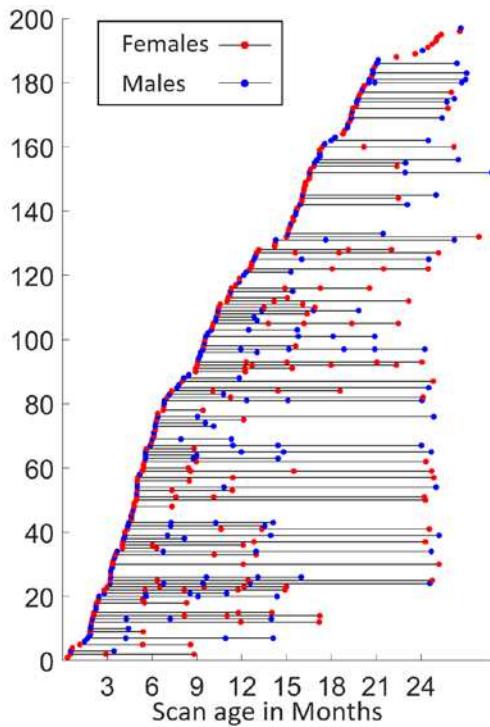
315 noted. The age-related increase of local efficiency was previously found from 18 months to 18  
316 years (27), 5 to 18 years (28), and 12 to 30 years (29), and is likely explained by progressive white  
317 matter maturation (27). This trajectory of local efficiency is not contradictory to the previous  
318 studies (31, 32), since they only measured the averaged local efficiency of all nodes to reflect  
319 network characterization, thus missing important characteristics of parcel-level local efficiency.  
320 This further stresses the importance of performing parcel-wise analyses and the significance of  
321 fine-grained infant cortical parcellations.

322 **4. Conclusion**

323 In summary, for the first time, this study constructed a comprehensive set of cortical surface-based  
324 infant-dedicated fine-grained functional parcellation maps. To this end, we developed a novel  
325 method for establishing functionally more accurate inter-subject cortical correspondences. We  
326 delineated age-specific parcellation maps at 3, 6, 9, 12, 18, and 24 months of age as well as an age-  
327 common parcellation map to facilitate studies involving infants at different ages. Our parcellation  
328 maps were demonstrated meaningful by comparing with known areal boundaries and through  
329 quantitative evaluation of homogeneity and variance of functional connectivity. Leveraging our  
330 infant parcellation, we provide the first comprehensive visualizations of the infant brain functional  
331 developmental maps on the cortex and reveal a complex multi-peak fluctuation functional  
332 development trend, which will serve as valuable references for future early brain developmental  
333 studies. Our generated fine-grained infant cortical functional parcellation maps will be released to  
334 the public soon to greatly advance pediatric neuroimaging studies.

335 **5. Methods**

336 **5.1 Subjects and Image Acquisition**



**Fig. 8.** Longitudinal distribution of scans. Each point represents a scan with its scanned age (in months) shown in the x-axis, with males in blue and females in red, and each horizontal line represents one subject, with males in blue and females in red.

337

338 Subjects in this study are from the UNC/UMN Baby Connectome Project (BCP) data90set (14).  
339 The BCP focuses on normal early brain development, where all infants were born at the gestational  
340 age of 37-42 weeks and free of any major pregnancy and delivery complications. In this study, 394  
341 high-resolution longitudinal structural MRI scans were acquired from 197 (90 males and 107  
342 females) typically developing infants, as demonstrated in Fig. 8. Images were acquired on 3T  
343 Siemens Prisma MRI scanners using a 32-channel head coil during natural sleeping. T1-weighted  
344 images (208 sagittal slices) were obtained by using the three-dimensional magnetization-prepared  
345 rapid gradient echo (MPRAGE) sequence: TR (repetition time)/TE (echo time)/TI (inversion time)  
346 = 2,400/2.24/1,600 ms, FA (flip angle) = 8°, and resolution = 0.8×0.8×0.8 mm<sup>3</sup>. T2-weighted

347 images (208 sagittal slices) were acquired with turbo spin-echo sequences (turbo factor = 314, echo  
348 train length = 1,166 ms): TR/TE = 3,200/564 ms, and resolution = 0.8×0.8×0.8 mm<sup>3</sup> with a variable  
349 flip angle. All structural MRI data were assessed visually for excessive motion, insufficient  
350 coverage, and/or ghosting to ensure sufficient image quality for processing.

351 For the same cohort, 1,064 high-resolution resting-state fMRI (rs-fMRI) scans were also  
352 acquired using a blood oxygenation level-dependent (BOLD) contrast sensitive gradient echo echo-  
353 planar sequence: TR = 800 ms, TE = 37 ms, flip angle = 80°, field of view (FOV) = 208×208 mm,  
354 72 axial slices per volume, resolution = 2×2×2 mm<sup>3</sup>, total volumes = 420 (5 min 47 s). The rs-  
355 fMRI scans include 524 anterior to posterior (AP) scans and 540 posterior to anterior (PA) scans,  
356 which are two opposite phase-encoding directions for better correction of geometric distortions.

## 357 **5.2 Structural MRI Processing**

358 All T1-weighted and T2-weighted MR images were processed using an infant-specific pipeline  
359 detailed in (15, 33), which have been extensively validated in many infant studies (21, 34-41). The  
360 processing procedure includes the following main steps: 1) Rigid alignment of each T2-weighted  
361 image onto its corresponding T1-weighted image using FLIRT in FSL (Smith et al., 2004); 2) Skull  
362 stripping by a deep learning-based method (42), followed by manual editing to ensure the clean  
363 skull and dura removal; 3) Removal of both cerebellum and brain stem by registration with an atlas;  
364 4) Correction of intensity inhomogeneity using the N3 method (43); 5) Longitudinally-consistent  
365 segmentation of brain images as white matter (WM), gray matter (GM), and cerebrospinal fluid  
366 (CSF) using an infant-dedicated deep learning-based method (44); and 6) Separation of each brain  
367 into left and right hemispheres and filling non-cortical structures.

## 368 **5.3 Resting-State fMRI Processing**

369 Infant rs-fMRI processing was conducted according to an infant-specific functional pipeline (31,  
370 45, 46). The head motion was corrected using FSL, as well as the spatial distortions due to gradient

371 non-linearity. The rs-fMRI scans were then registered to the T1-weighted structural MRI of the  
372 same subject using a boundary-based registration approach (47). All of the transformations and  
373 deformation fields were combined and used to resample the rs-fMRI data in the native space  
374 through a one-time resampling strategy. After conservative high-pass filtering with a sigma of  
375 1,000 s to remove linear trends in the data, individual independent component analysis was  
376 conducted to decompose each of the preprocessed rs-fMRI data into 150 components using  
377 MELODIC in FSL. An automatic deep learning-based noise-related component identification  
378 algorithm was used to identify and remove non-signal components to clean the rs-fMRI data (48).

379 **5.4 Cortical Surface Reconstruction and Mapping**

380 Based on the tissue segmentation results, inner, middle and outer cortical surfaces of each  
381 hemisphere of each MRI scan were reconstructed and represented by triangular meshes with correct  
382 topology and accurate geometry, by using a topology-preserving deformable surface method (33,  
383 49). Before cortical surface reconstruction, topology correction on the whiter matter surface was  
384 performed to ensure the spherical topology of each surface (50). After surface reconstruction, the  
385 inner cortical surface, which has vertex-to-vertex correspondences with the middle and outer  
386 cortical surfaces, was further smoothed, inflated, and mapped onto a standard sphere (51).

387 To ensure the accuracy in longitudinal analysis during infancy, it is necessary to perform  
388 longitudinally-consistent cortical surface registration (15). Specifically, 1) for each subject, we first  
389 co-registered the longitudinal cortical surfaces using Spherical Demons (52) based on cortical  
390 folding-based features, i.e., average convexity and mean curvature. 2) Longitudinal cortical  
391 attribute maps were then averaged to obtain the intra-subject mean surface maps. 3) For each  
392 hemisphere, all intra-subject mean surface maps were then co-registered and averaged to get the  
393 population-mean surface maps. 4) The population-mean surface maps were aligned to the HCP  
394 32k\_LR space through registration to the “fsaverage” space as in (53). By concatenating the three  
395 deformation fields of steps 1, 3 and 4, we directly warped all cortical surfaces from individual scan

396 spaces to the HCP 32k\_LR space. These surfaces were further resampled as surface meshes with  
397 32,492 vertices, thus establishing vertex-to-vertex correspondences across individuals and ages.  
398 All results were visually inspected to ensure sufficient quality for subsequent analysis. The inner  
399 and outer cortical surfaces were used as a constraint to resample the rs-fMRI time courses onto the  
400 middle cortical surface with 32,492 vertices using the HCP workbench (54), and the time courses  
401 were further spatially smoothed on the middle cortical surface with a small Gaussian kernel ( $\sigma =$   
402 2.55 mm).

403 **5.5 Generation of Fine-grained Cortical Functional Parcellation Maps**

404 In this section, we describe detailed steps for generating fine-scaled infant cortical functional  
405 parcellation maps (see Fig. 1). Specifically, we first describe the computation of the gradient  
406 density map of functional connectivity for each scan, followed by a function-based registration step  
407 based on gradient density maps. Then, we detail the computation of both “age-specific” and “age-  
408 common” parcellation maps based on the functional registration results and our evaluation scheme.  
409 At last, we introduce how we use the parcellation maps to discover the functional network  
410 organization development, as well as parcel homogeneity and local efficiency during infancy.

411 ***Computation of Individual Functional Gradient Density Map***

412 The gradient density of functional connectivity (7) identifies sharp changes of RSFC, thus  
413 intrinsically representing the transition from one functional parcel to another, and is widely used in  
414 generating meaningful fMRI-based cortical parcellations in adult studies (7-9). For each fMRI scan  
415 of each infant subject, the computation of the gradient density of functional connectivity on the  
416 cortical surface is summarized in the following steps. 1) For each fMRI scan, the functional  
417 connectivity matrix is built by pair-wise correlating each vertex with all other cortical vertices in  
418 the CIFTI file to create a 32k×64k RSFC matrix for each hemisphere. 2) Each RSFC matrix is  
419 transformed to z scores using Fisher’s r-to-z transformation. 3) For each fMRI scan, the z-  
420 transformed RSFC of each vertex is correlated with all cortical vertices within the same hemisphere,

421 creating a 2<sup>nd</sup> order correlation matrix (RSFC-2<sup>nd</sup>) sized 32k×32k for each hemisphere. 4) For some  
422 scan visits consisting of both AP and PA scans, all RSFC-2<sup>nd</sup> matrices of the same visit from the  
423 same subject are averaged, so that all subjects contribute equally, even they may have different  
424 numbers of scans in one visit. 5) The gradient of functional connectivity is computed on the RSFC-  
425 2<sup>nd</sup> as in (4), resulting in a 32k×32k gradient matrix per hemisphere. 6) By performing the  
426 watershed-based boundary detection (7) on the gradient matrix, we obtain 32k binary boundary  
427 maps per hemisphere. 7) The functional gradient density map is defined as the average of 32k  
428 binary boundary maps.

429 ***Cortical Surface Registration based on Functional Gradient Density***

430 Previous studies mostly computed population-based functional gradient density map, where  
431 cortical surfaces were usually co-registered to a common space using only cortical folding-based  
432 features. However, due to the highly-variable relationship between cortical folds and functions,  
433 especially in high-order association regions, researchers recently are getting more aware of the  
434 necessity of functional features-based registration (55, 56). To this end, in addition to cortical  
435 folding-based co-registration, we further use the gradient density of functional connectivity as a  
436 meaningful functional feature to perform a second-round of co-registration of cortical surfaces for  
437 the purpose of more accurate functional alignment.

438 Specifically, based on cortical folding-based surface co-registration, 1) the functional gradient  
439 density maps of all scans are averaged to generate the population-mean functional gradient density  
440 map. 2) To improve inter-individual cortical functional correspondences, the functional gradient  
441 density map of each scan is then aligned onto the current population-mean functional gradient  
442 density map using Spherical Demons (52) by incorporating functional gradient density as a feature.  
443 3) All warped functional gradient maps are then resampled and averaged to obtain the newly  
444 improved population-mean functional gradient density map with sharper and more detailed  
445 functional architecture. 4) Steps 2 and 3 are repeated iteratively until no visually observed changes

446 in the population-mean functional gradient density map (4 iterations in our experiment). After this  
447 procedure, all individual functional gradient density maps are co-registered, thus establishing  
448 functionally more accurate cortical correspondences across individuals.

449 ***Generation of Parcellation Maps based on Functional Gradient Density***

450 **Age-specific Parcellation Maps:** To capture the spatiotemporal changes of fine-grained cortical  
451 functional maps during infancy, we group all scans into 6 representative age groups, i.e., 3, 6, 9,  
452 12, 18, and 24 months of age based on the distribution of scan ages. For each age group, we compute  
453 the age-specific group-average functional gradient density maps by averaging the gradient density  
454 maps of all scans within the group, without any smoothing. Detailed information of each age group  
455 is reported in **Table 1**. A watershed method is then applied on each age-specific group-average  
456 functional gradient density map to generate the corresponding functional parcellation maps (7).  
457 This watershed segmentation algorithm starts by detecting local minima in 3-ring neighborhoods,  
458 and iteratively grows the region until reaching ambiguous locations, where vertices can be assigned  
459 to multiple regions. These locations appear to be borders that separate parcels and reflect putative  
460 boundaries of functional connectivity according to the functional gradient density maps.

461 **Age-common Parcellation Maps:** Ideally, the age-specific parcellation maps are the more  
462 appropriate representation of the cortical functional architecture at the concerned age. However,  
463 many neuroimaging studies involve infants across multiple ages, thus the age-specific parcellation  
464 maps may not be proper choices due to different parcel numbers and variation in parcel boundaries  
465 across ages, thus inducing difficulties in across-age comparisons. To facilitate infant studies  
466 involving multiple age groups, we also compute an age-common gradient density map, which is  
467 the average of all 6 age-specific functional gradient density maps without any smoothing, so that  
468 each age group contributes equally to the age-common map. According to the age-common  
469 functional gradient density map, we generate the age-common functional parcellation map using  
470 the watershed segmentation method as well. The subsequent parcellation evaluation, functional

471 network architecture and longitudinal development analyses are performed using the age-common  
472 parcellation maps.

473 **Table 1.** Demographic information of each age group from the longitudinal dataset under study.

Age Group	Age Range (days)	fMRI Scans	AP Scans	PA Scans	Structural MRI Scans (males/females)
<b>3M</b>	10~144 (97.7 $\pm$ 35.1)	109	55	54	52 (27/25)
<b>6M</b>	145~223 (183.3 $\pm$ 23.3)	172	85	87	56 (24/32)
<b>9M</b>	224~318 (278.6 $\pm$ 24.1)	139	67	72	54 (27/27)
<b>12M</b>	319~410 (366.4 $\pm$ 21.4)	151	76	75	57 (24/33)
<b>18M</b>	411~591 (494.9 $\pm$ 51.8)	244	119	125	91 (40/51)
<b>24M</b>	592~874 (723.6 $\pm$ 67.5)	249	122	127	84 (42/42)
<b>Total</b>	10~874 (410.9 $\pm$ 219.1)	1064	524	540	394 (184/210)

474

475 **5.6 Evaluation of Parcellation Maps**

476 **Reproducibility:** Ideally, a functional gradient density-based parcellation map should extract  
477 robust common gradient information that shows the transition between parcels. We thus test if the  
478 gradient density map is reproducible on different subjects. Therefore, randomly divided “generating”  
479 and “repeating” groups (7, 9) are used to calculate mean gradient density map, separately. These  
480 two maps are then binarized by keeping only 25% highest gradient density as in (7, 8), and the dice  
481 ratio overlapping index between the two binarized maps is calculated to evaluate the reproducibility  
482 of the functional gradient map. This process is repeated multiple times (1,000 times in this study)  
483 to get a reliable estimation.

484 **Homogeneity:** The functional gradient density-based parcellation identifies large gradients,  
485 representing sharp transition in functional connectivity pattern and avoiding large gradients inside  
486 parcels as much as possible. Meanwhile, a parcel that accurately represents a cortical area should  
487 not only be distinct from its neighbors in functional connectivity pattern, but also has a homogenous

488 functional connectivity pattern across all vertices inside. Therefore, we estimate the homogeneity  
489 of each parcel as in (7). Specifically, we first compute the mean correlation profile of each vertex  
490 across all subjects. Next, the correlation patterns of all vertices within one parcel is entered into a  
491 principal component analysis; the percentage of the variance that is explained by the largest  
492 principal component is used to represent the homogeneity of this parcel.

493 **Variance:** As the functional connectivity pattern within a parcel should be relatively uniform, we  
494 also measure the variability of the connectivity pattern within each parcel, with smaller variability  
495 indicating greater uniformity and hence higher parcellation quality. Specifically, for each parcel,  
496 we first obtain a matrix with each column representing subject-average z-score of functional  
497 connectivity profile of one vertex in the parcel. Then we compute the sum of standard deviation of  
498 each row to represent the variability of this parcel. The average variability of all parcels is used to  
499 represent the variability of the parcellation map.

500 As parcellation maps usually have different numbers, sizes and shapes in parcels, to have fair  
501 comparison and be consistent with (7, 8), we compare our parcellation maps with ‘null  
502 parcellations’. The null parcellations are generated by rotating by a random amount along x, y and  
503 z axes on the 32,492 spherical surfaces, which relocate each parcel while keeping the same number  
504 and size of parcels. We compare both variability and homogeneity of our parcellation and that of  
505 the random rotated null parcellations. Notably, in any random rotation, some parcels will inevitably  
506 be rotated into the medial wall, where no functional data exist. The homogeneity/variance of a  
507 parcel rotated into the medial wall is not calculated; instead, we assign this parcel the average  
508 homogeneity/variance of all random versions of the parcel that were rotated into non-medial-wall  
509 cortical regions.

510 **Variability Between Functional Gradient Density Maps:** A variability map visualizes the  
511 variability or dissimilarity between two functional gradient density maps, and is estimated as  
512 follows. For a vertex  $v$ , a surface patch centering at  $v$  is extracted (10-ring neighborhood in this

513 study), and two vectors  $\mathbf{p}_1$  and  $\mathbf{p}_2$  within this patch are then extracted from two functional gradient  
514 density maps. Their variability at  $v$  is computed as  $0.5 \times (1 - \text{corr}(\mathbf{p}_1, \mathbf{p}_2))$ , where  $\text{corr}(\cdot, \cdot)$   
515 stands for Pearson's correlation. As a result, the variability/dissimilarity is within the range of [0,  
516 1], where high value stands for high variability/dissimilarity and vice versa. In this study, we mainly  
517 measure the variability between functional gradient density maps in two aspects: 1) the temporal  
518 variability, which computes the variability of functional gradient density maps between two  
519 consecutive age groups to reflect the developmental changes of the gradient density maps; 2) the  
520 variability between the age-common functional gradient density map and each age-specific  
521 functional gradient density map, for quantitatively evaluating whether it is appropriate to use the  
522 age-common parcellation maps for all 6 age groups.

523 **5.7 Functional Development Analysis**

524 **Functional Network Detection:** To discover the developmental evolution of large-scale cortical  
525 functional networks, we employ a network discovery method (5) to each of the 6 age groups.  
526 Specifically, for each subject in each age group, given  $n$  parcels, we first compute the average time  
527 course of each parcel (excluding the medial wall), and compute the correlation of the average time  
528 courses between any two parcels. This results in a  $n \times n$  matrix, which is further binarized by  
529 setting the top 10% of the correlations to one and the rest to zero. For each age group, all  $n \times n$   
530 matrices are averaged across individuals independently. A clustering algorithm (57) is then applied  
531 to estimate networks of parcels with similar connectivity profiles.

532 To determine the optimal cluster number  $k$  for each age group, we employ the random split-half  
533 test to compute the stability for each  $k$ , with higher stability corresponding to more meaningful  
534 clustering results. Specifically, for each age group, we randomly split all subjects into two folds  
535 and run the clustering algorithm separately to obtain two independent clustering results  $c_1$  and  $c_2$ ,  
536 and the similarity between  $c_1$  and  $c_2$  is evaluated using the Amari-type distance (58). This  
537 experiment is repeated 200 times for each age group, and the resulted similarities are averaged to

538 represent the stability for  $k$ . During this process, the range of  $k$  is set to [2, 30] according to the  
539 existing literature of functional network discovery (5, 6).

540 **Parcel-wise Development:** We computed the homogeneity and local efficiency of each parcel in  
541 the age-common parcellation to characterize infantile parcel-wise developmental patterns regarding  
542 functional homogeneity and functional segregation, respectively. The homogeneity is computed as  
543 described in Section 3.4 for each subject, where higher parcel homogeneity indicates more unified  
544 connectivity pattern within the parcel. The local efficiency is computed using the GRETNA Toolkit  
545 (59) for each subject. Herein, multiple thresholds are used, keeping 50% to 5% connections with  
546 1% as a step, and the area under curve (AUC) is calculated to represent the local efficiency to avoid  
547 the influence of connectivity densities. The local efficiency corresponds to the mean information  
548 transfer efficiency between a particular parcel and all its connected nodes, which is proportional to  
549 the clustering coefficient. Parcels with higher local efficiency can more effectively share  
550 information to its connected parcels, and thus help build effective segregated networks. To have  
551 intuitive and spatiotemporally detailed views of their development, we use the sliding window  
552 technique to compute homogeneity and local efficiency in each age window by averaging all scans  
553 within the same age window. The windows are centered at each month, with a window width of 90  
554 days ( $\pm 45$  days) at 2 months of age, increasing 4 days in width for each following month and  
555 reaching 182 days ( $\pm 91$  days) at 2 years of age.

556 **Acknowledgment**

557 This work was partially supported by NIH grants (MH116225, MH117943, MH104324,  
558 MH109773, MH123202, MH127544). This work also utilizes approaches developed by an NIH  
559 grant (1U01MH110274) and the efforts of the UNC/UMN Baby Connectome Project Consortium.

560 **Competing Interests**

561 The authors declare no competing interests.

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