RESEARCH ARTICLE

Comparing the temporal relationship of structural and functional connectivity changes in different adult human brain networks: a single-case study [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Despite accumulated evidence for adult brain plasticity, the temporal relationships between large-scale functional and structural connectivity changes in human brain networks remain unclear.
Methods: By analysing a unique richly detailed 19-week longitudinal neuroimaging dataset, we tested whether macroscopic functional connectivity changes lead to the corresponding structural alterations in the adult human brain, and examined whether such time lags between functional and structural connectivity changes are affected by functional differences between different large-scale brain networks.
Results: In this single-case study, we report that, compared to attention-related networks, functional connectivity changes in default-mode, fronto-parietal, and sensory-related networks occurred in advance of modulations of the corresponding structural connectivity with significantly longer time lags. In particular, the longest time lags were observed in sensory-related networks. In contrast, such significant temporal differences in connectivity change were not seen in comparisons between anatomically categorised different brain areas, such as frontal and occipital lobes. These observations survived even after multiple validation analyses using different connectivity definitions or using parts of the datasets.
Conclusions: Although the current findings should be examined in independent datasets with different demographic background and by experimental manipulation, this single-case study indicates the possibility that plasticity of macroscopic brain networks could be affected by cognitive and perceptual functions implemented in the networks, and implies a hierarchy in the plasticity of functionally different brain systems.

Keywords

neural plasticity, Hebb's rule, resting state, DTI

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Introduction

Many neuroimaging studies have demonstrated substantial plasticity of functional and structural connectivity in adult human brains[1–3]. White matter microarchitecture is changed by a variety of training methods[4–11], macroscopic functional connectivity (FC) is affected by learning[2,12–15], and the location and strength of structural and functional connectivity changes are correlated[13,15,16].

However, the temporal relationship between changes in these two fundamental types of brain connectivity – specifically, the lag between functional and structural changes for a particular set of brain regions – is not yet fully understood. Unlike microscopic neural plasticity[17,18], even whether macroscopic FC changes lead to the corresponding structural connectivity (SC) changes for the same brain network remains unconfirmed. Moreover, even if such FC changes precede modulation of SC, it is still unclear whether the time lags between the occurrence of FC and SC changes are constant across functionally heterogeneous human brain networks.

Here, we hypothesised that, like Hebbian neural plasticity at a cellular level[17,18], changes in large-scale intrinsic FC occur in advance of the corresponding SC alterations. We further hypothesised that the time lags between FC and SC changes vary between different brain networks with difference cognitive and perceptual functions. Specifically, in brain networks related to primary perception, SC changes may take more time to catch up to FC changes in order to keep its perceptual functions robust against fluctuating external inputs; in contrast, brain networks for attention control may have more flexible SC changes to adapt themselves to varying tasks and situations, and the time lags between FC and SC changes could be shorter than other networks.

To test these hypotheses, we examined a unique open longitudinal neuroimaging dataset recorded from a single healthy adult male over 19 weeks of community living[19,20]. The density of the data collection (42 and 16 time points for FC and SC datasets, respectively) allowed us to characterise the temporal relationships between any FC and SC changes occurring in the time period. In addition, the data were effectively unaffected by neural plasticity induced by intensive experience of specific cognitive/motor/perceptual learning because no explicit training was conducted in the 19 weeks, and thus we were expected to be able to compare the temporal properties of spontaneous or environmentally induced neural plasticity between functionally different brain networks.

Results

Identification of connectivity showing significant increases

Using these data, we first built nine FC and SC matrices for nine representative brain cortical networks with different functions[21,22] for each recording day (Figure 1a). SC was defined

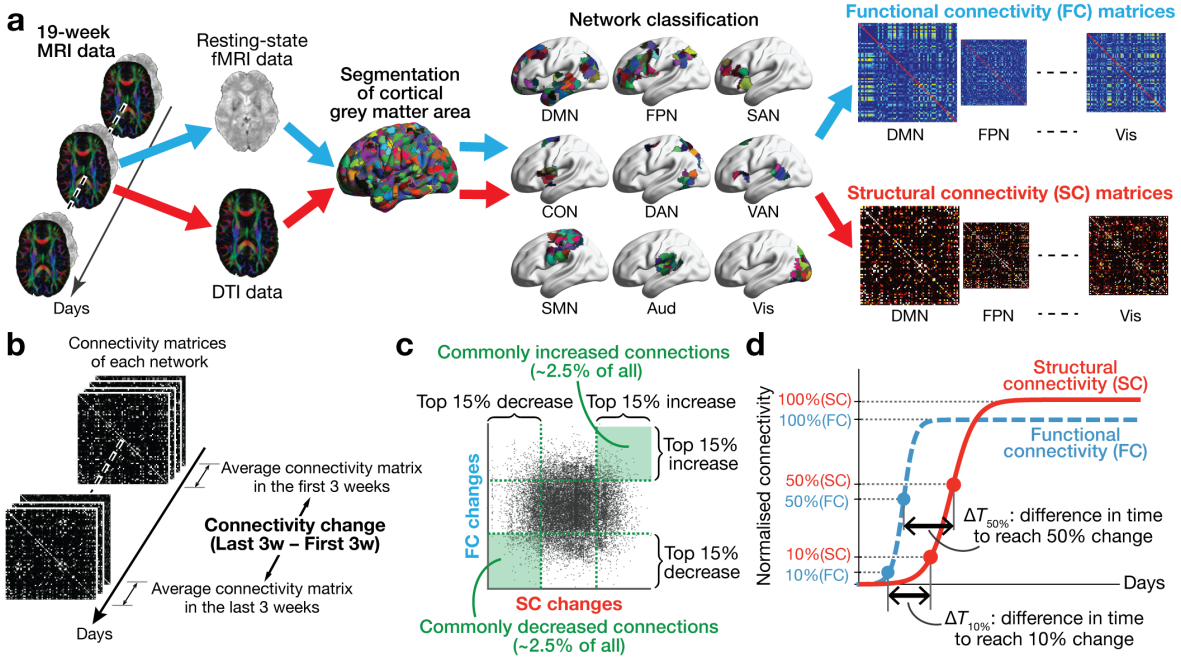

Figure 1. Analysis procedure. a. For each data-collection day, we constructed matrices of functional connectivity (FC) and structural connectivity (SC) for the nine networks whose nodes consisted of randomly-segmented similar-size cortical grey matter areas. DMN, default-mode network; FPN, fronto-parietal network; SAN, salience network; CON, cingulo-opercular network; DAN, dorsal-attention network; VAN, ventral attention network; SMN, sensory-motor network; Aud, auditory network; Vis, visual network. **b** and **c.** We calculated connectivity differences between the first and last three weeks (**b**), and selected brain connections both of whose FC and SC showed significant changes (**c**). There was no significant difference in average Euclidian lengths of the selected connections between the nine cortical networks (Supplementary File 1). **d.** After fitting logistic functions to mean connectivity of the selected brain connections, we compared temporal properties between FC and SC changes.

by the number of streamlines traced in diffusion-tensor imaging (DTI) data, and FC was calculated based on partial correlation of resting-state functional MRI (rsfMRI) signals, which represents SC more accurately than FC based on Pearson correlation[23,24].

We then selected brain connections for which both FC and SC showed significant increases in the period for each network (Figures 1b and 1c). In fact, the selected connections were included in top 2.5% significant increases in each network (Supplementary Table 1; Supplementary File 1), and their lengths did not significantly differ between the nine networks ($F_{8,1086}$ = 0.84, P = 0.57 in one-way analysis of variance (ANOVA); Supplementary Figure 1; Supplementary File 1).

Comparison of temporal patterns of connectivity changes

By fitting logistic functions to the mean connectivity changes of the selected connections, we calculated two time-lag indices to compare FC and SC changes within and between brain networks (Figure 1d): $\Delta T_{50\%}$ shows how earlier FC reached the half of the total connectivity increases in the 19 weeks than SC ($T_{50\%\_SC} - T_{50\%\_FC}$), whereas $\Delta T_{10\%}$ indicates how much later the SC changes started after FC changes had begun ($T_{10\%\_SC} - T_{10\%\_FC}$).

We confirmed significant goodness of fit of the logistic functions (adjusted $R^2 \geq 0.62$, $P_{uncorrected} \leq 0.004$, $P_{Bonferroni} < 0.05$; Figure 2a), and identified significant differences in the two time-lag indices across the nine networks ($F_{8,232} > 85.3$, $P < 10^{-4}$ in one-way ANOVA; Figure 2b). Apart from three attention-related networks (i.e., cingulate–opercular network (CON), dorsal attention networks (DAN), ventral attention network (VAN)), FC changes in the other six networks preceded SC ones with significant time lags ($t_{23} > 10.8$ for $\Delta T_{50\%}$, $t_{27} > 11.3$ for $\Delta T_{10\%}$, $P_{Bonferroni} < 0.05$ in two-tailed Welch's tests). In addition, default-mode (DMN), fronto-parietal (FPN), and salience networks (SAN) had significantly longer time lags than the three attention-related networks ($t_{34} > 6.2$ for $\Delta T_{50\%}$, $t_{54} > 5.3$ for $\Delta T_{10\%}$, $P_{Bonferroni} < 0.05$), but showed significantly shorter lags than remaining three sensory-related networks (SMN, Auditory, and Visual networks; $t_{41} > 3.6$ for $\Delta T_{50\%}$, $t_{43} > 4.2$ for $\Delta T_{10\%}$, $P_{Bonferroni} < 0.05$).

These observations about time lags between FC and SC changes were confirmed by directly comparing FC values at certain time points with SC values at the same/different time points (Supplementary Figure 2; Supplementary File 1). Linear regression analyses found that FC values in DMN/FPN/SAN could predict SC values that were observed one week after the FC values were recorded (adjusted R^2 = 0.79; $P_{Bonferroni} < 0.05$; Supplementary Figure 2a; Supplementary File 1), whereas FC values in SMN/Auditory/Visual could predict SC values that would be seen two weeks later (adjusted R^2 = 0.91; $P_{Bonferroni} < 0.05$; Supplementary Figure 2c; Supplementary File 1). In contrast, FC values in CON/DAN/VAN could predict SC values recorded on the same day (adjusted R^2 = 0.91; $P_{Bonferroni} < 0.05$; Supplementary Figure 2b; Supplementary File 1). Moreover, these time-lagged FC-SC relationships were robustly observed even after we removed outliers (adjusted $R^2 \geq 0.40$; three small boxes in Supplementary Figure 2, Supplementary File 1).

Validation analysis

We then examined the robustness of these observations by conducting three validation analyses.

First, we confirmed that these temporal differences between FC and SC increases were qualitatively reproduced when comparing FC decreases with SC decreases over the 19 weeks (Figures 2c and 2d, Supplementary Table 1, Supplementary Figure 3, Supplementary File 1)

Second, we also compared timings of connectivity changes after we matched the time points of FC data collections to those of SC data collections. Technically, we used sets of rsfMRI and DTI data only when both were recorded in the same day. Although this procedure reduced the number of FC time points from 42 to 16 and slightly mitigated fitting of the logistic functions, we could still observe qualitatively the same difference in the FC-SC time lags between different brain networks (Figures 3a and 3b, Supplementary Figure 4; Supplementary File 1).

Third, we repeated the entire analysis after re-defining SC by the mean fractional anisotropy (FA) value of the traced streamlines, and confirmed that the pattern of the FC-SC time lags was preserved (Figures 3c and 3d, Supplementary Figure 5, Supplementary Table 2; Supplementary File 1).

Comparison of the FC-SC time lags between anatomically different brain lobes

Finally, we examined whether such differences in FC-SC time lags were observed between anatomically categorised brain areas (here, frontal, parietal, temporal, and occipital lobes). Although logistic functions were well fitted to connectivity changes in each lobe (adjusted $R^2 \geq 0.60$, $P_{uncorrected} \leq 0.005$, $P_{Bonferroni} < 0.05$, Figures 4a and 4c), we did not find significant difference in either time index between different brain lobes ($F_{4,86} \leq 1.4$, $P \geq 0.21$ in one-way factorial ANOVA; Figures 4b and 4d).

Discussion

This single-case study shows that compared to attention-related networks, FC in DMN, FPN, and SAN is followed by SC changes at a longer latency, while SC in sensory-related networks has an even longer latency following FC changes. Such temporal differences seen between functionally distinct brain networks were not detected in comparisons between anatomically categorised brain areas. Although the current study is based on a dataset collected from a single participant and thus its generalisation power is limited, these observations were robust against multiple within-participant validation tests, and were preserved even after we used part of the data and adopted a different definition of connectivity.

We speculate that such differences in the temporal lag of functional and structural neural plasticity may be relevant to the cognitive function of each brain network. Shorter FC–SC time lags seen in the attention-related networks could reflect quick tuning of attention to the task mix required in the local environment; longer time lags seen in DMN and FPN may be

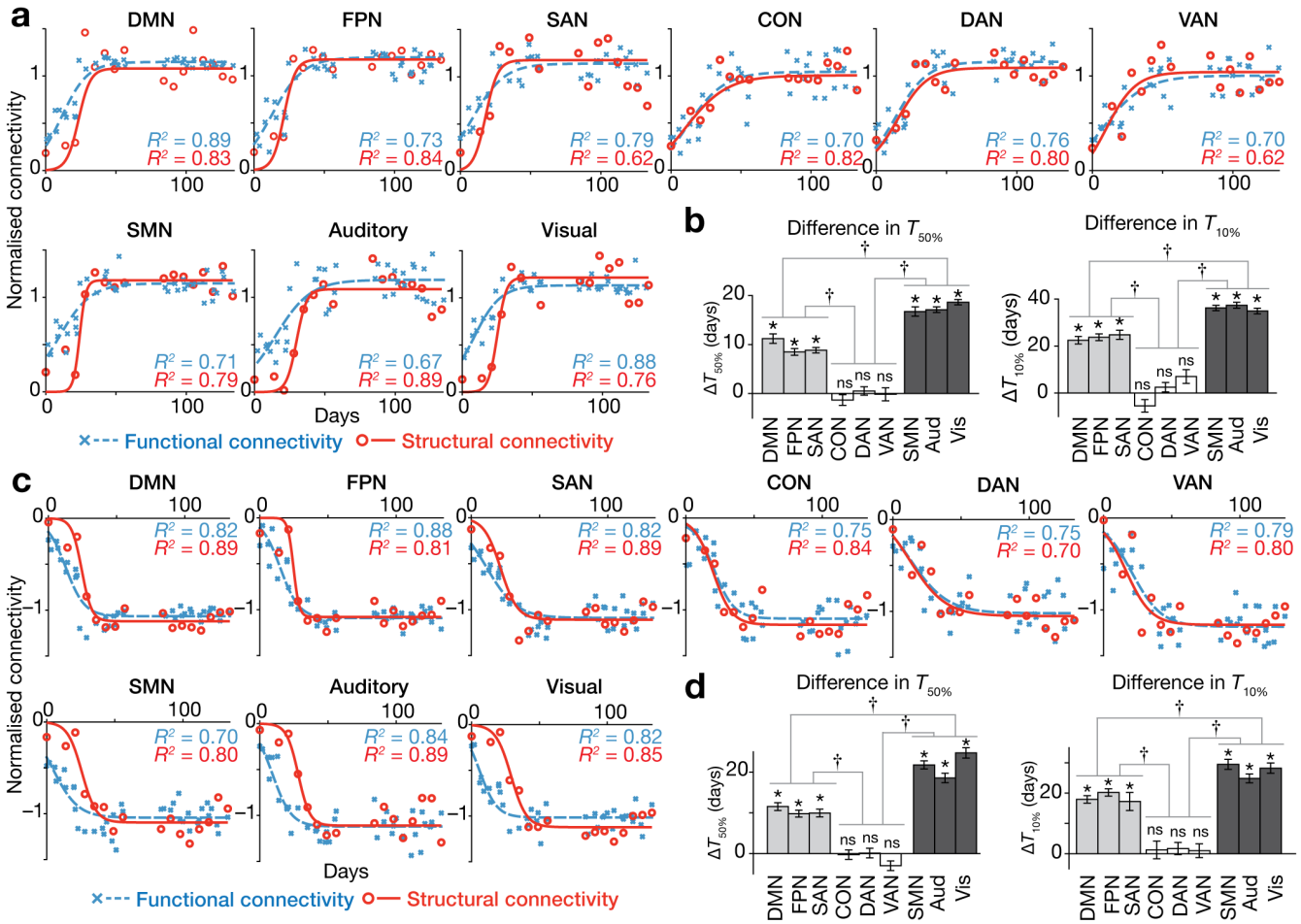

Figure 2. Comparison between functional connectivity (FC) and structural connectivity (SC) increases (a, b) and decreases (c, d). **a.** Blue dotted line and blue cross marks represents normalised FC changes, whereas red line and red circles shows SC changes. Each cross/circle corresponds to each FC/SC recording day. **b.** * indicates that $\Delta T_{50\%}$ and $\Delta T_{10\%}$ were significantly deviated from zero ($P < 0.05$ Bonferroni-corrected across the nine networks). † denotes significant differences in the time indices between the networks ($P < 0.05$ Bonferroni-corrected across 36 possible pairs of the nine networks). Error bars denote s.e.m. **c** and **d**. Panels **c** and **d** correspond to panels **a** and **b**, respectively. Logistic functions were fitted to connectivity decreases with significant accuracy (adjusted $R^2 \geq 0.70$, $P_{uncorrected} \leq 0.0013$, $P_{Bonferroni} < 0.05$; panel **c**). The two indices to compare FC and SC decreases showed qualitatively the same patterns as those for the connectivity increases.

consistent with the central role of these networks during rest and tasks, respectively[22,25], and might be important for keeping our behavioural and cognitive consistency. The longest lag of the sensory-related networks may make sensory processing systems more robust to changing and often noisy perceptual stimuli. Such speculation based on this exquisitely detailed observation dataset can now potentially be tested by directed experimental manipulations of different brain networks.

Biologically, the SC changes we identified may be related to myelination[1,26]. The SC changes were accompanied by significant opposite changes in radial diffusivity ($F_{1,108} > 13.6$, $P < 0.0004$ in two-way factorial ANOVA; Figure 4e) without substantial changes in axial diffusivity ($F_{1,108} < 2.8$, $P > 0.09$), which may indicate myelination changes[27]. Although we should be careful in inferring cellular mechanisms based on MRI data, the current observations could be interpreted in a context of activity-dependent myelination[1,10,26].

Investigating such temporal gaps between FC and SC changes for inter-network connections will be another interesting research theme. Proper coordination between different brain networks is critical for human brains to efficiently process a wide range of information and to complete various cognitive tasks[22,28], which implies that different inter-network connections may be associated with different cognitive/perceptual functions. Considering this implication with the current observations, such functional differences could affect plasticity of inter-network connections as well, which can be tested in future studies.

It should be noted that the aim of the current study was to investigate time lags between FC and SC changes, but not to

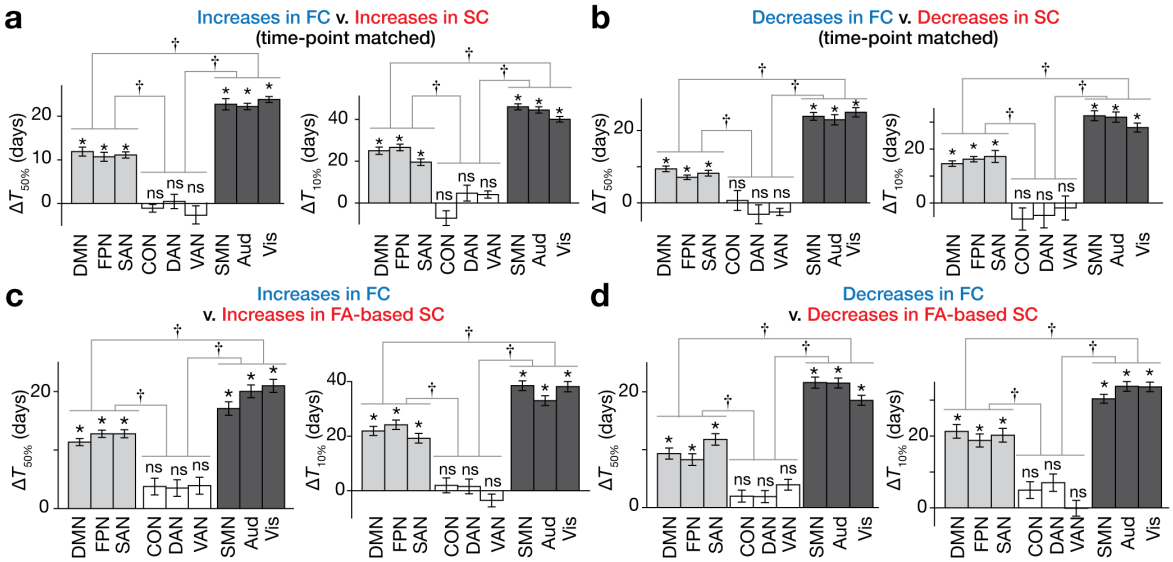

Figure 3. Results of validation analyses. The upper panels (**a, b**) show results of comparison between functional connectivity (FC) and structural connectivity (SC) changes (panel **a**, increases; panel **b**, decreases) when the dates of the data collection were matched between FC and SC (see also Supplementary Figure 4, Supplementary File 1). The lower panels (**c**, **d**) show results of the FC-SC comparisons when SC was defined by a mean fractional anisotropy (FA) value of the traced streamlines (panel **c**, increases; panel **d**, decreases; see also Supplementary Figure 5). Both of these two validation analyses yield qualitatively the same results as those seen in Figure 2. * and † represent the same statistical results as in Figure 2. Error bars denote s.e.m.

identify general characteristics of spontaneous connectivity changes. In fact, the current observations reflect approximately 2.5% of the entire brain connections estimated from the data (Supplementary Table 1; Supplementary File 1). Therefore, the current results do not necessarily suggest that such connectivity changes frequently occur even without any specific cognitive/perceptual training.

Our findings suggest that time lags between functional changes in brain networks and corresponding anatomical changes can be observed and reliably characterised; but that such lags are quite different between brain networks with different cognitive and perceptual functions. Although the generalisation power of this study is limited and further investigations employing independent datasets and experimental manipulations are necessary for validating the findings, this single-case report implies that plasticity of neural systems could be biased by functions implemented in the systems.

Methods

Data

The current study analysed open MRI data that were recorded from a healthy 45-year-old Caucasian male and shared in OpenfMRI[19,20]. In particular, we used resting-state fMRI (rsfMRI) datasets and diffusion-tensor image (DTI) datasets, which were obtained between 23 October 2012 and 5 March 2013 by Siemens 3T MRI scanner with a 32-channel head coil in the University of Texas. The rsfMRI data were acquired on 42 different days in the 19 weeks, whereas the DTI data were collected on 16 different days in the same period.

According to previous studies using the same dataset[19,20], the Office of Research Support of the scanning site decided that this data collection did not meet their requirements for human subject researches and thus approval of the institutional review board was not necessary.

The rsfMRI data were recorded using multi-band echo-planar imaging (EPI) sequence (Repetition Time, 1.16ms; Echo time, 30ms; Flip angle, 63°; voxel size, 2.4×2.4×2mm; 68 slices in the first 14 datasets and 64 in the others; scan time, 10min). The alteration of the slice number was due to an update of multiband sequence[18].

For each DTI dataset, two diffusion-weighted imaging (DWI) scans corresponding to two opposite gradient readout directions (LR/RL) were obtained with multi-band Stejskal-Tanner EPI sequence. In each scan, two shells with 30 directions were recorded (b = 1000 and 2000s/mm^2) with four low-b acquisitions interspersed every 15 frames (1.74×1.74×1.7mm; 72 axial slices; Repetition time, 5000ms; Echo time, 108ms).

For locational registration of MRI data and anatomical segmentation of grey matter (GM) regions, we also used a T1-weighted image obtained with a magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (0.8×0.8×0.8mm; Echo

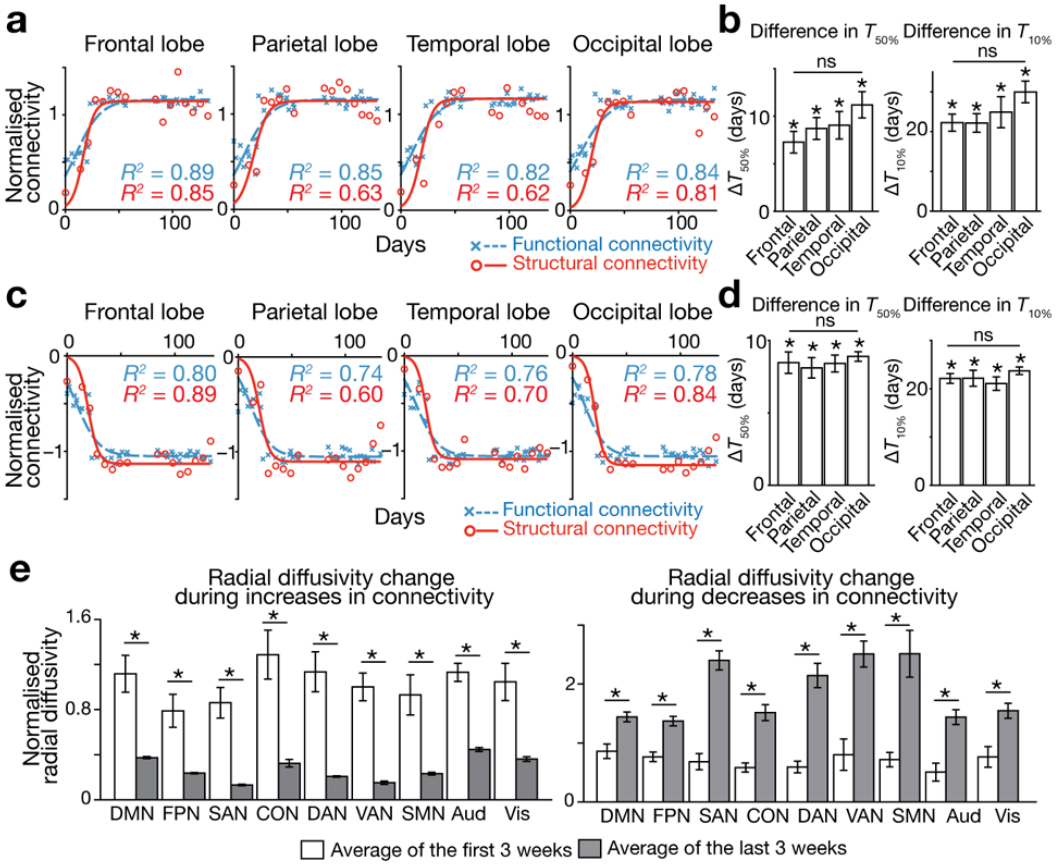

Figure 4. Anatomy-based comparison. a–d. Temporal patterns of functional connectivity (FC) and structural connectivity (SC) changes in different brain lobes. We examined FC–SC time lags between different brain lobes. The logistic functions showed significant goodness of fit in every case (adjusted $R^2 \geq 0.60$, $P_{uncorrected} \leq 0.005$, $P_{Bonferroni} < 0.05$, panels **a** and **c**). Although the FC–SC time lags significantly deviated from zero in both temporal indices in all the lobes ($t_{16} = 4.5$, $P_{uncorrected} = 0.003$, $P_{Bonferroni} < 0.05$ in two-tailed Welch's tests), there was no significant difference between the lobes ($F_{4,86} \leq 1.4$, $P \geq 0.21$ for panel **b,** $F_{4,116} \leq 0.76$, $P \geq 0.55$ for panel **d** in one-way factorial analysis of variance (ANOVA)). * represents $P_{Bonferroni} < 0.05$ in two-tailed Welch's tests. Error bars indicate standard errors. **e.** Comparison of radial diffusivity between the first and last three weeks of the data collection. Radial diffusivity (RD) for each SC was calculated as a mean RD value per the traced streamlines. RD values were defined by the mean of the second and third largest diffusivity (i.e., $(\lambda_2 + \lambda_3)/2$)[27]. We then normalised the RD values by that seen in the first recording day. For SC showing significant increases in the 19 weeks, the normalised RD values significantly decreased over the period ($F_{1,108} = 13.6$, $P = 0.0004$ in two-way factorial ANOVA, $t > 4.9$, $P_{uncorrected} < 0.002$, $P_{Bonferroni} < 0.05$ in post-hoc two-sample *t*-tests in the left). For SC showing significant decreases, the RD values significantly increased ($F_{1,108} = 33.5$, $P < 10^{-4}$ in two-way factorial ANOVA, $t > 4.4$, $P_{uncorrected} < 0.004$, $P_{Bonferroni} < 0.05$ in post-hoc two-sample *t*-tests in the right panel). Such significant changes were not observed in axial diffusivity, which was defined by the largest diffusivity (λ_1).

time, 2.14ms; Flip angle, 8°) on the first T1-scanning day in the current time period.

Cortical grey matter parcellation

As preparation for the following constructions of FC and SC matrices, using a random parcellation algorithm[29,30], we first divided cortical GM areas into 991 similar-size contiguous segments with respecting anatomical landmarks. Such relatively fine parcellation was adopted, because coarse segmentation is supposed to be insufficient for reducing self-loop anatomical connections[29] and representing detailed functional differences between brain regions.

Briefly, we first randomly divided a conventional GM parcellation map (here, automated anatomical labelling (AAL) parcellation)[31] to 1024 segments with similar numbers of continuous voxels. Using this segmented map as a template, we parcellated the participant's whole-brain GM image, which was constructed from the T1-weighted image using New Segment Toolbox[32] and DARTEL Toolbox[33] in SPM12. Finally, we excluded subcortical regions based on the AAL map[31], and obtained a cortical GM parcellation map consisting of 991 similar-size contiguous areas.

fMRI data preprocessing

The rsfMRI data were preprocessed in line with previous studies[23,34] using SPM12. After excluding the first five images to reduce effects of transient processes before the equilibrium of longitudinal magnetization, the data underwent realignment, slice-timing correction, and nonlinear normalisation to the

standard template image (ICBM 152). After regressing out effects of head motions and signals measured in white matter and ventricles, we then performed temporal band-pass filtering (0.01–0.1Hz) with in-house MATLAB scripts, and spatial smoothing in SPM 12 (Full width at half maximum, 8mm). Finally, for each of the 991 GM segmentations, we extracted time series of mean fMRI signals. These procedures were repeated for all the rsfMRI datasets, three of which were excluded for the following analyses because of their poor locational registration (identified by visual inspection) and/or large head movements (≥ 5mm).

DTI data processing

The DTI datasets were preprocessed using FSL Diffusion Toolbox (Release 5.0) and MRtrix3 (Version 3.0). First, we applied topup tool in FSL to the pairs of DWI images with opposite phase encoding, and corrected susceptibility-induced distortions by combining the pairs of images into a single one[35]. Then, eddy currents and movements in the DWI images were corrected by FSL's eddy tool[36]. Next, for the following probabilistic tractography based on 2nd order integration over Fibre Orientation Distributions (iFOD2) algorithm[37], a fibre Orientation Distribution Function (ODF) was reconstructed using non-negativity constrained spherical deconvolution technique implemented in dwi2response and dwi2fod tools in MRtrix3[38]. Based on the calculated ODF, we performed the iFOD2-based probabilistic tractography and built a whole-brain structural connectivity matrix using MRtrix3's tckgen and tck2connectome tools. In this tractography, we anatomically constrained the tracks to begin and terminate within the GM by specifying GM segments in the above-mentioned brain parcellation mask as seeds. We calculated 10^7 streamlines between all the 991 cortical GM segments. These procedures were repeated for every DTI scanning day.

Network-wise time series analysis

We classified the 991 cortical GM segments into nine large-scale cortical brain networks (Figure 1a)[21,22]. Technically, each GM area was given one network label when ≥50% of the segment overlaps a specific network area. The network area was defined as a collection of multiple 6mm-radius spheres around the network-specific coordinates used in previous studies[21,22]. GM segments showing no sufficient overlap with any network were labelled as undefined, and were excluded in the following analyses.

For each brain network, we repeated the following analysis.

First, for each recording day, we built an FC matrix by calculating partial correlations between fMRI signals of the GM segments in the network[23,24]. Partial correlation was adopted as a measure to estimate FC because connectivity based on the method is more comparable to anatomical connections than that based on Pearson correlation[23]. We also built an SC matrix by extracting SC between the target network regions from the whole-brain SC matrix constructed above. This procedure was repeated for all the time points.

Second, we searched for region pairs both of whose FC and SC showed significantly large increases in the 19-week period. For this purpose, we first normalised the connectivity values across the scanning period, and set the average at 0.5 and the standard deviation at 0.5 for all the brain connections. That is, almost all the connectivity values were included in a range between 0 and 1. We then calculated connectivity changes as differences between the mean connectivity in the first three weeks and that in the last three weeks (Figure 1b). To select top 2.5% connectivity increases, we identified connectivity whose FC and SC changes were simultaneously included in top 15% increases in each domain. This threshold was set because 15% is approximately a square root of 2.5%.

Mainly due to this normalisation process, connectivity values of the selected brain connections were highly likely to show monotonic increases: given that almost all the connectivity values ranged between 0 and 1, the first-three-week average of the selected connections should be around 0 and the last-three-week average should be around 1; moreover, considering the standard deviation was also constrained to be at 0.5, the connectivity values of the rest of the period (4th–16th week) were unlikely to under/overshoot the 0–1 range. Consequently, the connectivity values of the selected connections tend to show a roughly monotonic increase and asymptote trend at the end, which enables us to fit the following logistic functions and compare temporal changes between functional and anatomical connections.

Finally, for each connectivity type, we calculated the mean connectivity across the selected connections, and fitted the following logistic function to it:

$$\text{Connectivity} = a \Big/ \left(1 + e^{-\frac{t-c}{b}}\right),$$

where t denotes the day passed since the first data collection. After examining the goodness of fit by calculating adjusted R^2, we estimated when the connectivity change reached 10% ($T_{10\%} = c - 2\times(\ln 3)\times b$) and 50% ($T_{50\%} = c$) of the increases, and evaluated their differences between FC and SC ($\Delta T_{10\%} = T_{10\%\_SC} - T_{10\%\_FC}$; $\Delta T_{50\%} = T_{50\%\_SC} - T_{50\%\_FC}$).

The same analysis was performed for brain connections showing top 2.5% connectivity decreases.

Statistics

Whether the ΔT indices were deviated from zero across the nine networks was tested in one-way factorial analysis of variance (ANOVA) and subsequent two-tailed Welch's tests. Results of the Welch's tests were corrected for multiple comparisons in Bonferroni manner (α = 0.05/[9 network] ≈ 0.0056). Comparisons of the two ΔT indices between the nine networks were based on Welch's tests, whose statistical values were also corrected in Bonferroni manner (α = 0.05/[36 possible pairs of the nine networks] ≈ 0.0014). These statistical analyses were conducted on MATLAB r2015a (Mathworks, Inc).

Validation analyses using fractional anisotropy values

To examine the robustness of the current results, the entire analyses were repeated using fractional anisotropy (FA) values as SC rather than streamlines. For this purpose, we first obtained whole-brain FA value map from the preprocessed DTI datasets using FSL's dtifit tool. By applying MRtirx3's tck2connecome tool to the map, we estimated mean FA values of the traced streamlines between each pair of the GM segments, and built SC matrices consisting of the mean FA values. We performed the same time series analyses comparing these FA-based SC with FC.

Comparison of the FC-SC time lags between different brain lobes

We examined FC–SC time lags between different brain lobes. The randomly-segmented 991 cortical grey-matter areas were classified into one of four brain lobes (frontal, parietal, temporal and occipital lobes) based on AAL labels originally assigned to them. Except this difference in segmentation, the analysis was the same as that performed for the main analysis based on the nine brain networks. The SC was defined by the number of streamlines.

Data availability

fMRI data used in this study is available from OpenfMRI under the accession number ds000031 (MyConnectome).

Competing interests

No competing interests were disclosed.

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Supplementary material

Supplementary File 1: PDF containing the following Supplementary Figures and Tables.
Click here to access the data.

Supplementary Table 1: Proportion of the selected brain connections in all the possible connections in each network

Supplementary Table 2: Proportion of the selected brain connections in all the possible connections in each network (when structural connectivity was defined by fractional anisotropy (FA) values)

Supplementary Figure 1: Comparison of the average length of the selected brain connections

Supplementary Figure 2: Prediction of structural connectivity (SC) increases based on functional connectivity (FC) increases

Supplementary Figure 3: Prediction of structural connectivity (SC) decreases based on functional connectivity (FC) decreases

Supplementary Figure 4: functional connectivity (FC)/structural connectivity (SC) changes after the dates of the data collection were matched between FC and SC

Supplementary Figure 5: Temporal changes in functional connectivity (FC) and fractional anisotropy (FA)-based structural connectivity (SC)

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The authors compared functional connectivity (FC) changes with structural connectivity (SC) changes in nine different networks to test whether FC changes lead to SC changes and whether such time lags between SC and FC changes are different among different functional networks.

The idea to assume that changes in FC occur in advance of SC and that the time lags between SC and FC changes vary between different brain networks is interesting but there are some major points concerning measuring these time lags.

1. **Logical link between FC and SC changes.** The authors reason that a change in FC will, after some time lag, lead to a change in SC. However, Figure 1C shows that there is no correlation between the magnitude of SC change and FC change overall. Even within the 2.5% of chosen connections (very weak or very strong change in Figure 1C), the correlation seems low. It is possible that small SC changes lead to large FC changes. Therefore, differences in the normalised connectivity change between FC and SC might be due to delay but could also be due to a more complex relationship between FC and SC. This should be considered in the discussion section.

2. **Quantifying the number of nodes and connections that are studied.** The authors mention that nodes that had no significant overlap with any of the nine networks were removed: how many of the 991 nodes were excluded? Also, for supplementary tables 1 and 2, how many connections were observed in each of the nine networks? This is crucial to assess how many measurements form the basis for the average values and the standard error of the mean in Figure 2.

3. **Comparing SC and FC curves to detect time lags.** Observing the scatter plot in Fig.2, for all nine networks, SC changes and FC changes reach their maximum/minimum nearly at the same time points. The time lags delta T therefore critically depend on the fitting function that is used for the early change in values. First, it is currently unclear whether the logistic function provides the best fit compared to alternative functions and this should be tested looking, for example, at the cumulative log-normal function or others. Especially for SC, the logistic function fits often only relies on 3 or 4 data points at the early stages. The authors may consider other statistical approaches to test for time lags. Second, it seems that the time lags are largely due to differences between the FC and SC values at day 0. If the normalisation procedure would be updated so that the initial values or set to zero for both FC and SC, would time lags still occur? Third, the shown curves are average values based on maybe 10-50 connections (see the previous point). How consistent are the changes over time for the individual connections? That means, do changes correspond to the average changes that are shown or are the average driven by few outlier connections that show a much faster or slower increase/decrease than the other connections within a network? For this, it would be helpful to provide plots in the supplementary material to assess the consistency of changes for the connections.

4. **Quantifying change.** The authors only show the percentage of SC and FC changes in all figures. What is the magnitude of SC changes? In general, for a mature adult, the changes of SC would be expected to be relatively small without explicit training. How do the changes compare to the magnitude of changes observed in test-retest measurements of SC and FC?

5. **Prediction of SC from previous FC** (Supplementary Figures 2 and 3). To prove the existence of time lag and the efficiency of time lag, it is necessary to compare with the experiments without time lag (zero weeks difference) for these six networks as a baseline. In addition, it is currently unclear whether different time lags (3, 4, or 5 weeks) would not give the same or even better prediction performance. In short, it is currently unclear whether the prediction with a time lag that corresponds to the lag found through curve fitting gives a better prediction than alternative longer or shorter time lags.

Besides, some other points need clarification:

1. The first paragraph in Results states:"… which represents SC more accurately than FC based on Pearson Correlation". Does this mean, "… which represents FC more accurately than FC based on Pearson Correlation"?

2. The second paragraph in Results states that "In fact, the selected connections were included in top 2.5% significant increases in each network…". However, the supplementary tables 1 and 2 show that the percentage varies between the nine networks with a minimum of 1.6%.
3. In the third paragraph in Results, authors need to explain more about testing values and the meaning of subscripts, such as,, ,.

4. The results of axial diffusivity seem to be lacking in Figure 4e.

5. The authors firstly normalised the connectivity values and then selected connections. The authors should state the process of normalisation. Normalised by z-score or by Gaussian distribution? How many values were below 0 and above 1?

6. Supplementary Figure 1: What was the average length of un-selected connections? Are selected connections longer than un-selected ones?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

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Thank you for the invitation to comment on this article titled "Comparing the temporal relationship of structural and functional connectivity changes in different adult human brain networks: a single-case study".

This is a well considered and insightful case-study into the plasticity of the typical adult human brain during the absence of any explicit training. The authors show an impressive creativity with the data analyses applied here. By combining MRI measures of how the brains functional and structural architectures change over modest timescales (~5 months), the authors were able to provide evidence of several interesting phenomena within a single subject. First, most connections within the typical adult human brain are dynamic over short timescales, even in the absence of explicit training (fig1c). Second, by focusing on those connections whose functional and structural weights both change in the same direction (both increase or decrease), the authors show that changes in functional connectivity (FC) are

highly predictive of changes in structural connectivity (SC). Third, changes in FC consistently preceded changes in SC. Fourth, the lag between changes in the FC being reflected in the SC showed an interesting non-uniform pattern across the brain that was interpretable. Critically, this pattern was consistent across both analyses of the increasing or decreasing connectivity weights. Specifically, it seems that the anatomy of the sensory networks is relatively resilient to modulation in response to changes in the FC. This was in contrast to the higher order networks that appear to be readily available to modulate their SC in response to changes in FC.

The article is scientifically sound, however, it may benefit from some minor changes that are described below. It would be very exciting to replicate the findings from this case-study in future work involving multiple subjects.

Tractogram Filtering:
At this stage, the only methodological concern I have relates to the extracted measures of structural connectivity. While the use of metrics that go beyond simplistic tensor-based models is appropriate, raw streamline counts are known to be susceptible to systematic biases introduced by tractography algorithms. To get closer to the desired biologically meaningful metric, a final step of tractogram filtering could be added to your structural connectome pipeline. The developers at mrtrix have provided some very useful tools (tcksift & tcksfit2 - see attached citations[1-2]) that filter whole-brain tractograms by iteratively removing streamlines in order to minimise the difference between a voxels streamline density and the integrals of its Fibre Orientation Distribution (FOD) function. While the algorithm's cost function does relate to the global fit, the developers have demonstrated that several of the biases that occur during streamline propagation are significantly mitigated when filtering is applied. Finally, this approach is particularly desirable as the filtered streamline counts provide a measure of Apparent Fibre Density (AFD), a "biologically meaningful" metric that has a strong relationship to the underlying DWI data.

Minor Comments:

- *Effect Size*
It would be interesting to get a handle on the magnitude/effect size of the changes in the connectivities focused on. For example, could it be that the sensory networks seem more resilient (exhibit longer time lags) because larger scale anatomical changes are occurring than in the higher-order networks?

- *Interpretation*
I am wondering if others would agree with the interpretation that, if the experiment was continued or repeated then you wouldn't necessarily see those same connections in the top-right and bottom left segments of fig1c? Presumably, those connections focused on here would not keep increasing or decreasing as there must be floors and ceilings that determine the possible range of connection strengths. Instead, the positions of those functional and structural connectivities in fig1c may be in a constant degree of flux. If this is the case, it would be very interesting to quantify the probability that certain connectivities end up in certain segments of fig1c. This could be addressed across subjects in future work. It would be nice to see the possibility of non-stationarity in this feature set being described in the discussion.

- *Terminology*
It may be a good idea to replace the term 'Diffusion Tensor Imaging (DTI)' with 'Diffusion Weighted Imaging (DWI)' throughout, except for the section of the validation analysis that explicitly uses tensor

metrics. DWI refers to the MR modality, while DTI refers to a model that is often applied to DWI data.

- *Spelling / Grammar*
The 3rd paragraph of the introduction a sentence reads: "We further hypothesised that the time lags between FC and SC changes vary between different brain networks with **difference** cognitive and perceptual functions." It may read better like this: "We further hypothesised that the time lags between FC and SC changes vary between different brain networks with **different** cognitive and perceptual functions."

- *Spelling / Grammar*
The 1st paragraph of the results (page 4/10) read: "SC was defined by the number of streamlines traced in diffusion-tensor imaging (DTI) data...". It may be more accurate to replace the term 'DTI' with either 'the DWI' or 'the FOD space' as the tensor does not seem to have been used for streamline propagation.

- *Structure*
It may be sensible to move the analyses of radial and diffusivity out of the discussion and into the Validation section. These results support your main findings from a different perspective. There you could unpack your findings by describing the direction of the effects reported in the ANOVA. Critically, you could then return to this in the discussion and provide some context about the difference between the radial and axial diffusivity metrics, i.e., Axial=E1, Radial=mean([E2 E3]), and how these are specifically thought to describe different aspects of myelination. This may be helpful for future readers to contextualise the results, particularly if they are not familiar with DTI.

- *Data availability*
Are the DWI data publically available alongside the fMRI data?

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Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.