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CASE STUDY

Decoupling between the hand territory and the default mode network after bilateral arm transplantation: four-year follow-up case study

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Abstract Several studies have suggested both a local and network reorganization of the sensorimotor system following amputation. Transplantation of a new limb results in a new shifting of cortical activity in the local territory of the transplanted limb. However, there is a lack of information about the reversibility of the abnormalities at the network level. The objective of this study was to characterize the functional connectivity changes between the cortical territory of the new hand and two intrinsic network of interest: the sensorimotor network (SMN) and the default mode network (DMN) of one patient whom received bilateral forearm transplants. Using resting-state fMRI these two networks were identified across four different time points, starting four months after the transplantation surgery and during three consecutive years while the patient underwent physical rehabilitation. The topology of the SMN was disrupted at the first acquisition and over the years returned to its canonical pattern. Analysis of the DMN showed the normal topology with no significant changes across acquisitions. Functional connectivity between the missing hand's cortical territory and the SMN increased over time. Accordingly, functional connectivity between the missing hand's cortical territory and the DMN became anticorrelated over time. Our results suggest that after transplantation a new reorganization occurs at the network level, supporting the idea that extreme behavioral changes can affect not only the local rewiring but also the intrinsic network organization in neurologically healthy subjects. Overall this study provides new insight on the complex dynamics of brain organization.

Keywords Resting state · Motor network · Transplantation · Hand · Default mode network

Introduction

Since its first demonstration using functional magnetic resonance (fMRI) in the primary motor cortex (Biswal et al. 1995), resting state fMRI has become a powerful and increasingly popular tool to study long-range interactions in the brain. Resting state functional connectivity measures the synchrony of low frequency blood oxygenation level dependent (BOLD) fluctuations among anatomically distant brain areas, which characterize the neural baseline activity of the brain, and reflects functionally distinct networks (Beckmann et al. 2005). Resting state networks (RSN) exhibit correlated spontaneous fluctuations even in the absence of tasks or stimuli, suggesting independence among different networks (Fox et al. 2005). A number of studies have shown the consistency of the RSNs using a variety of analyses in healthy subjects (Damoiseaux et al. 2006) and its abnormalities in clinical populations (Hernandez-Castillo et al. 2013, 2015). The reliability of resting state networks in longitudinal data has also been tested in both younger adults (Chou et al. 2012) and elderly populations (Guo et al. 2012) showing very low within-subject variability across time. These studies suggest that resting state

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measurements are potentially suitable as biomarkers for monitoring disease progression and treatment effects in clinical trials and individual patients. In a recent report, Makin et al. (2015) investigated cortical reorganization after unilateral amputation at the network-level scale. They found that normally highly positive correlation between the missing hand's territory and the sensorimotor network (SMN) was significantly decreased after amputation. Instead, the area started to correlate more with the default mode network (DMN), even though in healthy individuals, these two networks are usually anticorrelated. These results indicate that the dramatic change in the sensorimotor system, as well as in the behavior of the subject after suffering the loss of a limb, can lead to changes in brain organization on the network level. Here we investigate whether this reorganization is reversible after limb transplantation and successful rehabilitation.

Several reports have suggested that cortical reorganization after amputation results in a shift in the cortical activity of unaffected muscles into the respective motor and sensory regions previously dedicated to the lost limb. Röricht et al. (1999) used focal transcranial magnetic stimulation in human amputees, finding increased response amplitudes in stump muscles and an enlarged area from which responses could be elicited from the skull on the respective motor cortex of the missing limb. Furthermore, studies involving primate amputees have shown that a mixture of shoulder, stump, trunk, and orofacial movements can be evoked from the deafferented cortex using intracortical microstimulation (Wu and Kaas 1999; Qi et al. 2000). Those initial findings have been challenged by newer studies that report that the stump muscle map area in upper limb amputees is not different from that of the intact muscle from the other side (Gagné et al. 2011), or expanded by showing that increases in the representation of displaced body parts in the deprived cortex of upper limb amputees, correlate with adaptive daily strategies of limb-usage (Makin et al. 2013). Reports using fMRI in patients who received transplantation of a new limb have shown that the local patterns of the BOLD signal within the sensorimotor cortex shift again, suggesting a possible reversibility mechanism (Giraux et al. 2001; Hernandez-Castillo et al. 2016) that might be modulated by the time between the loss of the limb and the transplantation of a new one (Brenneis et al. 2005). Based on the findings that amputation results in both local activity shifts and resting state changes, we hypothesized that after transplantation, the abnormal functional connectivity of the SMN resulting from amputation could return to its canonical pattern following rehabilitation. Here we present a single case-study functional connectivity analysis of a patient who underwent bilateral arm transplantation and rehabilitation over a period of four years.

Material and methods

Participant

A 52-year-old right-handed man suffered a high-voltage electrical burn causing the loss of his hands in January 2011. The patient underwent bilateral proximal forearm transplantation in May 2012. During the period of waiting for a suitable donor, the patient reported intermittent phantom pain. The donor was a 34-year-old brain-dead multiorgan donor. After the transplant, the patient followed a comprehensive rehabilitation program (Iglesias et al. 2016). The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire (Beaton et al. 2001) was used to assess behavioral recovery in the patient (DASH score on each rsfMRI acquisition: 1st =42; 2nd =36; 3rd =30; 4th =25). DASH is a 30-item questionnaire that looks at the ability of a patient to perform daily-life upper extremity activities. This questionnaire is self-reported and the score ranges from 0 to 100. The higher the score, the greater the respondent experiences disability/symptoms. By the date of preparation of this study, the patient was able to sign the informed consent and perform his daily activities independently. Ten right-handed male subjects were invited to participate as healthy controls (mean age 53, standard deviation 6.4). All participants in the control group self-reported not having any neurological or psychiatric disorders. The protocol was approved by the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán ethics committee. The participants gave signed informed consent prior to the beginning of the study.

Imaging acquisition

The patient underwent four MRI scanning starting four months after surgery at regular twelve-months intervals for three consecutive years. Brain imaging sequences were acquired with a 3 T GE Excite scanner (GE Healthcare Technologies, Waukesha, WI) equipped with a standard quadrature head coil. The acquisition included a high-resolution inversion recovery spoiled gradient-echo T1-weighted isotropic, volumetric sequence (3D SPGR $1 \times 1 \times 1$ mm^3, 180 slices TE/TR/TI = 2/7/400 ms, flip angle =15, matrix =$256 \times 256 \times 180$, FOV = $240 \times 240 \times 180$ mm^3) and a resting state functional image using a gradient-echo single-shot echo-planar imaging sequence (repetition time 3000 ms, echo time 50 ms, field of view 200 mm, matrix 64×64, 39 slices of $3.75 \times 3.75 \times 4$ mm thickness with no gap) of 180 volumes with whole brain coverage. Resting state fMRI data of ten age-matched healthy subjects were used to create the control RSNs. The control group underwent a single session MRI acquisition which included high resolution structural and resting state functional images following the same acquisition protocol as was used in the patient.

Seed locations

For functional connectivity analysis, we used three seed locations: right hand and left hand for the SMN and the posterior cingulate for the DMN. Seed locations for the bilateral hand knob area were selected based on independent data (Ejaz et al. 2015). In this study, nine right-handed subjects were instructed to perform finger movements with both hands. fMRI data analysis of the motor task was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB"s Software Library, www.fmrib.ox.ac.uk/fsl). The following preprocessing was applied: motion correction, brain extraction, spatial smoothing using a Gaussian kernel of FWHM 5 mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma =30.0 s). Time-series statistical analyses were carried out using FILM with local temporal autocorrelation correction. Z-transformed statistical images were thresholded at a height threshold of $Z > 7.0$ and the corresponding cluster size of 520 mm^3 to control for the family-wise error rate at $p < 0.01$. Clusters of significant activation were identified for right and left hand movement in the primary motor cortex. Based on previous literature, a third seed was defined for the default mode network in the posterior cingulate gyrus (Fox et al. 2005). All structural images were warped to the Montreal Neurological Institute (MNI) template, using the nonlinear registration method (Jenkinson et al. 2002). Coordinates of the local maxima in MNI space in mm: right hand X = 42, Y = −22, Z = 52; left hand X = −38, Y = −26, Z = 52; posterior cingulate X = −5, Y = −49, Z = 30.

Resting state preprocessing

The resting state fMRI (rsfMRI) preprocessing was performed using FSL (FMRIB Software Library (FSL), Oxford University, Oxford, UK) and included brain extraction, time shifting, motion correction, spatial smoothing (6 mm full-width at half-maximum Gaussian kernel), linear trend removal, and temporal filtering (band pass, 0.01–0.08 Hz). A regression technique was used to remove sources of variance, including white matter and cerebrospinal fluid (Fox et al. 2006). In addition, motion scrubbing was applied to scans that surrounded a minimum signal change of less than 0.5% and a frame-wise displacement of 0.5 mm (Power et al. 2012). rsfMRI images were coregistered to the corresponding structural image using rigid body transformation. In order to have a patient's common space, rsfMRI images of the patient were coregistered to one single structural image. After rigid alignment of rsfMRI images to structural images, spatial normalization of rsfMRI images to the MNI template was achieved by using the transformation field acquired during the structural image registration.

Functional connectivity analysis

Functional connectivity maps for each seed were created for each patient's time point and for the control group. Using MATLAB R2015a (The Mathworks, Inc., Natick, MA), the mean time course of each seed was extracted by calculating the average of all voxels within a sphere with a diameter of 12-mm centered on the previously defined coordinates. Functional connectivity maps were created by calculating a Pearson's linear correlation between the seed's average signal and the signal of every other voxel in the brain. Functional connectivity maps of all subjects in the control group were averaged to create the RSN control maps that represent the canonical form of each network.

We then wanted to determine the correspondence of the topology between the patient's RSN maps and the canonical RSN. For this, we calculated the spatial correlation between each canonical RSN map and each of the corresponding network maps of the patient. To determine the range of variation within the control group, we calculated the spatial correlation between the canonical RSN map and the RSN map of each individual in the control group. The spatial correlation was calculated using non-thresholded maps. In a second analysis we wanted to explore the coupling changes between the territory of the hand and both the SMN and the DMN. The canonical RSN maps were thresholded in the third quartile of the positive correlation and then binarized to be used as masks in the following procedure. The area of each seed was excluded from each corresponding RSN mask. The RSN masks were warped to the original patient space using the inverse transformation field acquired in the registration process. The average time series of each mask were extracted from the patient rsfMRI data, resulting in two time-series for the SMN (left and right) and a third for the DMN. To assess the intra-network coupling, Pearson's correlations were calculated between the average time series of each seed and the time series of the corresponding SMN. Coupling between the hand territory and the DMN was assessed by calculating the Pearson's correlation between the average time series of each hand knob seed and the time series of the DMN. Linear regression was performed to examine the association between the functional connectivity measurements and the DASH score.

Results

Correspondence of RSNs

To examine the topological changes in the patient's RSN over the course of rehabilitation progress, we compared his functional connectivity maps with the canonical RSN obtained from the control group (Fig. 1). Since the patient had to wait more than a year before transplantation, we expected that at

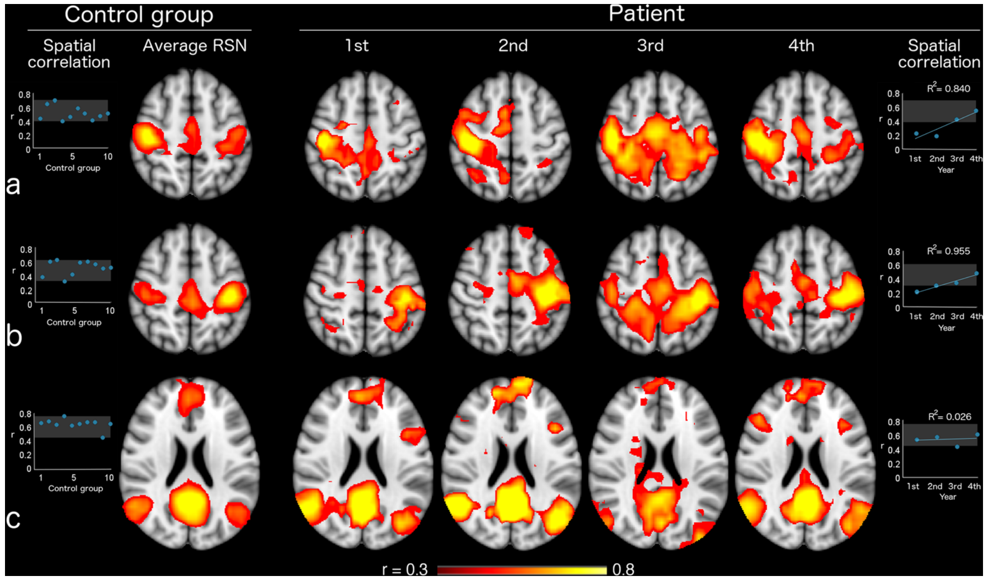

Fig. 1 Correspondence of RSNs. Functional connectivity maps for **a** left SMN, **b** right SMN and **c** DMN. The left section shows the average connectivity maps for the control group (canonical RSNs) and the scatter plots of the variability of the control group. The right section shows in consecutive order the patient's connectivity maps for each time point. Scatter plot in the right indicate the spatial correlation between the canonical RSNs and the individual patient's maps. The gray region in all scatter plots indicates the range of variability in the control group

the moment of the first rsfMRI acquisition, his SMN would be affected, thus showing an abnormal connectivity pattern; in contrast, his DMN would likely preserve its canonical organization (Makin et al. 2015). We also predicted that the abnormal connectivity pattern in the patient's SMN would change over the years. As expected, our results indicate that the patient's SMN was disrupted at the first MRI session, showing high correlation mostly in the seed area and no connectivity with the contralateral motor cortex or the premotor area. The shape of the patient's SMN shifted overtime to a more typical topology, showing high correlation with the premotor area in the second acquisition. By the third and fourth scanning sessions, a high correlation with the contralateral motor cortex was finally found (Fig. 1a, b). In contrast, the patient's DMN showed the typical topology since the first acquisition and no significant differences were found over time (Fig. 1c).

Coupling changes in the SNM and the DMN

Makin et al. (2015) showed that over time, the territory of an amputated limb decoupled from the SMN and started to show a correlation with the DMN. This suggests that over the years the missing hand's cortex territory gradually became decoupled from the sensorimotor network resulting in coupling increases with the default mode network. Based on this, we expected to find the opposite result in our patient. We calculated the functional connectivity within each RSN and its respective seed. As expected, the strength of the synchrony within the SMN showed a low correlation at the first time point, which then increased over the consecutive years, whereas the DMN showed a high correlation in all sessions (Fig. 2 upper row). The coupling between the hand territory and the DMN showed a positive correlation in the first acquisitions that became anticorrelated over time (Fig. 2 lower row).

Associations between functional connectivity changes and DASH score

We found a significant correlation between the DASH score and RSNs spatial correspondence of the left SMN ($r = -0.97$, $p = 0.02$), a trend in the right SMN ($r = -0.91$, $p = 0.08$) and no correlation in the DMN ($r = -0.12$, $p = 0.87$) see Fig. 3 upper row. The DASH score showed a correlation trend with the within-network connectivity in the left SMN ($r = -0.90$, $p = 0.09$) while the right SMN and DMN did not showed significant correlation (right SMN: $r = -0.85$, $p = 0.14$; DMN: $r = 0.32$, $p = 0.67$) see Fig. 3 middle row. The functional connectivity between the hand seed and the DMN showed no significant correlation (left, $r = 0.80$, $p = 0.19$; right $r = 0.81$, $p = 0.18$) see Fig. 3 lower row.

Discussion

In this study we characterized the changes in the functional connectivity between the hand area and the SMN and the DMN of a patient after bilateral forearm transplantation and four subsequent years of rehabilitation. Our results suggest a gradual reconstitution of the canonical topology of the SMN, as well as changes in functional connectivity between the bilateral hand territory and the DMN over the rehabilitation years.

In the healthy brain, correlated spontaneous activity known as RSNs occurs within spatially distinct, functionally related groups of cortical and subcortical regions (Seeley et al. 2009). After the loss of a limb, local cortical reorganization can be observed within the sensorimotor cortex. Makin et al. (2015) have shown that those local changes also affect the motor system beyond the hand area, resulting in abnormalities in

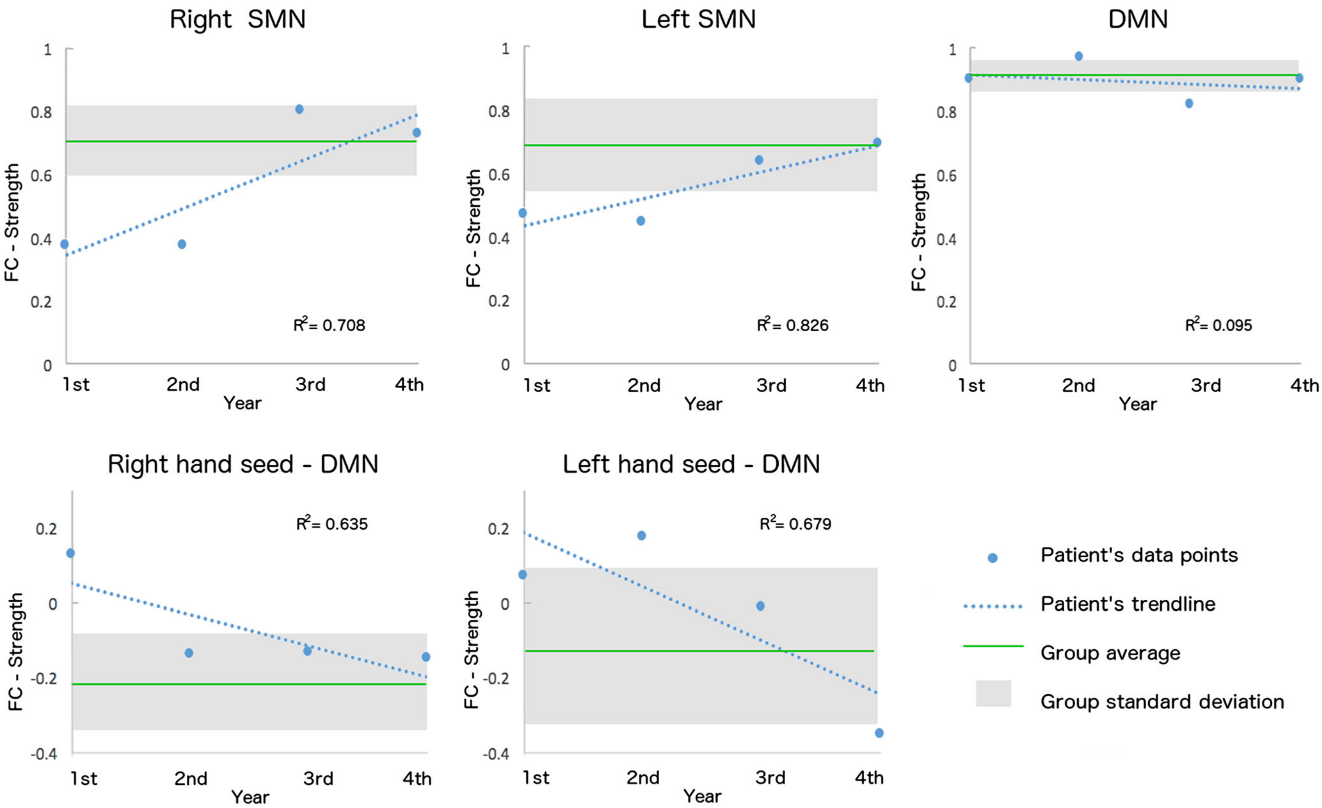

Fig. 2 Within/between-network correlation. Scatter plots showing Pearson's correlation of the temporal BOLD signal between the seed area and the RSNs. The upper row indicates the coupling between the three seeds and its corresponding RSN (within-network); The lower row indicates the coupling between SMN seeds and the DMN (between-network)

the RSNs mainly due to sensorimotor deprivation. Once a new limb is transplanted, shifts in the activation pattern occur in the sensorimotor cortex, suggesting a possible reversibility of the changes after amputation (Hernandez-Castillo et al. 2015). Our results expand previous reports by showing that a large-scale reorganization beyond the sensorimotor territory of the transplanted forearm gradually occurs paralleling to rehabilitation. Specifically, our analysis revealed that in the first rsfMRI acquisition after surgery, the patient exhibited a disruption in the motor network, showing decreased or no connectivity between the deprived hand area and the contralateral motor and premotor cortices. For several reasons, such as finding a suitable donor, our patient waited one year to receive the transplantation surgery. Since the sensorimotor cortex is not hard wired, but adapts to sensory experience (Barnes and Finnerty 2010), waiting for a long time before the transplantation surgery might result in changes in cortical rewiring causing the observed network disruption. Once the patient gained dexterity in using his new arms, the topology of the motor network shifted gradually back to the canonical topology which includes the bilateral primary motor cortices and the premotor area. Furthermore, we found correlation between the DASH score and the correspondence between the patient's SMN and the canonical shape. In other words, our results suggest that the topology of the patient's SMN can be associated with his disabilities/symptoms, and future research might find this measurement useful to evaluate the rehabilitation state or efficacy.

We also explored the functional connectivity between the territory of the hand and the default mode network. A recent study involving a large group of amputees has shown increases in the functional connectivity between the cortical territory of the lost limb and the default mode network (Makin et al. 2015). It is well known that in healthy subjects the SMN and the DMN are anticorrelated (Fox et al. 2005); however, the deprivation of inputs and outputs resulting from an amputation might drive the affected area to remain in a standby state, which will couple with the DMN which is more active during rest. As expected, in the first acquisition our patient showed a positive correlation between the hand territory and the DMN which became negative over time, showing the opposite effect with the SMN as previously discussed. This shows that the more active the hand's territory becomes, the less it is coupled with the DMN. The changes between the hand knob area and the DMN also showed a direct relationship with the rehabilitation of the patient; however, due to the low number of time points these correlations should be taken with prudence.

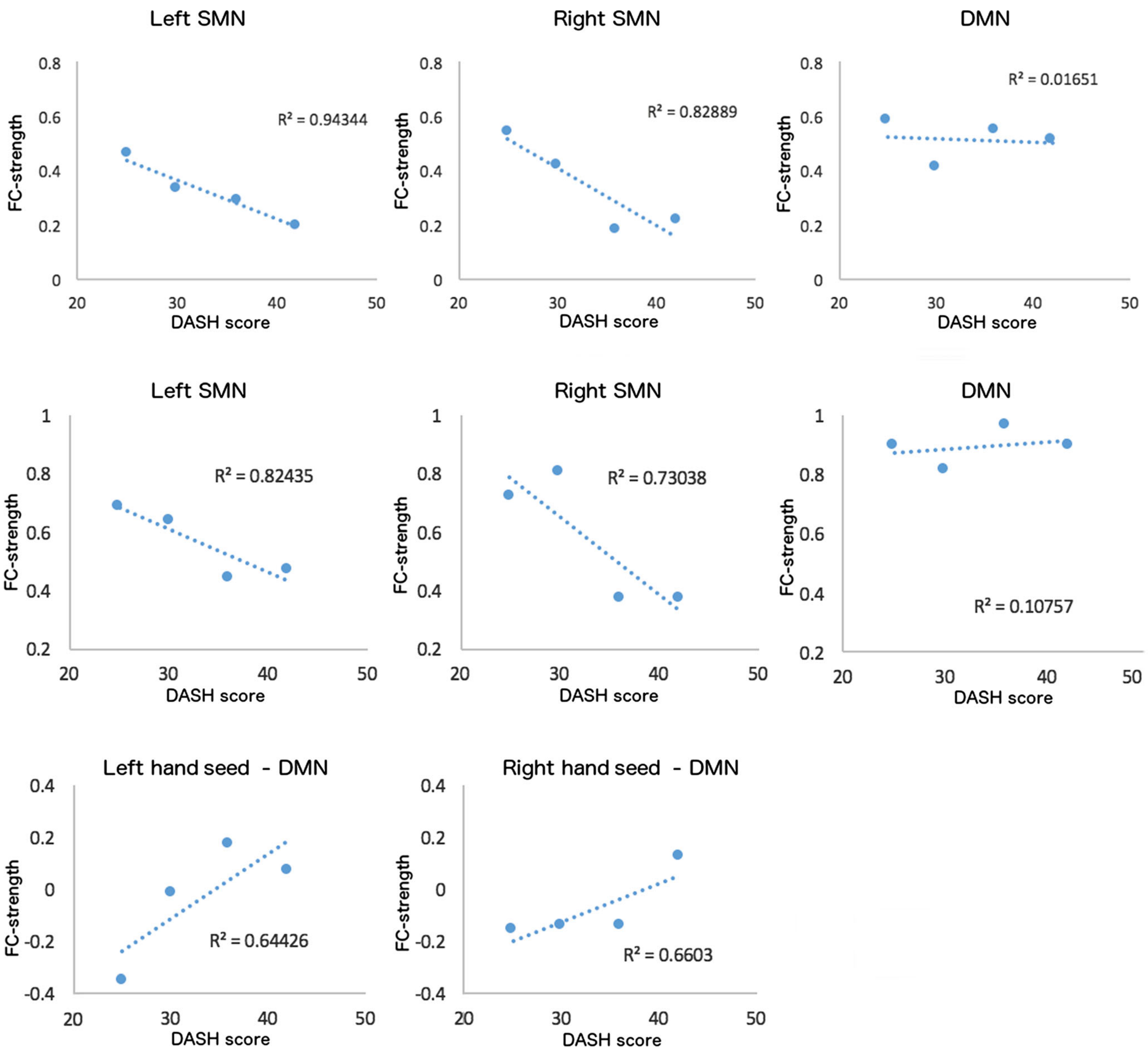

Fig. 3 Association of DASH score with functional connectivity changes. Scatter plots showing the linear regression of DASH score and the functional connectivity measurements; the upper row indicates the topological correspondence of RSNs; the middle row indicates the within network connectivity; the lower row indicates the between-network connectivity (see Methods)

A number of limitations should be noted. Studies acquiring data more frequently and for a longer period of time are needed to validate our results. Another limitation of this study is that we did not collect longitudinal data for the control group. Although resting state measurements have been shown to be reliable over time (Chou et al. 2012; Guo et al. 2012), some variation in the gradients of MRI scanner can appear over the years, so further studies should acquire longitudinal data from both patient and control groups to assess any possible variation in the equipment.

Overall, this case study shows that the functional connectivity of the hand knob changes in parallel to functional rehabilitation of the transplanted arms; however, more research is needed to clarify whether the new cortical organization represents a mechanism of reversibility or whether a new representation is rewired over the preserved sensorimotor system.

Conclusion

Here we showed a single-case report in which an abnormality of the SMN resulting from amputation one year before, reorganized to its canonical topology after limb transplantation and successful rehabilitation four years later. Similarly, the temporal signal of the hand's territory became decoupled from the DMN over the course of rehabilitation. Our findings support previous studies highlighting the network-scale reorganization in neurologically healthy subjects. Future studies might eventually characterize this reorganization in larger populations and provide insight into the complex dynamics of brain organization.

Compliance with ethical standards

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Conflict of interest The Authors declare they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Instituto Nacional de Neurología y Neurocirugía in Mexico City and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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