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Reduced functional connectivity within the primary motor cortex of patients with brachial plexus injury

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ABSTRACT

This study aims at the effects of traumatic brachial plexus lesion with root avulsions (BPA) upon the organization of the primary motor cortex (M1). Nine right-handed patients with a right BPA in whom an intercostal to musculocutaneous (ICN-MC) nerve transfer was performed had post-operative resting state fMRI scanning. The analysis of empirical functional correlations between neighboring voxels revealed faster correlation decay as a function of distance in the M1 region corresponding to the arm in BPA patients as compared to the control group. No differences between the two groups were found in the face area. We also investigated whether such larger decay in patients could be attributed to a gray matter diminution in M1. Structural imaging analysis showed no difference in gray matter density between groups. Our findings suggest that the faster decay in neighboring functional correlations without significant gray matter diminution in BPA patients could be related to a reduced activity in intrinsic horizontal connections in M1 responsible for upper limb motor synergies.

1. Introduction

Brain plasticity consists in the ability of the central nervous system (CNS) to modify in response to changes in behavior, as a consequence of skill acquisition or following central/peripheral injury (Buonomano and Merzenich, 1998; Kaas, 1991; Garraghty and Kaas, 1992). Although a growing body of studies shows that plasticity correlates positively with functional recovery following brain injury (review in Cramer et al., 2011), less is known about the mechanisms underlying functional recovery following peripheral lesion and surgical reconstruction.

Severe traumatic brachial plexus lesions with root avulsion (BPA) leads to motor and sensory function loss of the arm. Although the reconstruction of the original peripheral nerve pathways is not possible, nerve transfer can be performed to regain function. For instance, by connecting the distal denervated musculocutaneous (MC) nerve to the third to sixth thoracic intercostal (IC) nerves (Midha, 2004). Normally the IC nerves are connected to intercostal muscles, which are involved in volitional breathing and postural control. After successful reinnervation of the biceps muscle following intercostal-musculocutaneous (ICN-MC) nerve transfer, the ICN now innervates the biceps muscle. Initially, elbow flexion by biceps contraction can only be effected by respiratory effort, for instance sustained inspiration. In time however, volitional control becomes possible, implying a change in control. Following this surgical procedure, about two-thirds of patients regain biceps function with at least Grade 3 out of 5 according to the Medical Research Council scale (Seddon; Narakas and Hentz, 1988; Malessy et al., 1993; Malessy and Thomeer, 1998; Midha, 2004).

Applying transcranial magnetic stimulation (TMS) to the primary motor cortex (M1), Mano et al. (1995) and Malessy and Thomeer (1998) studied the change in control over the reinnervated biceps muscle some years after ICN-MC transfer performed in patients with BPA. M1 contains a map of movements organized somatotopically (Rasmussen and Penfield, 1950) with gross and largely separated

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body part subdivisions represented sequentially from lateral to medial precentral gyrus. Mano et al. (1995) and Malessy and Thomeer (1998) found in these operated patients that the biceps representation shifted from medial to a more lateral position (i.e a shift from the trunk area to the arm area) in M1. Although plausible hypotheses have been put forward to understand the role of brain plasticity in recovery of BPA patients after ICN-MC nerve transfer (Mano et al., 1995; Malessy and Thomeer, 1998; Malessy et al., 2003), it remains unclear which mechanisms underlie the shift from respiratory dependent biceps control to volitional biceps control and to what extent this functional change is a result of plastic changes in the brain.

Horizontal intrinsic connections between spatially distant and functionally different parts of M1 have been consistently revealed in animal models (Huntley and Jones, 1991; Jacobs and Donoghue, 1991; Sanes and Donoghue, 2000; Ziemann, 2004). These long-range horizontal connections were proposed to be involved in activity synchronization beyond cortical modules (Boucsein et al., 2011), fine motor synergy coordination (review in Schieber, 2001) and use-dependent motor learning (review in Sanes and Donoghue, 2000). Such horizontal network within M1 might also underlie plastic modifications induced by BPA and nerve transfer.

Resting-state fMRI has already been used to investigate how the human brain's functional organization is affected by BPA (Liu et al., 2013; Qiu et al., 2014). Herein we aim at the effects of BPA on local functional connectivity by exploring the decay of the functional correlations between neighboring voxels within M1. We find evidence that these correlations decay faster as a function of distance in BPA patients as compared to the control group in the M1 region corresponding to the arm but not to the face area. We also investigate whether such larger correlation decay in patients can be attributed to a gray matter diminution in M1 by means of structural imaging analysis. The lack of difference in gray matter density between BPA group and control together with the faster correlation decay in neighboring functional correlations in BPA patients suggests a reduced activity in intrinsic functional connections responsible for upper limb motor synergies in M1.

2. Material and methods

2.1. Subjects

Nine right-handed patients with a brachial plexus lesion (mean age 34.6, SD = 4.8; mean age at lesion: 18.8 ± 2.2) and eleven right-handed control subjects (mean age 35.4 ± 8 years), matched in age and sex with the patient's group participated in the study. All patients suffered a brachial plexus traction lesion with root avulsion on the right side. They were included in the study only if they had undergone successful Intercostal to Musculocutaneous (ICN-MC) nerve transfer, meaning there was at least some recovery of biceps function (grade of 1 or higher as measured with the Medical Research Council grade). At the time of the study they showed variable degrees of biceps function recovery (Mean: 3.0, SD 1–4, as measured with the Medical Research Council grade). The exclusion criteria were history of neurological trauma and additional surgical procedures aimed at regaining elbow flexion (e.g. Steindler flexorplasty), and general exclusion criteria for MRI scanning (such as claustrophobia, pacemaker, and metallic implants). The local ethics committee approved the study and the patients gave written informed consent in accordance with the declaration of Helsinki. Information about patients and controls are presented in Tables 1 and 2.

2.2. Experimental procedure

The volunteers were comfortably positioned inside the scanner during the experiment. Pillows were placed between the forehead of the subject and the coil to minimize head movement. Lower arms were positioned next to the body at a comfortable angle between 10° and 30° by using cushions. The palm of subjects' hands faced up to the extent that this was possible without causing discomfort. Subjects were instructed to keep their eyes closed, and not to think of anything in particular during resting-state scanning. The scanning time lasted for 5 min.

Table 1
Information of the patients with braquial plexus lesion. Injury type classification includes Avulsion (Av.) and Neurotmesis (Nt.) types. I1 is the time interval in months between lesion and surgery. I2 is the time interval in years between surgery and fMRI scan.

Id	Age at scan	Gender	Injury type	Age at lesion	I1	I2	Location
P01	35	M	Av. C5-T1	16	2	19	Leiden
P02	40	M	Av. C5-C7	35	11.2	5	Leiden
P03	36	M	Av. C5-T1	18	4	18	Leiden
P04	38	F	Av. C5-C7	22	2.8	16	FCDC
P05	33	F	Av. C5-C7	19	2	14	Leiden
P06	32	M	Av. C5-C7	26	5.1	6	FCDC
P07	40	M	Av. C6-C7 Nt. C5	23	3	17	Leiden
P08	40	M	Av. C6-T1 Nt. C5	26	1	14	FCDC
P09	26	M	Av. C5-T1	19	5	7	FCDC

2.3. Data acquisition

To reduce travel time and thereby maximize the willingness of the patients to participate in the study, data from control participants and from patients were acquired at two centers in the Netherlands. Six control and four patients underwent scanning at Donders Institute (DI) in Nijmegen and five controls and five patients, at the Leiden University Medical Center (LUMC). At the Donders Institute (DI) in Nijmegen, measurements were performed on a 3 T TIM Trio MR scanner (Siemens Medical Solutions, Erlangen, Germany). At the Leiden University Medical Center (LUMC), a 3 T Achieva scanner (Philips Medical Systems, Best, The Netherlands) was used. On both systems an eight-channel head coil, which was produced by the same vendor, was used for all data collection. Acquisition parameters were adjusted to be as equal as possible between the two scanners, while still having near optimal settings for each system.

Resting-state fMRI data were acquired with a 2D single-shot EPI sequence. The whole brain was covered by acquiring 38 axial slices (3.5 mm isotropic voxels, 0.35 mm interslice gap, 64 × 64 matrix). Flip angle = 85°, volume repetition time = 2180 ms, echo time = 30 ms. An in-plane parallel imaging acceleration factor of 2 was used. Online image reconstruction was performed using the GRAPPA [REF 37] and SENSE algorithms [REF 38] on the Siemens and Philips systems, respectively. A number of 220 volumes were acquired for a total acquisition time of 8 min.

2.4. Data analysis

2.4.1. Resting state fMRI data pre-processing

The statistical parametric mapping software package (SPM8, Wellcome Department of Cognitive Neurology, London) was used for

Table 2
Information of the control group. Control group and patients group match in age (p-value for unpaired t-test is 0.7996) and proportion of each gender (p-value for proportion z-test is 0.4132).

Id	Age	Gender	Location
C01	50	M	FCDC
C02	31	M	FCDC
C03	34	M	FCDC
C04	31	M	Leiden
C05	31	M	Leiden
C06	39	M	FCDC
C07	40	M	FCDC
C08	28	M	FCDC
C09	33	F	Leiden
C10	31	M	Leiden
C11	36	M	Leiden