NeuroImage: Clinical 2 (2013) 797–803

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Cortical thickness changes in the non-lesioned hemisphere associated with non-paretic arm immobilization in modified CI therapy

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ARTICLE INFO

Article history:
Received 4 February 2013
Received in revised form 7 May 2013
Accepted 8 May 2013
Available online 21 May 2013

Keywords:
Immobilization
Sensorimotor deprivation
Hemiparesis
Surface-based morphometry
Cortical thickness
Diffusion tensor imaging
Stroke
Learned non-use
Plasticity

ABSTRACT

Recent evidence suggests that immobilization of the upper limb for 2–3 weeks induces changes in cortical thickness as well as motor performance. In constraint induced (CI) therapy, one of the most effective interventions for hemiplegia, the non-paretic arm is constrained to enforce the use of the paretic arm in the home setting. With the present study we aimed to explore whether non-paretic arm immobilization in CI therapy induces structural changes in the non-lesioned hemisphere, and how these changes are related to treatment benefit. 31 patients with chronic hemiparesis participated in CI therapy with ($N = 14$) and without ($N = 17$) constraint. Motor ability scores were acquired before and after treatment. Diffusion tensor imaging (DTI) data was obtained prior to treatment. Cortical thickness was measured with the Freesurfer software. In both groups cortical thickness in the contralesional primary somatosensory cortex increased and motor function improved with the intervention. However the cortical thickness change was not associated with the magnitude of motor function improvement. Moreover, the treatment effect and the cortical thickness change were not significantly different between the constraint and the non-constraint groups. There was no correlation between fractional anisotropy changes in the non-lesioned hemisphere and treatment outcome. CI therapy induced cortical thickness changes in contralesional sensorimotor regions, but this effect does not appear to be driven by the immobilization of the non-paretic arm, as indicated by the absence of differences between the constraint and the non-constraint groups. Our data does not suggest that the arm immobilization used in CI therapy is associated with noticeable cortical thinning.

1. Introduction

It is estimated that 85% of stroke survivors sustain upper limb hemiparesis (Thorngren and Westling, 1990) with 30–60% experiencing permanent impairments of motor function (van der Lee, 2003). The need to improve long-term motor outcome, and the challenges involved in this endeavor, has long been recognized. The discovery of adult brain plasticity, together with the emergence of positive evidence for motor function improvement through repetitive training and practice, has driven a paradigm shift in the treatment of motor deficits after stroke (French et al., 2007; Taub et al., 2002). One concept, constraint induced movement therapy (CI-therapy), has received particularly strong resonance in the field. This is evidenced by several systematic reviews (e.g. Nijland et al., 2011; Peurala et al., 2012; Sirtori et al., 2009), and multi-centered trials (e.g. EXCITE, Wolf et al., 2007; Wolf et al., 2010) which suggest sustainable improvements of upper limb function through CI-therapy or its derivatives (e.g. Page, 2007; Sterr and Freivogel, 2003).

The signature CI-therapy intervention comprises 6 h of daily training with the paretic arm while constraining the non-paretic arm with a splint–sling constraint for 90% of waking hours (Taub et al., 1993). This daily regime is provided for 10 consecutive days spread over two weeks. The concept of linking paretic arm practice with constraining the non-paretic arm is rooted in theoretical assumptions. Specifically, CI-therapy assumes that increased paretic arm use, induced by a combination of massed practice and changes to the behavioral tendency to disuse the paretic limb spontaneously, promotes functional reorganization of the brain and the recovery of function. Through the constraint of the non-paretic arm during the intervention period, CI-therapy further aims to break the behavioral contingencies that perpetuate the conditioned non-use of the paretic arm (Sterr et al., 2002; Taub et al., 1993). It is presumed that the constraint

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2213-1582
http://dx.doi.org/10.1016/j.nicl.2013.05.005

makes a large contribution to the sustained improvements in the everyday life setting (Taub, 1994).

Several studies have explored the functional and structural changes induced by CI therapy (e.g. Cope et al., 2010; Liepert, 2006; Liepert et al., 2000; Liepert et al., 1998; Mark et al., 2006; Sawaki et al., 2008; Wittenberg et al., 2003). These studies generally indicated some use-dependent changes in the reorganized neural systems controlling paretic arm movements (e.g. Sawaki et al., 2008), as well as changes in gray and white matter density (e.g. Gauthier et al., 2008). It is assumed that these changes are driven by the increased use of the paretic hand through the daily shaping training and the concurrent constraint of the non-paretic arm. However, the constraint not only facilitates paretic arm use but also reduces the sensory input and motor output of the non-paretic arm. One might therefore question whether the constraint causes neuroplastic changes for the paretic as well as the non-paretic arm. More specifically, a recent neuroimaging study on the effects of arm immobilization (Langer et al., 2012) suggests that immobilizing the upper limb for a period of 2–3 weeks causes cortical thinning in the sensorimotor hand area contralateral to the immobilized limb. At the same time function in the non-immobilized (non-dominant) hand improves. Presumably these structural and behavioral effects are caused by activity-dependent changes in the neural representations of the immobilized and non-immobilized hands respectively.

The findings by Langer et al. (2012) are potentially very important for the concept of CI therapy. They not only support the idea that skill transfer from one hand to the other is facilitated by constraining one limb, but also suggest that the structural characteristics of the non-lesioned hemisphere are changed by this measure. The interaction between homologous motor representations in the two hemispheres during recovery is complex, and different theories have been put forward to explain the role of interhemispheric facilitation on the prediction of outcome (e.g. Carter et al., 2010; Murase et al., 2004; Takeuchi and Izumi, 2012; van Meer et al., 2012; van Meer et al., 2010). The constraint element of CI therapy might well interfere with these processes, in particular when applied in the post-acute phase. Understanding the effects of the constraint on the non-lesioned hemisphere is therefore important.

Based on Langer's findings, one might further predict that wearing the constraint would induce a reduction of cortical thickness in the sensorimotor cortex through the short-term deprivation of the sensorimotor representation of the non-paretic limb. At the same time, however, it is possible that the increased use of the paretic arm might induce use-related changes of the ipsilateral hand representation, which may be manifested in a cortical thickness increase. The present study therefore sought to examine structural changes in the non-lesioned hemisphere of 31 patients with chronic stroke undergoing CI therapy with (N = 14) or without constraint (N = 17). Using the Freesurfer software we conducted a cortical thickness analysis using a whole brain as well as a hypothesis-driven region of interest cortical thickness analysis for the non-lesioned hemisphere. We assumed that cortical thickness would change with the intervention and that this change should be greater in those wearing the constraint. We further predicted that wearing the constraint would facilitate skill transfer, and hence expected stronger treatment effects in the constraint group. In addition, we reasoned that if treatment effects are greater in those wearing the constraint, and constraint-wearing affects cortical thickness, then a significant correlation between treatment benefit and cortical thickness should be found.

2. Material and methods

2.1. Participants

31 patients with moderate to severe chronic upper-limb hemiparesis of the left (N = 15) or the right (N = 16) arm following first ever stroke participated in the study. Hemiparesis was caused by unilateral mixed lesions (illustrated in Inline Supplementary Fig. S1 in Appendix A), as determined by visual inspection of a trained neurologist (Appendix A.3). Details are summarized in Table 1.

Inline Supplementary Fig. S1 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.05.005.

Participants were recruited via General Practitioners (GP's), hospitals and online support communities. Patients were screened for cognitive and emotional problems in a clinical interview conducted by trained psychologists. Clinical levels of depression, seizures within 6 months prior to the study, a mini-mental state examination (MMSE) < 24, and severe aphasia were exclusion criteria. The minimum motor criterion for participation comprised the ability to produce a voluntary movement with any part of the hand no matter how small. Patients who exceeded Taub's criterion of 20° wrist- and 10° finger extension were excluded.

The study was approved by the local NHS Ethics Committee and the Ethics Committee of the University of Surrey. Written informed consent was obtained prior to participation, along with GP's assent for participation. Financial reimbursement was given for travel cost and accommodation when necessary.

2.2. Intervention

All patients received two weeks of modified CI therapy with or without the non-paretic arm constraint for a period of two weeks. Patients were advised to wear the constraint during their waking hours for the whole fortnight except for situations and activities that were excluded in the treatment contract. Shaping training for the paretic hand was given for either 3 or 1.5 h a day during weekdays (10 days in total), leading to four subgroups, 3 h with constraint (n = 7), 3 h without constraint (n = 10), 1.5 h with constraint (n = 7), and 1.5 h without constraint (n = 7). Group allocation was randomized. To analyze the effects of constraint wearing on cortical thickness, the 3 h and 1.5 h subgroups were collapsed for the two constraint conditions respectively.

Table 1
Participant demographics for cortical thickness analysis. Mean ± SEM. Only pre-morbid handedness significantly differed between groups.

	Total	Constrained	Un-constrained	*p*-Value
No. of participants (n)	31	14	17	–
Age (years)	57 ± 2	54 ± 3	59 ± 2	0.3
Gender (M/F)	20/11	11/3	9/8	0.3
Paretic hand (R/L)	16/15	9/5	7/10	0.3
Pre-morbid handedness (R/L)	24/7	8/6	16/1	0.03*
Chronicity (mths)	45 ± 8	51 ± 13	40 ± 10	0.5
Hours of therapy (3/1.5)	17/14	7/7	10/7	0.7
Constraint (Y/N)	15/16	–	–	–
Lesion side (R/L)	15/16	5/9	10/7	0.3
Lesion location (subcortical/cortico-subcortical)	18/13	6/8	12/5	0.2

* $p < .05$.