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Functional and structural cortical characteristics after restricted focal motor cortical infarction evaluated at chronic stage – Indications from a preliminary study

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HIGHLIGHTS

- TMS and DWI show changes in chronic stroke patients with minor motor symptoms.
- Affected hemisphere is less excitable to produce strong responses.
- At chronic stage, neuronal structure remains disrupted in the affected motor cortex.

ABSTRACT

Objective: To assess the inter-hemispheric differences in neuronal function and structure of the motor cortex in a small group of chronic stroke patients having suffered a restricted ischemic lesion affecting hand motor representation. GABAergic intracortical inhibition, known to be affected by stroke lesion, was also investigated.
Methods: Eight patients exhibiting little or no motor impairment were studied using transcranial magnetic stimulation (TMS) and diffusion weighted imaging (DWI) >15 months from diagnosis. Resting motor threshold (MT) for 50 μV and 2 mV motor evoked potentials, and short-interval intracortical inhibition (SICI) were measured from hand muscles. Apparent diffusion coefficients (ADCs) were analyzed from the DWI for the primary motor cortex (M1), the supplementary motor area (SMA) and thalamus for reflecting changes in neuronal organization.
Results: The MTs did not differ between the affected (AH) and unaffected hemisphere (UH) in 50 μV responses, while the MTs for 2 mV responses were higher ($p = 0.018$) in AH. SICI was weakened in AH ($p = 0.008$). ADCs were higher in the affected M1 compared to the unaffected M1 ($p = 0.018$) while there were no inter-hemispheric differences in SMA or thalamus.
Conclusions: Inter-hemispheric asymmetry and neuronal organization demonstrated abnormalities in the M1. However, no confident inference can be made whether the observed alterations in neurophysiological and imaging measures have causal role for motor rehabilitation in these patients.
Significance: Neurophysiological changes persist and are detectable using TMS years after stroke even though clinical symptoms have normalized.

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1. Introduction

Motor disability is among the most common consequences of ischemic stroke. Following focal ischemic damage, the reorganization of the cortical functions begins (Ward and Cohen, 2004). Some initial improvement after the acute phase occurs due to resolution of the perilesional edema and recovery of other tissue functions surviving the ischemia (Hallett, 2001). However, it is thought that the long-term recovery occurs primarily due to brain plasticity through functional and structural reorganization (Hallett, 2001; Hodics et al., 2006). For example, increased gray matter density and contralesional cortical thickness in the essential cortical motor areas has been correlated with improved arm function in chronic stroke (Gauthier et al., 2008; Sterr et al., 2013).

Lesions in the motor cortex, and the following recovery, cause functional changes in the cortex, in both the affected (AH) and unaffected hemisphere (UH) as well as in the interhemispheric connections (Chen and Schlaug, 2013; Cunningham et al., 2015; Li et al., 2015; Rossini et al., 2007; Ward and Cohen, 2004). In the acute phase after stroke, the cortical activity increases in the intact non-primary motor and non-motor areas of both hemispheres, whereas later on in well-recovering patients the activity is shifted towards the affected M1 and is reduced in other areas (Calautti et al., 2001a; Calautti et al., 2001b; Feydy et al., 2002; Ward et al., 2003; Ward and Cohen, 2004). The reorganization of the representation area of the paretic hand may occur during the first months after stroke and is usually seen as a mediolateral shift of representation in affected M1. Also an anteroposterior shift of representation towards sensory cortex and premotor areas may be seen (Fridman et al., 2004; Rossini et al., 2007; Traversa et al., 1997) indicating the recruitment of motoneurons from adjacent cortical areas. Interhemispheric inhibition is altered after stroke leading to increased activation in UH and increased inhibition in AH. Greater imbalance in interhemispheric inhibition and asymmetry in cortical activations has been related to poor recovery (Chen and Schlaug, 2013; Cunningham et al., 2015; Di Lazzaro et al., 1999; Li et al., 2015). Schaechter and Perdue (2008) demonstrated with functional MRI that in stroke patients with good recovery, cortical activity in the AH motor areas is enhanced depending on the demands of the motor task.

Significant effort has been committed to understanding the neurophysiological mechanisms of functional recovery from brain lesions such as stroke. The region adjacent to lesion demonstrates modified plasticity through remapped sensorimotor functions (Brown et al., 2009; Clarkson et al., 2010; Dijkhuizen et al., 2003). Stroke-related plasticity consists of mechanisms such as early dendritic branching and synaptogenesis, initial increase of cortical excitability via decreased GABA activity enabling use-dependent plasticity, and later on decrease in hyperexcitability (Hagemann et al., 1998; Jones and Schallert, 1992; Neumann-Haefelin et al., 1998; Shimizu et al., 2002; Stroemer et al., 1995; Ward et al., 2003). Stroke is known to increase tonic GABAergic transmission in perilesional cortical area, and a reduction of this inhibition produces early motor recovery after stroke (Clarkson et al., 2010). Counteracting the increased GABAergic inhibition by administering inverse agonist specific for GABA receptors or genetically lowering the number of GABA receptors have been reported to be beneficial for the recovery of motor function after stroke (Clarkson et al., 2010). Hence, the role of the changes in cortical excitability and inhibition in chronic stroke patients with restricted focal lesions and almost complete clinical recovery should be studied more precisely.

Transcranial magnetic stimulation (TMS), a painless non-invasive method, is suitable for investigating the neurophysiological effects of stroke due to its ability to probe corticospinal excitability as well as facilitatory and inhibitory mechanisms of the motor cortex (Rossini et al., 2015). The motor threshold (MT) based on the occurrence of motor evoked potentials (MEPs) induced by TMS is considered to be a common measure of general cortical excitability (Rossini et al., 2015). MT in the affected motor cortex has been shown to increase demonstrating a lowered level of excitation caused by the motor cortex lesion following stroke in the early state (Prashantha et al., 2013). In the long-term recovery, the cortical excitability in AH has been shown to exhibit a decrease in MT values approaching normal (Takechi et al., 2014; Traversa et al., 2000).

Primary motor cortex disinhibition is a characteristic sign of reorganization in the subacute stage after stroke enabling the recruitment of adjacent motoneurons and facilitating activity-dependent plasticity (Liepert et al., 2000). The intracortical GABA-related inhibition, called short-interval intracortical inhibition (SICI), can be studied by paired-pulse TMS using short inter-stimulus intervals (ISIs) (Chen et al., 1998; Kujirai et al., 1993). Intracortical facilitation (ICF) can be assessed with longer ISIs (Kujirai et al., 1993). Previously, SICI and ICF have been studied at different stages of stroke recovery (Cicinelli et al., 2003; Liepert et al., 2000; Malcolm et al., 2015) and a general finding is that SICI is decreased in the AH and normalization of inhibition is associated with successful recovery (Eliassen et al., 2008; Manganotti et al., 2002; Swayne et al., 2008). Interhemispheric inhibition is often imbalanced in unilateral stroke leading to disinhibition of UH and increased inhibition of AH through transcallosal fibers (Bütefisch et al., 2003).

In diffusion weighted imaging (DWI) apparent diffusion coefficient (ADC) map reflects the local diffusion of water molecules at each point with a single value (Le Bihan et al., 1986). Thereby in the ADC map, areas with restricted diffusion appear dark while unrestricted diffusion can be seen as bright. The mean ADC values in infarcted neuronal regions change over time; in the acute phase the ADC decreases, in the subacute phase the ADC returns near to normal values and in the chronic stage the ADC is higher than in the healthy tissue (Shen et al., 2011). Similar change has been observed in thalamus after middle cerebral artery infarcts (Hervé et al., 2005).

The aim of the present study was to understand the chronic phase characteristics of the neurophysiological motor cortical excitability and inhibition in patients with almost complete clinical recovery after restricted focal cortical infarction in the "hand knob" of the primary motor cortex. For this purpose, we studied the excitability, intracortical inhibition and facilitation of the motor cortex using navigated TMS (nTMS) over 15 months after stroke diagnosis in a small group of patients. To gain insight into the relation with parallel cortical anatomical changes, we also assessed ADC to study the local organization of the cortical neurons on the M1, where the lesions were located, and in the supplementary motor area (SMA) and thalamus.

2. Methods

2.1. Patients

The study was approved by the Research Ethics Committee of Kuopio University Hospital (95/2010). Patients were selected retrospectively from the patient register of Kuopio University Hospital from the years 2005–2009. Criteria for the first selection were the treatment period in the neurology clinic, ICD-10 diagnosis number I63 (stroke) and year of birth 1940 or later. After this, epicrisis from the neurology department and statements of CT- and MR images of selected stroke patients were read. CT and MRIs from patients having first ever unilateral stroke in the immediate vicinity of the anatomical primary hand motor area causing unilateral paresis symptoms in the acute phase were selected for re-evaluation by neuroradiologist. This criterion was set to enable the study of long-term plasticity in patients who had clearly intact areas in the close proximity of the lesion site. Selected patients