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Effect of median-nerve electrical stimulation on BOLD activity in acute ischemic stroke patients

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HIGHLIGHTS

- The study investigates the predictive value of a passive task in 3T fMRI in the early phase of stroke.
- The absence of BOLD activation during sensory stimulation in the acute phase is associated with poorer clinical recovery.
- The presence of BOLD activation in the early hours after stroke seems to be related to better clinical recovery.
- A subject-specific HRF for acute stroke patients provides reliable BOLD activation maps.

ABSTRACT

Objective: To investigate blood oxygenation level-dependent (BOLD) activation during somatosensory electrical stimulation of the median nerve in acute stroke patients and to determine its correlation with ischemic damage and clinical recovery over time.
Methods: Fourteen acute stroke patients underwent functional magnetic resonance imaging (fMRI) during contralesional median-nerve electrical stimulation 12–48 h after stroke. Findings were then validated by diffusion tensor imaging (DTI) and motor evoked potential by transcranial magnetic stimulation (TMS).
Results: Poor clinical recovery at three months was noted in four patients with no activation in the early days after stroke, whereas good clinical recovery was observed in eight patients with a normal activation pattern in the primary sensory motor area in the acute phase. In two patients BOLD activation correlated weakly with clinical recovery. Findings from TMS and DTI partially correlated with clinical recovery and functional scores.
Conclusions: Clinically relevant insights into the "functional reserve" of stroke patients gained with peripheral nerve stimulation during fMRI may carry prognostic value already in the acute period of a cerebrovascular accident.
Significance: BOLD activation maps could provide insights into the functional organization of the residual systems and could contribute to medical decision making in neurological and rehabilitative treatment.

1. Introduction

Ischemic stroke is a leading cause of mortality and disability in Western countries, particularly among the elderly (Sarti et al., 2000). In the acute phase, cerebral hypoxia causes irreversible neuronal damage; the reperfusion phase is critical for neuron survival in the neighbouring necrotic area (Maxwell and Lip, 1997) and represents the substrate for recovery or permanent disability. Functional imaging studies investigating possible predictive parameters of reversible damage have found that the activation of brain areas both close to and remote to lesions correlates with motor recovery in stroke patients (Cramer and Bastings, 2000; Ward et al., 2004; Gerloff et al., 2006). Functional imaging studies of the motor system have also revealed differences in motor task-related brain activation related to motor function recovery in

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stroke patients over and above control subjects in the contralesional sensorimotor and premotor cortex, ipsilesional cerebellum, bilateral supplementary motor area (SMA) and parietal cortex (Chollet et al., 1991; Weiller et al., 1992, 1993; Cramer et al., 1997; Seitz et al., 1998; Cramer and Bastings, 2000).

The damaged adult brain is able to compensate for motor deficits (Calautti and Baron, 2003). A shift of activation balance during the motor protocol towards the unaffected hemisphere appears to be associated with poorer initial recovery; conversely, the longer this physiological balance is maintained over time, the better the recovery (Calautti et al., 2001). Furthermore, on executing a given task with the affected hand, patients with a better post-stroke recovery have been noted to activate motor and premotor cortices bilaterally (Bütefisch et al., 2005; Gerloff et al., 2006).

The majority of neurophysiological and functional studies have investigated motor function recovery probably because it is more standardized and constitutes the chief clinical goal in stroke rehabilitation. However, one main limitation to these studies is the lack of reliability of motor performance assessment. In the acute stroke phase, patients are unable to perform any movement correctly or their motor activation may induce so much synkinetic activity that it may interfere with functional magnetic resonance imaging (fMRI) activation. To overcome these limitations, the use of a passive task with a standard method such as median-nerve stimulation in functional neuroimaging could be helpful for assessing non-cooperative patients during the acute stroke phase.

To date, the few studies on somatosensory stimulation in stroke patients (Taskin et al., 2006) have mainly applied magnetoencephalography (MEG) as a predictor of sensory or sensorimotor recovery (Tecchio et al., 2007; Assenza et al., 2009). Taskin et al. applied fMRI during passive stimulation of the affected and unaffected sides only in chronic patients; statistical parametric maps showed a reduced activation of the primary somatosensory cortex (SI) in response to stimulation of the affected side. However, no significant difference was detected in the activation of the secondary somatosensory cortex (SII) compared with stimulation of the unaffected side (Taskin et al., 2006). In Tecchio et al.'s study (2007), the absence of the somatosensory evoked field in MEG was associated with more severe ischemic damage and poor recovery.

Another method to assess brain damage load and motor pathway integrity and examine cerebral networks is diffusion tensor imaging (DTI) in combination with fMRI. This combined application is based on matching the functional connectivity of cerebral areas with its structural basis in order to study the propagation of stimuli across physiological pathways and to verify the correspondence between physiological and anatomical pathways in order to obtain prognostic information (Møller et al., 2007; Lindenberg et al., 2010). A wide variety of fiber tracking methods have been described. The main drawback of DTI is the uncorrected reconstruction of the fiber tracts driven by false trajectories. Because of the lack of a standard procedure, fMRI activation can play an important role in defining an appropriate seed region. This approach has been successfully applied in both healthy subjects (Staempfli et al., 2008) and patients with brain tumors (Kleiser et al., 2010). Nonetheless, there are several limitations to applying this method to stroke patients (Tang et al., 2010). Executing isolated joint movements without associated movements or spasticity may be difficult for stroke patients and head motion artifacts may appear on the MR images, whereas the effect of motor performance on BOLD signals in ipsilesional M1 may be minimal or absent.

To our knowledge, no data exist on the predictive value of sensory stimulation using 3T magnetic resonance (MR) in acute stroke patients. In this study we applied fMRI during electrical stimulation to compare sensorimotor system reorganization after stroke and evaluated clinical stroke recovery over time by means of neurological and disability scales. Specifically, we performed a block fMRI study during median-nerve stimulation in 14 acute stroke patients with different degrees of recovery to evaluate blood oxygenation level-dependent (BOLD) signal changes in SI and SII and to characterize the altered spatial activation patterns within the somatosensory network.

The motor network (areas and fibers) is fundamental for motor performance and recovery, whereas the sensory (or somatosensory) network is essential for sensory tactile and proprioceptive perception and constitutes an intrinsic component of the sensorimotor system. Sensory neurons are located not only in the main sensory areas (SI, area 1, 2, 3; and SII) but also in motor areas (MI) as well motor neurons are located in SI. The sensorimotor network is important for sensorimotor integration, which forms the functional basis of motor execution.

The first aim of our study was to investigate for correlations between functional sensory stimulation and a relatively new neurophysiology-MRI technique in stroke patients in relation to their clinical symptoms. The second aim of the study was to correlate the activation obtained by electrical sensory stimulation in the acute stroke phase with clinical sensorimotor recovery. The third aim was explorative in nature. We attempted to identify a possible association between cortical function impairment during sensory stimulation and white matter fiber integrity as revealed by DTI in the early stage of stroke and its predictive value for clinical recovery. The overarching objective was to devise a functional tool which could provide predictive values of sensorimotor recovery and quantify the "recovery reserve" in stroke patients in the acute phase.

2. Methods

2.1. Patients

Fourteen patients with acute stroke (8 men, 6 women; mean ± SD age, 61.9 ± 13.1 years, right-handed) were recruited from the stroke unit at our institution. Inclusion criteria were first stroke with a single hemispheric lesion as demonstrated by magnetic resonance imaging (MRI), moderate-to-severe hemiparesis, and age below 80 years. Patients or a family member gave written informed consent to participate in the study in accordance with the Declaration of Helsinki (Oldfield, 1971). The study design and protocol were approved by the Local Ethics Committee of the Verona University Department and Hospital. Nine patients presented with left hemispheric lesions and five with right hemispheric lesions. On the basis of MR and diffusion weighted imaging (DWI) findings, lesions were classified as cortical if they involved the gray matter and were limited to cortical structures or as subcortical if they involved the white matter, including the internal capsule and basal ganglia, putamen, or globus pallidus. Patients presenting with concomitant neuropathies or systemic vasculopathies or dementia were excluded from the study. According to this definition, most of the patients had mixed cortical and subcortical lesions, while only two patients presented subcortical lesions. Clinical neurological evaluations were performed at the time of fMRI recording, a few days after stroke (12–48 h after stroke) (t_0), one month after stroke (t_1), and four–five months after stroke (t_2). Clinical assessment of neurological impairment, neurological status and disability was performed using the European Stroke Scale (ESS) (Hantson et al., 1994), the National Institutes of Health scale (NIH) (Brott et al., 1989) and the Barthel Index (Mahoney and Barthel, 1965), respectively (Table 1). Tactile-thermal pain (tactile-thermal scale (TTS)) was evaluated on an arbitrary twelve-point scale (0–12; 12 being normal); the Kinesthetic Sensitivity Test (KST) was used as a diagnostic tool to identify poor kinesthetic function (Laszlo and Bairstow, 1985). The Motricity Index was measured to assess the motor function of the arm and