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Voxel-based lesion-symptom mapping of stroke lesions underlying somatosensory deficits

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ABSTRACT

The aim of this study was to investigate the relationship between stroke lesion location and the resulting somatosensory deficit. We studied exteroceptive and proprioceptive somatosensory symptoms and stroke lesions in 38 patients with first-ever acute stroke. The Erasmus modified Nottingham Sensory Assessment was used to clinically evaluate somatosensory functioning in the arm and hand within the first week after stroke onset. Additionally, more objective measures such as the perceptual threshold of touch and somatosensory evoked potentials were recorded. Non-parametric voxel-based lesion-symptom mapping was performed to investigate lesion contribution to different somatosensory deficits in the upper limb. Additionally, structural connectivity of brain areas that demonstrated the strongest association with somatosensory symptoms was determined, using probabilistic fiber tracking based on diffusion tensor imaging data from a healthy age-matched sample. Voxels with a significant association to somatosensory deficits were clustered in two core brain regions: the central parietal white matter, also referred to as the sensory component of the superior thalamic radiation, and the parietal operculum close to the insular cortex, representing the secondary somatosensory cortex. Our objective recordings confirmed findings from clinical assessments. Probabilistic tracking connected the first region to thalamus, internal capsule, brain stem, postcentral gyrus, cerebellum, and frontal pathways, while the second region demonstrated structural connections to thalamus, insular and primary somatosensory cortex. This study reveals that stroke lesions in the sensory fibers of the superior thalamocortical radiation and the parietal operculum are significantly associated with multiple exteroceptive and proprioceptive deficits in the arm and hand.

1. Introduction

Somatosensory deficits are common after stroke, with reported prevalence ranging from 11% to 85% (Connell et al., 2008; Tyson et al., 2008). While somatosensory symptoms after stroke may be discomforting and disabling by themselves, they further affect motor ability and overall rehabilitation after stroke. The somatosensory system plays a crucial role in motor performance by providing constant sensory feedback to be able to make adaptations in an on-going motor task (Rabin and Gordon, 2004). As a consequence, somatosensory dysfunction represents an important factor for motor and functional outcome after stroke (Meyer et al., 2014; Tyson et al., 2008).

Somatosensation comprehends all anatomical components of the central and peripheral nervous systems that receive and interpret sensory information from receptors in the joints, ligaments, muscles, and skin. The somatosensory system has two primary functions: exteroceptive and proprioceptive sensation (DeJong, 1979). Exteroceptive sensation includes somatosensory modalities such as light touch, pressure, pinprick and pain (DeJong, 1979), whereas proprioceptive sensation is

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the ability to recognize the location and movement of our limbs in space (Sherrington, 1907). Although somatosensory symptoms are present in a large number of stroke patients, detailed reports on the affected components of somatosensation are rare (Carey and Matyas, 2011; Connell et al., 2008; Tyson et al., 2008).

In contrast to the large amount of studies reporting on neural correlates of motor symptoms and recovery after stroke (Rehme et al., 2012; Ward et al., 2003), the relationship between lesion location and somatosensory deficits after stroke remains poorly understood. From primate studies, it is well-known that the ventral posterior lateral nucleus of the thalamus is an important brain structure in somatosensory processing, as both the dorsal and the anterolateral ascending tracts terminate in this nucleus (Martin and Jessel, 1991). Most somatosensory information enters the cerebral cortex through projections from the thalamus up to the primary somatosensory cortex (S1). Furthermore, small projections exist from the thalamus to the secondary somatosensory cortex (S2), the posterior parietal cortex and insular cortex (Burton and Jones, 1976). In humans, lesion studies using structural brain imaging revealed contributions of thalamus, lenticulocapsular region, corona radiata, and the brain stem to the occurrence of a somatosensory deficit (Georgiadis et al., 1999; Kim, 1992). With respect to the secondary somatosensory cortex in the human parietal operculum, several distinct cortical subdivisions were distinguished for either basic sensorimotor processing or higher order somatosensory processing (Eickhoff et al., 2010, Eickhoff et al., 2006b).

To the best of our knowledge, only two recent studies investigated the voxel-wise association between lesion location and a somatosensory deficit in patients after stroke (Baier et al., 2014; Preusser et al., 2014). It was found that impaired light touch perception was associated with lesions in S2, the anterior and posterior insular cortex, the putamen, and white matter connections reaching ventrally towards prefrontal brain areas (Dijkerman and de Haan, 2007; Preusser et al., 2014). The other voxel-wise association study, including patients with insular strokes, demonstrated that lesions in the posterior insular cortex are associated exclusively to impaired temperature perception (Baier et al., 2014). More detailed analysis of different somatosensory modalities has not been conducted as yet using modern voxel-based imaging methods. Thus, it remains unclear to what extent lesions in these brain areas affect other sensory modalities besides light touch and temperature perception. Therefore, the aim of the present study was to investigate, which brain regions are associated with the occurrence of different exteroceptive and proprioceptive somatosensory deficits in the acute phase after stroke, using voxel-based lesion-symptom mapping (VLSM).

2. Materials and methods

2.1. Patients

Thirty-eight consecutive adult patients were recruited for this study at the acute stroke unit of two University Hospitals in Belgium from October 2012 until September 2014. The inclusion criteria were (1) first-ever stroke (ischemic or hemorrhagic) as defined by the World Health Organization (World Health Organization MONICA Project, 1988); (2) assessment within the first week after stroke; (3) presence of motor and/or somatosensory deficit in the upper limb, using the Fugl–Meyer motor assessment upper extremity and somatosensory assessments as described below, and; (4) sufficient cooperation to perform the assessment. Patients were excluded if they (1) had a pre-stroke Barthel Index <95 out of 100; (2) had other serious neurological conditions with permanent damage; (3) had a subdural hematoma, tumor, encephalitis or trauma that led to similar symptoms as a stroke, and; (4) had serious communication, cognitive or language deficits, which could hamper the assessment. Patients signed a written informed consent form prior to participation. Ethical approval was obtained from the Ethics Committee of both University Hospitals in Leuven and Brussels.

2.2. Behavioral assessment

2.2.1. Testing procedure

Patients were assessed once within day 4 to day 7 after stroke onset using an MRI brain imaging protocol and clinical as well as more objective measures of somatosensory function. To ensure standardized data collection, the clinical testing was performed by only one trained physiotherapist (S.M.). Furthermore, patients' baseline characteristics were collected, and severity of stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS). The presence of visuo-spatial neglect was assessed with the star cancellation test (Friedman, 1992), the most sensitive paper-and-pencil measure of visuo-spatial neglect (Lindell et al., 2007). A cut-off score of <44 (out of 54 stars) was used to determine the presence of visuo-spatial neglect.

2.2.2. Somatosensory assessment

Somatosensory deficits in the affected upper limb were assessed using the Erasmus MC modifications of the (revised) Nottingham sensory assessment, the perceptual threshold of touch (PTT), and somatosensory evoked potentials (SSEP).

The Erasmus MC modification of the (revised) Nottingham sensory assessment (Em-NSA) assesses light touch, pressure, pinprick and proprioception in the affected upper extremity and has good to excellent intra-rater and inter-rater reliability (Stolk-Hornsveld et al., 2006). Light touch was applied with a cotton wool, pressure with the index finger and pinprick with a toothpick, all at predefined points of contact. Proprioception was assessed during passive movements of the different joints in the upper limb. Scores for each modality range on a continuous scale from 0 (complete loss of somatosensory function) to 8 (intact somatosensory function). A cut-off score of <7 indicates the presence of somatosensory deficit.

The perceptual threshold of touch (PTT) is the minimal stimulus level of touch that is detectable. A transcutaneous electric nerve stimulation (TENS) was applied with a portable device, the CEFAR Primo Pro (Cefar Medical AB, Sweden). Round electrodes, with a diameter of 3 cm, were attached to the index finger and bulb of the thumb of the affected upper extremity. A high-frequency constant current of 40 Hz with single square pulses of 80 μs pulse duration was applied. The amplitude was gradually increased from 0 mA with increments of 0.5 mA, until a tingling sensation was perceived. To evaluate the PTT impairment, individual scores were compared to age- and gender-matched cut-off norm-values (Eek et al., 2012). Impairment was defined as a threshold value above the predefined norm value and therefore PTT scores were classified into impaired or normal PTT. Good reliability has been established for this method in stroke patients (Eek and Engardt, 2003).

Somatosensory evoked potentials (SSEP) were measured following a standardized protocol (American Clinical Neurophysiology Society, 2006). A transcutaneous electrical stimulation (monophasic rectangular pulses) was delivered to the median nerve at the wrist with a pulse of 200 μs and a stimulation rate of 5.1 Hz. The cathode was placed between the tendons of the palmaris longus and flexor carpi radialis muscles, the anode was placed 2 to 3 cm distal to the cathode and the ground electrode was placed on the forearm. Sensory threshold was determined on the non-affected side and stimulation was performed at 3 times this sensory threshold for both the unaffected and the affected side. Stimulation was always above motor threshold and produced a clearly visible muscle twitch causing abduction of the thumb. Standard 10 mm cup electrodes, connected to a Medelec Synergy System, were placed at positions CP3 and CP4, according to the international 10–5 system (Oostenveld and Praamstra, 2001). The SSEP assessment was consecutively performed at the non-affected and the affected upper limb. The interside difference between interpeak cortical amplitude N20-P25 was calculated. To evaluate the SSEP impairment, these