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Understanding the role of the primary somatosensory cortex: opportunities for rehabilitation

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Abstract

Emerging evidence indicates impairments in somatosensory function may be a major contributor to motor dysfunction associated with neurologic injury or disorders. However, the neuroanatomical substrates underlying the connection between aberrant sensory input and ineffective motor output are still under investigation. The primary somatosensory cortex (S1) plays a critical role in processing afferent somatosensory input and contributes to the integration of sensory and motor signals necessary for skilled movement. Neuroimaging and neurostimulation approaches provide unique opportunities to non-invasively study S1 structure and function including connectivity with other cortical regions. These research techniques have begun to illuminate casual contributions of abnormal S1 activity and connectivity to motor dysfunction and poorer recovery of motor function in neurologic patient populations. This review synthesizes recent evidence illustrating the role of S1 in motor control, motor learning and functional recovery with an emphasis on how information from these investigations may be exploited to inform stroke rehabilitation to reduce motor dysfunction and improve therapeutic outcomes.

Keywords: Primary somatosensory cortex; rehabilitation; motor control; motor learning; neuroimaging; noninvasive brain stimulation; stroke

I. Introduction

The planning, execution, and control of motor behaviors is a complex neural process in part dependent on correct sampling of multiple sensory modalities from the body periphery (e.g., somatosensation, vestibular, etc.) and external environment (e.g., vision, hearing, etc.) (Hummelsheim, Bianchetti, Wiesendanger, & Wiesendanger, 1988; Riemann & Lephart, 2002; D.M. Wolpert, Pearson, & Ghez, 2013; Zarzecki, Shinoda, & Asanuma, 1978). Without correct processing and translation of sensory input, both before and during movement, motor outputs are abnormal and/or inaccurate. Thus, there is a tight link between sensory processing and movement production. Accordingly, emerging evidence suggests abnormal processing of somatosensory information by the primary somatosensory cortex (S1) contributes to deficits seen in neurological disorders typically classified by motor dysfunction (e.g. stroke, Parkinson's disease, dystonia, ataxia, etc.) (Elbert, et al., 1998; Hummelsheim, et al., 1988; Jacobs, Premji, & Nelson, 2012; Konczak & Abbruzzese, 2013; Rub, et al., 2003; D.M. Wolpert, et al., 2013).

There is a growing body of literature regarding the effects of altered S1 function on M1 activity and the control of movement. Increased M1 excitability has been noted in animal models of neurological conditions involving S1 damage, such as stroke (Harrison, Silasi, Boyd, & Murphy, 2013; Winship & Murphy, 2009) and idiopathic dystonia (Domenech, Barrios, Tormos, & Pascual-Leone, 2013). It is interesting to note that in the latter study, 46% of the rats with increased cortical excitability in M1 developed scoliosis, and that human patients with dystonia and Parkinson's disease demonstrate a higher prevalence of scoliosis than the general population (Domenech, et al., 2013). Lesions to sensorimotor areas, similar to injuries resulting from stroke, have resulted in difficulty with a battery of motor behavioral tasks assessing gross motor function and reflexes in rats (Gerlai, Thibodeaux, Palmer, van Lookeren Campagne, & Van

Bruggen, 2000; Kleim, Boychuk, & Adkins, 2007; McIntosh, Smith, Voddi, Perri, & Stutzmann, 1996), and impaired fine motor skills involving small objects in monkeys (Brinkman, Colebatch, Porter, & York, 1985; Hikosaka, Tanaka, Sakamoto, & Iwamura, 1985).

Studies have suggested that motor deficits observed after S1 lesions may not be due to difficulty with executing motor commands but rather attributed to disrupted learning of new motor tasks, as motor deficits are attenuated if the task had been learned prior to S1 injury (Pavlides, Miyashita, & Asanuma, 1993; Sakamoto, Arissian, & Asanuma, 1989; Sakamoto, Porter, & Asanuma, 1987). Another phenomenon that could affect motor function is the alteration of somatosensory maps within S1. Studies in rodents have found a shift in the sensory map after experimentally-induced stroke that results in an overlap with a portion of the motor representation where the neurons originally devoted to encode exclusively motor commands take on small role in sensory processing, reducing the capacity for involvement in the motor system (Harrison, et al., 2013; Winship & Murphy, 2009).

In the following sections, the importance of S1 to motor function will be considered using theoretical models, neuroimaging approaches, non-invasive neural stimulation technologies, and combined neuroimaging-neurostimulation paradigms. Finally, future clinical implications of a comprehensive understanding of the relationship between motor functioning and S1 structure, function, and connectivity will be discussed.

II. Modeling the role of S1 in sensorimotor integration

The balance between sensory input and motor output is essential for efficiently acting with the environment. For example when grasping a previously visualized object, first the visual information about the object's location must be identified based on input from the retina (e.g.

Becke, Muller, Vellage, Schoenfeld, & Hopf, 2015). Then it has to be integrated with the (currently available) visual and/or somatosensory information about the location and configuration of the agent's body. In addition, during the movement, the somatosensory input from the agent's effector also must be transmitted to the motor system in order to fine-tune the movement (e.g. Blakemore, Wolpert, & Frith, 1998; D. M. Wolpert, Ghahramani, & Jordan, 1995). In other words, during motor execution, real-time somatosensory feedback must be encoded and provided to the motor system through integrative loops for a precise motor control (see also Perruchoud, Murray, Lefebvre, & Ionta, 2014).

Nevertheless, the basic mechanisms, anatomo-functional neural underpinnings, and rehabilitation of sensorimotor function are still under investigation. In particular, current models of S1 function lack precision in defining the multifaceted role in processing afferent sensory information and regulating efferent motor commands of this cortical region. This section will review the available data on the anatomo-functional role of S1 in motor control, aiming at describing the reciprocal influence between (somato) sensory information and motor commands.

Two main features of S1 function deserve particular attention. First, S1 can drive movements in coordination with or independent of M1 activity. Converging evidence from animal research shows that rich fiber pathways interconnect S1 and M1 (Donoghue & Parham, 1983; Veinante & Deschenes, 2003; White & DeAmicis, 1977). These cortico-cortical connections are considered to modulate the relationship between sensory and motor components of sensorimotor processes (Petreanu, Mao, Sternson, & Svoboda, 2009; Xu, et al., 2012). Recent theorizations about the directionality of such an exchange between S1 and M1 emphasize the dominant (probably disinhibitory) role of M1 over S1, both in rodents (Lee, Kruglikov, Huang, Fishell, & Rudy, 2013) and humans (Gandolla, et al., 2014). In accordance with this view,

126 animal research showed that lesions of S1 are associated with increased excitability of M1
127 (Domenech, et al., 2013; Harrison, et al., 2013). Furthermore, clinical observations in humans
128 report increased peripheral somatosensory inflow facilitates functional reorganization of M1
129 (Hamdy, Rothwell, Aziz, Singh, & Thompson, 1998) and that the stimulation of S1 induces
130 shorter latencies to initiate movements (Sean K. Meehan, Dao, Linsdell, & Boyd, 2011). These
131 findings support a continuous mutual communication between sensory inflow and motor outflow
132 (Kleinfeld, Ahissar, & Diamond, 2006; Lee, Carvell, & Simons, 2008). Other evidence
133 conversely shows that S1 can drive motor commands without the intervention of M1. In
134 particular, the behavioral outcome in response to a specific somatosensory stimulus, further
135 associated with the earliest recorded cortical activity (in S1), can be triggered also by the
136 stimulation of the same S1 subregion with latencies shorter than those of the motor region
137 evoking the same movement, even when the motor region is pharmacologically inactivated
138 (Matyas, et al., 2010). In the same vein, motor deficits are less prominent if the movement is
139 learned prior to a lesion of S1 (Sakamoto, et al., 1989) and movement execution improves
140 following the administration of S1-facilitating drugs (McIntosh, et al., 1996).

141 The second important feature of S1 is that it is strictly interconnected with other primary
142 sensory cortices (e.g. visual and auditory; V1 and A1, respectively) and with subcortical
143 structures encoding different sensory modalities. Unlike conventional views of the primary
144 sensory cortices as unisensory regions, different perspectives propose that multisensory
145 integration processes begin to take place in these regions (Driver & Noesselt, 2008). The neural
146 underpinnings of such crossmodal integration may be provided by the cortico-cortical
147 connections between S1 and A1, described both in primates (Cappe & Barone, 2005) and
148 humans (Ro, Ellmore, & Beauchamp, 2013), as well as by the modulation of human S1 activity

in response to non-corresponding stimulation (Liang, Mouraux, Hu, & Iannetti, 2013), e.g. acoustic (Murray, et al., 2005) and visual information (Meyer, Kaplan, Essex, Damasio, & Damasio, 2011). In addition, subcortico-cortical connections transmit information about different sensory modalities to non-matching primary sensory areas (Henschke, Noesselt, Scheich, & Budinger, 2014).

In light of these findings, how can S1 contributions to movement control be modeled? In accordance with the multisensory nature of S1, initially multimodal sensory input must be combined with actual intentions and previous knowledge in order to initiate movements (Genewein & Braun, 2012). Current theoretical conceptualizations propose the existence of two internal movement prediction components. The first component can be defined as a "forward" model used by the nervous system to predict the behavioral outcome of a given motor command generated by M1 (Desmurget, et al., 2009). The forward model is based on a copy of the motor command generated in M1, defined as an "efference copy" that, instead of being sent to the periphery, is to be processed by parietal regions (Sirigu, et al., 1996). Simultaneously, the forward model contributes information to a so-called "feedforward model" used to anticipate the sensory consequence of the movement itself (D. M. Wolpert & Ghahramani, 2000). The feedforward model combines together the actual sensory consequences associated with an executed motor command and the sensory component of the predicted motor outcome (based on the forward model) to provide information on the potential mismatch between expected and real bodily states during the movement. In this way both the actual sensory information and the motor outcome are compared to the expected sensory consequences and the real movement, respectively. As a result of these recalibration mechanisms, the potential mismatch between the

actual and predicted sensorimotor states can be used to update subsequent motor commands and may be used as an error signal facilitate motor learning.

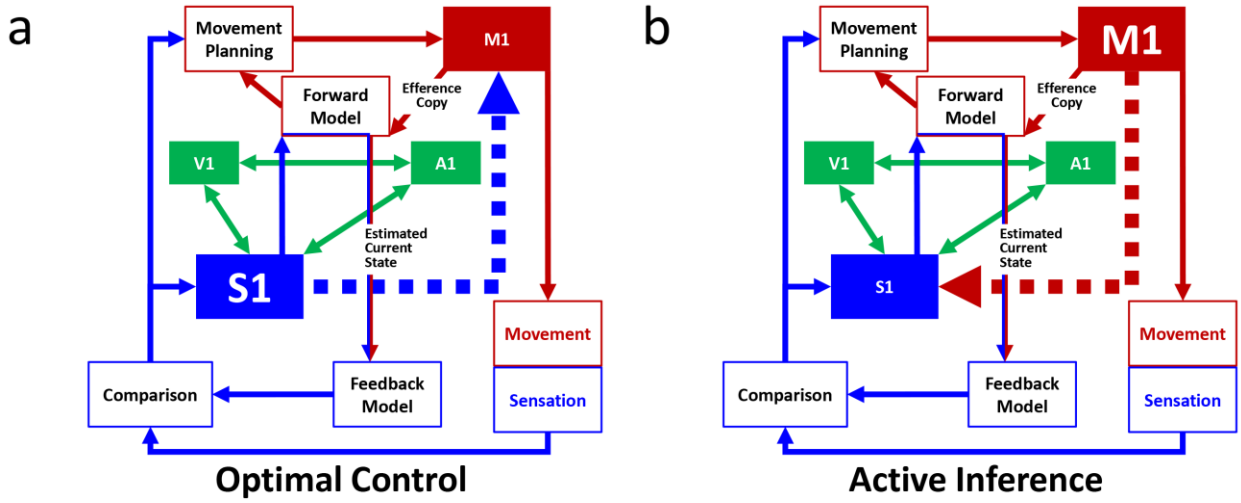

Figure 1. Theoretical model of information exchange between primary somatosensory (S1) and motor (M1) regions. According to the "optimal control" theory (a) S1 modulates M1 activity. According to the "active inference" theory (b), M1 modulates S1 activity. In addition, S1 exchanges and integrates information to and from other primary sensory areas, such as visual (V1) and auditory (A1).

Two different options may explain the reciprocal role the sensory and motor components of such a complex interaction (Figure 1). The so-called "optimal control" theory postulates that the motor command contains purely motor information (D. M. Wolpert, et al., 1995) and M1 only generates the movement (D. M. Wolpert & Kawato, 1998). In this view, the motor command contains purely motor information and the motor command is context-independent (Figure 1a). The alternative "active inference" theory proposes that, instead of being uniquely motor, the motor command also contains information used to predict the sensory consequences of the triggered movement (Figure 1b; Adams, Shipp, & Friston, 2013). According to this view, motor commands are context-dependent and modulate activity in S1. In other words, M1 activity has a direct effect on S1 activity both in terms of a facilitation of the M1-S1 connections and

stronger S1 self-inhibition (in order to diminish sensitivity to unrelated information), which has been recently demonstrated in the human brain (Gandolla, et al., 2014).

How to combine these two perspectives? It can be indeed hypothesized that the recruitment of one model or the other model depends on movement complexity. During simple movements, less reliance on sensory information is required and the system can rely on the optimal control model. On the other hand, increasing movement complexity would necessitate additional sensory information in order to successfully to adapt the movement to the increased requirements of the task and environment resulting in a greater potential of recruiting the active inference model.

Altogether, this body of evidence suggests that S1 is far from being an exclusively somatosensory processing area, but rather it is involved in merging and exchanging multimodal information through cortico-subcortical connections in order to fine tune sensations and movements in close cooperation with the motor cortex. Furthermore, the reviewed data highlight information flow between S1 and M1 changes in terms of directionality and quantity, suggesting that, rather than begin fixed, the relative weight of S1 and M1 contributions to movement execution normally vary according to context-dependent requirements. Advances in modeling the contributions of S1 to movement have provided a better understanding of the complex relationships underlying normal movement production. This improved understanding can now used to inform the study of the structural and functional substrates underlying abnormal movement in various neurologic conditions.

III. Imaging structural and functional differences in S1 after stroke

Recent development of advanced neuroimaging techniques has provided profound insights into the behavioral significance of structural and functional characteristics of the healthy and damaged brain. Bidirectional changes in brain structure and function underlie alterations in motor behavior. The clinical significance of examining the links between S1 structure and sensorimotor function is supported by evidence showing that approximately one-half of stroke patients in rehabilitation suffer from sensory discrimination impairments in the paretic hand (L. M. Carey & Matyas, 2011), and that integration of tactile afferent signals with motor commands is crucial for the performance of purposeful movements (Classen, et al., 2000).

Cytoarchitectically, S1 is housed within the postcentral gyrus, composed of 4 subareas: BA 3a, 3b, 1, and 2 (Jacobs, et al., 2012; Jones, Coulter, & Hendry, 1978; Rizzolatti & Kalaska, 2013; Vogt & Pandya, 1978) [Figure 2]. Afferent signals from cutaneous stimulation are transmitted first to area 3b (sometime referred to as 'S1 proper' (Kaas, 1983)), and then to the other areas of S1, as well as to M1, supplementary motor and premotor cortices, and somatosensory association areas (Brodmann's areas 5 and 7) (Canedo, 1997; Ghosh, Brinkman, & Porter, 1987; Jones, et al., 1978; Pons & Kaas, 1986; Vogt & Pandya, 1978). Studies have highlighted the potential importance of area 3a on influencing motor activity, as it receives inputs from group I muscle afferents and contributes axons to descending motor pathways (Canedo, 1997; Ghosh, et al., 1987; Zarzecki, et al., 1978). The somatosensory association areas, located in posterior parietal cortices, also influence motor activity. These association areas receive input from neurons in S1, as well as from the visual and auditory systems, and project to the supplementary motor and premotor cortices. It has been theorized that the function of these association cortices is to integrate somatosensory information with other sensory modalities in order to create a multi-dimensional representation of the external environment and influence

planned manipulation of objects (Andersen, Snyder, Bradley, & Xing, 1997; E. R. Kandel, 2000; Pandya & Seltzer, 1982; Saper, Iversen, & Frackowiak, 2000).

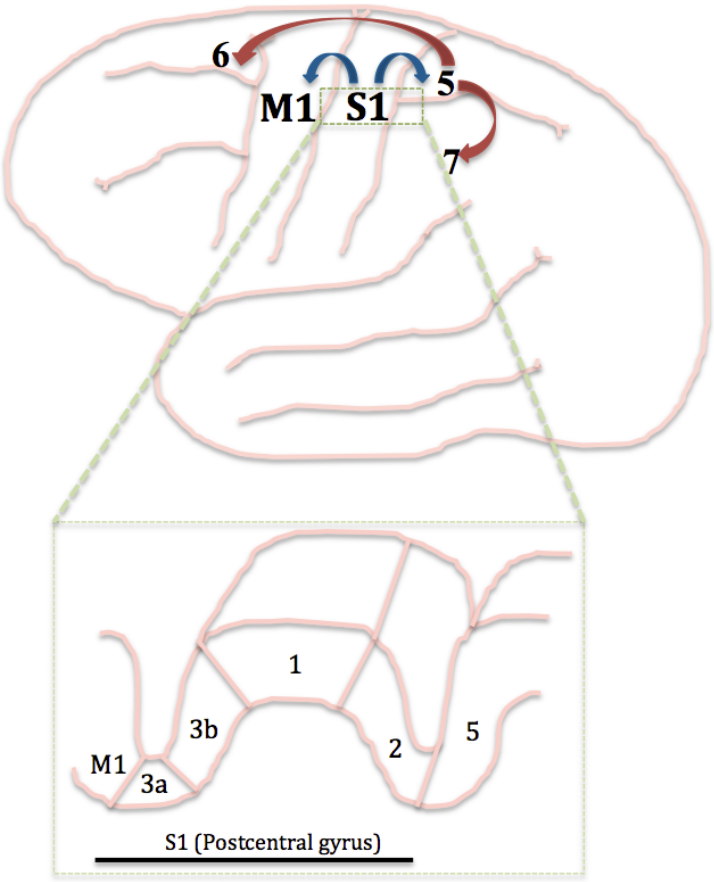

Figure 2: Projections between primary somatosensory (S1), motor (M1), and association cortices. Sensory information is projected directly from S1 to M1 and somatosensory association cortices (BA 5; blue arrows). Secondary projections occur from BA 5 to additional somatosensory cortices (BA 7) and premotor and supplementary motor cortices (BA 6; red arrows). Inset (dashed green box): cross-section of the cortex including M1, S1, and somatosensory association cortices. Cytoarchitecture of the subgroups of S1 (BA 3a, 3b, 1, and 2) is shown. Adapted from (E. Kandel, Schwartz, & Jessell, 2000; Saper, et al., 2000).

At a macrostructural level, a direct lesion to S1 or along the primary afferent sensory pathway is likely to result in some level of sensory dysfunction and, importantly, sensory impairments are usually paralleled by motor deficits (Taskin, et al., 2006; Yamada, et al., 2003). Often the resulting damage is not necessarily restricted to the local tissue damage at the primary

lesion location. Microstructural brain injury can occur due to secondary degeneration. Using diffusion tensor imaging (DTI), alterations in white matter tissue properties have been found in non-lesioned brain areas (Borich, Mang, & Boyd, 2012; Lindberg, et al., 2007). Structural properties of white matter, such as degree of myelination and axon diameter, influence the efficacy of signal transmission within the brain, thereby influencing functions associated with voluntary behavior (Seidl, 2014). As a result, post-stroke levels of impairment and motor recovery can be highly variable between individuals, and it is often difficult to parse out specific cause-and-effect relationships of brain structure and function with behavior.

Commonly, white matter tissue properties within the posterior limb of the internal capsule (PLIC) are altered after stroke (Werring, et al., 2000). Reports of abnormal ipsi- or contralesional PLIC tissue properties have been associated with greater levels of physical impairment (Borich, et al., 2012; Qiu, et al., 2011; Stinear, et al., 2007), reduced motor learning (Borich, Brown, & Boyd, 2013; Stinear, et al., 2007), lower levels of global motor function (Stinear, et al., 2007), and poorer hand dexterity (Borich, et al., 2012; Schaechter, et al., 2009). These changes may be partially explained by reduced transmission of sensory input in addition to motor output. Borstad and colleagues (2012) examined sensory component of the superior thalamic radiation (sSTR), which is upstream of the PLIC and includes all of the afferent connections of S1 (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004) in participants with chronic stroke. A strong correlation between the ipsi- and contralesional asymmetry of sSTR integrity and sensory function was observed, such that individuals with a larger asymmetry performed poorer on a measure of sensory discrimination with their paretic hand (Borstad, Schmalbrock, Choi, & Nichols-Larsen, 2012). These findings are in line with a study in children with congenital hemiplegia showing the status of sensorimotor thalamic projections were more

significantly correlated with paretic hand function than corticospinal tract connections (Rose, Guzzetta, Pannek, & Boyd, 2011). Despite recent experimental evidence, there remains a paucity of data evaluating the behavioral significance of changes in somatosensory tract structure in response to neurologic conditions.

Another white matter pathway commonly studied in individuals with stroke is the corpus callosum (CC), the largest commissural tract in the brain that connects homologous cortical regions of each hemisphere. The ability to produce skilled and coordinated movements relies on the dynamic interactions between the two hemispheres. The CC has a critical role in maintaining an appropriate balance of inter-hemispheric activity, which can be disrupted after stroke (Gupta, et al., 2006; Perez & Cohen, 2008) and has been linked to motor dysfunction (Jang, 2010; Lindenberg, Zhu, Ruber, & Schlaug, 2012). The CC can be divided into functionally and anatomically distinct segments according to the cortico-cortical tracts that pass through it connecting homologous regions between each hemisphere (Fling, Benson, & Seidler, 2011; Hofer & Frahm, 2006). Overall, previous studies have focused almost exclusively on the transcallosal segment that connects the two primary motor cortices (M1-M1), whereas studies of the sensory segment (S1-S1) are sparse. Borich and colleagues (2012) reported the microstructural integrity of CC sensory fibers, but not CC motor fibers, was reduced in individuals with chronic stroke compared to healthy age and gender-matched controls. However, no significant correlation with motor function was observed (Borich, et al., 2012). Based on these initial observations, further studies are necessary to better understand the functional significance of abnormal tissue properties of interhemispheric pathways after stroke and to verify the importance of S1 to S1 connections for motor function in this population.

An accumulating body of evidence suggests that, similar to the motor system, in healthy individuals the activation of S1 in one hemisphere modulates the activity of the contralateral S1. For example, functional magnetic resonance imaging (fMRI) studies conducted in monkeys (Lipton, Fu, Branch, & Schroeder, 2006) and in humans (Blankenburg et al., 2008; Hlushchuck & Hari, 2006; Kastrup et al., 2008; Eickhoff et al., 2008; Klingner et al., 2011) describe a corresponding increase in activation in the contralateral S1, and transient decrease in activation in the ipsilateral S1 during peripheral hand stimulation. This decrease in ipsilateral S1 activation correlates with reduced sensory perception in the opposite hand (Kastrup et al., 2008). Similar patterns have emerged in electrophysiological studies in humans (Ragert et al., 2011; Brodie et al., 2014). However, considerations of how sensory networks change after stroke are highly dependent on the time point studied as brain function is altered not only with damage but also by recovery from damage. One common finding after unilateral stroke is a shift in activation from ipsilesional to contralesional sensorimotor areas (Murase, Duque, Mazzocchio, & Cohen, 2004; Nowak, Grefkes, Ameli, & Fink, 2009); resolution of this hemispheric imbalance is associated with sensorimotor recovery (Cramer, 2008; Rossini, et al., 2007). This interhemispheric imbalance has been described specifically between the S1's in individuals with chronic stroke; the larger the imbalance, the poorer motor task performance (Calautti, et al., 2006). Resolution of the S1-S1 hemispheric imbalance has been reported in the acute phase post-stroke with recovery of sensory loss (L.M. Carey, et al., 2002) in individuals with chronic stroke before and after skilled sensorimotor training (J. R. Carey, et al., 2002; Schaechter, Moore, Connell, Rosen, & Dijkhuizen, 2006) and following intensive treatment with neuromuscular electrical stimulation of the paretic forearm (Kimberley, et al., 2004). These findings are in parallel to studies of laterality shifts in M1 with acute recovery (Zemke, Heagerty, Lee, & Cramer, 2003) and motor learning

(Boyd, Vidoni, & Wessel, 2010; Calautti & Baron, 2003). An additional point to consider when addressing interhemispheric imbalances in S1 is the possible relationship between asymmetries in S1 anatomy and function with handedness, similar to lateralization. Although hemispheric asymmetries in S1 anatomy (Soros, et al., 1999) and function (Jung, et al., 2003; Jung, Baumgartner, Magerl, & Treede, 2008) have been observed, it is currently unclear if these asymmetries are solely attributable to hand dominance.

Another common finding in fMRI experiments is a shift in primary sensorimotor activation towards the postcentral gyrus following stroke (Calautti, Leroy, Guincestre, & Baron, 2003; Cramer & Bastings, 2000; Laible, et al., 2012; Pineiro, Pendlebury, Johansen-Berg, & Matthews, 2001; Schaechter, et al., 2006). The behavioral significance of this posterior shift is elusive. Pineiro and colleagues proposed that it may potentially reflect an increased proprioceptive attentional process to offset motor impairment, or a recruitment of latent corticospinal fibers originating in S1 (Galea & Darian-Smith, 1994) to compensate for the limited output from M1 (Pineiro, et al., 2001). Schaechter and colleagues (2006) reported an increase in ipsilesional S1 activation was correlated with increased cortical thickness (structural plasticity) in the same area, but these increases were not correlated with motor outcome in the sample studied (Schaechter, et al., 2006). In a homogeneous group of patients with hand weakness but normal sensation, and no lesion within the S1, thalamus, or brainstem, a close relationship between improvements in hand function after constraint-induced movement therapy and increased peak changes in fMRI activation within the ipsilesional S1 was reported (Laible, et al., 2012). Conversely, individuals with direct damage to the ventroposterior nucleus of the thalamus show reduced activation in the ipsilateral S1 (Taskin, et al., 2006), and a negative correlation has been reported between touch discrimination and activation in ipsilesional S1,

particularly after sub-cortical stroke (L. M. Carey, et al., 2011). Thus, sensory network activity influences both sensory and motor function, and this activity appears to be closely related to therapy-induced gains in motor function seen after stroke.

IV. Non-invasive brain stimulation (NIBS) targeting S1 to improve sensorimotor function after stroke

Normalization of hemispheric excitability after stroke has been associated with sensorimotor functional recovery (Cramer, 2008; Rossini, et al., 2007) leading to experimental interventions to up- or down-regulate cortical activity in a targeted fashion in an effort to enhance functional recovery (Calautti & Baron, 2003).

One approach to enhance motor function by modulating S1 excitability relies on stimulating the peripheral somatosensory system. Indeed, several studies have shown that pairing repetitive peripheral nerve stimulation of the paretic upper extremity with training enhances motor performance after stroke (Celnik, Hummel, Harris-Love, Wolk, & Cohen, 2007; Conforto, et al., 2010; Klaiput & Kitisomprayoonkul, 2009; Knutson, et al., 2012; Wu, Seo, & Cohen, 2006). Furthermore, peripheral somatosensory stimulation can induce cortical reorganization of M1 (Hamdy, et al., 1998). Together, these findings have prompted investigation into the use of NIBS techniques that can directly modulate S1 excitability and modify connections between S1 and M1.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a safe, painless, and non-invasive technique used to the alter electrical activity of the underlying brain tissue by electromagnetic induction using a stimulating coil at the surface of the skull (Hallett, 2000). When applied as a single pulse

in healthy individuals, TMS over S1 transiently masks tactile sensation (Cohen, Bandinelli, Sato, Kufta, & Hallett, 1991; Hannula, et al., 2005; Seyal, Siddiqui, & Hundal, 1997) and disrupts sensorimotor performance (S. K. Meehan, Legon, & Staines, 2008). Studies investigating paired pulse TMS over S1 demonstrate amplified masking of a tactile sensation with a sub-threshold conditioning stimulus (Koch, Franca, Albrecht, Caltagirone, & Rothwell, 2006), and decreased sensorimotor performance with a suprathreshold conditioning stimulus (S. K. Meehan, et al., 2008). Essentially, these foundational studies confirmed linkages between S1 activity and somatosensory processing (Song, Sandrini, & Cohen, 2011) and reinforced the theoretical potential of S1 as a target to modify more complex sensorimotor behaviors. However, the behavioral consequences of S1 stimulation are more applicable when considering the longer-lasting modulatory effects of neuromodulatory forms of TMS.

Repetitive (r)TMS can be used to modulate local cortical excitability in a frequency and intensity-dependent manner (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Ridding & Ziemann, 2010; Siebner & Rothwell, 2003), for a period of time that outlasts the duration of stimulation (W.-H. Chen, et al., 2003). After stroke, high frequency (>5 Hz) or low frequency (≤1 Hz) rTMS may be used to increase ipsilesional or decrease contralesional excitability respectively. Given recent evidence of functional S1-S1 connections mediated by the CC in the human brain (Brodie, Villamayor, Borich, & Boyd, 2014), theoretically either of these rTMS approaches could be used to reestablish the balance of interhemispheric excitability after stroke (Fregni & Pascual-Leone, 2007; Nowak, et al., 2009). The majority of previous rTMS studies have focused on modulation of M1 excitability. However, S1 also possesses a high capacity for plastic change (Schaechter, et al., 2006), and emerging studies suggest that rTMS targeting can modulate S1 excitability, sensory function and motor control.

Excitatory rTMS protocols to modulate S1 excitability

High frequency (≥5Hz) rTMS applied over M1 increases cortical excitability, as measured by motor evoked potentials (MEPs) (Peinemann, et al., 2004). Similarly when applied over S1, 5Hz rTMS induces sustained increases in cortical excitability, indicated by larger SEPs in healthy individuals (Ragert, Becker, Tegenthoff, Pleger, & Dinse, 2004). Similar effects have also been observed with intermittent theta burst stimulation (iTBS) (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005), an excitatory form of patterned rTMS that results in longer-lasting effects with shorter stimulation durations compared to simple rTMS paradigms (Staines & Bolton, 2013). When applied over S1 in healthy individuals, iTBS increases SEP amplitudes (Katayama & Rothwell, 2007; Premji, Ziluk, & Nelson, 2010), but has not be shown to modulate M1 excitability (Katayama & Rothwell, 2007). Behavioral changes in sensation have been observed after excitatory rTMS including gains in spatial acuity (Ragert, et al., 2003; Tegenthoff, et al., 2005) and frequency discrimination (Pleger, et al., 2006) of the hand. Following 5Hz rTMS over the finger representation in S1, Tegenthoff and colleagues (2005) observed and expansion in the finger representation in healthy individuals that was correlated with improvements in tactile perception. Using fMRI, reorganization of activity sensorimotor network activity patterns within S1 and M1 were demonstrated following 5Hz rTMS over S1 that lasted for up to 120 minutes following stimulation (Pleger, et al., 2006) suggesting both local and remote changes can result from neuromodulation of S1.

The potential for rTMS of S1 to not only improve somatosensation but also enhance connectivity with other nodes within the sensorimotor network (e.g. M1) has important implications for motor learning. To induce persistent change in sensorimotor function, learning is required. Thus, motor learning is considered the basis of neurorehabilitation (Krakauer, 2006).

Ragert and colleagues (2003) showed enhanced perceptual learning following repeated applications of 5Hz rTMS over S1 in healthy individuals; however tactile discrimination was tested over several sessions on the same day of stimulation. When participants were re-tested 2 weeks later, their discrimination thresholds were at baseline levels (Ragert, et al., 2003). Similarly, Karim and colleagues (2006) reported learning of a spatial discrimination task, but not of a frequency discrimination task, was facilitated following the application of 15Hz rTMS over S1; yet again, all sensory testing was conducted on the same day of stimulation (Karim, Schuler, Hegner, Friedel, & Godde, 2006). Without significant improvements observed at a no-rTMS retention test, it is not currently possible to conclude that long-term memory consolidation and improved sensory function result from rTMS over S1 highlighting the need for study designs to incorporate delayed retention tests to defined the persistent impact of NIBS to S1 (Boyd & Linsdell, 2009; Dayan & Cohen, 2011; Robertson, Pascual-Leone, & Miall, 2004).

Recently, Brodie and colleagues (2014) applied 5Hz rTMS over ipsilesional S1 in individuals with chronic stroke followed immediately by motor skill practice of a serial visuomotor targeting task (Brodie, Meehan, Borich, & Boyd, 2014). The intervention was repeated daily for 5 days. Individuals who received rTMS over S1 showed a generalized improvement of skill performance across training that persisted at a no-rTMS retention test at 24 hours following the last practice session. Motor learning was associated with significant improvements in spatial acuity but not in upper extremity motor function or manual dexterity. Yet, to date, these findings have not been extended to determine whether pairing 1Hz rTMS over S1 with neurorehabilitation might enhance clinically meaningful outcomes and is an area of significant interest for future inquiry.

Inhibitory rTMS protocols

When applied at low frequencies (≤1Hz), rTMS applied over M1 decreases motor cortex excitability (R. Chen, et al., 1997). However, a number of reports of low frequency rTMS over S1 have not found a significant depression of SEP amplitudes in healthy individuals (Enomoto, et al., 2001; Ogawa, et al., 2004; Restuccia, Ulivelli, De Capua, Bartalini, & Rossi, 2007; Satow, et al., 2003). Instead, alterations in high-frequency oscillations, which represent changes in localized activity of intracortical inhibitory interneurons, have been observed (Katayama, Suppa, & Rothwell, 2010; Ogawa, et al., 2004; Restuccia, et al., 2007). However Ishikawa and colleagues (2007) reported inhibitory (c)TBS over S1 suppressed SEP amplitudes from the stimulated S1 for at least 13 minutes after the stimulation period. This suppression occurred in the absence of changes in M1 excitability bilaterally (Ishikawa, et al., 2007). In contrast, Zapallow and colleagues (2013) showed that cTBS over S1 increases intracortical inhibition between M1s for 45-60 minutes following stimulation in young healthy adults providing one potential mechanism by which S1 may influence M1 activity and basal motor control (Zapallow, et al., 2013).

The ability to transiently depress cortical activity within S1 of healthy individuals provides insights into the potential contributions of sensory dysfunction to sensorimotor impairment after stroke. For example, Vidoni and colleagues (2010) used 1Hz rTMS over S1 as a 'virtual lesion' in healthy adults prior motor skill practice over two days. During training and at a no-rTMS retention test, improvements in tracking performance were diminished in the stimulation group compared to a sham stimulation control group (Vidoni, Acerra, Dao, Meehan, & Boyd, 2010). Thus disrupting S1 activity prior to skill practice reduced motor skill learning further supporting a critical role of somatosensory information processing to motor function. .

In individuals with unilateral stroke, it is possible that down-regulation of specific areas within the contralesional hemisphere may alter interhemispheric competition, thereby reducing inhibition of the ipsilesional hemisphere mediated by the contralesional side (Fregni & Pascual-Leone, 2007; Nowak, et al., 2009). Meehan and colleagues (2011) showed that cTBS over contralesional M1 or over S1 paired with skill practice enhanced skill learning compared to practice alone. However, cTBS over contralesional M1 resulted in greater changes in velocity and acceleration, whereas cTBS over contralesional S1 resulted in faster time to initiate movement and in lower cumulative magnitude of each movement (Sean K. Meehan, et al., 2011). Contralesional S1 stimulation also induced substantial improvements in upper extremity motor function (Sean K. Meehan, et al., 2011). Taken together, neuromodulatory TMS targeting S1 can modulate both sensory and motor performance and, when applied over multiple sessions, can improve motor learning in both healthy individuals and patients with stroke making this NIBS approach an intriguing option to further investigate potential clinical applications aimed at enhancing sensorimotor function.

Transcranial direct stimulation

Transcranial direct stimulation (tDCS) is another method that enables the non-invasive manipulation of cortical excitability. During tDCS a low intensity current is run between two large surface scalp electrodes; the effects depend on current polarity. In the motor system, anodal tDCS over the motor cortex increases cortical excitability as measured by MEPs, cathodal tDCS has the opposite effect (Nitsche & Paulus, 2000). The spatial resolution of tDCS is significantly poorer than that of TMS, and as a result it is difficult to precisely target specific cortical areas such as M1 and S1. Nevertheless, studies have examined the effects of tDCS protocols on S1 excitability. The data characterizing the effect of anodal tDCS over the motor cortex is mixed;

one study reported significant increases in SEP amplitude (Matsunaga, 2004) while another failed to observe any effect (Dieckhofer, et al., 2006). Similar mixed results have been reported for the effects of anodal tDCS over S1 on somatosensation (Ragert, Vandermeeren, Camus, & Cohen, 2008; Rogalewski, Breitenstein, Nitsche, Paulus, & Knecht, 2004), Cathodal tDCS over S1 reduced SEP amplitudes (Dieckhofer, et al., 2006), and impaired tactile frequency discrimination (Rogalewski, et al., 2004). Cathodal tDCS over the motor cortex area has not been shown to affect SEPs (Matsunaga, 2004). Overall, current evidence is inconsistent regarding the efficacy of tDCS protocols to modify S1 excitability due to a paucity of studies and heterogeneous results. Limitations of tDCS (e.g. difficulty in target localization, inability to identify stimulation intensities across individuals, and differences in simulation parameters across studies) may explain these inconsistent findings. Therefore, it is possible that improvements in standardization of tDCS protocols will result in a better understanding of the potential of tDCS approaches to modulate S1 activity to support motor function and recovery.

Limitations of non-invasive brain stimulation

Although, NIBS over S1 is a promising approach to modulate sensorimotor activity and motor function, targeting S1 is associated with a number of challenges. It is more difficult to target this cortical region due to the lack of observable evoked peripheral responses during stimulation in comparison to targeting M1. While some researchers identify the hand representation in S1 by shifting the coil ~2cm posteriorly from the M1 hotspot, or using the international 10-20 system to visually approximate the location of S1, improved localization approaches are now available Stereotaxic neuronavigation utilizes structural MRI data to identify and target non-motor cortical regions based on known anatomical location. FMRI-based activation maps can also be used to identify a stimulation target based on functional activity

rather than anatomy. Defining appropriate stimulation intensities for S1 is another challenge. All rTMS protocols discussed calculated S1 stimulation intensities using a percentage of the resting or active *motor* thresholds – measures of M1 excitability. Future work is needed to identify optimal stimulation protocols specifically for S1. At this point, due to lack of consistency between methods, results have been variable. Nevertheless, evidence of the behavioral consequences of S1 stimulation continues to accumulate support the notion that S1 is integral to sensorimotor control and learning and may be a viable target for clinical applications of NIBS. It is important to note that despite encouraging mechanistic investigations, a large-scale randomized clinical trial evaluating the efficacy of NIBS targeting of S1 to improve motor function after stroke has yet to be conducted.

V. Combining TMS with neuroimaging to study effective connectivity after stroke

The correlative nature of neuroimaging techniques limits empirical characterization of causal interactions between behavior with brain structure and function. By using TMS to stimulate a cortical region of interest during a behavior of interest, it is possible to study causal influences of the stimulated region on task performance. However, the brain is comprised of intricate and complex neuronal networks that are dynamically modifiable (Sporns, Chialvo, Kaiser, & Hilgetag, 2004) thus complicating the interpretation of TMS-based results. It is not clear if the observed change in behavior is solely due to stimulation of the targeted cortical region or if it is a result of interactions within functional neural networks that may also be influenced by structural network organization. Neuroimaging can be performed before, during or after TMS to noninvasively map the spatiotemporal dynamics of TMS-induced cortical activation (Siebner, et al., 2009). For example, it is now common to use frameless stereotactic neuronavigation using previously acquired structural MRI data to spatially localize the individualized stimulation site

for each participant to enable reproducible targeting within and between TMS sessions (Bashir, Edwards, & Pascual-Leone, 2011; Julkunen, et al., 2009). Combined TMS-neuroimaging can also be used to refine neuromodulation approaches by individualizing stimulation parameters based on characteristics of brain network structure and function. For example, cortical activation patterns associated with somatosensory discrimination have been mapped after stroke using fMRI (L. M. Carey, et al., 2011). These task-based activation maps could used to personalize (r)TMS delivery based on each participant's unique cortical activity patterns.

Mapping reorganization of white and gray matter tissue and structural networks in stroke can also be performed prior to TMS. A recent report described smaller volumes of white matter underlying ipsilesional S1 predicted less motor task improvement following an intervention pairing high-frequency rTMS over the ipsilesional S1 followed by motor training of the paretic arm in individuals with chronic stroke (Brodie, Borich, & Boyd, 2014). However, there is currently a paucity of data combining neuroimaging with TMS to characterize S1 excitability as well as the structural and functional connections between S1 and M1. With the introduction of navigated TMS using structural MRI data, it is now possible to reproducibly target any cortical region of interest. However, it is not possible to use TMS alone to evoke a measurable response in S1, which limits the current understanding of how S1 excitability may be modulated by NIBS or task practice to support motor function in health or disease.

In contrast to performing imaging before or after NIBS, functional neuroimaging can be performed during TMS to evaluate immediate spatiotemporal cortical network dynamics of TMS-induced responses (R. J. Ilmoniemi, et al., 1997). This approach remains methodologically challenging due to technical aspects associated with acquiring functional imaging data in the harsh TMS environment (Risto J. Ilmoniemi & Kicic, 2010; Sato, Bergmann, & Borich, 2015).

Concurrent TMS- neuroimaging can uniquely investigate causal information flow through functional neural networks mediated by excitatory and inhibitory connections (Bortoletto, Veniero, Thut, & Miniussi, 2015). Yet, to date, no studies have been published in stroke using concurrent TMS-neuroimaging nor have studies used concurrent approaches to study local cortical excitability and regional connectivity in response to stimulation of S1 in general. This knowledge gap suggests there are substantial opportunities to improve our understanding of the neurobiological mechanisms of cortical reorganization both after stroke and response to rehabilitation interventions as well as further elaborate the salient interactions between S1 and M1 that underlie human sensorimotor control.

VI. Clinical implications and conclusions

Advances in neuroimaging and neurostimulation research are rapidly expanding our understanding of the role of the sensory system in the recovery from stroke. Moving forward the challenge will be to exploit our understanding of the role(s) of the sensory system in motor recovery to formulate novel therapeutic interventions. Critically, S1 is heavily connected with ipsilateral M1 as well as with the sensory association areas of the parietal cortex. It is now clear that the two sensory cortices are both neuroanatomically and functionally linked, such that they may mutually inhibit one another (Brodie, Villamayor, et al., 2014; Ragert, Nierhaus, Cohen, & Villringer, 2011). These extensive connections enable S1 to influence not only voluntary movements, but perhaps more importantly, motor learning. Indeed, S1 has a central role in theoretical conceptualizations of motor learning such as the internal model (Ito, 2000). The internal model posits that output from M1 is directly affected by input from S1, and that with task practice this relationship enables sensory information to refine the emerging motor plan

570 (Hwang & Shadmehr, 2005; Nowak, Glasauer, & Hermsdorfer, 2004; Thoroughman &
571 Shadmehr, 1999). This theoretical model is supported by findings from rTMS studies where non-
572 invasive brain stimulation was used to disrupt S1 function (Vidoni, et al., 2010). Altering sensory
573 function of healthy individuals with 1Hz rTMS over S1 results in more errors and slower
574 movements during physical practice; importantly these changes persist at a no-rTMS retention
575 test. These data indicate that learning a new motor task is influenced by sensory input, regardless
576 of the accuracy of this information.

577 It is clear that the nervous system is continually updating based on the afferent
578 information (Wei & Kording, 2009). Impaired somatosensation during task practice leads to the
579 development of an inaccurate internal model or motor plan and, in turn, degrades motor learning.
580 These data have important implications for people with centrally impaired sensation, such as
581 occurs after stroke, as they suggest that it is imperative to design novel therapies that focus on
582 remediation of sensory processing deficits. It is also important to consider the cognitive aspects
583 associated with sensorimotor control where movement planning, strategy and selection will exert
584 and influence on the sensorimotor interactions discussed in detail in this review. Similar to
585 sensory dysfunction observed in typical motor-based neurologic disorders, many of these
586 conditions also present with cognitive dysfunction that will influence motor control and motor
587 learning associated with the recovery of function.

588 Future work needs to focus on gaining a clearer understanding of the neuroanatomy of
589 sensory connectivity in both the damaged and healthy brain. To date it remains unclear what
590 proportion of the CST carries ascending sensory information. Similarly, it is only recently that
591 interhemispheric sensory to sensory connectivity has begun to be explored (Brodie, Villamayor,
592 et al., 2014; Ragert, et al., 2011). Little information currently exists that characterizes how brain

damage, such as stroke, affects connectivity between brain regions. Further, it is not known how patterns of recovery after stroke may impact the flow of sensory information within the brain. Without this information it will be difficult to design effective therapeutics that seek to shape trajectories of recovery following brain damage.

The present review clearly supports the concept that somatosensation, and central sensory processing in particular, is crucial for both motor learning in healthy adults and motor recovery after brain damage. We have demonstrated the intricate connections and functions of the sensory system, as they are understood to date. The data presented here also suggest that sensation is a necessary consideration in motor rehabilitation. These findings have implications for both learning theory and rehabilitation medicine, in particular regarding the importance of developing novel rehabilitation approaches to enhancing recovery of sensory loss after stroke. As discussed, future work should consider the impact of pairing interventions such as non-invasive brain stimulation over S1 or peripheral sensory stimulation with neurorehabilitation. In addition, it is clear that because of the complexity of the central sensory system that studies employing multimodal imaging and behavioral mapping approaches will yield the most useful data as we continue to discover more about the role(s) of somatosensation in recovery from brain damage.

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