Insight into motor control and motor impairment from stroke and beta oscillations

Ramina Adam,1,2* Silvia Isabella,3,4* and Jason L. Chan1,2*

1The Brain and Mind Institute, University of Western Ontario, London, Ontario, Canada; 2Graduate Program in Neuroscience, University of Western Ontario, London, Ontario, Canada; 3Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; and 4Program in Neurosciences and Mental Health, Hospital for Sick Children Research Institute, Toronto, Ontario, Canada

Submitted 29 January 2015; accepted in final form 15 July 2015

Adam R, Isabella S, Chan JL. Insight into motor control and motor impairment from stroke and beta oscillations. J Neurophysiol 114: 3033–3035, 2015. First published July 15, 2015; doi:10.1152/jn.00098.2015.—Beta oscillations are associated with motor function and are thought to play a role in movement impairment. In a recent magnetoencephalography (MEG) study, Rossiter et al. (J Neurophysiol 112: 2053–2058, 2014) found a disruption in the modulation of movement-related beta oscillations in stroke patients that correlated with motor impairment. We discuss how beta oscillatory measures characterize motor impairment, the implications of stroke variability, and the potential role of GABA in modulating oscillations following stroke and during stroke recovery.

NEURONAL OSCILLATIONS, which reflect the synchronized activity of large populations of neurons, have been implicated in brain function and behavior. Generally, oscillations enable the temporal control of neuronal firing and underlie communication within local and between distant brain areas. Distinct processes and functions have been attributed to oscillations within several frequency bands.

Oscillations in the beta frequency band (15–30 Hz) are particularly relevant to motor function and behavior. In the primary sensorimotor cortex and other motor areas, beta activity is observed at rest and is modulated by voluntary movement (Engel and Fries 2010; Pfurtscheller and Lopes da Silva 1999). During movement preparation and before movement initiation, a decrease in beta power originates in the primary sensorimotor cortex contralateral to movement. This movement-related beta desynchronization (MRBD) is followed by a postmovement beta rebound (PMBR) where beta power increases above baseline levels. MRBD is related to neural activation and movement preparation and execution, whereas PMBR is associated with sensory feedback or neural deactivation that inhibits movement.

The prominence of beta oscillations in normal movement suggests that this activity may be disrupted with motor impairment and damage to brain areas involved in motor control. Investigating pathological changes to oscillatory dynamics in patients with motor impairment can provide insight into the neurophysiological mechanisms for normal motor control and lead to therapeutic interventions. Stroke is a leading cause of physical disability and impairment in motor control, but its relation to beta activity is poorly understood.

In a recent article, Rossiter et al. (2014) used magnetoencephalography (MEG) to examine beta activity in primary motor cortex (M1) during unilateral movement in stroke patients and healthy participants. The authors hypothesized that beta oscillations would be affected by stroke both at rest and during movement and that greater motor impairment would correlate with reduced modulation of beta oscillations. MEG signals were recorded while 25 stroke patients and 32 healthy participants performed a hand grip task. In this task, patients and healthy participants were cued to isometrically grip a manipulandum using their affected hand or dominant hand, respectively, by the appearance of a “force thermometer,” which displayed continuous visual feedback about the force exerted. On each trial, participants maintained grip at a target force of 30% of their maximum grip strength (obtained before scanning) for 3 s.

The main finding was that MRBD was significantly reduced in stroke patients compared with healthy participants in the M1 contralateral to movement (ipsilesional). For the patient group, MRBD in contralateral M1 was also negatively correlated with motor impairment. The secondary result of this study involved the MRBD ratio, calculated as the MRBD in contralateral M1 divided by the MRBD in ipsilateral M1, which was used to compare MRBD across the two hemispheres. This ratio was lower in patients compared with participants and negatively correlated with the degree of impairment experienced by patients. In other words, MRBD was more consistent across hemispheres in patients with greater impairment.

Taking these results together, Rossiter et al. (2014) suggested that MRBD in contralateral M1 may play a role in the impairment of motor control following stroke. The authors also suggested that diminished MRBD may reflect changes in excitation and inhibition via altered levels of γ-aminobutyric acid (GABA) and experience-dependent plasticity during stroke recovery. In this Neuro Forum article, we comment on how different oscillatory measures characterize motor impairment, discuss the implications of variability in stroke, and expand on the possible role of GABA in modulating oscillatory changes after stroke.

Beta oscillations and motor impairment. The study by Rossiter et al. (2014) establishes an important association between beta oscillations and motor impairment following stroke. By examining the peak frequency and amplitude of beta oscillations...
tions at baseline and during the MRBD, they showed that MRBD was affected by stroke. This finding presents questions regarding additional parameters related to beta oscillations, which we hypothesize will further characterize and clarify the effects of stroke on impairments of motor control. For example, another possible conclusion from the reduction in MRBD with stroke is that stroke increases variability in the latency of the MRBD. If MRBD onset, maximum value, or return to baseline occur at different time points across trials, then the averaged time course will be longer in duration with lower values at each time point and the average amplitude of the MRBD time course will be lower. The MRBD differences found in stroke suggest that further analysis may reveal additional implications of stroke, especially on the timing of cortical oscillations. Consequently, a measure such as the area above the MRBD curve may provide additional information worthy of investigation, because it accounts for the width of the MRBD time course and is therefore more robust to differences in variability.

In addition to the MRBD, which begins before movement onset and is thought to be involved in movement preparation (Cheyne et al. 2012), we hypothesize that brain activity that occurs after movement onset, especially the PMBR, may be affected by stroke and be crucial for stroke recovery. Somatosensory loss after stroke is common, and sensory feedback mechanisms are known to be important for motor control and the recovery of function. A recent MEG study found that patients with acute stroke had reduced PMBR following tactile finger stimulation compared with healthy participants and that PMBR was correlated with hand function (Laaksonen et al. 2012). Thus potential deficits in sensory feedback following movement in stroke patients may be reflected by the PMBR.

Alternatively, the PMBR is associated with sustained contractions and holding periods following movement (Engel and Fries 2010), and we hypothesize that it may reflect the ability of stroke patients to maintain grip. In particular, Rossiter et al. (2014) examined the relationship between MRBD and two measures of motor impairment: maximum grip strength and a principal component analysis (PCA) score based on the Nine Hole Peg Test (NHPT) and Action Research Arm Test (ARAT). Although grip strength was not found to account for changes in MRBD, greater motor impairment measured using PCA was associated with less MRBD in contralateral M1. The absence of a relationship between grip strength and MRBD could be related to the tasks and beta parameters used. The NHPT and ARAT involve a series of movements, whereas maximal grip strength involves a sustained contraction. Although motor impairment measured by the PCA score may be sufficiently reflected by the MRBD, which occurs before movement onset, we hypothesize that a relationship may exist between impairment measured by grip strength and the PMBR, which is associated with sustained muscle contractions. Future studies investigating the PMBR may provide critical insight into the functional significance of oscillations in motor control.

Implications of stroke variability. For strokes with unilateral motor impairment, current functional magnetic resonance imaging (fMRI) literature indicates that there is widespread and bilateral neural activation across the motor system that is proportional to the degree of impairment (Ward et al. 2003). Poor motor performance is associated with less M1 activation in the contralateral hemisphere, and bilateral activation decreases over time with recovery. These findings suggest the presence of compensatory mechanisms in the ipsilateral hemisphere following stroke, and that recovery may be associated with reduced compensation in the ipsilateral hemisphere and improved function in the contralateral hemisphere.

The finding by Rossiter et al. (2014) that contralateral MRBD in patients is negatively correlated with motor impairment is an important result that supports the relationship between the fMRI blood oxygen level-dependent (BOLD) signal, cortical oscillations as measured by electroencephalography and MEG, and behavior, despite differences in primary measure and temporal resolution between the imaging modalities. However, no significant differences from healthy participants or correlations with impairment were found in the ipsilateral M1. Consequently, the correlation of MRBD ratio with motor impairment had to be driven by MRBD in the contralateral M1 rather than by MRBD in the ipsilateral M1. Indeed, a smaller β-value for the MRBD ratio correlation with impairment (β = 0.42) compared with the contralateral MRBD correlation with impairment (β = −0.52) indicates a dampening of the correlation when ipsilateral activity is included compared with contralateral activity alone. The absence of a relationship between ipsilateral M1 and the degree of impairment is contrary to fMRI studies that find bilateral M1 activation. We hypothesize that this null result may be explained by variability in the patient group studied. Indeed, heterogeneity in stroke recovery and compensatory mechanisms can be ascribed to patient variability in degree of impairment, time since stroke, lesion location, and lesion size (Di Pino et al. 2014).

Rossiter et al. (2014) addressed patient variability and found that time since stroke and patient age did not influence variability in beta parameters. In addition to these two factors, lesion location and lesion size are critical predictors of impairment and recovery. Although Table 1 in Rossiter et al. (2014) indicates different lesion locations across patients, all lesions were grouped together for analyses, and this may have contributed to patient variability. It is important to note that a larger patient population may be required to investigate location- or size-specific effects on M1 beta oscillations. For example, damage to the contralateral premotor cortex or supplementary motor area, which can compensate for lost motor function, or damage to hub regions that participate in multiple brain systems, such as the posterior medial frontal gyrus or dorsomedial prefrontal cortex, have been shown to produce more severe impairments than lesions at other locations (Di Pino et al. 2014; Warren et al. 2014) and may be associated with greater deficits in MRBD or changes in ipsilateral M1 activity. Neurotransmitters, such as GABA, are thought to play a role in mediating oscillations, and lesions to different locations may have different effects on GABA levels in the contralateral M1. Cortical lesions, including lesions to M1, may result in the loss of cortical GABAergic neurons, whereas subcortical lesions may result in a functional decrease in inhibition to modulate recovery (Blicher et al. 2015). Thus differences in neurotransmitter levels and changes in input to M1 because of lesions to different locations are likely to variably affect beta parameters. Furthermore, lesion size correlates with the degree of motor impairment experienced by a patient, how the brain functionally reorganizes after injury, and patient recovery (Di Pino et al. 2014). Ultimately, lesion

J Neurophysiol • doi:10.1152/jn.00098.2015 • www.jn.org
location and size are important factors in patient variability and impairment, and future studies investigating the link between these factors and beta parameters can help elucidate how the motor system uses beta oscillations in normal and abnormal motor control.

**GABA, beta oscillations, and stroke recovery.** The reduction in MRBD with stroke and its correlation with motor impairment have implications for understanding the mechanisms that underlie stroke recovery. Rossiter et al. (2014) briefly suggested that changes in oscillatory activity in patients may reflect excitatory and inhibitory processes involving GABA and experience-dependent plasticity. In this article, we expand on their discussion of the relationship between beta oscillations, GABA, stroke, and post-stroke recovery.

Indeed, increased GABA has been found to enhance MRBD in M1 in healthy participants (Hall et al. 2011; Muthukumaraswamy et al. 2012). Hall et al. (2011) administered diazepam, a GABA<sub>Α</sub> receptor modulator that increases GABAAergic drive, and concluded that MRBD is a GABA<sub>Α</sub>-mediated process. Muthukumaraswamy et al. (2012) used tiagabine, a GABA reuptake inhibitor that increases synaptic levels of GABA, and found enhanced MRBD but reduced PMBR. This suggested that PMBR may be mediated by a different receptor, GABA<sub>Β</sub>. These studies show that different aspects of movement-related beta oscillations may be variably affected by endogenous GABA levels due to the involvement of two different receptors. The reduced MRBD observed by Rossiter et al. (2014) indicates that stroke may affect GABA<sub>Α</sub> receptors or lower synaptic levels of GABA.

Accordingly, the time period immediately following stroke is characterized by a decrease in GABA<sub>Α</sub> and GABA<sub>Β</sub>-mediated inhibition (Di Pino et al. 2014). A decrease in GABA<sub>Α</sub> receptor expression could mediate the reduced MRBD observed following stroke in Rossiter et al. (2014). Furthermore, patients assessed 3–12 mo following stroke were found to have decreased GABA levels in M1 compared with healthy participants (Blicher et al. 2015). This is consistent with findings from Rossiter et al. (2014) and importantly supports a link between GABA and MRBD changes following stroke.

During stroke recovery, GABA levels may have a biphasic effect. Blicher et al. (2015) found that decreased GABA was associated with greater improvement in motor function during rehabilitation. This is consistent with acute decreases in GABA levels in healthy individuals that facilitate motor learning and neural plasticity (Stagg et al. 2011). In contrast, Rossiter et al. (2014) found that better motor function correlated with greater MRBD, which may be driven by chronically increased GABA (Hall et al. 2011; Muthukumaraswamy et al. 2012). It is possible that acute GABA decreases during motor learning may facilitate long-term increases in GABA levels to a pre-stroke state during recovery. In this case, MRBD would reflect the overall excitatory/inhibitory state of M1 and recovery in terms of level of impairment. As such, different measures of beta oscillations may be better associated with acute changes in GABA during motor learning. Future studies investigating different beta measures and the contributions of different GABA receptors to oscillation generation and motor learning could provide a better understanding of how beta oscillations relate to plasticity and stroke recovery.

**Conclusion.** Although the modulation of beta oscillations in primary sensorimotor cortex is prominently associated with voluntary movement and normal motor control, how these oscillations are disrupted with motor impairment and brain damage is poorly understood. The study by Rossiter et al. (2014) characterizes how beta oscillations relate to motor impairment following stroke and provides a foundation for future studies to investigate stroke-related changes in oscillatory dynamics during movement. The results of Rossiter et al. (2014) pose important questions regarding different measures of movement-related beta oscillations, the effect of lesion location and size on beta oscillations and impairment, and the role of GABA in modulating beta oscillations, with implications for neural plasticity and stroke recovery. Future studies addressing these questions can provide further insight into the neurophysiological mechanisms for normal motor control and inform the development of therapies for motor rehabilitation.