NeuroImage: Clinical 14 (2017) 344–353

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Hemispheric asymmetry in myelin after stroke is related to motor impairment and function

Bimal Lakhani[a], Kathryn S. Hayward[a,b,c], Lara A. Boyd[a,*]

[a]Department of Physical Therapy, University of British Columbia, Vancouver, BC V6T 1Z3, Canada
[b]Stroke Division, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, VIC 3084, Australia
[c]NHMRC Centre of Research Excellence in Stroke Rehabilitation and Brain Recovery, Australia

ARTICLE INFO

Article history:
Received 19 October 2016
Received in revised form 3 January 2017
Accepted 10 January 2017
Available online 16 January 2017

Keywords:
Stroke
Myelin
White matter
Biomarkers
Motor control
Accelerometry

ABSTRACT

The relationships between impairment, function, arm use and underlying brain structure following stroke remain unclear. Although diffusion weighted imaging is useful in broadly assessing white matter structure, it has limited utility in identifying specific underlying neurobiological components, such as myelin. The purpose of the present study was to explore relationships between myelination and impairment, function and activity in individuals with chronic stroke. Assessments of paretic upper-extremity impairment and function were administered, and 72-hour accelerometer based activity monitoring was conducted on 19 individuals with chronic stroke. Participants completed a magnetic resonance imaging protocol that included a high resolution T_1 anatomical scan and a multi-component T_2 relaxation imaging scan to quantify myelin water fraction (MWF). MWF was automatically parcellated from pre- and post-central subcortical regions of interest and quantified as an asymmetry ratio (contralesional/ipsilesional). Cluster analysis was used to group more and less impaired individuals based on Fugl-Meyer upper extremity scores. A significantly higher precentral MWF asymmetry ratio was found in the more impaired group compared to the less impaired group ($p < 0.001$). There were no relationships between MWF asymmetry ratio and upper-limb use. Stepwise multiple linear regression identified precentral MWF asymmetry as the only variable to significantly predict impairment and motor function in the upper extremity (UE). These results suggest that asymmetric myelination in a motor specific brain area is a significant predictor of upper-extremity impairment and function in individuals with chronic stroke. As such, myelination may be utilized as a more specific marker of the neurobiological changes that predict long term impairment and recovery from stroke.

1. Introduction

Improved medical management of stroke has resulted in decreasing mortality rates (Grefkes and Ward, 2014). As a result, the number of individuals living with long-term disability as a result of stroke is rising (Krueger et al., 2015). Due to the heterogeneity of clinical presentation following stroke, it is imperative to identify biomarkers that may predict long-term impairment and function in order to appropriately individualize clinical rehabilitation goals and objectives (Bernhardt et al., 2016). With advances in diagnostic and prognostic tools, it is necessary to isolate modalities that can predict long-term outcomes for individuals with stroke, and to understand the underlying neurobiology that contributes to the predictive value of those measures.

Neuroimaging can be utilized to aid in the identification of biomarkers that may predict recovery status in individuals with stroke. White matter imaging is often used as a predictor of stroke recovery (Feng et al., 2015; Stinear et al., 2012). Diffusion tensor imaging (DTI) can be performed within 10 days post stroke to quantify initial post stroke structural degeneration (Werring, 2000). Such indices have been found to strongly predict upper-extremity motor function at both 3- and 6-months post stroke (Puig et al., 2010; Stinear et al., 2012). The combination of acute corticomotor function, derived from DTI and motor evoked potentials, using transcranial magnetic stimulation, has also been demonstrated to strongly predict recovery from upper-extremity impairment after stroke (Byblow et al., 2015). Although these modalities are predictive of long-term upper-extremity impairment, the underlying neurobiological bases driving the relationship between white matter microstructure and motor capacity remains unclear. While relationships between white matter integrity, quantified with DTI, and motor impairment have been established after stroke, it is

Abbreviations: AC, Activity Count; ANCOVA, Analysis of Covariance; AR, Asymmetry Ratio; CST, Corticospinal Tract; DTI, Diffusion Tensor Imaging; FM, Fugl-Meyer; GRASE, Gradient and Spin Echo; MANCOVA, Multivariate Analysis of Covariance; MR, Magnetic Resonance; MWF, Myelin Water Fraction; UE, Upper Extremity; WMFT, Wolf Motor Function Test.

* Corresponding author at: University of British Columbia, Department of Physical Therapy, 212-2177 Wesbrook Mall, Vancouver, BC V6T 1Z3, Canada.
E-mail address: lara.boyd@ubc.ca (L.A. Boyd).

http://dx.doi.org/10.1016/j.nicl.2017.01.009

important to note that DTI measures are not a specific marker for myelination (Arshad et al., 2016). While DTI can grossly identify water movement, it is unable to differentiate between individual white matter substrates, which may produce the observed signal. Multiple structural features can be individually or collectively responsible for the observed changes in DTI measures, including: 1) axonal membrane status, 2) myelin sheath thickness, 3) number of intracellular neurofilaments and microtubules, and 4) axonal packing density (Alexander et al., 2007; Beaulieu, 2002). To understand the neurobiological components contributing to the change in motor outcome observed there is a need to adopt neuroimaging techniques that can quantify these structural features.

Myelin formation has been identified as a specific target for therapeutic intervention following stroke, as recovery of axonal fibres is not complete without adequate myelination (Mifsud et al., 2014). Oligodendrocytes are responsible for initiating a cascade of events that result in the formation of myelin. Acute cerebral ischemia, such as that caused by a stroke, causes a rapid breakdown of oligodendrocytes and demyelination (Tekkök and Goldberg, 2001), which greatly limits overall axonal integrity in the lesioned area (Saab and Nave, 2016). Although animal work has underlined the importance of active myelination on motor recovery after stroke (Chida et al., 2011; McKenzie et al., 2014), it is unclear how these findings transfer to humans.

Until recently, technical limitations prevented the imaging of myelin in vivo. Myelin water fraction (MWF) can be derived in humans non-invasively in vivo from multi-component T2-relaxation imaging (Alonso-Ortiz et al., 2014; Prasloski et al., 2012b). Formalin-fixed human brains yield T_2 distributions similar to those found in vivo, and histopathological studies show strong correlations between MWF and staining for myelin (Laule et al., 2004; Moore et al., 2000). With the development of non-invasive imaging techniques, myelin can be quantified in the human brain (Prasloski et al., 2012b), both cross-sectionally and longitudinally (Lakhani et al., 2016) Work from the Human Connectome Project and others have identified that the primary motor and sensory regions are among the most densely myelinated and most easily delineated in the human brain, allowing for more reliable automatic identification and parcellation of myelinated regions (Glasser et al., 2016; Glasser and Van Essen, 2011; Nieuwenhuys and Broere, 2016). In addition, myelination of corticospinal projections from these regions may vary based on the length of the tract and the size the axon. As such, quantification of corticospinal tract (CST) myelin using in vivo neuroimaging has not been validated to date (Glasser and Van Essen, 2011). Previous work from our group did not reveal a relationship between ipsi- and contralesional CST MWF, measured from the posterior limb of the internal capsule, and motor function or impairment (Borich et al., 2013). In order to limit variability arising from CST tract heterogeneity between individuals with stroke, the current study focused on the most well defined, myelinated regions of interest, located in precentral and postcentral areas.

Recent work has demonstrated that oligodendrocyte precursor cell proliferation and myelin structure are associated with motor learning in rodent models (Gibson et al., 2014; Xiao et al., 2016). In particular, this work emphasized the possibility that functional motor activity may influence myelination of redundant neural pathways and improve conduction velocity via more efficient neural synchrony (Fields, 2015). The current study will extend previous lines of inquiry by exploring the relationship between real-world activity in the upper-extremity to myelination in humans. The ability to use the stroke-affected upper-limb in 'everyday tasks' is cited as a primary goal for individuals living with stroke (Barker and Brauer, 2005; Barker et al., 2007). Monitoring upper-extremity usage after stroke using accelerometers is a low-cost, non-invasive way to measure functional activity and to quantify overall real-world activity (Hayward et al., 2015). Use of the stroke affected upper-limb correlates with long-term motor impairment as greater activity generally results in reduced impairment (Gebruers et al., 2014; Lang et al., 2007; Shim et al., 2014). Identifying relationships between accelerometer based measures of activity and myelination will inform future investigations about the potential specificity of myelin as predictive biomarker for understanding what people can do, via measurement of impairment and function, versus what people actually do in the real-world.

Given the important relationships between white matter, activity and post-stroke impairment as well as the recent advances in imagining techniques, it is imperative to consider the contribution of myelination to post-stroke impairment, function and activity in humans. In order to identify potential differences in myelination based on the level of impairment after stroke, the current study identified 'more impaired (M)' and 'less impaired (L)' groups of participants. Therefore, the primary objective of the current investigation is to understand whether MWF in sensorimotor regions of interest is a biomarker of long term impairment, function or arm use in a population of individuals living with chronic stroke. Furthermore, we sought to identify if there were differences in MWF in sensorimotor regions of interest between individuals classified as 'more impaired' versus those who were 'less impaired'.

2. Methods

2.1. Participants

Twenty-two participants were enrolled in this study. Participants were included if they were between the ages of 45 and 85, had been clinically-diagnosed with a first time, ischemic infarct at least six months (chronic) prior to their enrollment in the study (Table 1). Participants completed a magnetic resonance (MR) screening form and were excluded if they had any strict contraindications to MR scanning. Consent from each participant was obtained according to the declaration of Helsinki; the clinical ethics boards at the University of British Columbia approved all aspects of the study.

2.2. Clinical testing

Upper-extremity motor impairment was quantified using the UE portion of the Fugl-Meyer (FM-UE; Fugl-Meyer et al., 1975) scale (0–66, where higher scores indicate less impairment). Hemiparetic motor function was assessed using the Wolf Motor Function Test (WMFT; Wolf et al., 2001) which consisted of 15 timed movement tasks. For each task, the task rate (repetitions/60 s) was calculated using Eq. (1) in order to be more sensitive to individuals with moderate to severe functional impairment (Hodics et al., 2012). If an individual was not able to complete one repetition of a task within 120 s, then a task rate of zero was recorded.

$$\text{Task rate} = \frac{60(\text{s})}{\text{Performance Rate}} \quad (1)$$

2.3. Activity monitoring

Activity monitoring was conducted using Actical Accelerometers (Philips, Amsterdam, Netherlands). Actical accelerometers have been shown to be reliable indicators of day-to-day activity in individuals with chronic stroke (Rand et al., 2009). A device was placed on each upper-extremity at the wrist crease. Activity monitors were worn continuously for three consecutive days (72 h) following the initial assessment. Data was sampled at 32 Hz and was time-locked into 15 s epochs. For each 15 s epoch, data was rectified and integrated within the Actical Software package and stored as an activity count (AC) which represents the intensity of the activity performed during that interval (Rand et al., 2009, 2010). Activity counts were averaged over the three days. In order to accommodate for the variability of day-to-day activity, an activity count asymmetry ratio (activity-AR) was calculated (Eq. (2)), where an index > 1 indicated greater activity of the ipsilesional limb compared