Spring 5-10-2019

Using Electrophysiology to Investigate Changes in Brain Activation in Individuals with Chronic Stroke

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USING ELECTROPHYSIOLOGY TO INVESTIGATE CHANGES IN BRAIN ACTIVATION IN INDIVIDUALS WITH CHRONIC STROKE

by

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DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
In Linguistics

The University of New Mexico
Albuquerque, New Mexico

May 2019

DEDICATION

In memory of Anne Alexander and Jerry Hudspeth, whose unconditional love and acceptance helped provide the foundation of the woman I am.
In memory of Oliver Ender Russell, you will not be forgotten.

&

In dedication to individuals who have experienced a stroke and their families. Your courage and tenacity inspire me to never give up.

&

In dedication to Lenorah, Matthew, Jackson, Mark, Madison, Piper, Ava, Isabelle, and Lena. Keep your dreams as big as the stars. I can't wait to see how you make this world your own. I love you more than words can express.

ACKNOWLEDGEMENTS

There are so many people who have earned my gratitude throughout this process. I am so happy to have a space to thank everyone. I would like to start by acknowledging and thanking my committee members: Drs. Holly Jacobson, Jill Morford, Rick Arenas, and Jessica Richardson. Thank you for the time and wisdom you have invested in me during this process. I have appreciated your support, encouragement, and belief in me.

I would also like to acknowledge my co-workers and the students with whom I have worked for the past six years. Each of you has helped me grow as a clinician and person. Christie, thank you for always bringing a fresh perspective and a laugh to our meetings. Janet, thank you for all of your help with data collection. I knew that with your care and attention to detail any data you helped with was in good hands! Vic and Isabel – thank you for the many hours long phone calls, evening and weekend Skype work dates, text check-ins, and pet photos to make me smile. You helped keep my sanity intact. I am lucky to have two such incredible friends.

To my family, thank you for encouraging me to always pursue my dreams and then supporting me throughout the process. Thank you for putting up with my stubbornness. I am so grateful for the visits and phone calls. Thank you for providing a space to vent on the bad days and celebrate on the good days.

Jacob, my wonderful spouse. You moved all the way across the country so that I could keep pursuing my dreams. You've single-handedly kept a roof over our heads, kept us fed and clothed, and handled all of the day to day aspects of our life so that I could focus on my PhD. You made me laugh and smile and keep going on the days when all I wanted to do was curl up in a ball and pretend the world did not exist. Our relationship brings me joy daily, and I am so glad that you are my partner in life. Thank you for being so generous with your time and energy. Thank you for your relentless positivity and unwavering faith in me. I love you, and I absolutely could not have done this without you.

And finally, thank you to Jessica. How do I adequately convey the depths of gratitude for a decade of friendship and mentoring? How do I explain the ways you have inspired me? You were the first person to put a face on this vague dream I had of wanting to do research. You helped me see that we are what researchers look like and that being a university professor wasn't just a pipe dream for a southern girl from the middle of nowhere. You have helped me become not just a better researcher, speech-language pathologist, supervisor, and teacher, but more importantly, a better person with more compassion and empathy for others. I am awed by the depth of your commitment to the community and individuals you work with. Thank you, for investing in me, for believing in me, for supporting me. Thank you for including me in your family. I can't wait to see where the next decade of friendship and collaboration takes us!

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ABSTRACT

Many individuals who have experienced a stroke also experience persistent decrements in several domains, such as sensorimotor, language, and cognition. While rehabilitation for these deficits is helpful even decades after a stroke, there is limited information available to determine the most effective pairing of treatment with individual deficits. Further, despite decades of neuroimaging research, our understanding of optimal recovery patterns following stroke is relatively poor. In order to improve outcomes for individuals living with chronic deficits due to stroke, neurophysiological biomarkers corresponding to recovery patterns and treatment response are needed. Electroencephalography (EEG) holds great potential for identifying biomarkers as it directly measures brain activation, and is non-invasive, reliable, replicable, and portable. Further, almost all individuals post-stroke are able to tolerate EEG recording. In addition, different methods of analyzing EEG data allow multiple information streams to be gleaned from a single dataset.

In this study, 27 persons with chronic stroke (PWCS) and 27 neurologically healthy controls completed speech, language, cognitive, and sensorimotor behavioral assessments. Participants also completed two EEG sessions approximately one month apart which included recording of brain activity at rest and during language, cognitive, and motor tasks. Spectral EEG and event-related potential (ERP) analyses revealed significant differences between neurologically healthy controls and PWCS both at rest and during an auditory oddball task. Test-retest reliability measured across a one-month interval varied by group, task, and electrode montages or regions of interest from poor to excellent. The spectral EEG analysis showed changes previously reported during the acute and sub-acute phase of recovery persist into the chronic phase. ERP analysis demonstrated that individuals with a wide range of post-stroke deficits perform significantly differently during a cognitive task. However, no statistically significant differences were observed between healthy controls and this mixed group during language tasks. Finally, reliability findings indicate some tasks and measures may be appropriate for use in determining treatment response. These results provide support for the use of EEG as a biomarker in the chronic phase in a general stroke population. Future research should investigate the utility of EEG in specific subgroups of persons with chronic stroke.

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Chapter 1

Shared Introduction

Stroke is a leading cause of adult disability in the United States and is the only leading cause for which prevalence has increased across the past two decades (US Burden of Disease Collaborators, 2013). Each year, approximately 795,000 individuals in the US experience a stroke, and approximately 650,000 are stroke survivors (Benjamin et al., 2019). While strokes can occur at any age, older individuals are at greater risk of stroke than younger individuals. The higher incidence of stroke in older adults combined with an aging population in the US means stroke prevalence is expected to continue to increase in the coming decades. Stroke carries with it high economic costs. In 2015, the total cost of stroke, in terms of both direct expenses related to medical care and indirect expenses such as wages lost due to disability, was approximately $45 billion. This is expected to more than double by 2035, increasing to approximately $129 billion (Benjamin et al., 2019). Still, these numbers underestimate the burden of stroke, as they only include costs directly related to the individual who had the stroke. Strokes have wide-ranging effects on the family unit as well. Often a spouse or close relative must assume caregiving responsibilities that limit opportunities to work for pay, volunteer, access education, or engage in social and recreational activities (Grawburg, Howe, Worrall, & Scarinci, 2013), further driving up stroke-related costs.

Post-Stroke Impairments

Stroke recovery is generally divided into three phases: acute, sub-acute, and chronic. Variability exists regarding the definition of onset and length of each phase, but among rehabilitation professionals, the acute phase is generally recognized as the period

beginning one day after stroke and extending one to two weeks after the stroke. The sub-acute phase begins after the first or second week and extends up to six months post-stroke. Finally, the chronic phase begins six months to one year after stroke and extends to the individual's death (Bernhardt et al., 2017; Kiran, 2012). A range of functional impairments are observed in the acute phase and contribute to the high cost of stroke. For example, a population study of individuals living in the UK who had a first-time stroke reported the following immediately post-stroke: 26% experienced visual field cuts, 20% experienced visual neglect, >70% experienced upper and/or lower limb motor impairment, ~30% experienced upper and/or lower limb sensory impairment, 45% experienced swallowing impairment, 41% experienced motor speech impairment, 23% experienced language impairment, 48% experienced urinary incontinence, and 44% experienced cognitive impairment (Lawrence et al., 2001). An examination of the number of different impairments and the proportion of individuals experiencing each reveals that many individuals post-stroke experience more than one kind of impairment. Indeed, in this sample, only 6% of individuals had one or two impairments, whereas a staggering 50% experienced 6-10 impairments. It is difficult to determine how comparable these percentages are between the US and UK, as there seems to be no similar population-based study of acute stroke deficits for the US. In addition, much of the information in the literature regarding prevalence of post-stroke deficits in the US is several decades out of date. More recent studies generally do not present results in a way that is comparable to Lawrence and colleague's report.

Individuals who have a stroke experience a great deal of spontaneous recovery in the first six months to one year following their stroke. Despite this, many stroke survivors

do not regain full functioning in all areas of initial impairment, and therefore require continued rehabilitation to reduce the impact of disability. These persistent deficits that last for the remainder of a stroke survivor's life are referred to as chronic impairments. Systematic investigations of the prevalence of multiple chronic post-stroke deficits are lacking, although some studies report the prevalence of a single chronic post-stroke impairment. Depression and other mood disorders are a common consequence of stroke, with 33% - 50% of individuals reporting post-stroke depression (Hackett & Pickles, 2014; Kouwenhoven, Kirkevold, Engedal & Kim, 2011). Cauraugh and Kim (2003) reported 60% of their chronic stroke sample experienced some kind of motor impairment, although prevalence of specific diagnoses varied. When investigating other domains, approximately 33% of stroke survivors experienced impaired hand sensation (Bowden, Lin, & McNulty, 2014), approximately 30% experienced cognitive impairment (Henon et al., 2001; Pohjasvaara et al., 1998), and approximately 30% of stroke survivors experienced chronic aphasia (e.g., Berthier, 2005; Go et al., 2014, Maas et al., 2012; Simmons-Mackie, 2018), a communication disorder that diminishes spoken and/or written language production and/or comprehension abilities. Aphasia results in limitations of activity and participation, poorer quality of life, and higher incidence of depression compared to post-stroke individuals without aphasia matched for social support, well- being, and physical ability (Hilari, 2011; Hilari et al., 2012; Wallace, 2010). Further, aphasia incurs an additional economic cost (above the cost of stroke with other disabilities) in terms of medical treatment (~$2,200) in the first year following stroke (adjusted for 2019 inflation; Ellis, et al., 2012). Individual response to aphasia treatment varies and restoration of communication abilities in the chronic phase is rare.

Despite the documented negative impacts of aphasia on recovery and quality of life, these individuals are often excluded from general stroke research due to their language difficulties.

Optimal Brain Reorganization Post-Stroke

In the healthy brain, the left and right hemispheres are highly interconnected and in constant communication both at rest and during completion of a variety of tasks. Specific brain areas are recognized as necessary (but not sufficient) for completion of particular tasks or processing of stimuli. For example, literate adults develop highly specialized activation of the left fusiform gyrus (which spans occipital and temporal lobes) during word viewing and reading, so that it is now referred to as the "visual word form area" (e.g., McCandliss, Cohen, Dehaene, 2003). This activation is specifically observed as greater in the left than right hemisphere. Specialized activation of the left fusiform gyrus allows for fast and efficient processing of visual word forms independent of case, font, size, and other non-essential visual features such as color. In addition to brain regions being specialized, they are also highly interconnected. Widely distributed functional networks (and not just specialized brain areas) are brought online during tasks. Different regions are able to inhibit activation in the corresponding (or homologous) region in the opposite hemisphere in order to bring online the most efficient network for completing a given task. In regard to the previous example, the left fusiform gyrus inhibits the right homologue during word viewing or reading tasks. Conversely, the right fusiform gyrus inhibits the left homologue during viewing of faces, as this processing has been localized to the right fusiform gyrus (e.g., Kanwisher, McDermott, & Chun, 1997).

There is a long history of studying this inhibition (referred to variously as interhemispheric inhibition, balance, or symmetry) in stroke, specifically in individuals with post-stroke aphasia or motor deficits. (Review of the literature will focus on motor and aphasia research, although interhemispheric inhibition is also being investigated in other domains such as cognition.) A stroke disrupts the natural system of mutual inhibition in the brain, and homologous regions in the opposite hemisphere may restrict the contribution of surviving tissue around the brain lesion (perilesional tissue) that is specialized for a given behavior, potentially leading to less efficient processing. For example, in healthy individuals, left hemisphere frontal, temporal, and parietal areas are primarily responsible for language processing. These areas inhibit right hemisphere homologues during language production and processing. Inhibition is enacted via the corpus callosum, the largest white matter structure in the brain, which connects the two hemispheres. In a normally functioning brain, fibers originating in the left hemisphere (referred to as glutamatergic fibers because they release the neurotransmitter glutamate) travel through the corpus callosum and activate inhibitory interneurons in the right hemisphere. These inhibitory interneurons then reduce activation in right hemisphere homologues. Following damage to left hemisphere language areas, homologous right hemisphere areas receive less, or no, inhibition (due to the death or disconnection of glutamatergic fibers) and may increase their level of activation during language production and processing, bringing online a less efficient language system.

A similar process is observed in the motor cortex following stroke. Research shows that primary motor cortex of the non-lesioned hemisphere exerts much greater inhibition of the motor cortex in the lesioned hemisphere than is observed in healthy

brains. Further, this increased inhibition is related to decrements in performance on motor tasks during both the sub-acute and chronic phases (Murase, Duque, Mazzocchio, & Cohen, 2004; Ward, Brown, Thompson & Frackowiak, 2003). Clinicians have sought to use this knowledge to develop treatment methods for motor recovery (such as constraint induced motor therapy [CIMT]; Kwakkel, Veerbeek, van Wegen, & Wolf, 2015) that leverage our understanding of beneficial and maladaptive brain changes (Xerri, Zenno-Azogui, Sadlaoud, & Sauvajon, 2014). However, despite the large body of research examining brain activation following behavioral rehabilitation (i.e., physical, occupational, or speech-language therapy), there is still no consensus regarding the role of the contralesional hemisphere in stroke recovery (Bertolucci, Chisari, & Fregni, 2018; Turkeltaub et al., 2012), although it is likely to be individualized and dependent on lesion anatomy and size. Further, response to treatment is difficult to predict with current knowledge and pairing treatments with individual deficits is not straightforward.

Measuring Post-Stroke Recovery

Many technologies are available for measuring brain structure and function. Positron emission tomography (PET) and computed tomography (CT) are primarily used in clinical settings, while structural or functional magnetic resonance imaging (sMRI; fMRI), electroencephalography (EEG), and transcranial doppler (TCD) have mixed clinical and research usage. Others, such as near infrared spectroscopy (NIRS) and magnetoencephalography (MEG), are used primarily for research. Each technology has benefits and limitations compared to the others, but all have the potential to provide insight into post-stroke recovery. Despite the wealth of information gained from studies

using these imaging technologies, there is a lack of neurophysiological biomarkers that can improve prognosis and individualization of rehabilitation planning.

Currently, two of the best predictors of stroke recovery are lesion site and size (Stinear & Ward, 2013). Research has shown that individuals with larger lesions experience poorer recovery over time (e.g., Hope, Seghier, Leff, & Price, 2013), as do individuals with right hemisphere strokes (e.g., Aszalos, Barsi, Vitrai, & Nagy, 2002). In contrast, individuals with specific behavioral deficits may exhibit different patterns of recovery. For example, in a sample of individuals with aphasia, posterior left hemisphere lesions were most predictive of poor outcome (Fridriksson, Richardson, Fillmore, & Cai, 2012), while in the motor recovery literature, one of the best predictors of function is the degree of damage to the corticospinal tract (Burke Quinlan, et al., 2014). While structural MRI data such as lesion site and size are strong predictors of overall recovery following stroke, these measures cannot assess the functioning of intact tissue. Indeed, research regarding the role of the right hemisphere in recovery suggest that lesion size is a key factor in whether right hemisphere activation is compensatory or maladaptive. But lesion site and size are not the only variables that ought to be considered when attempting to predict or report on stroke recovery. Previous research has also suggested that intact blood flow in brain regions around the lesion (Richardson et al., 2011) or degree of interhemispheric connection (Burke Quinlan et al., 2014) may also play an important role. Further research into these additional variables may help elucidate the role of the intact brain in recovery.

Task-related fMRI (task-fMRI), such as picture naming or finger tapping while in the scanner, is most commonly used to image recovery and treatment-induced brain

changes (Breier et al., 2007; Davis & Harrington, 2006; Fridriksson, 2010; Fridriksson et al., 2012; Hillis, 2006; Hodics, Cohen, & Cramer, 2006; Leger et al., 2002; Meinzer et al., 2006; Meinzer et al., 2007; Page et al., 2009; Peck et al., 2004; Postman-Caucheteux et al., 2010; Richardson et al., 2012; Rosen et al., 2000; Schaechter et al., 2002; Takahashi et al., 2008; You et al., 2005), but inferences are difficult to make with this clinical population. Blood flow in the brain during task completion (referred to as the hemodynamic response) in healthy controls follows a well-described pattern. Beginning 1-2 seconds after task onset and peaking 4-6 seconds after task onset, there is an increase of blood flow to regions engaged in completing the task (Bandettini et al., 1992). However, the hemodynamic response, upon which MRI signals are based, is altered following stroke and blood flow does not necessarily follow the canonical time pattern (Altamura et al, 2009; Krainik, Hund-Georgiadis, Zysset, & von Cramon, 2005). Analysis of brain activation which relies upon typical blood flow timing assumptions may not adequately characterize brain activation changes in people post-stroke (Bonakdarpour, Parrish, & Thompson, 2007; Richardson et al., 2011; Thompson et al., 2017; Wierenga et al., 2006). Also, individual variability due to error production and/or the differential effort required to complete tasks makes interpretation difficult (Price, Crinion, & Friston, 2006; Veldsman, Cumming, & Brodtmann, 2015).

Task-fMRI research has been useful for confirming that the brain *can* change in individuals with chronic stroke, but current knowledge and the unique characteristics of this population do not allow straightforward testing of brain reorganization hypotheses. Resting state fMRI (rest-fMRI), where participants are asked to rest quietly without performing a task or thinking about anything in particular, may be a promising alternative

to task-fMRI for understanding brain reorganization following stroke. Investigation of resting state networks reveals disruptions not just in areas adjacent to the lesion, but in distributed nodes in the left and right hemisphere (for a review see Rehme & Grefkes, 2013). Additionally, several research teams have identified motor and language-specific networks (Baldassare, Metcalf, Shulman, & Corbetta, 2019; Sandberg, 2017; Thiel & Vahdat, 2015; Vahdat, Darainy, & Ostry, 2014). In motor specific networks, individuals post-stroke show reduced communication among network nodes compared to healthy controls (Bhajaj, Butler, Drake, & Dhamala, 2015; James, Lu, & VanMeter, 2009). Additionally, individuals with aphasia generally have fewer connections and more right-lateralized networks compared to healthy controls (Sandberg, 2017). In a sample of individuals with acute stroke, more right-lateralized networks following stroke correspond to more severe aphasia (Guo et al., 2018). An alarming finding with rest-fMRI (and corroborated with other imaging modalities) is the fact that spared and seemingly healthy perilesional tissue is hypo-connected in people with post-stroke deficits in a way that corresponds directly to severity of those deficits (Chen & Schlaug, 2013; Gleichgerrcht et al., 2016; James et al., 2009; Sandberg, 2017). Still, like task-fMRI, rest-fMRI is an indirect measure of brain activation, complicating the inferences which can be drawn from this modality.

EEG approaches have long been used to study stroke recovery (e.g., Assenza et al., 2013; Cillessen et al., 1994; Cuspineda et al., 2003; de Vos, van Maarseveen, Brouwers, & van Putten, 2008; Dobel et al., 2002; Dubovik et al., 2013; Faught, 1993; Finnigan et al., 2004; Finnigan, Walsh, Rose & Chalk, 2007; Finnigan, Wong, & Read, 2016; Friederici, Von Cramon, & Kotz, 1999; Gorisek et al., 2016; Hagoort, Brown, &

Swaab, 1996; Hagoort, Wassenaar & Brown, 2003; Hensel et al., 2004; Ilvonen et al., 2003; Laganaro, Python, & Toepel, 2013; Leon-Carrion et al., 2009; Nicolo et al., 2015; Petrovic et al., 2017; Pettigrew et al., 2005; Pulvermuller, Mohr, & Lutzenberger, 2004; Schaul, Green, Peyster, & Gotman, 1986; Schleiger et al., 2014; Sheorajpanday et al., 2009; Sheorajpanday et al., 2011; Song et al., 2015; Spironelli & Angrilli, 2015; Spironelli, Angrilli, & Pertile, 2008; Swaab, Brown, & Hagoort, 1997; Szelies, Mielke, Kessler, & Heiss, 2002; ter Keurs, Brown, Hagoort, & Stegeman, 1999). EEG is reliable, replicable and portable, all important factors for use in clinical settings. EEG also has the added benefit of being safe for almost all individuals who have experienced a stroke. Critically, EEG directly measures electrical brain activation via scalp electrodes, providing excellent temporal resolution of activation compared to other modalities. Furthermore, EEG is already used clinically to monitor some patients post-stroke, which would help ease the transition to more widespread use. Clinical EEG systems are designed to output measures online which means the data is quickly available for clinical decision-making.

Finally, EEG findings have been validated against the gold standard of MRI to ensure results are consistent across imaging modalities. Indeed, entire books have been written on the topic of successfully integrating EEG and MRI during research (e.g., Mulert & Lemieux, 2009). Validation specific to persons with stroke has also been conducted. For example, correlations between EEG measures and 1-month outcomes were equivalent to correlations between blood flow in the brain measured by MRI and 1-month outcomes, and outperformed correlations between white-matter structural MRI and 1-month outcomes (Finnigan et al., 2004). At a single timepoint, EEG measures at

ipsilesional and contralesional locations correlated with stroke severity and lesion size (Wu et al., 2016). When examining rest-fMRI and EEG, Deligianni and colleagues (2014) reported that EEG data was significantly better at predicting fMRI data than fMRI data was at predicting EEG. Together, this body of validation work suggests that EEG corresponds strongly with MRI data, and that EEG data provides additional valuable information about brain function beyond what is available through MRI alone.

Due to EEG's reliability, replicability, portability, safety, low-cost, and relationship with gold standard neuroimaging, it is well-suited for use in clinical populations such as stroke, where there is a dire need to better understand optimal recovery patterns in order to provide the most appropriate rehabilitation. In addition, the development of sensitive and reliable neurophysiological biomarkers via EEG may help clinicians make more informed treatment decisions and improve prognosis for individuals with chronic post-stroke deficits. EEG also provides a great deal of flexibility in data analysis, with two commonly used analysis methods (spectral EEG and event-related potential) providing complementary but distinct information. The same data can be subjected to both analytic methods, although that is rarely done for the same population. In the following papers, we will examine both methods of EEG analysis in the same population of healthy controls and people post-stroke. We are including individuals with post-stroke aphasia in our sample (and carefully characterizing their language performance) because aphasia is a relatively common deficit, occurring in approximately one-third of chronic stroke survivors. Unfortunately, much of the general stroke literature actively excludes individuals with aphasia due to reported difficulties with consent, greatly limiting our understanding of how individuals with aphasia recover from stroke,

and whether their experience is similar to or different from individuals with other post-stroke deficits.

Chapter 2

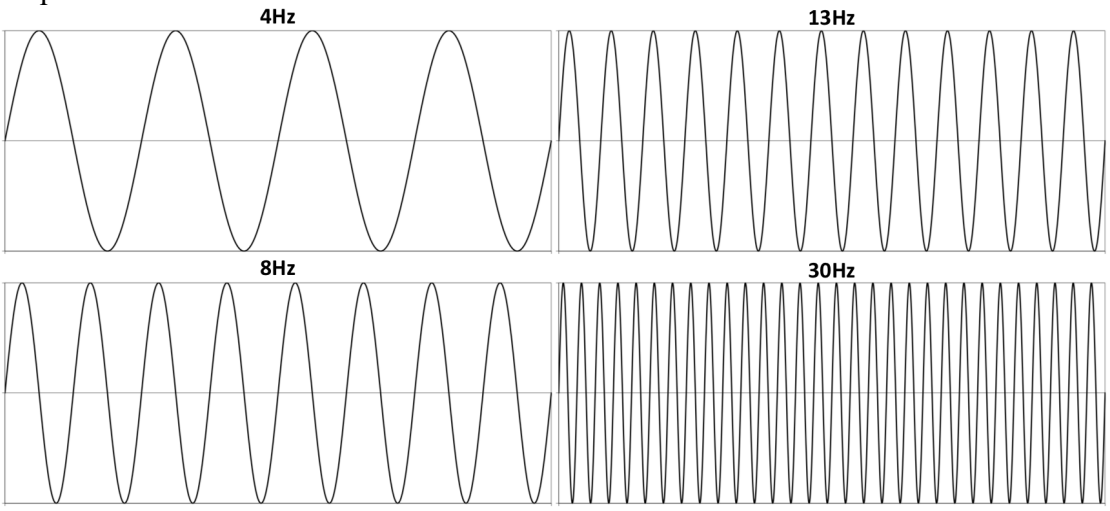
Introduction

Spectral EEG

Neural activity is observed even when individuals are resting quietly and not engaged in a task. Research using rest-fMRI has identified multiple functional networks that engage during on-task behavior, as well as a default mode network which seems to be most active when there is no task to be completed (e.g., Damoiseaux et al., 2006; De Luca et al., 2006; Greicius, Krasnow, Reiss, & Menon, 2003; Rosazza & Minati, 2011). Findings from these investigations demonstrate that functionally related brain regions communicate even when not engaged for task completion. Similar findings have been observed using spectral EEG (sEEG) to measure the rate (or frequency) at which brain regions are activated.

Historically in sEEG analysis, the speed of brain activation has been divided into four frequency bands: delta (1-4Hz), theta (~4-8Hz), alpha (~8-13Hz), and beta (~13-30Hz) (see **Figure 1**). Because populations of neurons and different brain regions carry

Figure 1. Examples of 4Hz, 8Hz, 13Hz, and 30Hz sine waves that demonstrate dividing frequencies between each classic band.



on multiple “conversations” at once, recordings of brain activation will simultaneously show activity in each of the frequency bands. Power is calculated to quantify the amount of activity occurring in a frequency band. To calculated power, a fast Fourier transform (FFT) is used to decompose the signal into amplitude at each frequency, and the amplitude value is squared. Then, segments of activity are summed to determine the power in a frequency band. In neurologically healthy adults, slow wave delta is associated with sleep states and theta activity is associated with rest and inhibition of unrelated brain regions during a task. Alpha and beta activation are higher frequency or fast wave activation. Alpha activity is associated with relaxed states while beta activity is associated with on task behaviors. For individuals in the acute and sub-acute phases post-stroke, slow wave activity is increased relative to fast wave activity, even when patients are awake and engaged in a task. sEEG can also be used to measure coherence, or the strength of communication between brain areas, by determining the similarity of power in different regions (Ruchkin, 2005). The more strongly two regions are connected, the larger the correlation between their measured power values, and the greater the coherence between the regions.

sEEG Corresponds to General Functional Recovery after Stroke

As noted above, EEG has been widely used to study stroke recovery in the acute (1 day to 1-2 weeks) and sub-acute (1-2 weeks to 3-6 months) phases (for a review, see Finnigan & van Putten, 2013). A wide range of sEEG measures derived from resting-state EEG recordings have been reported, from Z-scores of the frequency bands, to relative power, to measures of the relationship between activation in network nodes or hemispheres (coherence). Across studies, sEEG variables measured shortly after stroke

onset are correlated with functional outcomes (e.g., modified Rankin Scale [mRS; van Swieten et al., 1988], Canadian Neurological Scale [CaNS; Cote et al., 1989], NIH Stroke Scale [NIHSS; Goldstein, Bertels, & Davis, 1989]) in the sub-acute and chronic phases (de Vos et al., 2008; Dubovik et al., 2013; Finnigan et al., 2007; Leon-Carrion et al., 2009; Nicolo et al., 2015; Sheorajpanday et al., 2011). That is, increased delta and/or theta activity, decreased alpha and/or beta activity, or reduced coherence is related to more severe impairments in motor skills, cognition, and language. A few studies have reported that sEEG measures are equally or more strongly related to functional outcomes than behavioral measures such as the Rankin and modified Rankin Scale (mRS), Canadian Neurological Scale (CaNS), or NIH stroke scale (NIHSS) scores at onset, both within the first 72 hours (Cuspineda et al., 2003), and at one year post-stroke (Cillessen et al., 1994).

Given these results confirming a relationship between sEEG measures and functional recovery, Assenza and colleagues (2013) sought to determine if sEEG measures could predict "effective recovery" following stroke in a sample of 42 patients (20 healthy controls were enrolled for comparison). Effective recovery was calculated for each individual as the change in NIHSS score from baseline (T0) to 6 months after stroke (6mo) divided by the difference between control NIHSS scores and the individual's NIHSS score at stroke onset ($ER = NIHSS_{T0} - NIHSS_{6mo}/NIHSS_{T0} - NIHSS_{Control}$). Regression analysis revealed two predictors of recovery at six months: delta power in the contralesional hemisphere and baseline NIHSS score. Further analyses revealed that increased delta power in the contralesional hemisphere was associated with a decrease in

inter-hemispheric coherence (i.e., a weakening of the relationship between activation in the left hemisphere and activation in the right hemisphere).

Despite the demonstrated relationship between sEEG changes and recovery, the large number of sEEG measures used limits generalizability across studies. A recent study sought to determine which measures corresponding to functional recovery most accurately classify participants as healthy controls or persons with stroke (PWS) in the sub-acute phase (Finnigan et al., 2016). The measures examined included power in delta, theta, alpha, and beta frequency bands relative to total power across the spectrum (1-30Hz), delta/alpha ratio (DAR), delta+theta/alpha+beta ratio (DTABR) (sometimes also referred to as the power ratio index, PRI; e.g., Finnigan et al., 2007; Leon-Carrion et al., 2009), and delta+theta/total power ($Q_{slowing}$). In a sample of 28 neurologically healthy controls and 18 individuals in the acute phase post-stroke, all sEEG measures were significantly different between the two groups. Consistent with previous findings, relative delta, relative theta, DAR, DTABR, and $Q_{slowing}$ were significantly greater in individuals who had experienced a stroke than in healthy controls. Relative alpha and beta power showed the opposite pattern. Despite these significant differences, DAR was the only measure which classified individuals into the correct group with 100% accuracy, with a reported cut-off of 3.7. In their sample, any individual with a DAR greater than 3.7 had experienced a stroke, and any individual with a DAR less than 3.7 had not.

sEEG Corresponds to Early Recovery of Specific Stroke-Induced Deficits

In addition to informing on the prognosis of overall stroke recovery, sEEG may provide prognostic value for the recovery of specific stroke-induced deficits such as aphasia, cognition, or motor impairments in the acute and sub-acute phases. For example,

increased left hemisphere frontal theta and decreased left hemisphere occipital alpha were predictive of improvements in language abilities in a group of 23 patients with aphasia eight weeks after stroke (Szelies et al., 2002). Additionally, during the first year of stroke recovery, decreased left hemisphere slow wave delta activity corresponded to language recovery, but similar decreases were not observed in the second year following stroke. This was interpreted as confirmation that spontaneous recovery was not a factor after the first year (Hensel et al., 2004). In a study examining working memory in individuals with Broca's aphasia, two networks (one theta and one gamma) implicated in working memory were shown to be disrupted (Gorisek et al., 2016). Importantly, the gamma network (which the authors hypothesized was related to the phonological loop of working memory) was more severely impacted than the theta network, which was also consistent with the speech and language difficulties observed in this population. Similar investigations examining recovery of cognitive functions in individuals without aphasia have also demonstrated the prognostic value of sEEG. In particular, frontal delta and whole-head alpha power are predictive of cognitive outcomes in the sub-acute phase of stroke (Schleiger et al. 2014), and sEEG values may not return to baseline even when behavioral performance does (Petrovic et al., 2017).

sEEG in the Chronic Phase of Recovery

There is clear and consistent evidence that sEEG measures correspond to both general and deficit-specific recovery in the acute and sub-acute phases, but far less research has been performed regarding these measures and their relationship to behavioral deficits in the chronic phase of recovery, or their sensitivity to measuring response to treatment. There is some evidence that sEEG differences observed in the

acute and sub-acute phases are maintained into the chronic phase. For example, a study examining the relationship between perceived daytime sleepiness and sEEG in patients with chronic left or right hemisphere stroke revealed greater power in delta and theta bands compared to healthy controls which was not related to perceived sleepiness (Herron et al., 2014). Similarly, Spironelli, Manfredi, and Angrilli (2013) found in a sample of 11 individuals with chronic nonfluent aphasia that the strength of high beta band activity (21-28Hz) during language tasks was greater in right hemisphere central electrodes than left hemisphere central electrodes, a reversal of the pattern seen in healthy controls. Additionally, reduced beta activity was observed in posterior left hemisphere electrodes. Unlike controls, individuals with aphasia demonstrated greater high beta activity in left hemisphere frontal electrodes, suggesting that reorganization of language processing relies greatly on anterior regions, at least in individuals with mild nonfluent aphasia. Given the differences in spectral power and coherence observed in the acute and sub-acute phase, and that these measures are related to functional recovery, it is reasonable to suspect that sEEG in the chronic phase could prove useful as a diagnostic tool or as a biomarker of treatment response.

sEEG to Measure Treatment Response

Some researchers have examined sEEG before and after rehabilitation, either in the sub-acute or chronic phase (Rozelle & Budzynksi, 1995; Stojanovic et al., 2013; Wu et al., 2015). An early single case study of an individual with chronic post-stroke aphasia investigated the use of sEEG as a biofeedback method and examined its impact on functional outcomes (Rozelle & Budzynski, 1995). Following biofeedback training, the

participant showed significantly less slow wave activity, and improvements were observed in speech, language, motor, mood, and cognitive domains.

More recently, two studies have investigated treatment response; one in a sample of individuals with motor deficits (Wu et al., 2015), and one in a sample of individuals with aphasia (Stojanovic et al., 2013). In a study of 12 individuals with upper limb motor weakness following stroke, Wu and colleagues (2015) found that prior to treatment, connectivity of the primary motor cortex in the lesioned hemisphere accounted for 78% of the variance in functional outcomes. Participants completed a course of 28 days of intensive motor rehabilitation, and the connectivity of primary motor cortex was a good measure of gains, accounting for ~60% of the variance. Stojanovic and colleagues (2013) compared the hemispheric and regional symmetry in 32 individuals with aphasia before and after treatment. Prior to treatment, hemispheric and regional asymmetry were increased, and variability was decreased, compared to healthy controls. Following treatment the differences between groups was significantly decreased, but only for individuals who demonstrated good recovery. Taken together, these studies provide preliminary evidence that sEEG variables may be useful in prognosis and measuring treatment response. However, these studies were completed in the sub-acute phase, when spontaneous recovery may still be ongoing. Therefore, it is possible that the sEEG variables measured here were tracking spontaneous rather than treatment-induced recovery.

Clinical Utility of Biomarkers

An important step in the translation of sEEG measures from research to clinical practice is ensuring they possess adequate psychometric properties. Key psychometric

features for EEG normative data development include selecting an appropriate control sample and establishing the reliability of measures over time (Gordon et al., 2005; Prichep, 2005). In addition, normative data must be reported with sufficient detail to fully describe the sample (Mitrushina, Boone, Razani, D'Elia, 2005). Despite the large number of studies that report analyses with sEEG variables, few report the descriptive features of the data with enough detail for readers to judge the adequacy of the data.

However, there is a long history of investigating variability in EEG and sEEG, with the majority of research focusing on variability in children, since maturation causes significant changes in brain function (e.g., Fein et al., 1983; Fein et al., 1984; Gasser, Bacher, & Steinberg, 1985; Matousek & Peterson, 1973a, b; van Dis et al., 1979). Investigations into sEEG variability in adults have also been conducted, and generally reveal good stability for healthy populations, with greater reliability for spectral power measures than coherence measures (Corsi-Cabrera, Solis-Ortiz, & Guevara, 1997; Gudmundsson et al., 2007; Kondacs & Szabo, 1999; Oken & Chiappa, 1988; Salinsky, Oken, & Morehead, 1991; Suarez-Revelo et al., 2015). The electrode montage (i.e., combination of electrodes) can have a significant impact on reliability, especially for coherence measures. These results are promising as they indicate that reliable norms can be established for sEEG measures. However, for these measures to be clinically useful, acceptable specificity and test-retest reliability must be demonstrated for specific patient populations. Despite the fact that no information regarding test-retest reliability is available for individuals post-stroke in any recovery phase, several studies have compared sEEG measures across time (e.g., Rozelle & Budzynksi, 1995; Stojanovic et al., 2013; Wu et al., 2015). Defining specificity and reliability of sEEG measures post-

stroke is critical to ensuring appropriate application of these measures and preventing research waste (for a discussion of research waste see Ioannidis et al., 2014).

Purpose of the Study

The long-term goal of this research is to establish a sensitive biomarker that would allow targeted pairing of rehabilitation to deficits and would improve diagnosis and prognosis of chronic stroke-induced deficits. Currently, there are several barriers preventing the translation of sEEG from research to clinical practice. First, despite the existence of large databases of sEEG measures in controls and the utilization of these databases for comparisons with other neurologically disordered populations (e.g., ADHD/ADD, mental health disorders, traumatic brain injury), comparisons of healthy controls and individuals chronically post-stroke are lacking. Furthermore, there is limited evidence regarding the reliability and stability of sEEG measures in older controls and individuals in the chronic phase post-stroke. The current study aims to address these barriers by pursuing the following specific aims:

1. Identify differences in spectral power and coherence between individuals in the chronic phase post-stroke and neurologically healthy controls.
2. Define intra- and inter-individual variability of spectral power and coherence measures in individuals in the chronic phase post-stroke and neurologically healthy controls.

Methods

Participants

Healthy Controls

Twenty-seven (17 female, 10 male) healthy individuals participated in this study (**Table 1**). Participants were screened to ensure no history of neurological disease or injury that might affect brain function. Potential participants with a diagnosis of significant psychiatric mood disorders were excluded, but individuals with mild depression and anxiety were allowed to participate, as many individuals with chronic stroke also experience depression and anxiety. Participants completed the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), and if bi- or multi-lingual, the Language Experience and Proficiency Questionnaire (LEAP-Q; Marian, Blumenfeld, & Kaushanskaya, 2007). All healthy control participants were right-handed. Seven reported speaking at least one other language, including French, Spanish, Italian, and German. No control participants reported learning another language prior to English, and all reported English as their primary language at the time of participation. The average age of participants was 63 years (*SD* = 13.2 years). Control participant ages ranged from 22 to 88 and were selected to match persons with stroke. The average education was 16.9 years (*SD* = 2.6). Participants completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), Wechsler Adult Intelligence Scales - Picture Completion subtest (WAIS-PC; Wechsler, Coalson, & Raiford, 2008), Discourse Production Test (DPT; MacWhinney, Fromm, Forbes, & Holland, 2011), aprosodia battery (AB; based on Ross & Monnot, 2011), subtests of the Apraxia Battery for Adults - 2 (ABA-2; Dabul, 2000), and an in-house sensorimotor assessment including

Table 1. Demographics for neurologically healthy controls and persons with stroke.

	Healthy Controls
Sex	17 Female; 10 Male
Age (years)	63 (±13) *Range: 22-88*
Education (years)	17 (±3) *Range: 12 - 22*
Handedness	27 Right; 0 Left
Bi/Multilingual	7
	Persons with Stroke
Sex	10 Female; 17 Male
Age (years)	57 (±14) *Range: 25-87*
Education (years)	15 (±3) *Range: 7 - 22*
Handedness	27 Right; 0 Left*
Bi/Multilingual	3
Number of Strokes	1.4 (±1) *Range: 1 - 5*
Time post onset in months (since most recent stroke)	72 (±71) *Range: 12 - 275*
Lesioned Hemisphere	20 Left; 7 Right
Aphasia Diagnosis	13
Cognitive Deficit†	14
Sensorimotor Deficit	20

*All PWS were right-handed prior to their stroke. Due to motor impairment, some participants used their left hand at the time of the study.

†Two participants did not complete cognitive testing due to withdrawing from the study and fatigue.

sensory perception, proprioception, range of motion, and muscle tone (**Table 2**). Testing was completed to ensure participants' performance was within the range of neurologically typical individuals. Participants completed two sessions of EEG recording, approximately one month apart. Three participants were unable to complete the follow-up EEG due to changes in schedules; these participants are included in the normative data set and comparison with participants with stroke but are not included in the reliability analysis.

Persons with Chronic Stroke

Twenty-seven (10 female, 17 male) persons who had experienced one or more strokes also participated in this study (**Table 1**; referred to as persons with chronic stroke, PWCS). We included participants with multiple strokes to ensure that our results are maximally applicable to the general rehabilitation population served by practicing therapists, as one of the strongest risk factors for stroke is a history of prior stroke. Seventeen individuals experienced left hemisphere stroke, 7 experienced right hemisphere stroke, and 3 experienced left and right hemisphere strokes. (Participant reporting of stroke location was confirmed via medical records, CT, or MRI scans when available). Thirteen individuals were diagnosed with aphasia, 14 had cognitive impairment, and 20 had sensory and/or motor deficits (**Table 2**). All participants were at least one-year post-stroke to ensure that spontaneous recovery was not a factor in the reliability analysis. Participants completed the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), and if bi- or multi-lingual, the Language Experience and Proficiency Questionnaire (LEAP-Q; Marian, Blumenfeld, & Kaushanskaya, 2007). All stroke participants were right-handed prior to their stroke, although many individuals relied on

the left hand after their stroke due to motor impairments. Three participants with stroke reported speaking more than one language (Spanish and Azteca) and one participant reported Spanish as their first language, although English was the primary language for all participants at the time of testing and had been for many years. The average age of PWCS was 56.6 (SD = 14.2 years). PWCS ages ranged from 25 to 87. Average education was 15.2 years (SD = 3.3 years). PWCS completed the same assessments as healthy controls in addition to the Western Aphasia Battery - Revised (WAB-R; Kertesz, 2006), Boston Naming Test (BNT; Kaplan, Goodglass & Weintraub, 2001), and Discourse Comprehension Test (DCT; Brookshire & Nicholas, 1997). Participants completed two sessions of EEG recording, approximately one month apart. One participant was unable to complete the follow up EEG recording due to a change in schedule. As with controls, this participant is included in all analyses except reliability.

EEG Recording

EEG data was recorded from 64 active electrodes placed in an elastic cap according to the 10-10 International system of classification. The ground electrode was located at Fpz with the reference electrode at CPz. Eye movement was recorded via vertical electro-oculography using paired electrodes placed above and below the left eye, while heart rate was recorded via electrodes placed on the left and right collarbones. Data were recorded on a BrainVision actiCHamp system with a 500Hz sampling rate and online bandpass filtering from .01 - 100Hz. Participants were seated in front of a computer in a dimly lit room. Resting-state EEG was recorded for two minutes with eyes open (*eyes open rest*) and two minutes with eyes closed (*eyes closed rest*). During the eyes-open recording, participants were asked to fixate on a white cross presented on a

Table 2. Test scores for healthy controls and persons with chronic stroke

			Control	PWCS
Sensori-Motor	**Sensory**	Palm Sensation (2)	2 (+/- 0)	1.7 (+/- 0.6)
		Proprioception (11)	10.9 (+/- 0.2)	9 (+/- 3.3)
	Range of Motion (ROM); Strength	Left Hand Function (6)	6 (+/- 0)	5.8 (+/- 0.7)
		Right Hand Function (6)	6 (+/- 0)	5.1 (+/- 1.7)
		Left ROM (199)	197.2 (+/- 3)	150 (+/- 72.4)
		Right ROM (199)	197.5 (+/- 1.9)	137.7 (+/- .72.3)
	Fine Motor; Coordination	Left Index Finger Tap	49.3 (+/- 8.3)	40.8 (+/- 14.5)
		Right Index Finger Tap	53.2 (+/- 8.8)	36.5 (+/- 20.2)
		L Index/Middle Finger Tap	45.5 (+/- 18.2)	31.5 (+/- 15.9)
		R Index/Middle Finger Tap	49.5 (+/- 15.9)	26.7 (+/- 21.9)
		L/R Index Finger Tap	59.1 (+/- 15.1)	30.5 (+/- 26.6)
		L Foot Tap	27.6 (+/- 8.7)	29.6 (+/- 7.5)
		R Foot Tap	36.4 (+/- 7.5)	27.5 (+/- 11.3)
		L/R Foot Tap	47.8 (+/- 10)	37..4 (+/- 17.3)
Cognitive		RBANS	97.3 (+/- 13)	71.5 (+/- 19.2)
		WAIS - PC	13 (+/- 3.1)	9.6 (+/- 4)
Emotion	**Aprosodia Battery - Reception**	Word ID (12)	10.88 (+/- 1.2)	8.7 (+/- 2.8)
		Monosyllabic ID (12)	10.2 (+/- 1.1)	8.1 (+/- 2.1)
		Asyllabic ID (12)	9.16 (+/- 2.1)	6.6 (+/- 2.9)
		Facial Expression (14)	12.6 (+/- 1.22)	10.8 (+/- 2.2)
		Verbal Scenario (14)	12.5 (+/- 1.3)	10.6 (+/- 2.8)
		Attitude (20)	16.2 (+/- 2.2)	15 (+/- 2.5)
	- Expression	Emotion Semantics (20)	19.8 (+/- 0.4)	18 (+/- 2.2)
Language	**Main Concept (MC) Analysis**	MC Composite (216)	127.5 (+/- 20.5)	87.7 (+/- 49.8)
		Accurate/Complete (72)	35 (+/- 7.2)	22.4 (+/- 14.9)
		Accurate/Incomplete (72)	4.5 (+/- 2.5)	4.6 (+/- 2.9)
		Inaccurate/Complete (72)	6.5 (+/- 3.3)	5.1 (+/- 3.3)
		Inaccurate/Incomplete (72)	0.5 (+/- 0.9)	0.8 (+/- 1.2)
		Absent (72)	25 (+/- 7.3)	33.6 (+/- 17.6)
	Motor Speech	Increasing length	.1 (+/- 0.2)	2.52 (+/- 2.9)
		Limb/oral apraxia (50)	50 (+/- 0)	47.9 (+/- 2.9)
		Multiple Repetition (30)	29.8 (+/- 0.7)	26.3 (+/- 7.1)
		WAB-R-AQ (100)		84.9 (+/- 17.9)
		BNT (60)		45.2 (+/- 15.7)
	Discourse Comprehension	Main Idea – Total (12)		10.9 (+/- 1.73)
		Detail – Total (12)		9.3 (+/- 2.2)

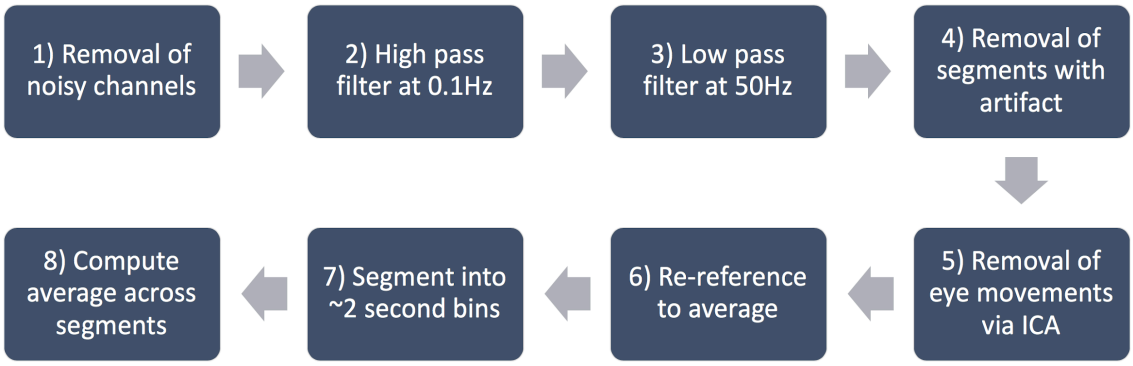
RBANS – Repeatable Battery for the Assessment of Neuropsychological Status; WAIS-PC – Weschler Adult Intelligence Scales – Picture Completion; WAB-R-AQ – Western Aphasia Battery - Revised – Aphasia Quotient; BNT – Boston Naming Test

black background to limit eye movement artifacts. Participants also completed cognitive, language, and motor tasks, but the discussion here is limited to the resting state data.

Data Processing

Standard offline pre-processing (see **Figure 2**) using BrainVision Analyzer 2.1 was conducted to ensure adequate data quality. First, noisy channels were identified and discarded through visual inspection. Specifically, electrodes were examined for spike

Figure 2. Pre-processing steps carried out in BrainVision Analyzer 2.1.



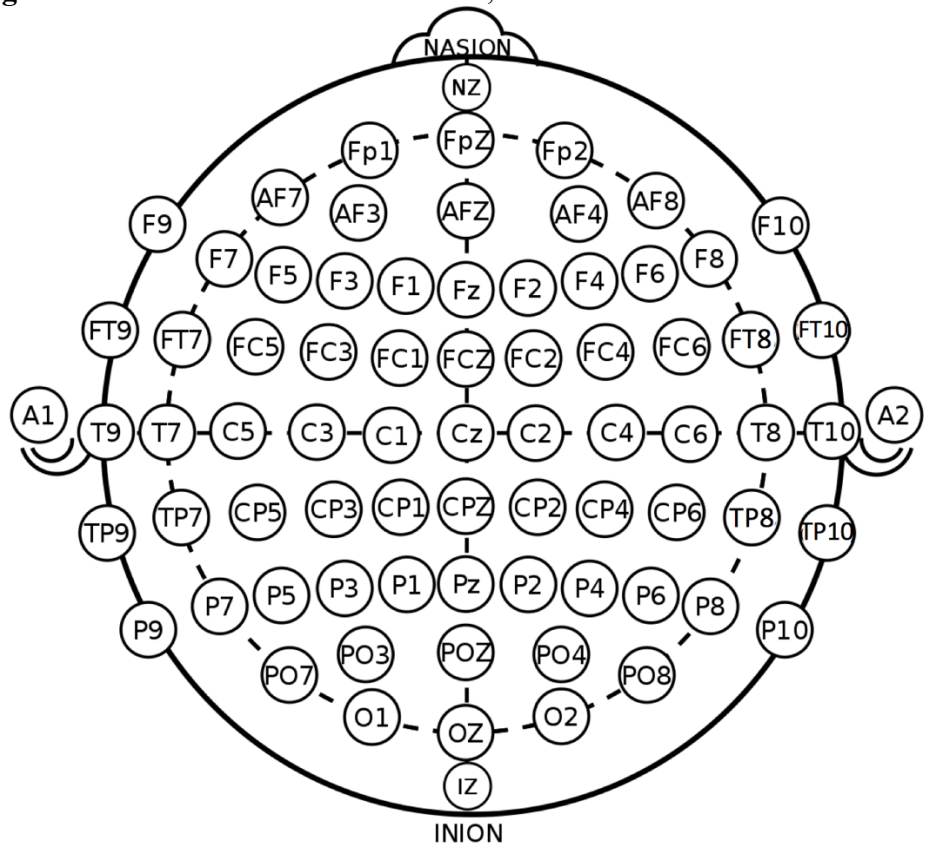
artifacts and high frequency electrical noise which is often due to poor contact between the electrode and scalp (e.g., Finnigan et al., 2007). The following data processing steps were conducted as described by Finnigan, Wong, and Read (2016). Next, data were high (.5Hz) and low (40Hz) pass filtered using infinite impulse response zero-phase shift Butterworth filters to minimize distortion and preserve phase information (Hamming, 1998; Oppenheim, 1999). After filtering, bad segments (i.e., muscle activity) were manually rejected and independent components analysis was conducted to remove eye movement artifacts (Makeig, Bell, & Jung, 1996). Data were then epoched into 2048ms bins and epochs with data values greater than +/-100 microvolts and/or changes in value greater than +/-25 microvolts were rejected. For both neurologically healthy controls and PWCS, no more than 20% of data in a given channel was rejected. Data were then

subjected to a fast Fourier transform (FFT) with Hanning window and tapering at the beginning and end of the window totaling 10% of the epoch length.

Following processing, the absolute sum of spectral power in the four classic frequency bands (delta: 1-4Hz; theta: 4.5-7.5Hz; alpha: 8-13Hz; beta: 13.5-30Hz) was calculated, as well as the absolute sum of total spectral power from 1-30Hz. Relative power was then calculated as absolute power in each frequency band divided by absolute power in the full spectrum (as in Finnigan et al., 2016). Commonly reported ratios were calculated, including delta/alpha ratio (DAR; Claassen et al., 2004), delta+theta/alpha+beta ratio (DTABR; Sheorajpanday et al., 2011), and delta+theta/total spectral power ($Q_{Slowing}$; Finnigan et al., 2016; Lodder & Van Putten, 2013). All measures were calculated for each electrode separately, then averaged across electrodes. Calculations were performed for the following electrode montages: whole brain (all 64 electrodes), clinical (19 electrodes corresponding to 10-20 International system locations), left hemisphere (excluding midline electrodes), right hemisphere (excluding midline electrodes), anterior (excluding all C*n* electrodes), posterior (excluding all C*n* electrodes), left hemisphere language (including F7, FT7, FC5, T7, C5,TP7, CP5, P5), right hemisphere language (including F8, FT8, FC6, T8, C6,TP8, CP6, P6), motor (including FC5, FC3, FC1,FCz, FC2, FC4, FC6, C1, Cz, C2), and cognitive (including Fp1, AF3, AF7, F7, AFz, Fpz, AF4, AF8, F8). See **Figure 3** for electrode locations and labels. These montages have been previously reported in the literature or were of interest because they correspond to common chronic post-stroke deficits. Electrodes for the language, motor, and cognitive networks were selected as the electrodes that overlay brain regions implicated in each behavior based on Koessler and colleagues' findings

(2009). Inter-hemispheric coherence was calculated for the following pairs: 1) left hemisphere - right hemisphere, 2) left hemisphere language - right hemisphere language, 3) anterior left hemisphere – anterior

Figure 3. Electrode locations and labels, as viewed from above the head.



right hemisphere (excluding midline and C*n* electrodes), and 4) posterior left hemisphere - posterior right hemisphere (excluding midline and C*n* electrodes). Intra-hemispheric coherence was calculated for the following pairs: 1) anterior left hemisphere - posterior left hemisphere (excluding C*n* electrodes), and 2) anterior right hemisphere - posterior right hemisphere (excluding C*n* electrodes).

Data Analysis

All statistical analyses were conducted using SPSS. First, descriptive statistics (mean, median, standard deviation, range, skew, and kurtosis) were calculated for the control and stroke participant groups and normality was assessed using skew and

kurtosis. Student's t-tests to compare differences between groups were planned. While many variables reported here violate the assumption of normality, previous research has shown parametric statistics such as the t-test to be robust to violations of normality (using Bradley's definition of robustness where deviation from $p = .05$ is $\leq \pm.005$; 1978). Simulation studies have demonstrated the robustness of the t-test in the face of non-normal distributions when the absolute value of skew (the spread of the data) is less than 2, and the absolute value of kurtosis (the "peakiness" of the data) is less than 9 (Boneau, 1960; Bradley, 1982; Posten, 1978; Schmider et al., 2010). Data with skew or kurtosis outside the range for which t-tests are robust were assessed using the Mann-Whitney U test. Several comparisons with and without acceptable skew and kurtosis values were calculated with both t-tests and Mann-Whitney U tests. Results showed that the statistical significance of comparisons was dependent on the use of the most appropriate statistical test, so we did not default to the use of a single test with our data. This is consistent with previous research (Herron et al., 2014; Sheorajpanday et al., 2009; Hensel et al., 2004; Nolfe et al., 2006). Homogeneity of variance was assessed using the Levene's test. For variables that violated the homogeneity of variance assumption, Welch's t-tests were used (Ruxton, 2006). Between-group comparisons were conducted using the data from the first recording session. Effect size calculations (Cohen's *d* for t-tests and η^2 for Mann-Whitney U-tests) were conducted for all comparisons, and medium to large effects are reported as they are likely to correspond to behaviorally relevant between-group differences. Cohen's *d* and η^2 have a different range of possible values, so for ease of interpretation, both the numeric value and commonly accepted estimates of effect size (small, medium, or large) are reported (Cohen, 1988). Holm-Bonferroni correction for

multiple comparisons (Holm, 1979) was used to reduce the chance of spurious significant differences. Coherence was calculated using Pearson correlations.

Finally, the reliability of measures for which statistically significant group differences were observed was calculated between sessions one and two via intra-class correlations (ICC; Koo & Li, 2016). ICCs are widely used to evaluate the psychometric properties of newly developed assessment instruments, as well as intra- and inter-rater reliability, depending on the specific test parameters selected. The interpretation of the ICCs conducted for this study differ from the more commonly known Spearman and Pearson correlations. A Spearman or Pearson correlation is used to assess how strongly related two variables are with each other. This does not require that the variables be similar in value, only that the values change together in a predictable, linear manner. However, the ICCs conducted here assessed the exactness of the match between, for example, whole brain relative delta power at session one and whole brain relative delta power at session two during eyes closed rest. The closer these values are to each other, the stronger the correlation, and the more stable the measure over time. For readability, only the point estimates are reported in the text; however, 95% confidence intervals are reported in tables to allow readers a more nuanced interpretation of reliability.

Results

Eyes Open Rest

Descriptive Statistics

Full descriptive statistics for each sEEG measure and montage of interest are reported in Appendix A (**Tables A1-A2**). For descriptive statistics only, the whole brain montage is the only montage reported in the text in order to improve readability. The

whole brain montage was chosen since whole brain values are most frequently reported in the literature. Mean relative delta power was 0.386 (*SD* = .092) in controls and 0.354 (*SD* = 0.115) in PWCS. Mean relative theta power was 0.114 (*SD* = 0.025) in controls and 0.168 (*SD* = .094) in PWCS. Mean relative alpha power was 0.151 (*SD* = 0.054) in controls and 0.185 (*SD* = 0.098) in PWCS. Mean relative beta power was 0.285 (*SD* = .089) in controls and 0.218 (*SD* = .098) in PWCS. Mean DAR was 3.236 (*SD* = 1.321) in controls and 3.05 (*SD* = 2.118) in PWCS. Mean DTABR was 1.399 (*SD* = 0.601) in controls and 1.897 (*SD* = 1.386) in PWCS. Mean $Q_{slowing}$ was 0.491 (*SD* = 0.106) in controls and 0.515 (*SD* = 0.141) in PWCS.

Between-Group Comparison

Inspection of skew and kurtosis revealed skew values greater than +/-2 for all relative theta power montages, so Mann-Whitney U tests were used for theta power rather than t-tests. Consistent with the mean and standard deviations reported above, no significant differences were observed between neurologically healthy controls and PWCS for relative delta power, relative alpha power, delta/alpha ratio, delta+theta/alpha+beta ratio, and $Q_{slowing}$ (see **Figure 4**; **Table 3**). After correcting for multiple comparisons,

Figure 4. Time frequency plot displaying delta, theta, alpha and beta power for neurologically healthy controls (left) and persons with chronic stroke (right) during *eyes open rest*.

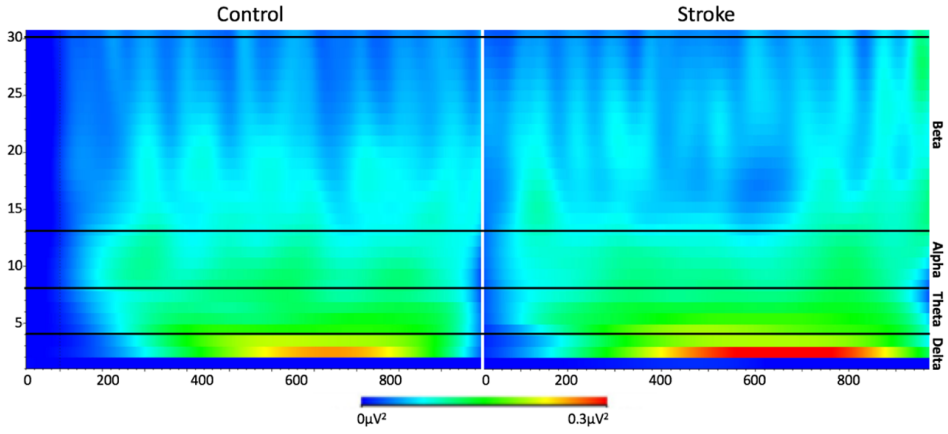


Table 3. Test statistic, p-value, and effect size for between group comparisons during *eyes open rest*. Comparisons that survived correction for multiple comparisons are bolded. Comparisons that were not statistically significant but showed a medium or large effect size are italicized.

	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Whole Brain	$t = 1.121$ $p = 0.267$ $d = 0.307$	*$U = 211$* *$p = 0.013$* *$\eta^2 = 0.119$*	$t = -1.543$ $p = 0.131$ $d = 0.426$	*$t = 2.625$* *$p = 0.011$* *$d = 0.721$*	$t = 0.385$ $p = 0.702$ $d = 0.105$	$t = -1.685$ $p = 0.101$ $d = 0.466$	$t = -0.626$ $p = 0.534$ $d = 0.171$
Left Hemisphere	$t = 1.017$ $p = 0.314$ $d = 0.279$	*$U = 204$* *$p = 0.009$* *$\eta^2 = 0.132$*	$t = -1.456$ $p = 0.153$ $d = 0.402$	*$t = 2.604$* *$p = 0.012$* *$d = 0.715$*	$t = 0.416$ $p = 0.679$ $d = 0.114$	$t = -1.783$ $p = 0.083$ $d = 0.493$	$t = -0.746$ $p = 0.459$ $d = 0.206$
Right Hemisphere	$t = 0.970$ $p = 0.337$ $d = 0.266$	*$U = 241$* *$p = 0.05$* *$\eta^2 = 0.074$*	$t = -1.583$ $p = 0.122$ $d = 0.437$	*$t = 2.289$* *$p = 0.026$* *$d = 0.628$*	$t = 0.175$ $p = 0.862$ $d = 0.048$	$t = -1.458$ $p = 0.154$ $d = 0.403$	$t = -0.503$ $p = 0.617$ $d = 0.138$
Anterior	$t = 1.222$ $p = .227$ $d = 0.335$	*$U = 228$* *$p = 0.029$* *$\eta^2 = 0.092$*	$t = -1.307$ $p = 0.199$ $d = 0.361$	$t = 1.588$ $p = 0.118$ $d = 0.335$	$t = 0.200$ $p = 0.842$ $d = 0.055$	$t = -1.434$ $p = 0.160$ $d = 0.396$	$t = -0.298$ $p = 0.767$ $d = 0.082$
Posterior	$t = 1.157$ $p = 0.253$ $d = 0.317$	***U* = 189** ***p* = 0.004** ***η^2* = 0.160**	$t = -1.627$ $p = 0.112$ $d = 0.449$	***t* = 3.329** ***p* = 0.002** ***d* = 0.915**	$t = 0.432$ $p = 0.668$ $d = 0.118$	$t = -1.794$ $p = 0.082$ $d = 0.496$	$t = -0.771$ $p = 0.444$ $d = 0.211$
LH – Language	$t = 0.925$ $p = 0.359$ $d = 0.254$	*$U = 241$* *$p = 0.05$* *$\eta^2 = 0.074$*	$t = -1.343$ $p = 0.185$ $d = 0.368$	$t = 1.862$ $p = 0.069$ $d = 0.254$	$t = 0.291$ $p = 0.772$ $d = 0.080$	$t = -1.521$ $p = 0.137$ $d = 0.421$	$t = -0.568$ $p = 0573$ $d = 0.157$
RH – Language	$t = 0.583$ $p = 0.562$ $d = 0.160$	*$U = 255$* *$p = 0.088$* *$\eta^2 = 0.074$*	$t = -1.395$ $p = 0.170$ $d = 0.385$	$t = 1.949$ $p = 0.057$ $d = 0.160$	$t = -0.141$ $p = 0.889$ $d = 0.039$	$t = -1.279$ $p = 0.210$ $d = 0.354$	$t = -0.670$ $p = 0.506$ $d = 0.184$
Motor	$t = 1.523$ $p = 0.134$ $d = 0.418$	*$U = 229$* *$p = 0.03$* *$\eta^2 = 0.091$*	$t = -1.732$ $p = 0.092$ $d = 0.479$	*$t = 2.018$* *$p = 0.049$* *$d = 0.553$*	$t = 1.043$ $p = 0.302$ $d = 0.286$	$t = -1.488$ $p = 0.146$ $d = 0.412$	$t = -0.374$ $p = 0.710$ $d = 0.103$
Cognitive	$t = 0.941$ $p = 0.351$ $d = 0.258$	*$U = 243$* *$p = 0.055$* *$\eta^2 = 0.074$*	$t = -0.819$ $p = 0.418$ $d = 0.226$	$t = 0.922$ $p = 0.361$ $d = 0.258$	$t = -0.338$ $p = 0.737$ $d = 0.093$	$t = -1.228$ $p = 0.226$ $d = 0.339$	$t = -0.107$ $p = 0.915$ $d = 0.029$
Clinical	$t = 0.867$ $p = 0.390$ $d = 0.238$	*$U = 217$* *$p = 0.017$* *$\eta^2 = 0.109$*	$t = -1.344$ $p = 0.187$ $d = 0.371$	*$t = 2.702$* *$p = 0.009$* *$d = 0.742$*	$t = 0.198$ $p = 0.844$ $d = 0.054$	*$t = -1.814$* *$p = 0.079$* *$d = 0.502$*	$t = -0.773$ $p = 0.443$ $d = 0.212$

relative theta and relative beta power were significantly different between groups for the posterior montage, and effect size calculations showed large effects for both (theta: U = 189, p = .004, eta^2 = .16; beta: t = 3.329, p = .002, d = .915). Non-significant comparisons with medium effect sizes for relative theta power were observed in the whole brain (eta^2 = .12), left hemisphere (eta^2 = .13), right hemisphere (eta^2 = .07), anterior (eta^2 = .09), left hemisphere language (eta^2 = .07), motor (eta^2 = .09), and clinical (eta^2 = .11) montages. Non-significant comparisons with medium effect sizes were also observed for relative beta power in whole brain (d = .72), left hemisphere (d = .72), right hemisphere (d = .63), motor (d = .55), and clinical (d = .74) montages. Finally, a medium effect size was seen for DTABR in the clinical montage (d = .50). For all reported comparisons, relative theta power and DTABR values were higher in PWCS than controls, while relative beta power values were higher in controls than PWCS.

Coherence

Inter- and intra-hemispheric coherence during *eyes open rest* is reported in **Table 4**. For inter-hemispheric coherence, all correlations were statistically significant and strong in both groups. Inter-hemispheric coherence in controls was generally strongest between either the whole left and right hemispheres (r = .886 to .965) or between the left and right posterior regions (r = .692 to .967), depending on sEEG measure. Strong correlations were observed for intra-hemispheric coherence in controls for all measures and locations except theta coherence between left anterior and posterior regions (r = .469).

Inter- and intra-hemispheric coherence was generally strong for PWCS. Inter-hemispheric coherence between left and right hemispheres in PWCS showed the

Table 4. Inter- and intra-hemispheric coherence as measured by Pearson correlations for neurologically healthy controls and persons with stroke for sEEG measures during *eyes open rest*. All correlations were statistically significant.

Controls							
Inter-hemispheric Coherence							
	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Left vs. Right	.923	.955	.965	.886	.920	.936	.934
Anterior Left vs. Right	.824	.843	.794	.757	.837	.871	.835
Posterior Left vs. Right	.922	.692	.967	.914	.906	.935	.948
Language Left vs. Right	.800	.688	.843	.733	.862	.828	.836
Intra-hemispheric Coherence							
	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Left Anterior vs. Posterior	.827	.469	.780	.735	.806	.784	.801
Right Anterior vs. Posterior	.890	.692	.803	.752	.875	.882	.875
PWS							
Inter-hemispheric Coherence							
	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Left vs. Right	.927	.971	.968	.878	.924	.889	.931
Anterior Left vs. Right	.834	.924	.889	.870	.756	.853	.887
Posterior Left vs. Right	.753	.937	.892	.826	.702	.710	.835
Language Left vs. Right	.822	.924	.872	.753	.775	.695	.857
Intra-hemispheric Coherence							
	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Left Anterior vs. Posterior	.746	.924	.769	.492	.821	.776	.829
Right Anterior vs. Posterior	.820	.922	.934	.737	.676	.863	.852

strongest correlation for all sEEG measures (r = .878 to .971). Similarly, intra-hemispheric coherence was significant across all locations and measures. Strong correlations were seen for PWCS for all measures except beta coherence between left anterior and right regions (r = .492).

Reliability

Test-retest reliability of all sEEG measures for healthy controls during *eyes open rest* ranged from poor to good (**Table 5**). Reliability was poor for theta in the left hemisphere, right hemisphere, posterior, left hemisphere language, right hemisphere language, and cognitive montages (ICCs between .327 and .494); and for delta in the right hemisphere language montage (ICC = .496). All other montages and sEEG measures demonstrated moderate (39/70 correlations) to good (24/70 correlations) reliability in healthy controls. The montages with highest reliability in controls were the clinical, left hemisphere, whole brain, and motor (no single montage showed better reliability than all others for all sEEG measures).

PWCS in general demonstrated better reliability than healthy controls. All correlations ranged from moderate to excellent in terms of the degree of reliability. For PWCS, moderate reliability was observed in six out of 70 correlations (for theta and DAR only), good reliability was observed in 46 of 70 correlations (across all measures), and excellent reliability was observed in 17 of 70 correlations (for alpha, beta, DAR, and DTABR). In PWCS, the montages with the highest reliability were posterior, whole brain, right hemisphere, and clinical.

Table 5. Intra-class correlation coefficients for neurologically healthy controls and persons with stroke during *eyes open rest*. *Moderate*, good, and *excellent* reliability are shown.

Control

	Delta	Theta	Alpha	Beta	DAR	DTABR	$Q_{slowing}$
Whole Brain	*.601*	*0.534*	**.769**	*0.692*	**.812**	*.741*	**.874**
	.277-.804	.174-.768	**.534-.893**	*.403-.854*	**.599-.915**	*.491-.879*	**.733-.943**
Left Hemisphere	*.571*	0.441	**.810**	*0.650*	**.803**	*.718*	**.859**
	.232-.788	*.057-.712*	**.609-.913**	*.336-.833*	**.598-.91**	*.448-.868*	**.705-.936**
Right Hemisphere	*.553*	0.494	*.703*	*0.678*	**.792**	*.723*	**.846**
	.211-.777	.116-.745	*.431-.859*	*.381-.847*	**.563-.906**	*.461-.870*	**.679-.93**
Anterior	*.566*	*0.629*	*.718*	*0.712*	**.770**	*.663*	**.815**
	.231-.784	*.312-.820*	*.457-.867*	*.438-.865*	**.531-.894**	*.362-.839*	**.623-.915**
Posterior	*.584*	0.460	*.737*	*0.622*	*.742*	**.759**	**.863**
	.252-.795	.072-.725	*.484-.877*	*.294-.818*	*.496-.879*	**.521-.888**	**.713-.938**
LH – Language	*.547*	0.460	*.743*	*0.586*	*.712*	**.751**	**.841**
	.203-.773	.089-.722	*.43-.887*	*.244-.798*	*.363-.874*	**.51-.884**	**.672-.928**
RH – Language	.496	0.327	*.696*	*0.604*	**.761**	*.676*	**.791**
	.12-.747	0-.642	*.42-.855*	*.275-.806*	**.525-.889**	*.38-.846*	**.575-.904**
Motor	*.593*	*0.770*	**.760**	**0.755**	*.714*	*.650*	**.851**
	.261-.8	*.539-.893*	**.52-.888**	**.509-.886**	*.448-.864*	*.336-.832*	**.69-.933**
Cognitive	*.564*	0.442	*.724*	*0.649*	*.706*	*.595*	*.719*
	.229-.782	.059-.713	*.461-.87*	*.341-.831*	*.433-.861*	*.262-.802*	*.458-.867*
Clinical	*.621*	*0.512*	**.801**	*0.671*	**.839**	**.757**	**.868**
	.303-.815	*.141-.756*	**.597-.908**	*.37-.844*	**.66-.927**	**.516-.887**	**.723-.94**

PWS

	Delta	Theta	Alpha	Beta	DAR	DTABR	$Q_{slowing}$
Whole Brain	**.868**	**0.813**	***.933***	**0.894**	**.884**	***.932***	***.919***
	.718-.941	**.62-.914**	***.852-.97***	**.771-.953**	**.754-.948**	***.85-.97***	***.823-.964***
Left Hemisphere	**.854**	**0.856**	***.936***	**0.873**	**.826**	**.895**	***.917***
	.692-.934	**.697-.935**	***.859-.972***	**.729-.943**	**.639-.921**	**.776-.953**	***.818-.963***
Right Hemisphere	**.829**	*0.728*	***.908***	**0.877**	**.862**	***.957***	**.898**
	.646-.922	*.471-.872*	***.793-.959***	**.737-.945**	**.71-.937**	***.904-.981***	**.781-.954**
Anterior	**.827**	**0.763**	***.900***	**0.828**	**.818**	**.895**	**.883**
	.641-.921	**.53-.89**	***.785-.955***	**.644-.922**	**.627-.916**	**.773-.953**	**.752-.948**
Posterior	**.872**	**0.810**	***.942***	***0.911***	***.916***	***.943***	***.902***
	.728-.942	**.614-.913**	***.872-.974***	***.807-.96***	***.816-.963***	***.875-.975***	***.786-.956***
LH – Language	**.774**	*0.717*	**.889**	**0.791**	*.743*	**.774**	**.883**
	.542-.896	*.445-.867*	**.761-.951**	**.572-.904**	*.49-.88*	**.548-.895**	**.749-.948**
RH – Language	**.812**	*0.728*	**.829**	**0.854**	**.869**	**.895**	**.882**
	.615-.914	*.467-.872*	**.648-.922**	**.692-.934**	**.72-.941**	**.774-.953**	**.749-.947**
Motor	**.799**	**0.750**	***.900***	**0.778**	**.789**	**.893**	**.855**
	.587-.908	**.504-.883**	***.770-.957***	**.549-.898**	**.571-.903**	**.768-.952**	**.697-.934**
Cognitive	**.763**	*0.748*	**.887**	**0.759**	*.705*	**.858**	**.835**
	.524-.89	*.499-.883*	**.759-.949**	**.519-.888**	*.43-.861*	**.703-.935**	**.656-.925**
Clinical	**.866**	**0.758**	***.939***	**0.883**	**.893**	***.928***	***.923***
	.715-.94	**.523-.887**	***.867-.973***	**.751-.948**	**.77-.952**	***.841-.968***	***.832-.966***

Eyes Closed Rest

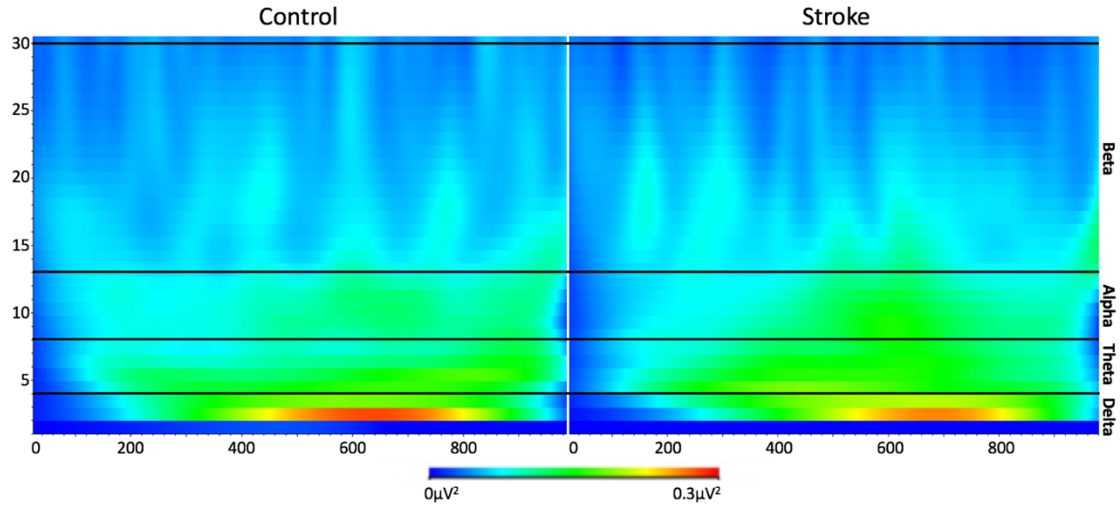
Descriptive Statistics

Descriptive statistics for the whole brain montage are reported here (see Appendix A, **Tables A3-A4** for full descriptive statistics). Mean relative delta power was 0.271 (*SD* = .117) in controls and 0.284 (*SD* = 0.124) in PWCS. Mean relative theta power was 0.104 (*SD* = 0.028) in controls and 0.171 (*SD* = .099) in PWCS. Mean relative alpha power was 0.271 (*SD* = 0.117) in controls and 0.284 (*SD* = 0.124) in PWCS. Mean relative beta power was 0.244 (*SD* = .071) in controls and 0.176 (*SD* = .066) in PWCS. Mean DAR was 1.863 (*SD* = 1.431) in controls and 2.084 (*SD* = 1.824) in PWCS. Mean DTABR was 1.044 (*SD* = 0.654) in controls and 1.765 (*SD* = 1.565) in PWCS. Mean $Q_{slowing}$ was 0.420 (*SD* = 0.126) in controls and 0.488 (*SD* = 0.155) in PWCS.

Between-Group Comparison

Again, no significant differences were observed between individuals with stroke and neurologically healthy controls for relative delta power, relative alpha power, delta/alpha ratio, delta+theta/alpha+beta ratio, or $Q_{slowing}$ (**Figure 5; Table 6**). After correcting for multiple comparisons, relative theta power was significantly different between groups for all montages. Mann-Whitney U tests were used with relative theta power for the right hemisphere language (*U* = 210, *p* = .012, eta^2 = .12) and cognitive (*U* = 203, *p* = .008, eta^2 = .13) montages as unacceptably large skew and kurtosis values were observed. For these montages, effect size calculations indicated a medium effect. For the montages with acceptable skew and kurtosis, t-values ranged from *t* = 3.712 (*p* = .001, *d* = 1.03; motor montage) to *t* = 3.061 (*p* = .005, *d* = .85; right hemisphere montage), all with corresponding large effect sizes. Relative beta power was also

Figure 5. Time frequency plot displaying delta, theta, alpha and beta power for neurologically healthy controls (left) and persons with chronic stroke (right) during *eyes closed rest*.



significantly different between groups for all montages (from $t = 3.912$, $p < .001$ for the posterior montage to $t = 2.32$, $p = .024$ for the right hemisphere language montage). Effect size calculations for relative beta power showed large effects for whole brain ($d = .98$), left hemisphere ($d = 1.07$), posterior ($d = 1.08$), and clinical ($d = .97$) montages and medium effects for right hemisphere ($d = .77$), anterior ($d = .78$), left hemisphere language ($d = .7$), right hemisphere language ($d = .64$), motor ($d = .8$), and cognitive ($d = .68$) montages. Non-significant between-group differences with medium effect sizes for DTABR were observed in whole brain ($d = .60$), left hemisphere ($d = .68$), anterior ($d = .59$), posterior ($d = .61$), left hemisphere language ($d = .61$), cognitive ($d = .64$), and clinical montages ($d = .62$). Finally, for $Q_{slowing}$, three non-significant difference with medium effect sizes were observed in the left hemisphere ($d = .57$), posterior ($d = .52$) and clinical ($d = .51$) montages. Relative beta power was higher in healthy controls than PWCS for all montages; however, PWCS had larger relative theta power, DTABR, and $Q_{slowing}$ than healthy controls.

Table 6. Test statistic, p-value, and effect size for between group comparisons during *eyes closed rest*. Comparisons that survived correction for multiple comparisons are bolded and comparisons not statistically significant but with a medium or large effect size are italicized.

	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Whole Brain	*t* = -0.16 *p* = 0.987 *d* = 0.004	***t* = -3.317** ***p* = 0.002** ***d* = 0.919**	*t* = -0.391 *p* = 0.697 *d* = 0.107	***t* = 3.559** ***p* = 0.001** **0.979**	*t* = -0.493 *p* = 0.624 *d* = 0.135	*t = -2.173* *p = 0.037* *d = 0.601*	*t* = -1.749 *p* = 0.086 *d* = 0.480
Left Hemisphere	*t* = -0.448 *p* = 0.656 *d* = 0.123	***t* = -3.411** ***p* = 0.002** ***d* = 0.944**	*t* = -0.251 *p* = 0.802 *d* = 0.069	***t* = 3.876** ***p* < 0.001** **1.065**	*t* = -0.766 *p* = 0.447 *d* = 0.210	*t = -2.460* *p = 0.019* *d = 0.680*	*t = -2.095* *p = 0.041* *d = 0.574*
Right Hemisphere	*t* = 0.245 *p* = 0.808 *d* = 0.067	***t* = -3.061** ***p* = 0.005** ***d* = 0.848**	*t* = -0.494 *p* = 0.624 *d* = 0.136	***t* = 2.814** ***p* = 0.007** **0.773**	*t* = -0.377 *p* = 0.708 *d* = 0.103	*t* = -1.827 *p* =0.081 *d* = 0.498	*t* = -1.380 *p* = 0.174 *d* = 0.378
Anterior	*t* = 0.064 *p* = 0.950 *d* = 0.017	***t* = -3.342** ***p* = 0.002** ***d* = 0.926**	*t* = -0.261 *p* = 0.795 *d* = 0.072	***t* = 2.829** ***p* = 0.007** **0.778**	*t* = -0.501 *p* = 0.619 *d* = 0.137	*t = -2.145* *p = 0.039* *d = 0.593*	*t* = -1.638 *p* = 0.108 *d* = 0.449
Posterior	*t* = -0.182 *p* = 0.856 *d* = 0.050	***t* = -3.197** ***p* = 0.003** ***d* = 0.885**	*t* = -0.270 *p* = 0.788 *d* = 0.074	***t* = 3.912** ***p* < 0.001** **1.075**	*t* = -0.653 *p* = 0.516 *d* = 0.179	*t = -2.193* *p = 0.036* *d = 0.607*	*t = -1.912* *p = 0.062* *d = 0.524*
LH – Language	*t* = -0.127 *p* = 0.900 *d* = 0.035	***t* = -3.449** ***p* = 0.002** ***d* = 0.956**	*t* = -0.205 *p* = 0.838 *d* = 0.056	***t* = 2.535** ***p* = 0.014** **0.696**	*t* = -0.681 *p* = 0.499 *d* = 0.187	*t = -2.203* *p = 0.035* *d = 0.609*	*t* = -1.736 *p* = 0.089 *d* = 0.476
RH – Language	*t* = 0.002 *p* = 0.998 *d* = 0.001	***U* = 210** ***p* = 0.012** ***η*² = 0.121**	*t* = -0.676 *p* = 0.502 *d* = 0.186	***t* = 2.320** ***p* = 0.024** **0.637**	*t* = -0.692 *p* = 0.492 *d* = 0.189	*t* = -1.715 *p* = 0.097 *d* = 0.475	*t* = -1.394 *p* = 0.169 *d* = 0.382
Motor	*t* = 0.594 *p* = 0.555 *d* = 0.163	***t* = -3.712** ***p* = 0.001** ***d* = 1.027**	*t* = -0.752 *p* = 0.456 *d* = 0.206	***t* = 2.893** ***p* = 0.006** **0.796**	*t* = 0.126 *p* = 0.900 *d* = 0.035	*t = -1.941* *p = 0.060* *d = 0.536*	*t* = -1.403 *p* = 0.167 *d* = 0.385
Cognitive	*t* = -0.372 *p* = 0.711 *d* = 0.102	***U* = 203** ***p* = 0.008** ***η*² = 0.133**	*t* = 0.149 *p* = 0.882 *d* = 0.041	***t* = 2.454** ***p* = 0.018** **0.675**	*t* = -0.982 *p* = 0.331 *d* = 0.269	*t = -2.306* *p = 0.027* *d = 0.638*	*t* = -1.806 *p* = 0.077 *d* = 0.495
Clinical	*t* = -0.143 *p* = 0.887 *d* = 0.039	***t* = -3.356** ***p* = 0.002** ***d* = 0.929**	*t* = -0.293 *p* = 0.771 *d* = 0.080	***t* = 3.515** ***p* = 0.001** **0.966**	*t* = -0.619 *p* = 0.538 *d* = 0.170	*t = -2.236* *p = 0.032* *d = 0.619*	*t = -1.872* *p = 0.067* *d = 0.513*

Coherence

Inter- and intra-hemispheric coherence during *eyes closed rest* is reported in **Table 7**. Similar to *eyes open rest*, all correlations for inter-hemispheric coherence were statistically significant and ranged from moderate to strong for both groups. Inter-hemispheric coherence in controls was highest between left and right hemispheres for all sEEG measures (r = .927 to .986). In addition, relative alpha power had the largest correlations for each inter-hemispheric coherence calculation (r = .946 to .986) than other sEEG measures (r = .720 to .963). For healthy controls, all intra-hemispheric coherence correlations were strong, but there was no consistent pattern.

For PWCS, inter-hemispheric coherence was highest between anterior left and right hemisphere regions, except for relative theta power (r = .777 to .948). Relative theta power (r = .901 to .959) had the largest correlations for each inter-hemispheric coherence calculation than any other sEEG measure. A single moderate correlation was observed for PWCS in DAR (r = .475) between posterior left and right hemispheres. Unlike controls, intra-hemispheric coherence in PWCS showed a consistent pattern, with correlations for intra-hemispheric left hemisphere anterior and posterior regions consistently smaller than correlations between right hemisphere regions. Lowest coherence (and the only moderate correlation) was seen in the left hemisphere for relative beta power.

Reliability

Test-retest reliability of all measures for healthy controls during *eyes closed rest* ranged from poor to excellent (**Table 8**). Control reliability was poor for relative delta in the right hemisphere (ICC = .488), anterior (ICC = .478), left hemisphere language

Table 7. Inter- and intra-hemispheric coherence as measured by Pearson correlations for neurologically healthy controls and persons with stroke for sEEG measures during *eyes closed rest*. All correlations were statistically significant.

Controls							
Inter-hemispheric Coherence							
	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Left vs. Right	.957	.938	.986	.927	.963	.963	.960
Anterior Left vs. Right	.946	.835	.962	.883	.954	.942	.951
Posterior Left vs. Right	.921	.864	.946	.891	.931	.940	.932
Language Left vs. Right	.893	.768	.929	.729	.912	.910	.893
Intra-hemispheric Coherence							
	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Left Anterior vs. Posterior	.938	.661	.926	.742	.936	.911	.928
Right Anterior vs. Posterior	.873	.795	.925	.821	.893	.907	.894
PWS							
Inter-hemispheric Coherence							
	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Left vs. Right	.902	.959	.905	.769	.881	.817	.908
Anterior Left vs. Right	.920	.948	.930	.777	.918	.895	.937
Posterior Left vs. Right	.639	.901	.624	.672	.475	.551	.720
Language Left vs. Right	.778	.915	.817	.675	.768	.718	.826
Intra-hemispheric Coherence							
	Delta	**Theta**	**Alpha**	**Beta**	**DAR**	**DTABR**	**$Q_{slowing}$**
Left Anterior vs. Posterior	.727	.905	.809	.454	.741	.797	.822
Right Anterior vs. Posterior	.782	.950	.818	.739	.801	.881	.847

Table 8. Intra-class correlation coefficients for neurologically healthy controls and persons with stroke during *eyes closed rest*. *Moderate*, good, and *excellent* reliability are shown.

Control

	Delta	Theta	Alpha	Beta	DAR	DTABR	$Q_{slowing}$
Whole Brain	*.518*	**0.865**	*.515*	**0.782**	***.932***	**.827**	**.848**
	.153-.758	**.712-.939**	*.148-.757*	**.56-.899**	***.85-.97***	**.644-.921**	**.681-.931**
Left Hemisphere	*.516*	**0.814**	*.506*	**0.753**	**.895**	**.801**	**.833**
	.146-.759	**.616-.915**	*.13-.753*	**.507-.885**	**.776-.953**	**.596-.908**	**.651-.924**
Right Hemisphere	.488	**0.824**	*.529*	*0.747*	***.957***	**.812**	**.846**
	.118-.74	**.636-.92**	*.169-.765*	*.501-.882*	***.904-.981***	**.616-.914**	**.678-.93**
Anterior	.478	*0.748*	.476	**0.781**	**.895**	**.759**	**.815**
	.096-.736	*.504-.882*	.095-.735	**.556-.899**	**.773-.953**	**.518-.888**	**.617-.915**
Posterior	*.533*	**0.868**	*.522*	**0.789**	***.943***	**.846**	**.860**
	.175-.767	**.718-.941**	*.155-.761*	**.574-.903**	***.875-.975***	**.68-.93**	**.704-.937**
LH – Language	.478	*0.539*	*.514*	*0.535*	**.774**	*.676*	*.737*
	.101-.735	*.182-.771*	*.143-.757*	*.173-.769*	**.548-.895**	*.389-.844*	*.482-.877*
RH – Language	.367	*0.698*	*.580*	*0.575*	**.895**	*.743*	**.805**
	0-.668	*.413-.858*	*.239-.794*	*.224-.792*	**.774-.953**	*.49-.88*	**.599-.911**
Motor	*.559*	**0.841**	.442	**0.818**	**.893**	**.866**	**.850**
	.217-.78	**.665-.928**	.064-.711	**.623-.917**	**.768-.952**	**.715-.94**	**.687-.932**
Cognitive	*.517*	*0.607*	.480	*0.685*	**.858**	*.675*	*.737*
	.144-.76	*.274-.809*	.093-.738	*.396-.851*	**.703-.935**	*.377-.846*	*.48-.878*
Clinical	.499	**0.856**	*.506*	*0.745*	***.928***	**.831**	**.826**
	.124-.748	**.694-.935**	*.135-.752*	*.494-.881*	***.841-.968***	**.649-.923**	**.639-.921**

PWS

	Delta	Theta	Alpha	Beta	DAR	DTABR	$Q_{slowing}$
Whole Brain	**.868**	**0.858**	**.871**	**0.879**	**.873**	***.932***	***.926***
	.722-.941	**.691-.937**	**.725-.942**	**.737-.946**	**.731-.943**	***.85-.97***	***.836-.967***
Left Hemisphere	**.838**	**0.874**	**.867**	**0.853**	**.788**	**.895**	***.907***
	.664-.926	**.734-.943**	**.718-.94**	**.691-.933**	**.574-.902**	**.776-.953**	***.797-.959***
Right Hemisphere	**.878**	**0.833**	**.862**	**0.885**	***.918***	***.957***	***.930***
	.74-.945	**.634-.926**	**.707-.938**	**.754-.949**	***.819-.964***	***.904-.981***	***.847-.969***
Anterior	**.805**	**0.782**	**.782**	**0.765**	**.817**	**.895**	**.888**
	.599-.911	**.545-.901**	**.558-.9**	**.51-.893**	**.623-.917**	**.773-.953**	**.762-.95**
Posterior	**.898**	***0.906***	***.908***	***0.940***	***.903***	***.943***	***.942***
	.766-.955	***.788-.959***	***.799-.959***	***.867-.974***	***.792-.957***	***.875-.975***	***.872-.974***
LH – Language	**.765**	*0.742*	**.765**	*0.733*	*.709*	**.774**	**.820**
	.534-.891	*.494-.879*	**.53-.891**	*.472-.875*	*.442-.862*	**.548-.895**	**.629-.918**
RH – Language	**.839**	**0.799**	**.783**	**0.797**	**.889**	**.895**	**.893**
	.663-.927	**.589-.908**	**.559-.9**	**.587-.907**	**.76-.95**	**.774-.953**	**.771-.952**
Motor	**.801**	**0.812**	**.863**	*0.741*	**.813**	**.893**	**.884**
	.597-.908	**.581-.917**	**.709-.938**	*.493-.878*	**.619-.914**	**.768-.952**	**.751-.948**
Cognitive	**.758**	*0.625*	*.670*	*0.749*	**.774**	**.858**	**.855**
	.519-.888	*.306-.818*	*.373-.842*	*.422-.892*	**.543-.896**	**.703-.935**	**.687-.935**
Clinical	**.862**	**0.850**	**.865**	**0.871**	**.879**	***.928***	***.912***
	.707-.938	**.655-.935**	**.713-.939**	**.715-.943**	**.742-.946**	***.841-.968***	***.808-.961***

(ICC = .478), right hemisphere language (ICC = .367), and clinical (ICC = .499) montages as well as for relative alpha in the anterior (ICC = .474), motor (ICC = .442), and cognitive (ICC = .480) montages. All other montages and sEEG measures demonstrated moderate (27/70 correlations), good (32/70 correlations), or excellent (4/70 correlations) reliability in healthy controls.

PWCS in general demonstrated better reliability than healthy controls. All correlations ranged from moderate to excellent in terms of the degree of reliability. For PWCS, moderate reliability was observed in seven out of 70 correlations (for theta, alpha, beta, and DAR), good reliability was observed in 49 of 70 correlations (across all measures), and excellent reliability was observed in 14 of 70 correlations (for theta, alpha, beta, DAR, and DTABR). In PWCS, the montage with the most consistent reliability was the posterior montage, as it showed excellent reliability for all sEEG measures except relative data power, which demonstrated good reliability.

Discussion

In this sample of 27 healthy controls and 27 persons with chronic stroke, we found no significant between-group differences during *eyes open rest* for relative delta and alpha power, delta/alpha ratio, delta+theta/alpha+beta ratio, or quantitative slowing. However, significant differences were observed in relative theta and beta power during *eyes open rest* in the posterior montage. Significant differences were also observed during *eyes closed rest* for all montages of interest in relative theta and beta power. Importantly, we reported acceptable stability of all sEEG measures over time, depending on electrode montage. Better stability was observed for all measures in the *eyes closed rest* condition, which is unsurprising since it is less prone to artifactual noise like eye

movements or other muscle activation. In particular, during *eyes closed rest* the posterior montage consistently had the best reliability.

Comparison with Previous Literature

Much of the previous literature investigating sEEG in individuals who have experienced a stroke is limited to the acute and sub-acute phases of recovery. These studies have generally reported significant differences between PWCS and neurologically healthy controls, with the most consistent results reported for relative delta power and delta/alpha ratio. In contrast, no significant differences were found for these measures here (and in fact, healthy controls had numerically higher delta and DAR values than our chronic PWCS). As a check, we examined previously published research to determine if our values for relative delta, relative alpha, DAR, and DTABR had been previously reported in the literature. While many studies have investigated these variables, relatively few report descriptive statistics adequate to determine the observed range. Nevertheless, examination of three articles (Finnigan et al., 2007; Leon-Carrion et al., 2009; Sheorajpanday et al., 2011) showed the values observed here have been reported previously (although not within a single study). Two acute studies (Finnigan et al., 2007; Sheorajpanday et al., 2011) reported values matching and exceeding our largest observed data points, but no values matching the lower end of those we observed. In contrast, Leon-Carrion and colleagues (2009) included non-acute participants and reported values matching our smallest observed data points, but no values matching the higher end. Importantly, Leon-Carrion and colleagues reported values of a mixed group of individuals with stroke and traumatic brain injury, and only included 5 participants with

stroke. Given this limited sample, it is perhaps unsurprising they did not report the full range of values found here.

We also examined the prior research for a range of values reported for neurologically healthy controls. Again, although multiple studies include a healthy control comparison group, descriptive statistics were reported in such a way that only a single comparison can be made. Finnigan and colleagues (2016) reported that no healthy controls in their sample of 28 individuals had a DAR above 3.56, which is lower than the highest DAR observed in our sample (5.69). However, the authors specifically stated that further research was needed to determine whether their values were confirmed in a different sample. One possible explanation for the difference is our use of less stringent inclusion criteria than Finnigan and colleagues. For example, we did not exclude individuals who were diagnosed with mild depression or anxiety, or individuals who scored in the borderline or low average range on the RBANS. Our rationale for including controls with mild depression or anxiety is the high prevalence of depression and anxiety in both the general population, and more importantly, in individuals who have experienced a stroke. Excluding controls with depression and/or anxiety might artificially limit the range of "normal" DAR that could be observed in neurologically intact individuals and would also make the samples less comparable, potentially leading to confounds. Similarly, individuals with borderline or low average RBANS scores were included because they had not been diagnosed with any developmental or learning disorder and did not have a history of any kind of neurological disease. Individuals with these cognitive profiles undeniably represent one facet of neurologically "normal"

performance, and to exclude them would artificially limit the variability seen in neurologically healthy controls.

Few studies have examined sEEG in persons with stroke in the chronic phase. In contrast to studies completed during the acute and sub-acute phases where EEG is exclusively recorded during *eyes closed rest* or *eyes open rest*, studies in the chronic phase have recorded EEG during completion of motor, cognitive, and language tasks (Herron et al., 2009; Spironelli & Angrilli, 2009; Spironelli et al., 2013). These studies have reported statistically significant differences between controls and persons with stroke in delta, theta, and beta power. To our knowledge, this is the first study to examine sEEG in individuals with chronic stroke at rest. Our results confirm the observation in the acute and sub-acute phases that changes in delta and alpha immediately post-stroke tend to normalize over time (e.g., Hensel et al., 2004). We are also the first to demonstrate that previously reported differences in theta and beta at rest (Assenza et al., 2014; Cuspineda et al., 2007; Finnigan et al., 2016; Gorisek et al., 2016; Song et al., 2015; Spironelli et al., 2013) persist into the chronic phase indefinitely. The differences between our resting state power results and previously reported task-based power results suggest that engaging in a task may trigger a paradoxical slowing of overall brain activity for individuals who have experienced a stroke. Although outside the scope of the current investigation, this will be the focus of future research, as we currently possess a dataset of task-based EEG recordings in this sample of participants, allowing for direct investigation of the effect of task engagement on the speed of brain activity.

sEEG for Outcome Measurement

Some studies have examined changes in sEEG over time as a response to treatment (e.g., Rozelle & Budzynksi, 1995; Stojanovic et al., 2013; Wu et al., 2015). However, to date there has been no evidence that sEEG measures in PWS are stable over time and therefore appropriate for use as repeated measures. This study is the first to report on the stability of sEEG measures over one month. This time period was selected as many research studies involving a treatment component last approximately one month from pre-treatment assessment to post-treatment assessment. Our results suggest that sEEG measures, particularly during *eyes closed rest*, demonstrate appropriate stability to be used to track changes over time. Interestingly, we found the best reliability, the largest magnitude differences, and the most reliably significant between-group differences in the posterior montage. A prior study also reported that the largest between-group differences observed in their sample of controls and PWS occurred in a set of posterior left hemisphere electrodes (Hensel et al., 2004). This suggests that a posterior montage may be most amenable to measuring treatment response or other change over time.

Correlation with Function

Although not the focus of the current study, an exploratory analysis investigating the correlation between sEEG measures and performance on behavioral tasks was conducted, as this result has been frequently reported in the literature. Due to its exploratory nature, only *eyes closed rest* data in the whole brain, clinical and posterior montages for relative theta and beta power was examined due to the significant differences with large effect sizes observed for these. Pearson correlations were conducted between relative theta or beta power and performance on motor (contralesional

index finger tapping), cognitive (RBANS index score), and language (production of main concepts during story-telling) assessments. For all measures, a lower score represents worse behavioral performance. Negative correlations were observed between relative theta power and main concept production in whole brain (r = -.684), clinical (r = -.678), and posterior left hemisphere (r = -.679) montages. A negative correlation was also observed for the RBANS (r = -.411) in the posterior left hemisphere. Positive correlations were observed between relative beta power and main concept production in whole brain (r = .569), clinical (r = .563), and posterior left hemisphere (r = .516) montages. Positive correlations were also observed between the RBANS and clinical (r = .413) and posterior left hemisphere (r = .516) montages. The negative correlations between theta power and behavioral measures mean that as theta power increases, discourse and cognitive performance decreases. The positive correlations between beta and behavioral measures mean that as beta power increases, discourse and cognitive performance also increases. These results provide an important assurance that the between-group differences observed are functionally relevant. They also provide additional support for a continued relationship between sEEG and behavioral function in the chronic phase of stroke recovery.

These results additionally highlight the importance of the behavioral measures selected to quantify functional abilities. No significant correlations were observed for contralesional index finger tapping despite a large number of participants exhibiting motor deficits. While this lack of significant correlation is possibly a reflection of no relationship between motor function and sEEG measures, it is more likely that contralesional index finger tapping was not sensitive enough to detect the relationship,

especially given the significant correlations for language and cognitive tasks. Indeed, not all participants with motor deficits demonstrated slowed finger tapping. A more global measure of function, or perhaps a combination of multiple measures, might be required to more sensitively quantify sensorimotor deficits.

In addition, the main concept score was selected as the measure of language function because the WAB-R aphasia quotient (one of the most widely used standardized aphasia assessments) did not demonstrate a linear relationship with theta and beta power, due in large part to ceiling effects. The WAB-R is scored out of 100 points, and the cut-off of performance that distinguishes individuals with aphasia from those without is 93.8. This means that the entire range of "normal" performance is constrained to less than seven points in comparison to the range of 93 points to quantify aphasic performance. In contrast, the main concept composite score, which quantifies the accuracy and completeness of story retelling, has demonstrated sufficient sensitivity to describe both impaired and control discourse across a wide range of performance (Dalton & Richardson, 2019). Within the field of aphasiology, there have been calls to utilize functional communication measures, such as discourse performance, as primary outcome measures in treatment studies, since these changes correspond more directly to outcomes desired by persons with aphasia (Brady et al., 2016). This exploratory analysis provides further support for those calls. This result also provides continued evidence for the sensitivity of posterior brain regions to changes following stroke, highlighting the need for more research into the features of posterior brain structure and connectivity which may contribute to these findings.

Future Directions

Future research should examine changes in sEEG before and after treatment of chronic, stroke-induced deficits to determine if these measures are sensitive to changes in response to treatment, and to determine if baseline sEEG measures are able to predict treatment response. To date only a single treatment case study has been published examining this topic, and the treatment was a biofeedback protocol with unknown efficacy (Rozelle & Budzynski, 1995) rather than a more commonly used and potentially more efficacious behavioral therapy. Additionally, as a field, improvements in reporting methodology and basic descriptive statistical information regarding data are needed, even if only in supplemental materials. By providing this information to readers, we can increase the confidence in reported results and strengthen the inferences that can be drawn from published findings. Ideally, a database, such as those already established for healthy controls and some populations with disorders (e.g., Brain Research and Integrative Neuroscience Network, http://www.brainnet.net; Patient Repository for EEG Data + Computational Tools; http://predict.cs.unm.edu), would be established to allow for sharing of data and use of big data analytics that are currently unavailable for individuals with stroke.

Finally, research into the mechanisms behind increased slow wave and decreased fast wave activity in chronic stroke should be investigated. There is evidence demonstrating that theta band synchrony is associated with cognitive control in healthy adults (Cavanagh & Frank, 2014), and is altered in some disordered populations (e.g., Cavanagh, Meyers, & Hajcak, 2017). If, for example, increased theta post-stroke is related to increased cognitive control effort required to navigate everyday life, this could

contribute to patient reported experiences of fatigue and increased effort. On the other hand, if increased theta is a result of the cognitive control network being co-opted to participate in non-standard tasks, this could indicate that there is less capacity for cognitive control mechanisms to be engaged, which would have implications for rehabilitation success.

Conclusion

Within the field of stroke rehabilitation, and especially within the field of aphasiology, there is great need for improved individualization of rehabilitation. One of the primary limiting factors in achieving this goal is the lack of sensitive measures that can predict treatment response. Simply looking at an individual's behavioral profile has proven to be insufficient to determine the most appropriate treatment course that will result in greatest functional recovery. This is especially critical for adults engaging in rehabilitation, as insurance companies impose annual limits on total therapy hours (often forcing individuals to choose between occupational, physical, and speech therapy). By improving individualization of treatment and thereby maximizing outcomes, individuals post-stroke will be more likely to experience meaningful improvements in everyday living. Given the persistence of stroke-induced changes into the chronic phase as demonstrated here and elsewhere, as well as the stability of these measures, sEEG shows great potential to be one such measure.

Chapter 3

Introduction

Event-Related Potentials

Perhaps the most widely utilized methodology in EEG research is the event-related potential (ERP) analysis. ERPs take advantage of the fact that the brain automatically processes information as it is presented. By marking the time at which a specific stimulus is presented to participants (typically auditorily or visually) and recording brain activation following stimulus presentation, ERPs allow inferences to be made regarding the timing and general location of processing. While activation for any given trial may be variable, averaging across many trials and many participants cancels out activity that is random and unrelated to stimulus processing, revealing a clear timeline of activation related to stimulus response. Of particular interest in ERP analysis is identification of ERP "components" corresponding to positive or negative peaks in the electrical signals recorded from the brain. Generally, early ERP components (occurring prior to ~150ms after stimulus onset) are associated with basic sensory (e.g., color, shape, brightness, tone frequency, loudness) processing of stimuli, while later components are associated with cognitive processing (e.g., attention, memory, language, executive). For example, the N400 is a cognitive-linguistic ERP component comprised of a typically negative-going peak that occurs around 400ms after stimulus presentation. It was first described by Kutas and Hillyard (1980) and was elicited in response to an unexpected word occurring at the end of a sentence (for example, "He cut his food with a toothbrush."). Since that time there have been hundreds of investigations of the N400 in healthy control and clinical populations that indicate it is involved in processing semantic

meaning, among other tasks (for discussion see Kutas & Federmeier, 2011; Lau, Phillips, & Poeppel, 2008). Researchers have identified numerous other ERP components corresponding to different aspects of sensory and cognitive processing in healthy controls (for an excellent tutorial see Luck & Kappenman, 2012). These components have been leveraged to better understand how the brain processes incoming information in healthy controls. ERP analysis has also been widely used to understand how brain processing is changed following a range of diseases and disabilities.

ERPs in Individuals Post-Stroke

Examination of ERPs in individuals who have had a stroke provides insight into neural adaptation when structural and functional connectivity is altered. Many such studies have been conducted (for a review see Hernandez, 2015; Monge-Pereira et al., 2017). These investigations encompass a wide range of tasks and behaviors, including: auditory processing, emotion processing, memory, language, motor imagery, motor planning, and movement execution (e.g., Daly et al., 2006; Dejanovic et al., 2015; Ilvonen et al., 2003; Kohlmetz et al., 2001; Laganaro, Python, & Toepel, 2013; Li, Yan, & Wei, 2013; Ofek et al., 2013; Sheppard et al., 2017; Stahlhut, Grotemeyer, Husstedt, Evers, 2014). Overall, studies report differences in the latency, amplitude, and topographic distribution of ERP components for persons with chronic stroke (PWCS) compared to neurologically healthy controls. Some studies have investigated stroke recovery broadly, while others have focused on specific stroke-induced deficits. While many investigations of cognitive ERPs include broadly defined stroke populations, cognitive-linguistic ERP investigations have generally constrained criteria to include

populations with specific features (for example, only individuals with post-stroke aphasia, or only individuals with mild stroke).

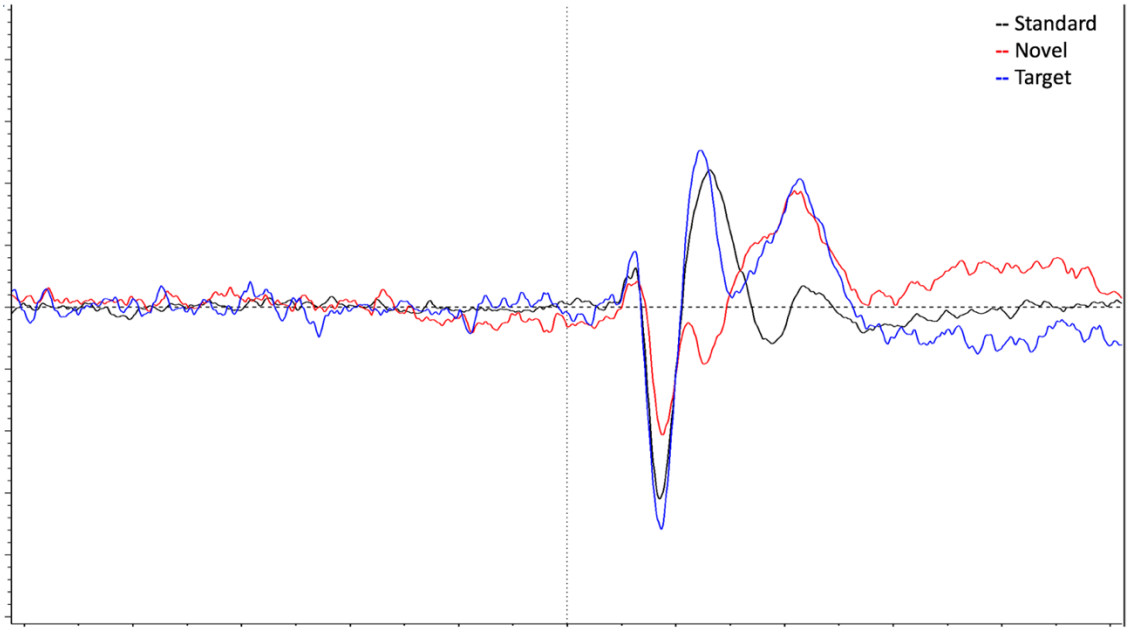
Measuring Cognition with ERP Post-Stroke

Attention

Many stroke researchers have investigated attention using the P300 (or P3) component (e.g., Dejanovic et al., 2015; Ehlers, Herrero, Kastrup, & Hildebrandt, 2015; Korpelainen et al., 2000; Molnar, Osman-Sagi, Nagy, & Kenez, 1999; Nolfe, Cobianchi, Mossuto-Agatiello, & Giaquinto, 2006). The P300 is a typically positive going peak occurring around 300ms after stimulus onset. It is centered over the midline and posterior to the midpoint of the skull (referred to as the vertex). It is elicited by presenting a commonly occurring "standard" stimulus, an infrequently occurring "target" stimulus, and (optional) infrequently occurring "novel" stimuli that differ from both the standard and target. The P300 can be elicited in response to either visual or auditory stimuli and differs in a well-described manner according to gender and age. There are two distinct constituents, the P3a and P3b. The P3a occurs slightly earlier than the P3b and is stronger in response to novel than target stimuli. It is thought to correspond to involuntary attentional processes (e.g., Picton, 1992), or stimulus processing and inhibition (Linden, 2005). The P3a also has a more fronto-medial, rather than posterior, distribution. In contrast, the P3b occurs slightly later, across a larger time window, and is more posterior in distribution than the P3a. It is more strongly elicited in response to the target stimulus, which highlights its involvement in conscious attentional and memory processes, because the stimulus must be attended to and then compared to a target exemplar stored in memory.

Because the P300 indexes conscious and unconscious attentional processes, can be elicited in a non-linguistic manner, and can be elicited without a behavioral task that requires an overt response, it is useful for examining recovery post-stroke when cognitive and/or language deficits may be present. Research has shown smaller P300 amplitude and longer latency following stroke (**Figure 6**; e.g., Dejanovic et al., 2014). Additional examination of changes in the P300 indicates that lesion location (e.g., temporal, parietal, frontal) also affects amplitude (Picton, 1992). Furthermore, the P300 shows a well-described pattern of age-related change, with longer latencies observed as age increases. This is an important consideration when studying diseases, such as stroke, that tend to occur in a more elderly population.

Figure 6. Example of the P300 response in an auditory oddball paradigm. The black trace corresponds to activation in response to the frequently occurring tone. The red trace corresponds to activation in response to novel sounds. The blue trace corresponds to activation in response to the target tone.



Language

Another important aspect of cognition is language production and processing. Language abilities can be directly disrupted by damage to language dominant areas in the brain, or indirectly through damage to areas of the brain responsible for cognitive processes that underlie language abilities, such as memory and attention. Research with individuals post-stroke has sought not only to describe how language processing changes following stroke (e.g., Angrilli & Spironelli, 2005; Angrilli et al., 2015; Chang et al., 2016; D'Arcy et al., 2003; Dobel et al., 2002; Friederici et al., 1999; Hagoort et al., 1996; Hagoort et al., 2003; Kawohl, Bunse, & Willmes, 2010; Kielar, Meltzer-Asscher, & Thompson, 2012; Kojima & Kaga, 2003; Laganaro et al., 2013; Robson, et al., 2017; Pulvermuller et al., 2004; Sheppard et al., 2017; Swaab et al., 1997; ter Keurs et al., 1999; Wilson et al., 2012), but also how language recovery manifests in the brain (e.g., Cobianchi & Giaquinto, 2000), and whether ERP analyses can be used to inform treatment response or predict treatment recovery (e.g., Barbancho et al., 2015; D'Arcy et al., 2003; Laganaro et al., 2008). These studies almost exclusively limit inclusion criteria to individuals who have been diagnosed with aphasia. While this has provided important and useful information regarding aphasia specifically, limiting inclusion/exclusion criteria in this manner prevents us from characterizing the contribution of other cognitive processes, such as working memory and attention, to language production and processing.

The N150 and N350 are ERP components that can be elicited in response to presentation of single words (Spironelli & Angrilli, 2015). The N150 is a negative-going peak that occurs posteriorly and is left-lateralized. It is related to early word recognition

(supported by the visual word form area discussed in chapter 1). Unlike controls, when completing orthographic, rhyme, and semantic relatedness judgment tasks, persons with post-stroke aphasia demonstrated an N150 that was either bilaterally distributed or lateralized to the right hemisphere (Spironelli & Angrilli, 2015). The N350 is also a negative-going peak that is left-lateralized, but its distribution is more frontal than the N150. The N350 is related to processing word-specific phonological features (Spironelli & Angrilli, 2015). Again, in contrast to controls, individuals with post-stroke aphasia demonstrated an N350 that was centered over spared anterior and posterior left hemisphere language areas. For both components, individuals with post-stroke aphasia also demonstrated decreased amplitude compared to healthy controls.

Predicting recovery post-stroke.

P300. Investigations of attentional and linguistic ERPs during stroke recovery, or in response to therapy, are promising with regards to their use as biomarkers of treatment response and general recovery. In one study, amplitude and latency immediately following a stroke were significantly different from healthy controls and showed a divergence during the first year of stroke recovery, such that latency became more normalized while amplitude showed no significant normalization (Dejanovic et al., 2015). In contrast, Korpelainen and colleagues (2000) found only a latency change in the P300 in the acute phase post-stroke, which was related to the severity of post-stroke depression. However, Korpelainen and colleagues only included individuals with minor strokes (i.e., small lesions, mild deficits), while Dejanovic and colleagues enrolled a consecutive sample regardless of severity, potentially accounting for these different findings. Yamagata and colleagues (2004) investigated the P300 in individuals with

subcortical strokes and found significant differences in P300 amplitude between participants with and without apathy. However, no control group was enrolled in this study, so it is unclear if differences existed between the individuals with stroke and healthy controls. A study examining whether the P300 indexed recovery in individuals with global aphasia (and therefore persons with larger lesions and more severe symptoms) found that presence of the P300 at stroke onset corresponded with better recovery at six months (Nolfe et al., 2006). The authors also reported that the P300 in this population of individuals with severe strokes was not stable over the first sixth months of recovery. Participants might show a P300 response in one month, but not the next. If this finding of instability holds for all individuals it might explain some of the variability in P300 changes following stroke, as individuals in the acute and subacute phases of recovery were included in the studies reviewed above.

The P300 is also associated with functional recovery and positive outcomes in response to treatment. In their study, Ehlers and colleagues (2015) found that larger P300 amplitude at frontal locations (P3a) corresponded with better recovery (e.g., discharge from acute care to sub-acute rehabilitation versus discharge to a nursing home). P300 amplitude was also correlated with improvement on a measure of activities of daily living. Based on their results, the authors suggested that degree of impairment in attention, as indexed by P3a amplitude, predicted poor versus good rehabilitation outcomes. Finally, the P300 can be directly altered through administration of pharmacological agents (Yamaguchi, Matsubara, & Kobayashi, 2004), which indicates that it may also be amenable to alterations induced by neurorehabilitation. Taken together, the body of work on P300 in PWS in early phases of recovery demonstrates that

ERP measures offer a fruitful avenue for understanding cognitive recovery after a stroke, and perhaps more importantly, improving prognosis and individualization of rehabilitation.

N150 and N350. Language ERPs have also been examined during recovery and in response to treatment, although participants were limited to individuals with post-stroke aphasia. In persons with very mild nonfluent aphasia, behavioral recovery as measured by the Aachen Aphasia Test (AAT; Huber, Poek, & Willmes, 1984) correlated with a return of left lateralization during language processing (e.g., Spironelli et al., 2008). One study reported that behavioral language improvements measured during recovery were indexed by both a return to the "normal" pattern of ERPs shown by controls in some participants, and emergence of ERP components with divergent topography and amplitude compared to controls in other participants (Laganaro et al., 2008). This study only included four PWAs (two conduction, one transcortical sensory, one unclassified), which did not allow for an investigation of possible patient factors that contribute to normalized versus divergent patterns of recovery. However, these findings have been replicated in additional research. For example, Wilson and colleagues (2012) reported that following therapy, the topography of the N400 shifted in a group of chronic, primarily fluent PWAs, from right-lateralized towards a more left-lateralized component, which the authors attributed to compensatory recovery mechanisms, and not normalization. Finally, Barbancho and colleagues (2015) administered the drug memantine to individuals with fluent and nonfluent chronic aphasia both alone and in conjunction with aphasia therapy. When participants received the drug intervention only, the ERP demonstrated reduced amplitude, and when participants received memantine

plus therapy, the ERP amplitude increased. In both cases, changes in ERP amplitude were correlated with improvements on behavioral measures of language. However, only individuals who received both the drug and behavioral therapy intervention demonstrated changes in ERP amplitude that persisted over time.

Purpose of the Study

The published literature on both cognitive and language ERPs supports their use to elucidate changes in processing after stroke, to track recovery during the acute and sub-acute phases, and to measure treatment response, whether it be pharmacological or therapy-induced. The long-term goal of the current research is to establish sensitive biomarkers that would allow targeted pairing of rehabilitation to deficits and would improve diagnosis and prognosis of chronic stroke-induced deficits. However, the P300 is not well-characterized in individuals with chronic stroke, and the N150 and N350 have not been investigated in samples that also include individuals without chronic stroke-induced aphasia to determine if they are sensitive to non-linguistic cognitive changes. Further, there is limited evidence regarding the reliability and stability of cognitive and linguistic ERP components in individuals with chronic stroke.

We will characterize the P300, N150, and N350 in a mixed population of individuals with left and right hemisphere strokes and a variety of post-stroke deficits. Our rationale for doing so here is two-fold. First, improved normative information regarding ERP changes in chronic post-stroke is needed. The most efficient way to develop norms is through databases to which many individuals can contribute. Guidelines for the development of such databases suggest that it is important to maximize the variability of participants who are included, in order to have robust generalizability and

reduce the chance of statistically significant, but clinically insignificant, differences (Prichep, 2005). This paper represents the first step in developing robust norms by pairing assessment of chronic stroke deficits in multiple behavioral domains with cognitive ERPs. Future research will then be able to use this well-characterized population, and its planned expansion, to investigate the impact of specific or co-occurring deficits on a variety of ERP components. Second, behavioral assessments are often insensitive to mild but functionally debilitating changes in cognition (for an example in persons with post-stroke aphasia, see Fromm et al., 2017). By selecting only individuals who score beyond a certain cut-off on standardized assessments, we limit our ability to learn about the full range of behavioral impairments experienced by individuals with chronic stroke, and potentially mischaracterize individuals as unimpaired when they are in fact experiencing functional difficulties. The aim of the current study is to address these gaps in the literature by pursuing the following specific aims:

1. Characterize the mean amplitude in attention and language ERPs in an English-speaking control population.
2. Characterize the mean amplitude in attention and language ERPs in an English-speaking PWCS population of mixed stroke hemisphericity and impairments.
3. Identify differences in mean amplitude in cognitive and language ERPs between controls and PWCS.
4. Report reliability of mean amplitude in cognitive and language ERPs in controls and PWCS.

Methods

Participants

Healthy Controls

Twenty-seven (17 female, 10 male) healthy individuals participated in this study (**Table 1**). Participants were screened to ensure no history of neurological disease or injury that might affect brain function. Potential participants with a diagnosis of significant psychiatric mood disorders were excluded, but individuals with mild depression and anxiety were allowed to participate, as many individuals with chronic stroke suffer from depression and anxiety. Participants completed the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), and if bi- or multi-lingual, the Language Experience and Proficiency Questionnaire (LEAP-Q; Marian, Blumenfeld, & Kaushanskaya, 2007). All healthy control participants were right-handed, and seven reported speaking at least one other language, including French, Spanish, Italian, and German. No control participants reported learning another language prior to English, and all reported English as their primary language at the time of participation. The average age of participants was 63 years (*SD* = 13.2 years). Control participant ages ranged from 22 to 88 and were selected to match persons with stroke. Average education was 16.9 years (*SD* = 2.6). Participants completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), Wechsler Adult Intelligence Scales - Picture Completion subtest (WAIS-PC; Wechsler, Coalson, & Raiford, 2008), Discourse Production Test (DPT; MacWhinney, Fromm, Forbes, & Holland, 2011), aprosodia battery (AB; based off of Ross & Monnot, 2011), subtests of the Apraxia Battery for Adults - 2 (ABA-2; Dabul, 2000), and an in-house sensorimotor assessment

including sensory perception, proprioception, range of motion, and muscle tone (**Table 2**). Testing was conducted to ensure participants' performance was within the range of neurologically typical individuals. Participants completed two sessions of EEG recording, approximately one month apart. Three participants were unable to complete the follow-up EEG due to changes in schedules, these participants are included in the normative data set and comparison with participants with stroke but are not included in the reliability analysis. Please see for complete demographics for each group.

Persons with Stroke

Twenty-seven (10 female, 17 male) persons who had experienced one or more strokes also participated in this study (**Table 1**). We included participants with multiple strokes to ensure that our results are maximally applicable to the general rehabilitation population served by practicing therapists, since one of the strongest risk factors for stroke is a history of prior stroke. Seventeen individuals experienced left hemisphere stroke, 7 experienced right hemisphere stroke, and 3 experienced left and right hemisphere strokes (participant reporting of stroke location was confirmed via medical records, CT, or MRI scans when available). Thirteen individuals were diagnosed with aphasia, 14 had cognitive impairment, and 20 had sensory and/or motor deficits (**Table 2**). All participants were in the chronic phase (greater than one-year post-stroke) to ensure that spontaneous recovery was not a factor in change over time. Participants completed the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), and if bi- or multi-lingual, the Language Experience and Proficiency Questionnaire (LEAP-Q; Marian, Blumenfeld, & Kaushanskaya, 2007). All stroke participants were right-handed prior to their stroke. Three participants with stroke reported speaking more than one language (Spanish and/or

Azteca) and one participant reported Spanish as their first language, although English was the primary language for all participants at the time of testing and had been for many years. The average age of PWCS was 56.6 years (SD = 14.2 years). PWCS ages ranged from 25 to 87. Average education was 15.2 years (SD = 3.3 years). PWCS completed the same assessments as healthy controls, as well as the Western Aphasia Battery - Revised (WAB-R; Kertesz, 2006), Boston Naming Test (BNT; Kaplan, Goodglass & Weintraub, 2001), and Discourse Comprehension Test (DCT; Brookshire & Nicholas, 1997). Participants completed two sessions of EEG recording, approximately one month apart. One participant was unable to complete the follow up EEG recording due to a change in schedule. As above, this participant is included in all analyses except reliability.

EEG Recording

EEG data was recorded from 64 active electrodes in an elastic cap placed according to the 10-10 International system of classification. The ground electrode was located at Fpz with the reference electrode at CPz. Eye movement was recorded via vertical electrooculography using paired electrodes placed above and below the left eye, while heart rate was recorded via electrodes placed on the left and right collarbones. Data were recorded on a BrainVision actiCHamp system with a 500Hz sampling rate and online bandpass filtering from .01 - 100Hz.

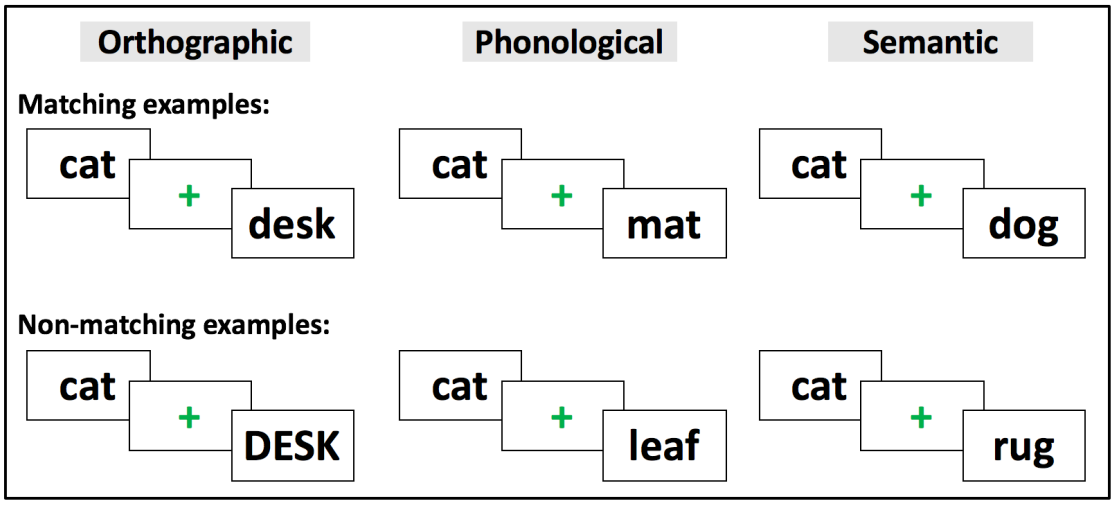
Behavioral Tasks

Participants were seated in front of a computer in a dimly lit room while completing the EEG recording. The sequence of tasks during recording was: rest, auditory oddball task, lexical decision task, semantic relatedness task, orthographic matching task, rhyme judgment task, emotion recognition task, motor imagery task, and

go/no-go task. We will limit our discussion to one cognitive task (auditory oddball) and three language tasks (orthographic matching, rhyme judgment, and semantic relatedness). During the auditory oddball task (Polich, 1998), individuals heard a commonly occurring low frequency tone (standard) which was interspersed with a rarely occurring high frequency tone (target) and oddball noises (novel) consisting of short segments of environmental or non-speech sounds (e.g., bark, meow, cough, laugh, sigh) as described by Cavanagh and colleagues (Cavanagh et al., 2018). Participants were asked to count the number of high tones they heard but were not required to make any behavioral responses while the sounds were presented. This task was used to investigate the P3a and P3b components. One hundred and twenty standard tones, 30 target tones, and 30 novel sounds were presented across two approximately 5-minute blocks.

During the language tasks (which we will refer to as orthographic, phonological, and semantic), word pairs were presented on the screen one at a time for one second to ensure participants with aphasia would be able to successfully process the stimuli. Participants were instructed to push one keyboard button if the words were related in meaning (semantic), rhymed (phonological), or matched in case (orthographic) and were instructed to push a different keyboard button if the words were not related in meaning, did not rhyme, or the case did not match (see **Figure 7**; Spironelli & Angrilli, 2015). Words were presented in white text on a black background to reduce visual fatigue. Word pairs were separated by a green plus sign, which helped visually cue participants with stroke that they should compare the two words according to the directions for that particular task. In the present study, only brain activity to the first word in each pair is evaluated, consistent with investigation of the N150 and N350 as reported by Spironelli

Figure 7. Examples of the orthographic, phonological, and semantic tasks completed by participants.



and Angrilli (2015). This also has the benefit of providing a larger dataset for averaging because no trials have to be discarded for incorrect or missing behavioral responses. Sixty word-pairs were included in each task, 30 matched and 30 non-matched, lasting approximately ten minutes.

Data Processing

Standard offline pre-processing (see **Figure 2**) using BrainVision Analyzer 2.1 was conducted to ensure adequate data quality. First, noisy channels were identified and discarded through visual inspection. Specifically, electrodes were examined for spike artifacts and high frequency electrical noise which is often due to poor contact between the electrode and scalp (e.g., Finnigan et al., 2007). The following data processing steps were conducted as described by Finnigan, Wong, and Read (2016). Next, data were high (.5Hz) and low (40Hz) pass filtered using infinite impulse response zero-phase shift Butterworth filters to minimize distortion and preserve phase information (Hamming, 1998; Oppenheim, 1999). After filtering, bad segments (i.e., muscle activity) were manually rejected and independent components analysis was conducted to remove eye

movement artifacts (Makeig, Bell, & Jung, 1996). Data were then epoched into 2048ms bins and epochs with data values greater than +/-100 microvolts and/or changes in value greater than +/-25 microvolts were rejected. For both neurologically healthy controls and PWCS, no more than 20% of data in a given channel was rejected. For the oddball task, epochs were calculated 1024 ms before and after sound presentation separately for the standard, novel, and target stimuli. For the language tasks, epochs were calculated 1024ms before and after the first word in a pair appeared on screen. Epochs were calculated separately for orthographic, phonological, and semantic tasks.

For these six datasets (orthographic, phonological, semantic, standard, novel, and target), the mean activation was calculated for each electrode by participant, and then averaged across participants to yield mean control and mean PWCS activation. The mean control waveform for the novel and target datasets were visually examined to identify the time windows for statistical comparison, taking into account previously published research. When identifying time windows of interest for each component, only peaks in the healthy control waveforms were examined in order to protect against experimenter bias (e.g., not selecting time windows with apparent visual differences between controls and PWCS to maximize likelihood of significant differences). Mean amplitude and standard deviation were calculated at each electrode. While previous literature has primarily reported on peak amplitude or peak latency, we chose mean amplitude as it is a less biased measure of activation (Clayson, Baldwin, & Larson, 2013) and is more robust to the presence of high frequency noise in the signal (Luck, 2014). Recent texts have therefore encouraged the use of mean amplitude to reduce the risk of bias and improve validity of reported findings (Luck & Gaspelin, 2017).

P3a and P3b

P3a and P3b times were selected based on a symmetric window around the largest positive peak in Fz (for P3a) and Pz (for P3b) occurring between 300-800ms (e.g., Conroy & Polich, 2007). Mean amplitude was calculated between 375-450ms for P3a and between 440-480ms for P3b. In order to compare our results with previously published findings in stroke (e.g., Dejanovic et al., 2015; Ehlers et al, 2015; Korpelainen et al., 2000; Nolfe et al, 2006; Stahlhut et al, 2014; Yamagata, Yamaguchi, & Kobayashi, 2004), we first examined mean amplitude in Fz, Cz, and Pz (for results reporting we will refer to these as historical). An additional set of electrodes were selected to examine activation away from the midline (referred to as expanded electrodes) due to the mixed hemisphericity of strokes in our PWCS group, and to leverage the density of our recording array. This expanded set of electrodes include F3, F4, C3, C4, P3, and P4.

N150 and N350

For the language tasks, mean amplitude of the N150 was calculated between 130-150ms and mean amplitude of the N350 was calculated between 300-500ms (based on Spironelli & Angrilli, 2015). In order to evaluate between-group differences, electrodes were assigned to regions of interest (ROIs). One set of ROIs were chosen to closely match ROIs reported by Spironelli and Angrilli (2015) to allow comparison of our results with previously published literature. These ROIs are: 1) left anterior (Fp1, AF7, F7); 2) left posterior (P3, P7, O1); 3) right anterior (Fp2, AF8, F8); and 4) right posterior (P4, P8, O2). We were able to use the Spironelli and Angrilli ROIs exactly for the posterior regions. However, the montage used by Spironelli and Angrilli included electrodes F9 and F10 in the anterior ROIs, which were not present in our electrode montage.

Therefore, we used Fp1 and Fp2 rather than F9 and F10 for calculation of the anterior ROIs. A second set of ROIs were also selected in order to leverage the granularity of the relatively dense electrode array used in this study. These expanded ROIs are: 1) left orbito-frontal (Fp1, AF3, AF7); 2) left antero-medial (F1, F3, FC1, FC3); 3) left antero-lateral (F5, F7, FC5, FT7); 4) left postero-medial (CP1, CP3, P1, P3); 5) left postero-lateral (CP5, TP7, P5, P7); 6) left occipital (PO3, PO7, O1); 7) right orbito-frontal (Fp2, AF4, AF8); 8) right antero-medial (F2, F4, FC2, FC4); 9) right antero-lateral (F6, F8, FC6, FT8); 10) right postero-medial (CP2, CP4, P2, P4); 11) right postero-lateral (CP6, TP8, P6, P8); 12); and right occipital (PO4, PO8, O2).

Data Analysis

All statistical analyses were conducted using SPSS. First, descriptive statistics (mean, median, standard deviation, range, skew, and kurtosis) were calculated for the control and stroke participant groups, and normality of MA distributions was assessed using skew and kurtosis for each ROI. Student's t-tests to compare differences between groups were planned. While many variables reported here violate the assumption of normality for use of t-tests, previous research has shown parametric statistics such as the t-test to be robust to violations of normality (using Bradley's definition of robustness where deviation from $p = .05$ is $\leq \pm.005$; 1978). Simulation studies have demonstrated such robustness when the absolute value of skew (the spread of the data) is less than 2, and the absolute value of kurtosis (the "peakiness" of the data) is less than 9 (Boneau, 1960; Bradley, 1982; Posten, 1978; Schmider et al., 2010). Data with skew or kurtosis outside the range for which t-tests are robust were assessed using the Mann-Whitney U test. Homogeneity of variance was assessed using the Levene's test. For variables that

violated this assumption, Welch's t-tests were used (Ruxton, 2006). Between-group comparisons were conducted using data from the first recording session. Examination of skew and kurtosis revealed that the distribution of mean amplitude was generally amenable to use of the t-test. Effect size calculations (Cohen's *d* for t-tests and η^2 for Mann-Whitney U-tests) were conducted for all comparisons that were statistically significant prior to correcting for multiple comparisons. Cohen's *d* and η^2 have a different range of possible values, so for ease of interpretation, both are reported with an estimate of the size of the effect: small, medium, or large (Cohen, 1988). Holm-Bonferroni correction for multiple comparisons were used to reduce the chance of spurious significant differences (Holm, 1979).

For the N150 and N350, effect sizes for all individual electrodes were calculated to determine which electrode(s) might be powering group differences. Additionally, while averaging across electrodes helps reduce the number of variables entered into analysis, it may also conceal differences among electrodes within a single ROI. Given the large number of comparisons and experimental nature of this analysis, results are reported via effect sizes, rather than test statistics and p-values. It is hoped that this method will allow identification of electrodes that maximally contribute to between-group differences and could help reduce dimensions of comparison in future research, while improving specificity (such as is available for the P300 components).

Finally, reliability of mean amplitude for each electrode or ROI was calculated between sessions one and two using intra-class correlation (ICC) coefficients (Koo & Li, 2016). ICCs are widely used to evaluate the psychometric properties of newly developed assessment instruments, as well as intra- and inter-rater reliability, depending on the

specific test parameters selected. The interpretation of the ICCs conducted for this study differ from the more commonly known Spearman and Pearson correlations. A Spearman or Pearson correlation is used to assess how strongly related two variables are with each other. This does not require that the variables be similar in value, only that the values change together in a predictable, linear manner. However, the ICCs conducted here assessed the exactness of the match between, for example, the value of mean amplitude at AFz in session one and the value of mean amplitude at AFz in session two in response to target tones. The closer these values are to each other, the stronger the correlation, and the more stable the measure over time. For readability, only the point estimate of the ICC is reported in the text, but 95% confidence intervals are reported in the tables to allow for more nuanced interpretations of reliability.

Results

P3a

Descriptive statistics in healthy controls

Historical. See Appendix B (**Table B1-B4**) for full P3a descriptive statistics. For healthy controls, positive mean amplitude was observed in response to target (M = 2.016μV, SD = 2.211) and novel sounds for Fz (M = 23.359μV, SD = 1.756), target (M = 1.679μV, SD = 2.478) and novel (M = 1.661μV, SD = 2.393) sounds for Cz, and target sounds for Pz (M = 1.734μV, SD = 2.068). A negative mean amplitude was observed to novel sounds in Pz (M = -0.471μV, SD = 1.978).

Expanded. When examining the expanded electrodes, controls demonstrated positive mean amplitude in response to target sounds for all electrodes, ranging from 0.596μV (SD = 1.186) in electrode P3 to 1.357μV (SD = 1.921) in F3. In response to

novel sounds, controls demonstrated positive amplitudes in F3, F4, C3, and C4 (ranging from 0.809μV, SD = 0.809 to 2.513μV, SD = 1.504). Negative mean amplitudes were observed to novel sounds in P3 (-1.436μV, SD = 1.294) and P4 (-1.229μV, SD = 1.753).

Descriptive statistics in PWCS

Historical. Positive mean amplitude in response to target and novel stimuli was also observed for PWCS in Fz (1.281μV, SD = 1.552 and 2.017μV, SD = 1.850, respectively), Cz (1.254μV, SD = 1.328 and 1.442μV, SD = 1.445, respectively), and Pz (.953μV, SD = 1.378; target only). Again, negative mean amplitude was observed in response to novel sounds in Pz (-0.273μV, SD = 1.478).

Expanded. Following the same pattern as seen above in controls, PWCS showed positive mean amplitude in response to target sounds for all expanded electrodes (ranging from 0.036μV, SD = 1.237 to 1.199, SD = 1.822μV), except P3 (-0.407μV, SD = 1.883). Positive mean amplitude in response to novel sounds was observed in F3, F4, C3, and C4, ranging from 0.539μV (SD = 1.470) to 1.588μV (SD = 1.598). Mean amplitude for PWCS in response to novel tones was negative for P3 (-1.234μV, SD = 1.866) and P4 (-0.501μV, SD = 1.207).

Between group comparisons

Historical. Overall, healthy controls had a larger, more positive mean amplitude than PWCS (**Table 9**). A statistically significant difference with medium effect size in mean amplitude was observed in electrode Fz in response to novel sounds ($t = 2.733$, $p = .009$, $d = .744$).

Expanded. When examining the expanded set of electrodes, none reached statistical significance for mean amplitude after correcting for multiple comparisons.

Table 9. Test statistic, p-value, and effect size for between group comparisons during P3a. Comparisons that survived correction for multiple comparisons are bolded. Comparisons that were not statistically significant but showed a medium or large effect size are italicized.

	Target	**Novel**
	Historical	
	$t = 1.414$	***t* = 2.733**
Fz	$p = 0.164$	***p* = 0.009**
	$d = 0.385$	***d* = 0.744**
	$t = 0.786$	$t = 0.406$
Cz	$p = 0.436$	$p = 0.687$
	$d = 0.214$	$d = 0.111$
	$t = 1.634$	$t = -0.418$
Pz	$p = 0.108$	$p = 0.678$
	$d = 0.445$	$d = 0.114$
	Expanded	
	$t = 1.545$	*t = 2.167*
F3	$p = 0.129$	*p = 0.035*
	$d = 0.424$	*d = 0.596*
	$t = -0.318$	$t = 1.826$
F4	$p = 0.752$	$p = 0.075$
	$d = 0.087$	$d = 0.497$
	$t = 1.748$	$t = 1.513$
C3	$p = 0.086$	$p = 0.136$
	$d = 0.476$	$d = 0.412$
	$t = 1.256$	$t = 0.112$
C4	$p = 0.215$	$p = 0.911$
	$d = 0.110$	$d = 0.031$
	t = 1.994	$t = -0.464$
P3	*p = 0.051*	$p = 0.645$
	d = 0.543	$d = 0.126$
	$t = 0.801$	$t = -1.777$
P4	$p = 0.427$	$p = 0.081$
	$d = 0.218$	$d = 0.484$

Several electrodes exhibited medium effects sizes and may be of interest for future research. In particular, mean amplitude in P3 showed a medium effect in response to target sounds ($t = 1.994$, $p = .051$, $d = .543$) and in F3 showed a medium effect in response to novel sounds ($U = 244$, $p = .057$, $\eta^2 = .070$). For both electrodes mean amplitude was larger in healthy controls than PWCS (and in fact PWCS showed negative mean amplitude in P3).

Reliability in healthy controls

Historical. When examining the reliability of electrodes Fz, Cz, and Pz, inadequate reliability was observed for all electrodes and variables in response to target tones (**Table 10**). In contrast, moderate to good reliability for controls was observed in response to novel tones. Moderate reliability of mean amplitude (ICC = .678) was seen for Fz and good reliability was seen for Cz (ICC = .848) and Pz (ICC = .846).

Expanded. Similar to the historical electrodes, no electrodes in the expanded set showed adequate reliability in response to target sounds. Moderate reliability was seen for controls to novel sounds in F4 (ICC = .542), C4 (ICC = .675), P3 (ICC = .649), and P4 (ICC = .610). Inadequate reliability was observed for controls in response to novel tones in F3 and C3.

Reliability in PWCS

Historical. When examining the reliability of electrodes Fz, Cz, and Pz, inadequate reliability was observed for all electrodes and variables in response to target tones. For PWCS, moderate reliability in response to novel sounds was seen only for Fz (ICC = .709) and Cz (ICC = .731).

Table 10. Intra-class correlation coefficients for neurologically healthy controls and persons with stroke during P3a. *Moderate*, good, and *excellent* reliability are shown.

	Target		**Novel**	
	Con	**PWS**	**Con**	**PWS**
Historical				
Fz	-	.031	**.678**	**.709**
		0-.347	**.388-.846**	**.429-.864**
Cz	.011	-	**.848**	**.731**
	0-.376		**.681-.931**	**.46-.877**
Pz	.055	-	**.846**	.413
	0-.41		**.68-.93**	.016-.697
Expanded				
F3	.006	-	.497	**.775**
	0-.374		.128-.748	**.551-.895**
F4	-	.012	**.542**	**.721**
		0-.28	**.199-.77**	**.386-.877**
C3	.410	.041	.415	**.723**
	0-.701	0-.365	.021-.697	**.464-.87**
C4	-	.023	**.675**	**.763**
		0-.341	**.388-.844**	**.518-.892**
P3	.005	-	**.649**	**.820**
	0-.306		**.349-.83**	**.632-.917**
P4	.031	.011	**.610**	**.593**
	0-.302	0-.306	**.276-.811**	**.258-.801**

Expanded. PWCS demonstrated moderate to good reliability in all expanded electrodes. Moderate reliability was demonstrated for F4 (ICC = .721), C3 (ICC = .723), and P4 (ICC = .593). Good reliability was demonstrated for F3 (ICC = .775), C4 (ICC = .763), and P3 (ICC = .820).

P3b

Descriptive statistics in healthy controls

Historical. See Appendix B (**Tables B5-B8**) for full P3b descriptive statistics. For healthy controls, positive mean amplitude was observed in response to target and novel sounds for Fz (1.334μV and 2.877μV, respectively), Cz (1.466μV and 1.265μV, respectively), and Pz (2.72μV and .402μV, respectively).

Expanded. Controls demonstrated positive mean amplitude in response to target sounds for all electrodes, ranging from 0.228μV (SD = 1.912) in F4 to 1.634μV (SD = 1.903) in P3. In response to novel sounds, controls demonstrated positive amplitudes in F3, F4, C3, and C4 (ranging from 0.668μV, SD = 1.242 to 1.942μV, SD = 1.277). Negative mean amplitudes were observed to novel sounds in P3 (-0.65μV, SD = 1.524) and P4 (-0.403μV, SD = 1.512).

Descriptive statistics in PWCS

Historical. Positive mean amplitude in response to target and novel stimuli was also observed for PWCS in Fz (1.044μV, SD = 1.850 and 1.891μV, SD = 2.215, respectively), Cz (1.240μV, SD = 1.487 and 1.463, SD = 1.869μV, respectively), and Pz (1.449μV, SD = 1.809 and 0.344μV, SD = 1.610, respectively).

Expanded. Following the same pattern, positive mean amplitude in response to target sounds was observed for all expanded electrodes and ranged from 0.135μV (SD = 2.238) to 0.885μV (SD = 1.950) in PWCS. Positive mean amplitude in response to novel sounds was observed in all but one electrode, ranging from 0.018μV (SD = 1.462) in P4 to 1.606μV (SD = 1.829) in F3. A negative mean amplitude was observed in P3 (-0.987μV, SD = 2.633).

Between group comparisons

Historical. No significant differences in mean amplitude survived correction for multiple comparisons (**Table 11**). However, medium effects in mean amplitude were seen in Pz (t = 2.404, p = .020, d = .654) to target tones and Fz (t = 1.918, p = .061, d = .522) to novel tones. For both, healthy controls had a larger, positive mean amplitude than PWCS.

Expanded. No significant differences in mean amplitude survived correction for multiple comparisons in the expanded set. A medium effect was observed in P3 (t = 2.651, p = .011, d = .722) in response to target tones, and mean amplitude in P3 was larger for healthy control than PWCS. No significant differences or medium to large effect sizes were observed in response to novel sounds for mean amplitude.

Reliability in healthy controls

Historical. Cz and Pz demonstrated moderate reliability (**Table 12**) in response to target and novel sounds (Cz: ICC = .538 and .588, respectively; Pz: ICC = .653 and ICC = .635, respectively), while Fz demonstrated good reliability in response to target tones only (ICC = .753).

Table 11. Test statistic, p-value, and effect size for between group comparisons during P3b. Comparisons that survived correction for multiple comparisons are bolded. Comparisons that were not statistically significant but showed a medium or large effect size are italicized.

	Target	Novel
	Historical	
	t = 0.524	*t = 1.918*
Fz	*p* = 0.603	*p = 0.061*
	d = 0.143	*d = 0.522*
	t = -0.091	*t* = -0.409
Cz	*p* = 0.928	*p* = 0.684
	d = 0.025	*d* = 0.111
	t = 2.404	*t* = 0.123
Pz	*p = 0.020*	*p* = 0.902
	d = 0.654	*d* = 0.034
	Expanded	
	t = 0.551	*t* = 0.773
F3	*p* = 0.584	*p* = 0.443
	d = 0.151	*d* = 0.213
	t = -0.973	*t* = 1.342
F4	*p* = 0.335	*p* = 0.185
	d = 0.340	*d* = 0.365
	t = 1.476	*t* = 0.541
C3	*p* = 0.146	*p* = 0.591
	d = 0.402	*d* = 0.147
	t = -1.488	*t* = 0.021
C4	*p* = 0.143	*p* = 0.983
	d = 0.405	*d* = 0.006
	t = 2.651	*t* = 0.575
P3	*p = 0.011*	*p* = 0.567
	d = 0.722	*d* = 0.157
	t = 1.531	*t* = -1.040
P4	*p* = 0.132	*p* = 0.303
	d = 0.417	*d* = 0.283

Table 12. Intra-class correlation coefficients for neurologically healthy controls and persons with stroke during P3b. *Moderate*, good, and *excellent* reliability are shown.

	Target		**Novel**	
	Con	**PWS**	**Con**	**PWS**
Historical				
Fz	**.753** **.510-.885**	.425 .056-.698	.497 .132-.744	**.686** **.395-.851**
Cz	**.538** **.187-.769**	**.554** **.187-.784**	**.588** **.249-.798**	**.709** **.442-.862**
Pz	**.653** **.343-.834**	.447 .063-.716	**.635** **.317-.824**	.428 .04-.704
Expanded				
F3	**.587** **.247-.8**	-	-	**.661** **.355-.838**
F4	**.632** **.323-.82**	**.605** **.136-.829**	.143 0-.517	**.711** **.445-.863**
C3	**.622** **.293-.818**	.389 0-.68	**.531** **.163-.768**	**.504** **.135-.75**
C4	.189 0-.527	**.525** **.169-.764**	**.539** **.185-.77**	**.592** **.259-.8**
P3	**.806** **.602-.911**	.390 .011-.676	**.581** **.245-.794**	**.837** **.661-.926**
P4	**.575** **.24-.79**	.266 0-.601	.470 .083-.732	.482 .103-.738

Expanded. Mean amplitude reliability in response to target tones was moderate to good in all electrodes (ICC from .575 to .806) except C4 (ICC = .189). In contrast, only moderate reliability of mean amplitude in response to novel tones was seen for C3 (ICC =.531), C4 (ICC = .539), and P3 (ICC = .581).

Reliability in PWCS

Historical. PWCS demonstrated moderate reliability in Fz to novel sounds and Cz to both target (ICC = .554) and novel sounds (ICC = .709).

Expanded. For PWCS, moderate reliability in response to target sounds was seen in F4 (ICC = .605) and C4 (ICC = .525). Reliability was stronger for PWCS in response to novel sounds, as moderate reliability was observed for F3 (ICC = .661), F4 (ICC = .711), C3 (ICC = .504), and C4 (ICC = .592) and good reliability was observed for P3 (ICC = .837).

N150

Descriptive statistics in healthy controls

Spironelli and Angrilli. See Appendix B (**Table B9-B14**) for full N150 descriptive statistics. For healthy controls, negative mean amplitude was seen in the left anterior (-0.459μV, SD = 1.429) and right anterior (-0.033μV, SD = 1.396) ROIs during the *orthographic* task. During the *phonological* task, negative mean amplitude was also seen for left anterior (-0.517μV, SD = 1.582) and right anterior (-0.265μV, SD = 1.627) ROIs. The *semantic* task also showed negative mean amplitude in left anterior (-0.760μV, SD = 1.488) and right anterior (-0.311μV, SD = 1.332) ROIs. Positive mean amplitude was measured in left and right posterior ROIs, ranging from .164μV (SD = 2.020) in *orthographic* to 3.676μV (SD = 2.256) in *phonological*.

Expanded. When examining the expanded set of ROIs, healthy controls showed negative mean amplitude during the *orthographic* task in left orbito-frontal, left antero-medial, left antero-lateral, right orbito-frontal, right antero-medial, and right antero-lateral ROIs, ranging from -0.182μV (SD = 1.269) to -0.482μV (SD = 1.555). During the *phonological* task, negative mean amplitude was observed in left and right orbito-frontal, antero-medial, and antero-lateral ROIs, ranging from -0.327μV (SD = 1.080) to -0.606μV (SD = 1.648). During the *semantic* task, negative mean amplitude followed the same pattern as orthographic and phonological, with amplitude ranging from -0.265μV (SD = 1.162) to -0.732μV (SD = 1.570). Positive mean amplitude during the *orthographic* task was seen in left postero-medial, left postero-lateral, left occipital, right postero-medial, right postero-lateral, and right occipital ROIs ranging from 0.065μV (SD = 0.835) to 1.579μV (SD = 1.140). Positive mean amplitude during the *phonological* task was observed in the same ROIs as in the orthographic, with amplitude ranging from 0.205μV (SD = 0.841) to 1.759μV (SD = 1.269). Again, positive mean amplitude was observed in the posterior left and right ROIs during the *semantic* task, ranging from 0.221μV (SD = 0.732) to 1.640μV (SD = 1.142).

Descriptive statistics in PWCS

Spironelli and Angrilli. In PWCS, negative mean amplitude was observed in left anterior (-0.128μV, SD = 1.693) and right anterior (-0.279μV, SD = 1.427) ROIs during the *orthographic* tasks. During the phonological task, negative amplitude was only seen in left anterior (-0.593μV, SD = 1.838) and right anterior (-0.762μV, SD = 1.324) ROIs. Again, for the *semantic* task, negative mean amplitude was seen only in the left (-0.581μV, SD = 2.065) and right (-0.451μV, SD = 1.426) anterior ROIs. For PWCS,

positive mean amplitudes ranged from 0.049μV (SD = 1.991) in *orthographic* to 4.289μV (SD = 1.775) in *phonological*.

Expanded. During the *orthographic* task in PWCS, negative mean amplitude was observed for the left orbito-frontal, left antero-medial, left antero-lateral, right orbito-frontal, right antero-medial, and right antero-lateral ROIs, ranging from -0.044μV (SD = 1.374) to -0.357μV (SD = 1.569). During the *phonological* task, negative mean amplitude in PWCS followed the same pattern as in controls - left and right orbito-frontal, antero-medial, and antero-lateral ROIs, although PWCS amplitude ranged from -0.441μV (SD = 1.179) to -0.967μV (SD = 1.445). During the *semantic* task, negative mean amplitude was observed in left and right orbito-frontal, left and right antero-lateral, and left antero-medial ROIs, ranging from -0.109μV (SD = 1.212) to -0.619μV (SD = 1.859). Positive mean amplitude ranging from .032μV (SD = 1.004) to 2.223μV (SD = 1.082) during the *orthographic* task was seen in left antero-medial, left postero-medial, left postero-lateral, left occipital, right postero-medial, right postero-lateral, and right occipital ROIs. Positive mean amplitude during the *phonological* task ranged from 0.231μV (SD = 0.837) to 2.631μV (SD = 1.071) in left and right postero-medial, left and right postero-lateral, and left and right occipital ROIs. Finally, during the *semantic* task, positive mean amplitude was seen in right antero-medial, left and right postero-medial, left and right postero-lateral, and left and right occipital ROIs, ranging from 0.005μV (SD = 1.515) to 2.149μV (SD = 1.284).

Between group comparisons

Spironelli and Angrilli. No significant differences in mean amplitude between controls and PWCS were observed for the left and right anterior and posterior ROIs (**Table 13**). Further, no comparisons had moderate or large effect sizes.

Expanded. No significant differences survived correction for multiple comparisons in the expanded ROI set. However, the left postero-lateral ROI demonstrated medium effects during the orthographic (t = -2.112, p = 0.040, d = 0.580) and semantic tasks (t = -2.708, p = .009, d = .743). Investigation of descriptive statistics revealed that for both ROIs, PWCS had larger, positive mean amplitudes than healthy controls.

Single electrodes. Effect sizes for the between-group comparison were calculated for each electrode and task separately. No medium or large effect sizes were observed in single electrodes during the orthographic and phonological tasks. Medium effect sizes were observed in F3 (d = .711), FC5 (d = .509), F1 (d = .553), F5 (d = .515), and FC3 (d = .573) during the *semantic* task.

Reliability in healthy controls

Spironelli and Angrilli. In healthy controls, during the *orthographic* task (**Table 14**), moderate reliability was seen in the left anterior (ICC = .661), right anterior (ICC = .762), and right posterior (ICC = .589) ROIs. Excellent reliability was seen in the left posterior ROI (ICC = .907). During the *phonological* task, moderate reliability was observed in the right anterior (ICC = .655) and posterior (ICC = .525) ROIs, with good reliability in the left posterior (ICC = .837) ROI. During the *semantic* task, moderate reliability was again observed in the right hemisphere ROIs (ICC = .623, anterior;

Table 13. Test statistic, p-value, and effect size for between group comparisons during N150. Comparisons that survived correction for multiple comparisons are bolded. Comparisons that were not statistically significant but showed a medium or large effect size are italicized.

	Orthographic	Phonological	Semantic
Spironelli & Angrilli ROIs			
Left Anterior	t = -0.748 p = 0.458 d = 0.211	t = -0.353 p = 0.726 d = 0.099	t = 0.157 p = 0.876 d = 0.044
Left Posterior	t = 0.208 p = 0.836 d = 0.057	t = 0.338 p = 0.736 d = 0.093	t = -0.314 p = 0.755 d = 0.086
Right Anterior	t = 0.615 p = 0.541 d = 0.174	t = 0.359 p = 0.721 d = 0.101	t = 1.184 p = 0.242 d = 0.335
Right Posterior	t = -0.924 p = 0.360 d = 0.253	t = -0.365 p = 0.716 d = 0.100	t = -1.103 p = 0.275 d = 0.302
Granular ROIs			
Left Orbito-Frontal	t = -0.289 p = 0.774 d = 0.080	t = -0.238 p = 0.813 d = 0.066	t = 0.508 p = 0.613 d = 0.141
Left Antero-Medial	t = 0.112 p = 0.911 d = 0.031	t = -1.051 p = 0.298 d = 0.289	t = -0.030 p = 0.976 d = 0.008
Left Antero-Lateral	t = -0.769 p = 0.445 d = 0.212	t = -0.917 p = 0.365 d = 0.251	t = -0.149 p = 0.882 d = 0.041
Left Postero-Medial	t = 0.131 p = 0.896 d = 0.036	t = 0.824 p = 0.414 d = 0.227	t = -0.111 p = 0.912 d = 0.030
Left Postero-Lateral	*t = -2.112* *p = 0.040* *d = 0.580*	t = -1.523 p = 0.134 d = 0.419	*t = -2.708* *p = 0.009* *d = 0.743*
Left Occipital	t = 0.106 p = 0.916 d = 0.029	t = 0.543 p = 0.590 d = 0.150	t = -0.115 p = 0.909 d = 0.032
Right Orbito-Frontal	t = 0.262 p = 0.794 d = 0.073	t = 0.420 p = 0.677 d = 0.116	t = 1.258 p = 0.214 d = 0.349
Right Antero-Medial	t = -0.009 p = 0.993 d = 0.002	t = -0.725 p = 0.472 d = 0.200	t = -0.023 p = 0.982 d = 0.006
Right Antero-Lateral	t = -0.176 p = 0.861 d = 0.048	t = -0.939 p = 0.352 d = 0.259	t = 0.551 p = 0.584 d = 0.152
Right Postero-Medial	t = 0.978 p = 0.333 d = 0.269	t = 1.137 p = 0.261 d = 0.314	t = 0.069 p = 0.946 d = 0.019
Right Postero-Lateral	t = -0.132 p = 0.895 d = 0.036	t = 0.199 p = 0.843 d = 0.055	t = -0.200 p = 0.842 d = 0.055
Right Occipital	t = 0.089 p = 0.929 d = 0.024	t = 0.538 p = 0.593 d = 0.147	t = -0.139 p = 0.890 d = 0.038

Table 14. Intra-class correlation coefficients for neurologically healthy controls and persons with stroke during N150. *Moderate*, good, and *excellent* reliability are shown.

	Orthographic		**Phonological**		**Semantic**	
	Control	**PWCS**	**Control**	**PWCS**	**Control**	**PWCS**
Spironelli & Angrilli ROIs						
Left Anterior	**.661**	.378	.433	.292	**.798**	-
	.356-.84	0-.687	.033-.713	0-.641	**.582-.909**	
Left Posterior	**.907**	**.703**	**.837**	**.762**	**.887**	**.621**
	.795-.96	**.422-.86**	**.658-.927**	**.529-.889**	**.752-.95**	**.292-.817**
Right Anterior	**.762**	.344	**.655**	.069	**.623**	.432
	.509-.894	0-.664	**.316-.845**	0-.638	**.267-.829**	.039-.714
Right Posterior	**.589**	**.674**	**.525**	.365	**.583**	**.696**
	.225-.805	**.376-.845**	**.168-.764**	0-.664	**.246-.797**	**.417-.856**
Granular ROIs						
Left Orbito-Frontal	**.742**	.401	**.618**	.481	**.831**	.364
	.485-.881	0-.694	**.284-.818**	.09-.742	**.644-.924**	0-.671
Left Antero-Medial	**.759**	**.736**	**.593**	.499	**.747**	**.573**
	.515-.89	**.476-.877**	**.257-.803**	.141-.745	**.488-.885**	**.229-.79**
Left Antero-Lateral	**.661**	.413	**.601**	.196	**.638**	.424
	.329-.844	.011-.697	**.262-.809**	0-.547	**.308-.829**	.052-.698
Left Postero-Medial	**.758**	.351	**.613**	-	**.687**	.372
	.509-.89	0-.658	**.279-.815**		**.4-.853**	0-.672
Left Postero-Lateral	**.778**	**.614**	**.614**	**.556**	**.534**	.496
	.55-.899	**.294-.811**	**.277-.816**	**.218-.778**	**.156-.773**	.116-.747
Left Occipital	**.889**	**.757**	**.833**	**.818**	**.894**	**.728**
	.757-.952	**.515-.887**	**.646-.926**	**.627-.916**	**.766-.953**	**.464-.873**
Right Orbito-Frontal	**.828**	.266	**.798**	.194	**.734**	.479
	.641-.923	0-.609	**.583-.909**	0-.552	**.467-.878**	.109-.737
Right Antero-Medial	**.751**	**.636**	**.763**	.458	**.718**	**.653**
	.494-.887	**.315-.825**	**.522-.892**	.097-.718	**.439-.871**	**.345-.834**
Right Antero-Lateral	**.733**	.341	**.670**	-	**.582**	.441
	.466-.878	0-.652	**.36-.846**		**.241-.797**	.057-.712
Right Postero-Medial	**.731**	**.571**	**.704**	.463	**.768**	.465
	.466-.876	**.22-.79**	**.424-.862**	.1-.722	**.527-.895**	.08-.728
Right Postero-Lateral	**.826**	**.758**	**.736**	**.764**	**.715**	**.718**
	.637-.922	**.514-.888**	**.469-.879**	**.534-.89**	**.435-.869**	**.455-.866**
Right Occipital	***.907***	**.720**	**.874**	**.681**	**.836**	**.759**
	.787-.96	**.458-.868**	**.725-.944**	**.397-.847**	**.655-.927**	**.523-.887**

ICC = .583, posterior), while good reliability was observed in the left hemisphere ROIs (ICC = .798, anterior; ICC = .887, posterior). Overall, the left posterior ROI showed the strongest reliability.

Expanded. During the *orthographic* task, moderate reliability (ICC ranging from .661 to .742) was observed in left orbito-frontal, left antero-lateral, right antero-lateral, and right postero-medial ROIs. Good reliability (ICC ranging from .751 to .889) was observed in left antero-medial, left postero-medial, left postero-lateral, left occipital, right orbito-frontal, right antero-medial, and right postero-lateral ROIs. Finally, excellent reliability (ICC = .907) was observed in the right occipital ROI. During the *phonological* task, moderate reliability (ICC ranging from .601 to .736) was observed in the left orbito-frontal, left antero-medial, left antero-lateral, left postero-medial, left postero-lateral, right antero-lateral, right postero-medial, and right postero-lateral ROIs. Good reliability (ICC ranging from .763 to .874) was observed in left occipital, right orbito-frontal, right antero-medial and right occipital ROIs. During the *semantic* task, moderate reliability (ICC ranging from .534 to .747) was observed in left antero-medial, left antero-lateral, left postero-medial, left postero-lateral, right orbito-frontal, right antero-medial, right anter-lateral, and right postero-lateral ROIs. Good reliability (ICC ranging from .768 to .894) was observed in left orbito-frontal, left occipital, right postero-medial, and right occipital ROIs. Across all tasks, the right occipital ROI, followed by the left postero-lateral ROI, showed the strongest reliability.

Reliability in PWCS

Spironelli and Angrilli. During the *orthographic* task, PWCS demonstrated moderate reliability in the left (ICC = .703) and right (ICC = .674) posterior ROIs.

During the *phonological* task, good reliability was seen only for the left posterior ROI (ICC = .762). During the *semantic* task, moderate reliability was observed for the left (ICC = .621) and right (ICC = .696) posterior ROIs. Similar to controls, the left posterior ROI showed the strongest reliability for PWCS.

Expanded. During the *orthographic* task, moderate reliability (ICC ranging from .571 to .736) was observed in the left antero-medial, left postero-lateral, right antero-medial, right postero-medial, and right occipital ROIs. Good reliability was observed only in the right postero-lateral ROI (ICC = .758). During the *phonological* task, moderate reliability was observed in the left postero-lateral (ICC = .556) and right occipital (ICC = .681) ROIs. Good reliability was observed in the left occipital (ICC = .818) and right postero-lateral (ICC = .764) ROIs. During the semantic task, moderate reliability (ICC ranging from .573 to .728) was observed in left antero-medial, left occipital, right antero-medial, and right postero-lateral ROIs.

N350

Descriptive statistics in healthy controls

Spironelli and Angrilli. See Appendix B (**Table B15-B20**) for full N350 descriptive statistics. In healthy controls during the *orthographic* task, mean amplitude was negative in the left anterior (-0.539μV, SD = 1.398) and right anterior (-0.653μV, SD = 1.229) ROIs and positive in the left posterior (0.070μV, SD = 1.286) and right posterior (2.992μV, SD = 1.787) ROIs. During the *phonological* task, negative mean amplitude was observed in left anterior (-0.660μV, SD = 1.154) and right anterior (-0.883μV, SD = 1.178) ROIs, while positive mean amplitude was observed in left posterior (0.240μV, SD = 1.139) and right posterior (3.380μV, SD = 1.648) ROIs. The *semantic* task has the

same pattern, where left anterior (-0.561μV, SD = 0.857) and right anterior (-0.721μV, SD = 0.939) ROIs showed negative and left posterior (0.094μV, SD = 1.236) and right posterior (3.362μV, SD = 1.691) ROIs showed positive mean amplitude.

Expanded. For healthy controls, negative mean amplitude was observed during the *orthographic* task in left orbito-frontal, left occipital, right orbito-frontal, right antero-medial, right antero-lateral, right postero-lateral, and right occipital ROIs with values ranging from -0.134μV (SD = 1.672) to -.773μV (SD = 1.293). During the *orthographic* task, mean amplitude was positive in left antero-medial, left antero-lateral, left postero-medial, left postero-lateral, and right postero-medial with values ranging from 0.008μV (SD = 0.766) and 1.625μV (SD = 0.954). During the *phonological* task, negative mean amplitude was observed in left orbito-frontal, left antero-medial, left antero-lateral, right orbito-frontal, right antero-medial, and right antero-lateral ROIs (from -0.118μV, SD = 0.812 to -1.023μV, SD = 1.160) while positive mean amplitude was observed in left postero-medial, left postero-lateral, left occipital, right postero-medial, right postero-lateral, and right occipital ROIs ranging from 0.110μV (SD = 0.924) to 1.586μV (SD = 0.934). During the *semantic* task, negative mean amplitude ranged from -0.026μV (SD = 1.572) to -0.874μV (SD = 0.922) in left orbito-frontal, left antero-medial, left antero-lateral, left occipital, right orbito-frontal, right antero-medial, and right antero-lateral. Positive mean amplitude during the *semantic* task, ranging from 0.058μV (SD = 0.966) to 1.481μV (SD = 1.067), was observed in left postero-medial, left postero-lateral, right postero-medial, right postero-lateral, and right occipital.

Descriptive statistics in PWCS

Spironelli and Angrilli. In PWCS during the *orthographic* task, mean amplitude was negative in the left anterior (-0.039μV, SD = 1.149) and right anterior (-0.667μV, SD = 1.493) ROIs while mean amplitude was positive in left posterior (0.324μV, SD = 1.572) and right posterior (3.905μV, SD = 1.167) ROIs. During the *phonological* task, mean amplitude was negative only in the left posterior ROI (-0.676μV, SD = 2.113). Positive mean amplitude in left anterior, right anterior and right posterior ROIs during the *phonological* task ranged from 0.200μV, (SD = 1.334) to 3.275μV (SD = 1.558). Mean amplitude during the *semantic* task was negative in left (-0.559μV, SD = 1.597) and right (-0.745μV, SD = 1.108) anterior ROIs and positive in left (0.584μV, SD = 1.551) and right (4.122μV, SD = 1.242) posterior ROIs.

Expanded. For PWCS, negative mean amplitude was observed during the *orthographic* task in left orbito-frontal, left antero-medial, right orbito-frontal, right antero-medial, and right antero-lateral ROIs ranging from -0.168μV (SD = 0.895) to -0.517μV (SD = 1.533). Positive mean amplitude during the *orthographic* task was seen in left antero-lateral, left postero-medial, left postero-lateral, left occipital, right postero-medial, right postero-lateral, and right occipital ROIs ranging from 0.148μV (SD = 1.136) to 2.212μV (SD = 1.636). During the *phonological* task, negative mean amplitude ranged from -0.055μV (SD = 1.308) to -0.721μV (SD = 2.442) in left orbito-frontal, left occipital, right orbito-frontal, right postero-latral, and right occipital ROIs while positive amplitude ranged from 0.033μV (SD = 1.220) to 1.785μV (SD = 1.266) in left antero-medial, left antero-lateral, left postero-medial, left postero-lateral, right antero-medial, right antero-lateral, and right postero-medial. Finally, during the *semantic* task, negative

mean amplitude ranged from -0.229μV (SD = 1.452) to -0.897μV (SD = 1.219) in left orbito-frontal, left antero-medial, left antero-lateral, right orbito-frontal, right antero-medial, and right antero-lateral ROIs while positive mean amplitude ranged from 0.238μV (SD = 0.791) to 2.234μV (SD = 1.642) in left postero-medial, left postero-lateral, left occipital, right postero-medial, right postero-lateral, and right occipital.

Between group comparisons

Spironelli and Angrilli. No significant differences in mean amplitude were observed between controls and PWCS (**Table 15**). Additionally, no comparisons exhibited medium to large effect sizes.

Expanded. Again, no significant differences were observed between controls and PWCS in the expanded ROI list. Comparisons with medium effect sizes were observed in *orthographic* left orbito-frontal ($t = 2.183$, $p = .034$, $d = 0.601$) and *phonological* left postero-medial ($t = 2.279$, $p = .027$, $d = .627$) mean amplitude. Inspection of descriptive statistics revealed that controls had a more negative mean amplitude in the left orbito-frontal ROI and a more positive mean amplitude in the left postero-medial ROI than PWCS.

Single electrodes. A large effect was observed during the *orthographic* task in C3 ($d = .954$). In addition, medium effects were observed during the *orthographic* task in CP1 ($d = .614$), O2 ($d = .524$), P8 ($d = .613$), CP2 ($d = .564$), C1 ($d = .582$), CP3 ($d = .739$), P1 ($d = .504$), PO8 ($d = .516$). During the *phonological* task, medium effects in single electrodes were seen in CP1 ($d = .611$), P1 ($d = .501$), P2 ($d = .526$), POz ($d = .513$), and CPz ($d = .506$). During the semantic task, a single medium effect was observed in O2 ($d = .5$).

Table 15. Test statistic, p-value, and effect size for between group comparisons during N350. Comparisons that survived correction for multiple comparisons are bolded. Comparisons that were not statistically significant but showed a medium or large effect size are italicized.

	Orthographic	Phonological	Semantic
Spironelli & Angrilli ROIs			
Left Anterior	$t = 0.767$ $p = 0.447$ $d = 0.211$	$t = -1.378$ $p = 0.175$ $d = 0.388$	$t = -0.007$ $p = 0.994$ $d = 0.002$
Left Posterior	$t = -0.283$ $p = 0.779$ $d = 0.078$	$t = -0.712$ $p = 0.480$ $d = 0.196$	$t = -1.269$ $p = 0.210$ $d = 0.349$
Right Anterior	$t = 0.734$ $p = 0.466$ $d = 0.203$	$t = -0.552$ $p = 0.583$ $d = 0.156$	$t = 0.081$ $p = 0.936$ $d = 0.023$
Right Posterior	$U = 316$ $p = 0.533$ $\eta^2 = 0.007$	$U = 314$ $p = 0.510$ $\eta^2 = 0.008$	$U = 278$ $p = 0.194$ $\eta^2 = 0.032$
Granular ROIs			
Left Orbito-Frontal	**$t = 2.183$** **$p = 0.034$** **$d = 0.601$**	$t = -0.691$ $p = 0.493$ $d = 0.192$	$t = 0.667$ $p = 0.508$ $d = 0.185$
Left Antero-Medial	$t = 0.226$ $p = 0.822$ $d = 0.062$	$t = 0.675$ $p = 0.503$ $d = 0.186$	$t = 0.981$ $p = 0.331$ $d = 0.270$
Left Antero-Lateral	$t = -1.178$ $p = 0.244$ $d = 0.324$	$t = -0.412$ $p = 0.682$ $d = 0.114$	$U = 275$ $p = 0.176$ $\eta^2 = 0.035$
Left Postero-Medial	$t = -0.044$ $p = 0.965$ $d = 0.012$	*$t = 2.279$* *$p = 0.027$* *$d = 0.627$*	$t = 0.849$ $p = 0.400$ $d = 0.233$
Left Postero-Lateral	$U = 339$ $p = 0.831$ $\eta^2 = 0.001$	$t = -0.054$ $p = 0.957$ $d = 0.015$	$t = -0.484$ $p = 0.631$ $d = 0.134$
Left Occipital	$t = -0.633$ $p = 0.529$ $d = 0.174$	$t = -1.412$ $p = 0.164$ $d = 0.389$	$t = -1.426$ $p = 0.160$ $d = 0.392$
Right Orbito-Frontal	$t = -0.034$ $p = 0.973$ $d = 0.009$	$t = -0.930$ $p = 0.357$ $d = 0.258$	$t = 0.075$ $p = 0.940$ $d = 0.021$
Right Antero-Medial	$t = -1.481$ $p = 0.145$ $d = 0.408$	$t = 1.193$ $p = 0.239$ $d = 0.329$	$t = 1.301$ $p = 0.199$ $d = 0.358$
Right Antero-Lateral	$t = -1.744$ $p = 0.087$ $d = 0.479$	$t = 0.664$ $p = 0.510$ $d = 0.183$	$t = 0.621$ $p = 0.538$ $d = 0.171$
Right Postero-Medial	$t = -0.269$ $p = 0.789$ $d = 0.074$	$t = -0.269$ $p = 0.789$ $d = 0.074$	$t = -0.031$ $p = 0.975$ $d = 0.008$
Right Postero-Lateral	$t = 0.352$ $p = 0.726$ $d = 0.289$	$t = -1.047$ $p = 0.300$ $d = 0.289$	$t = -1.077$ $p = 0.287$ $d = 0.297$
Right Occipital	$t = 0.441$ $p = 0.661$ $d = 0.465$	$t = -1.694$ $p = 0.096$ $d = 0.465$	$t = -1.495$ $p = 0.141$ $d = 0.411$

Reliability in healthy controls

Spironelli and Angrilli. In healthy controls, moderate-good reliability (**Table 16**) was observed for mean amplitude in left anterior (*orthographic* and *phonological* tasks), left posterior (all tasks), and right anterior (*semantic* task) ROIs.

Expanded. Test-retest reliability of mean amplitude in all ROIs for healthy controls during *orthographic*, *phonological*, and *semantic* tasks ranged from poor to good. Moderate reliability was most frequently observed (18/36 correlations), ranging from .503 in *semantic* right postero-lateral ROI to .745 in *orthographic* left antero-medial ROI. Fifteen out of 36 correlations for mean amplitude showed good reliability, ranging from .754 (*semantic* left occipital) to .866 (*semantic* left postero-lateral). The ROI with the strongest reliability for mean amplitude was left postero-medial.

Reliability in PWCS

Spironelli and Angrilli. Adequate reliability was only seen in the left and right posterior ROI for PWCS. Moderate reliability was observed during the *phonological* task (ICC = .731) in the left posterior ROI. Good reliability was seen during the *orthographic* task in left posterior (ICC = .887) *semantic* task in left posterior (ICC = .772), and *semantic* task in right posterior (ICC = .755) ROIs.

Expanded. PWCS in general demonstrated poorer reliability of mean amplitude than healthy controls. Two correlations (*phonological* left orbito-frontal and *phonological* right antero-lateral) were not significant, and an additional nine correlations demonstrated poor reliability. Moderate reliability was observed for 11 correlations (ranging from .511 in *semantic* right orbito-frontal to .71 in *semantic* right antero-medial). Good reliability was observed for 13 correlations, ranging from .762 (*phonological* right occipital) to .89

Table 16. Intra-class correlation coefficients for neurologically healthy controls and persons with stroke during N350. *Moderate*, good, and *excellent* reliability are shown.

	Orthographic		**Phonological**		**Semantic**	
	Control	**PWS**	**Control**	**PWS**	**Control**	**PWS**
Spironelli & Angrilli ROIs						
Left Anterior	**.518** **.159-.757**	.089 0-.507	**.505** **.146-.749**	.232 0-.587	.486 .107-.741	.254 0-.624
Left Posterior	**.721** **.453-.869**	**.887** **.755-.95**	**.875** **.733-.944**	**.731** **.464-.876**	**.752** **.51-.884**	**.772** **.538-.896**
Right Anterior	.408 0-.702	.354 0-.679	.462 .056-.736	.253 0-.616	**.555** **.193-.786**	.266 0-.621
Right Posterior	.032 0-.413	-	.102 0-.475	-	-	**.755** **.506-.888**
Granular ROIs						
Left Orbito-Frontal	.470 .083-.732	**.540** **.163-.78**	**.530** **.177-.764**	.329 0-.65	.434 .053-.707	.461 .05-.736
Left Antero-Medial	**.745** **.5-.881**	**.773** **.535-.897**	**.828** **.644-.922**	**.662** **.351-.841**	**.820** **.632-.918**	**.756** **.503-.889**
Left Antero-Lateral	**.755** **.517-.885**	.356 0-.666	**.581** **.252-.792**	.477 .094-.738	**.713** **.441-.865**	.436 .037-.715
Left Postero-Medial	**.853** **.692-.934**	**.598** **.25-.808**	**.836** **.656-.926**	.426 .039-.705	**.866** **.713-.94**	**.675** **.369-.848**
Left Postero-Lateral	**.773** **.542-.896**	**.857** **.696-.937**	**.861** **.709-.937**	**.858** **.695-.937**	**.680** **.386-.849**	**.839** **.661-.928**
Left Occipital	**.626** **.305-.819**	**.890** **.763-.952**	**.775** **.547-.896**	**.556** **.188-.785**	**.754** **.516-.885**	**.655** **.347-.836**
Right Orbito-Frontal	**.512** **.137-.757**	**.550** **.172-.786**	**.606** **.28-.808**	.461 .047-.737	**.574** **.229-.791**	**.511** **.114-.765**
Right Antero-Medial	**.741** **.485-.88**	**.667** **.364-.843**	**.778** **.555-.897**	.498 .111-.752	**.733** **.463-.877**	**.710** **.435-.865**
Right Antero-Lateral	**.679** **.383-.848**	.462 .06-.732	**.744** **.491-.881**	.260 0-.606	**.786** **.56-.902**	.408 .001-.699
Right Postero-Medial	**.851** **.672-.934**	**.617** **.278-.818**	**.557** **.22-.779**	**.785** **.554-.903**	**.717** **.448-.867**	**.683** **.389-.851**
Right Postero-Lateral	.407 .018-.69	**.883** **.744-.948**	**.717** **.447-.867**	**.793** **.57-.907**	**.503** **.136-.75**	**.777** **.545-.899**
Right Occipital	**.599** **.265-.804**	**.827** **.625-.924**	**.787** **.567-.902**	**.762** **.52-.891**	**.820** **.609-.92**	**.841** **.661-.93**

(*orthographic* left occipital). Mean amplitude in the left postero-lateral ROI had the most consistently high reliability. For PWCS, only a single correlation showed moderate reliability - left occipital during the *orthographic* task.

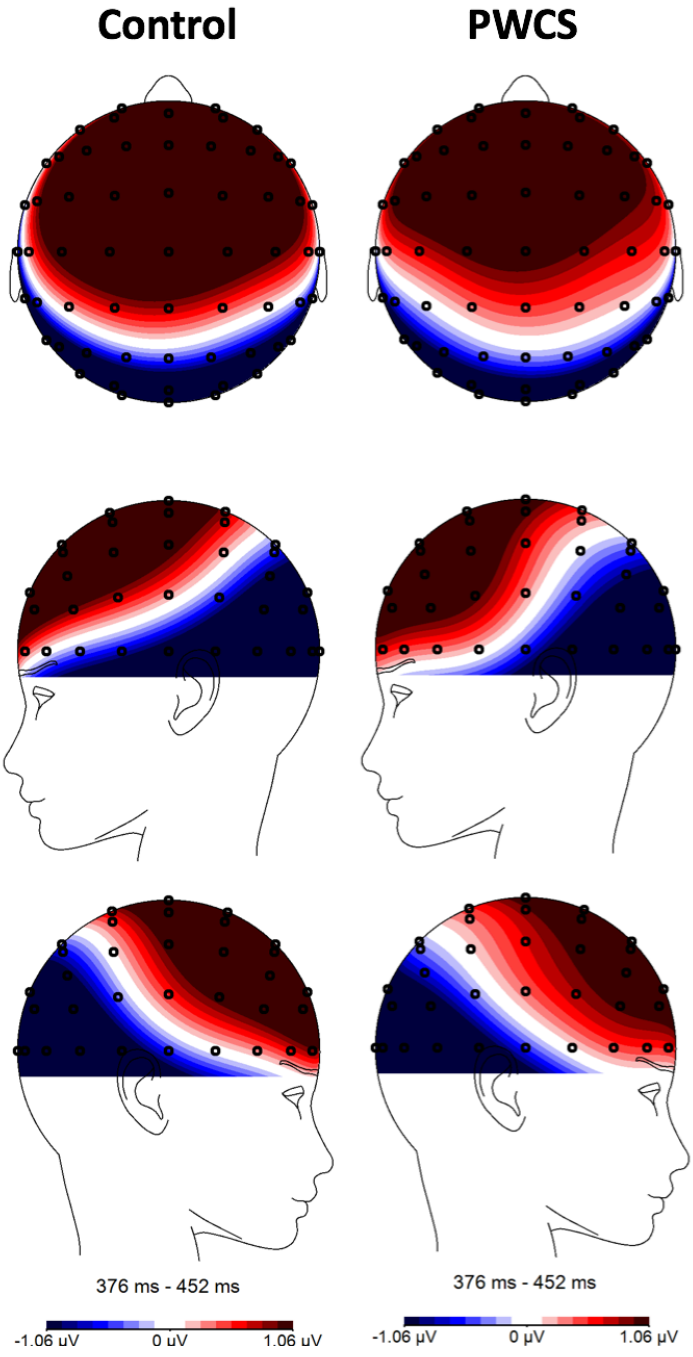
Discussion

This study investigated changes in cognitive and language ERP components in persons with chronic stroke of mixed hemisphericity and behavioral impairments. In our sample of 27 healthy controls and 27 persons with chronic stroke, statistically significant differences were observed in mean amplitude for the P3a component only. However, comparisons with medium to large effects were seen in all four components. Acceptable stability was found for mean amplitude in each component, although the specific electrodes and ROIs varied.

Attention ERPs

In healthy controls in the P3a window, we found larger positive amplitudes in frontal electrodes in response to novel sounds than in response to target sounds (**Figure 8**). Amplitude in frontal and central electrodes was highest in the midline. Amplitude decreased compared to frontal electrodes, but was still positive in central electrodes, and decreased and became negative in posterior electrodes. This distribution matches the typical P3a reported in the literature and provides confirmation that healthy controls were complying with the task. In PWCS, the same pattern of positive mean amplitude values was observed in frontal electrodes, with greater amplitude in response to novel sounds than target sounds. Mean amplitude was largest in midline electrodes and also demonstrated decrements from frontal to central to posterior electrodes as described for controls. The significant reduction in mean amplitude to novel sounds observed in Fz

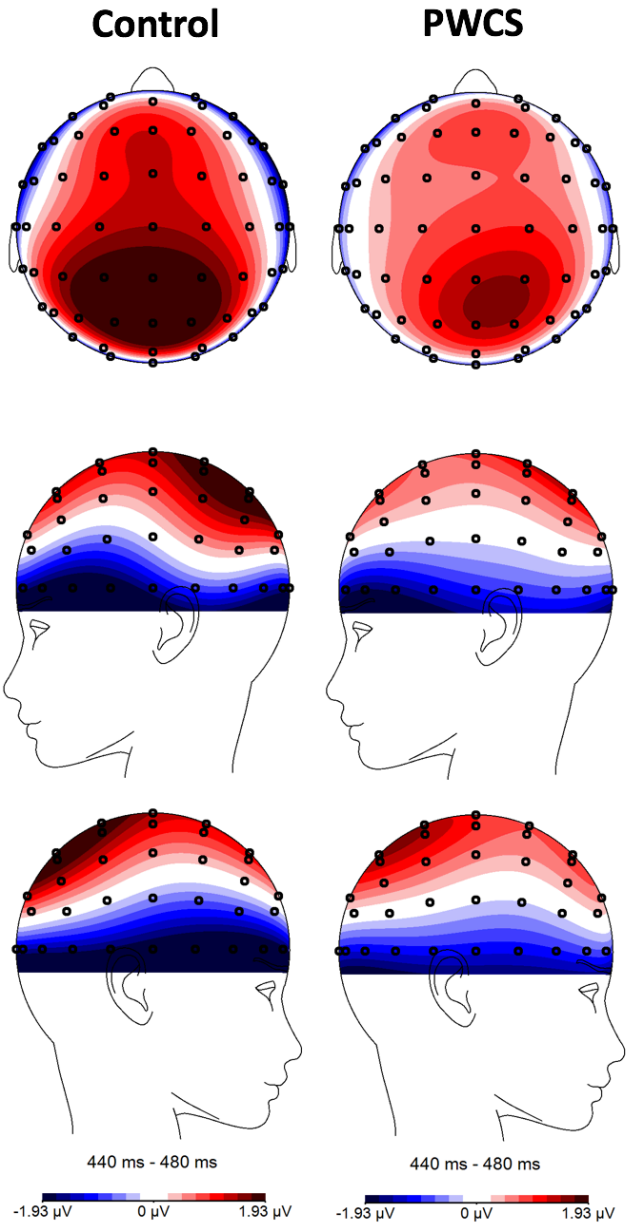
Figure 8. Topographic maps of activation during the P3a in healthy controls and PWCS.



confirms that PWCS continue to exhibit changes in the P3a well into the chronic phase of recovery. Additionally, the medium effect in F3 suggests that the typically bilateral activation observed in the P3a may continue to be altered in chronic stroke.

In healthy controls during the P3b window (**Figure 9**), we found larger positive amplitudes in posterior electrodes in response to target sounds as compared to novel sounds. Amplitude was greater in midline electrodes than left or right electrodes. In addition, left hemisphere electrodes had numerically larger values than right hemisphere values, although no comparisons were run to determine if these differences were statistically significant. Amplitude was largest in posterior electrodes, then central

Figure 9. Topographic maps of activation during the P3b in healthy controls and PWCS.



electrodes, with the smallest values observed in frontal electrodes, although mean amplitude remained positive. These results are consistent with the typical P3b reported in the literature. In PWCS, mean amplitude was larger in posterior electrodes in response to target compared to novel sounds. Midline electrodes also displayed larger mean amplitude than lateral electrodes. However, while mean amplitude in midline electrodes decreased from posterior to anterior, the opposite pattern was observed in left and right lateralized electrodes, with amplitude increasing posterior to anterior. Additionally, mean amplitude in left hemisphere electrodes was numerically smaller than in right hemisphere electrodes, although again no statistical comparisons were conducted. The reduction of mean amplitude to target sounds observed in electrode Pz suggests that PWCS may continue to exhibit changes in the P3b well into the chronic phase of recovery. Additionally, the medium effect in electrode P3 suggests that PWCS also have a reduction in posterior left hemisphere activation compared to controls.

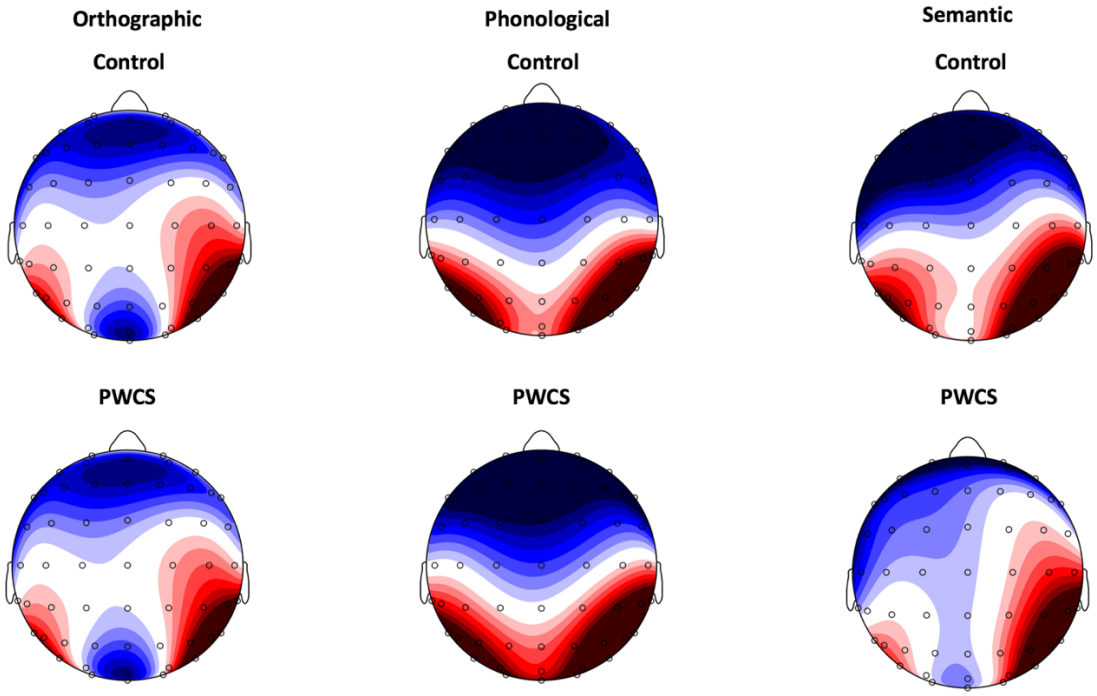
Although our investigation did not yield a large number of statistically significant results, those we did observe provide support for two major conclusions. First, use of a three stimuli oddball paradigm is sufficiently sensitive to identify changes in individuals post-stroke in a sample with varying stroke characteristics and behavioral impairments. Second, the P300 ERP complex continues to be altered in individuals who are years, and in some instances, decades post-stroke (consistent with Dejanovic et al., 2015). This neurophysiological finding is also consistent with behavioral reports of chronic attention deficits post-stroke (Barker-Collo et al., 2010; Hyndman & Ashburn, 2003) which negatively impact function (McDowd et al., 2003). Future research should investigate

whether ERP measurement of attention via the P300 component is more sensitive to deficits than traditional behavioral measures.

Language ERPs

Examination of mean amplitude in healthy controls and PWCS in the N150 window (**Figure 10**) revealed negative amplitudes across anterior ROIs and positive amplitudes across posterior ROIs in both the Spironelli and Angrilli and expanded set. This is not consistent with previous research which has reported a posterior distribution of the N150 (Spironelli & Angrilli, 2015). Although we selected the time window for investigation in this study based on Spironelli and Angrilli's report where N150 peaked 130-150ms after stimulus onset, peak latency can be unstable (Spencer, 2005), and this window may not have adequately reflected the N150 latency of the populations included here. Indeed, after examining the brain activation in healthy controls during the language

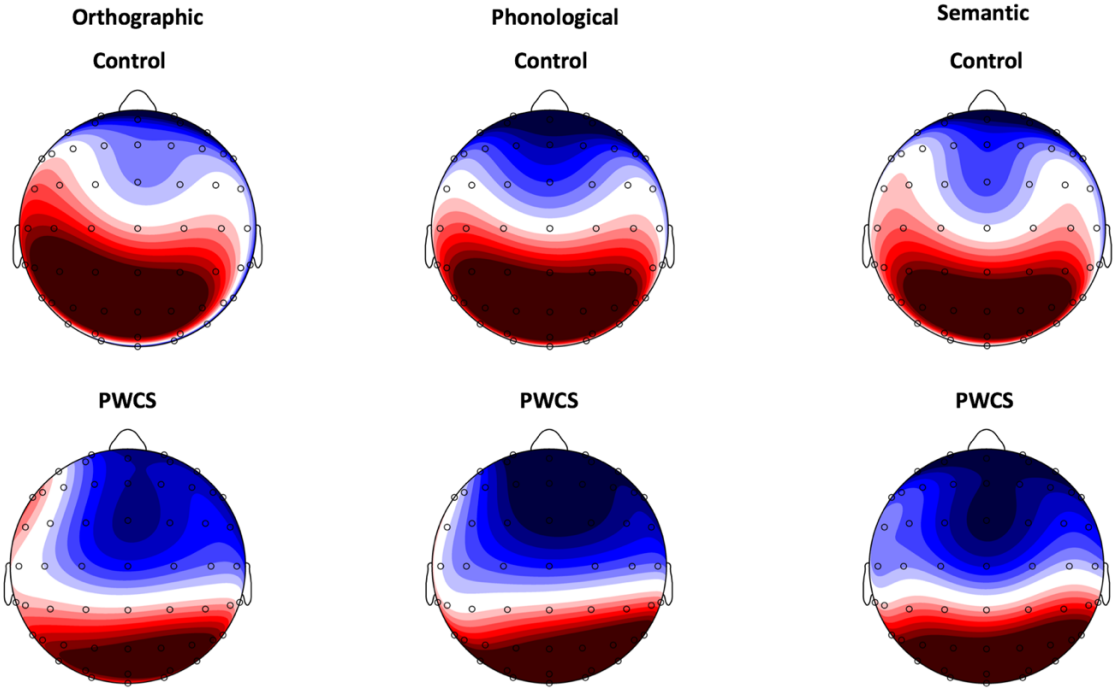
Figure 10. Topographic maps of activation during the N150 in healthy controls and PWCS.



tasks, it appears that the N150 peak in our population may appear slightly later: from ~140ms to ~170ms. Our results provide important evidence that the N150 may occur across a wider timeframe in both controls and PWCS than was previously reported by Spironelli and Angrilli.

In contrast to the N150 results, examination of mean amplitude in healthy controls in the N350 window (**Figure 11**) did reflect the expected, generally anterior, distribution of this component (Spironelli & Angrilli, 2015). Completion of the orthographic task yielded a more distributed pattern of activation across anterior and posterior ROIs, with numerically greater activation in right hemisphere ROIs than left. Both the phonological and semantic tasks demonstrated similar patterns of activation, with negative mean amplitudes restricted to right and left anterior ROIs (except the left occipital ROI in semantic, which also had a negative mean amplitude). For both tasks, orbito-frontal ROIs demonstrated the largest mean amplitudes (numerically larger on the left than right).

Figure 11. Topographic maps of activation during the N350 in healthy controls and PWCS.



Lateralization of activation in all three tasks differs from previously reported. We report numerically larger mean amplitude in right hemisphere ROIs in healthy controls for all tasks as opposed to the left. However, the topographic distribution of activation for the orthographic and semantic tasks is generally consistent between the studies. Mean amplitude of the N350 in PWCS during the orthographic task was negative in left and right anterior ROIs, but not in right hemisphere posterior ROIs. During the phonological task, PWCS had negative mean amplitudes in left and right orbito-frontal ROIs, and also had negative mean amplitude in several left and right posterior ROIs. The largest negative mean amplitudes were observed in the left and right posterior ROIs, rather than the anterior ROIs. Finally, during the semantic task, PWCS demonstrated negative mean amplitudes in left and right frontal ROIs, with amplitude larger in the right hemisphere than left. Similar to healthy controls, our lateralization (and topographic distributions) results differ from those previously reported.

There are some key differences between our study and Spironelli and Angrilli that may contribute to our different findings. First, with regard to the lack of significant differences between groups, and the descriptive differences in amplitude and distribution for PWCS, the characteristics of our stroke population diverge sharply from that enrolled in Spironelli and Angrilli's study. We included individuals with left and right hemisphere strokes and different behavioral deficits because we were interested in whether a cognitive-linguistic task might be sensitive to changes in both language and underlying cognitive processes. These results indicate that the N350 may be of marginal use in a mixed sample and may only be appropriate when variability is reduced along some factor. We also report findings for healthy controls that differ from previous reports. One

possible explanation is that Spironelli and Angrilli studied these components in individuals who are speakers of Italian. It is possible that differences in the transparency of written linguistic features differs between the two languages. For example, English orthography has a much more opaque mapping onto phonology than does Italian orthography onto phonology (Seymour, Aro, & Erskine, 2003), which may result in different patterns of neural activation for reading. In addition, participants in this study viewed each word for a longer period of time, which may have changed the strategy by which participants completed the task. Research in fMRI reveals that reading in English speakers, and differential timing of stimulus presentation for reading, results in activation of a wide array of bilateral areas, with some exhibiting sensitivity to differences in timing (Mechelli, Friston, & Price, 2000).

Stability of Mean Amplitude

Investigation of the stability of mean amplitude over time in the selected cognitive and language components revealed differing patterns of reliability. Historical and expanded electrodes showed some evidence of a task-specific reliability response in P3a, as adequate reliability for controls was observed in response to novel, but not target, sounds in P3a. PWCS demonstrated this task specificity in the historical electrodes, but not in the expanded set. In contrast, task specificity was not observed for either group for the P3b. In the N150 window used here, controls generally demonstrated better reliability than PWCS. However, given the uncertainty around whether this time frame actually captured the N150 ERP component in our study, it is difficult to interpret this in a meaningful way. Finally, during the N350 window, moderate to good reliability was observed in many ROIs in both controls and PWCS. Our results indicate that mean

amplitude exhibits adequate reliability for use over time in these components, although care should be taken when selecting specific electrodes or ROIs.

Variability Post-Stroke

In this sample, we observed very large standard deviations relative to the mean (often double or greater) for both healthy controls and PWCS. This within-group and within-individual variability likely contributed greatly to the lack of statistically significant differences in the study, and, in some instances, inadequate reliability. While variability due to broad inclusion criteria reduced power here, it was necessary to include individuals with a wide range of stroke deficits. Providing normative information regarding the general stroke population allows future comparisons to be made when investigations are limited to a single behavioral deficit, or when investigating the effects of co-morbid impairments.

The variability observed in both individuals with aphasia and healthy controls suggests that alternative analyses may need to be considered when investigating ERPs. In particular, some method of quantifying variability, to see if it differs between groups and could potentially identify group membership would be particularly useful (standard deviation cannot be used in this manner, as it is dependent on the value of the mean). One of the most commonly used measures of variability is the coefficient of variation; however, it is not appropriate for use in data that contain both positive and negative numbers, or for data that take values close to zero. There are several other measures of variability currently available (e.g., median absolute deviation, maximum absolute deviation, entropy) that may be more appropriate for ERP data and should be investigated in future research. In fact, some recent investigations have posited that variability in

neural activation indexes a system's capacity for processing information, with greater variability relating to greater capacity. A recent EEG study in traumatic brain injury (TBI) reported reduced variability in comparison to controls (Beharelle, Kovacevic, McIntosh, & Levine, 2012). This reduced variability was related to behavioral performance on an attention task, where those with greater variability showed better performance across both control and TBI groups. However, it is likely also the case that once variability increases beyond a certain value, the positive relationship between variability and behavioral performance fails to hold, after which point increasing variability is maladaptive. Indeed, evidence for this switch is seen in individuals with schizophrenia (e.g., Gallinat et al., 2003; Winterer et al., 2006). Further research is needed to determine whether the increased variability reported in PWCS here is consistent, varies with lesion severity, and/or corresponds to functional behavioral performance. The P3a may be an ideal component for such investigations, as its amplitude is strongly related to overall variability in the signal (e.g., Winterer et al., 2003). This knowledge has the potential to greatly contribute to prognosis and treatment prediction, as measuring frontal variability through P3a amplitude could be accomplished in approximately 10 minutes with a small electrode montage that would be clinically feasible.

Future Directions and Conclusion

The results and limitations reported here, combined with previous research, suggest several avenues of exploration for the future. First, it may be valuable to investigate the N150 at a later latency to see if it is able to capture cognitive processing that the N350 was not able to. In addition, the data reported here only investigate

activation in response to the first word in a pair. This did not require participants to make any decisions regarding the stimuli, and it may be that a higher task demand is required before underlying cognitive processes can be observed during language tasks to elicit cognitive-linguistic ERPs. In addition, the method of stimulus presentation may have an impact on participants' success in completing the behavioral tasks. In this study, as in previous research (Spironelli & Angrilli, 2015), written words were presented on the computer screen. However, many individuals post-stroke have some degree of reading difficulty (alexia), particularly if they experienced a more posterior stroke (and most individuals in the Spironelli & Angrilli sample had frontal strokes). Research investigating the effects of stimulus presentation modality could reveal cognitive-linguistic competencies that might otherwise be difficult to detect.

Second, an important feature of the P300 was not investigated in this study. Previous research has reported a very clear age effect whereby P300 latency increases as age increases. We did not consider age in this study because our participant groups were matched on age, so any age-related pattern was expected be present in both groups and therefore would be washed out during analysis. However, the wide age range included in the study may have also contributed to our lack of significant findings. Including a large age range would have a smearing effect on the distribution of the P3 peak, as some healthy controls would be likely to have earlier peaks while others would be more likely to display later peaks. The net effect would be a reduction in peak amplitude and a widening of the tails of the distribution, thereby increasing standard deviation. Future research may benefit from limiting inclusion criteria to a specific age range (although this would also limit generalizability) or dividing participants into age bins. In addition,

research in the future should examine whether individuals post-stroke demonstrate the same pattern of age effects as healthy controls, or if the presence of stroke disrupts amplitude and latency to such an extent that normal aging effects are no longer observable.

Finally, and perhaps most importantly, our results provide a characterization of the changes in cognitive ERPs in a broad stroke sample, which was previously lacking in the chronic phase. This characterization will allow future studies to become progressively more fine-grained by providing a stroke baseline for comparison. For example, much research is needed to characterize changes as a result of single versus co-morbid deficits. It is currently unknown how increasing numbers of deficits are reflected in the magnitude of change in brain activation. These factors may be linearly related such that, as successive impairments are loaded onto an individual, brain activation changes by a set amount each time. However, and potentially more likely due to the complexity of the neural system, brain activation may change in an exponential manner where each additional deficit causes an increasingly large change in brain activation (these are not the only possible relationships but are used as examples). Understanding how the presence, number, and degree of impairment impacts brain activity, and therefore functional performance, will be a critical step in improving rehabilitation. Combining this information with current knowledge regarding lesion anatomy (such as site and size) will also be valuable and may provide better insight into the intact brain's role in recovery.

Chapter 4

Shared Discussion

As discussed in Chapter 1, there is currently no consensus on the optimal pattern of recovery following a stroke. Many studies have reported greater recovery and better functional outcomes when perilesional regions responsible for processing specific information prior to a stroke continue to be recruited for that processing after the stroke (e.g., Burke Quinlan et al., 2014; Naeser et al., 2005; Postman-Caucheteux, 2010; Rosen et al., 2000; Saur et al., 2006). However, some studies have also demonstrated better recovery when contralesional areas, rather than perilesional, are recruited (e.g., Burke & Cramer, 2013; Schlaug, Marchina, & Norton, 2008). Contributing to the lack of consensus regarding optimal recovery is a dearth of sensitive measures that directly index brain activation. While MRI can provide important information about the structure and function of the brain, brain activation is inferred from changes in blood flow rather than directly measured. This is warranted in healthy control populations, as the relationship between oxygen and glucose consumption and resultant increases in blood flow are well described. However, the canonical patterns of blood flow response are altered in individuals with stroke, making inferences about brain activation less certain. EEG has been widely used to investigate brain activation and changes after stroke, and as a direct measure of the electrical activation of neural populations, it has great potential to serve as a marker of biophysiological function. While previous research has demonstrated changes in both sEEG and ERP in the acute and sub-acute phases following stroke (Finnigan & van Putten, 2013; Hernandez, 2015; Monge-Pereira et al., 2017), relatively few reports have investigated changes that persist into the chronic phase. The results

reported here extend our understanding of how sEEG and ERP measures are altered in the chronic phase following stroke and provide evidence that EEG variables may continue to be potential biomarkers years and decades after a stroke.

Establishing Normative Data

One of the primary goals of this research was to establish preliminary normative values for power and mean amplitude in healthy controls and a population of individuals who exhibited a wide range of stroke and behavioral impairment characteristics. For both manuscripts, we provide descriptive statistics that will allow readers to better evaluate the raw data under analysis here and the appropriateness of the statistical methods utilized. Previous research in both sEEG and ERP has generally lacked adequate reporting of descriptive statistics, which makes it difficult to determine whether findings are comparable across studies, and what the range of values for healthy controls or PWCS might be for power and mean amplitude. We also report effect sizes in addition to test statistics and p-values, in order to facilitate discussion of statistically significant versus practically significant differences; keeping in mind that not all statistically significant results equate to meaningful differences in performance or functional abilities. Finally, we reported on the test-retest reliability, or stability, of sEEG and ERP measures over time. Given that many researchers have used repeated sessions of sEEG or ERP to evaluate functional recovery or assess response to treatment, the lack of reliability data on these measures was a critical gap in the literature. For both EEG analyses we demonstrated adequate reliability for use as repeated measures, although care must be taken to ensure that the specific montages, electrodes, or ROIs of interest demonstrate adequate reliability.

In addition to facilitating comparisons with future research, we expect the normative data reported for this broad stroke population will be used in investigations that narrow the focus onto a specific deficit or constellation of deficits. To this end, we also provided a detailed description of the number of motor, cognitive and language impairments observed in our sample, as well as estimates of the severity of the various impairments. Consistent with previous reports, most of our sample experienced deficits in more than one domain, and several experienced deficits in all three domains. Given the rich interconnectedness of the brain, it is important to consider how a lesion in one area might impact multiple behavioral domains, and the data reported here provide a place to start these investigations.

sEEG versus ERP Results

Significant differences in sEEG and ERP variables were observed in this sample. During sEEG, relative delta and relative beta power showed clear patterns of difference from healthy controls and moderate to excellent reliability, particularly for *eyes closed rest*. During ERP, results of P300 also showed clear differences between PWCS and healthy controls that was stimulus-specific and had moderate to good reliability. Results for the N150 and N350 showed the fewest between-group differences, and generally poorer reliability. Because power and mean amplitude of the P300 demonstrated more consistent differences from controls, and also generally better reliability, they may be more appropriate for investigations of biomarkers in the immediate future. However, further research is needed to determine whether the N150, N350, or another ERP component (or complex of components) might be able to measure different types of cognitive ability in the same task (such as attention and language). Identifying a single

paradigm that could provide useful information about multiple domains would decrease the time required for assessment while potentially increasing prognostic accuracy.

EEG as a Marker of Target Engagement

One of the most frustrating aspects of neurorehabilitation for individuals, family members, and therapists is the length of time required for significant gains to be achieved. Interest in therapeutic adjuvants for post-stroke rehabilitation, such as non-invasive brain stimulation (e.g., Fridriksson et al., 2018) or pharmacology (e.g., Kessler, Thiel, Karbe, & Heiss, 2000), to enhance recovery has gained ground due to the intractable nature of chronic deficits. The goal of treatment adjuvants is to increase the magnitude of behavioral treatments and/or reduce the time needed to achieve improvements. Unfortunately, the limitations in our understanding of optimal recovery patterns make it difficult to design theoretically motivated investigations. Additionally, current studies have primarily used behavioral measures to determine the impact of therapeutic adjuvants on functional outcomes. This is problematic given the host of unanswered questions, particularly for non-invasive brain stimulation, regarding optimal dosage parameters and targets. Without directly measuring how the brain is changing, even or perhaps especially if those changes do not initially induce behavioral effects, it will be difficult to determine appropriate dosing parameters and maximize the potential benefits of adjuvants.

Identification of biomarkers may provide insights into the specific brain regions that should be targeted for excitation or inhibition, which could then be applied generally to behavioral rehabilitation strategies. For example, noninvasive brain stimulation has been studied as a potential mechanism to improve aphasia rehabilitation (although we

focus our discussion here on aphasia, this is also being studied in motor rehabilitation). In these studies, excitatory transcranial direct current stimulation (tDCS) has almost exclusively been applied to the left hemisphere. On the other hand, inhibitory transcranial magnetic stimulation (TMS) is often applied to right hemisphere language homologues, consistent with theories of interhemispheric inhibition. Results from these brain stimulation studies are mixed. Inhibitory TMS to the right hemisphere consistently results in language improvements (Otal et al., 2015), while a recent review of tDCS studies determined there was no evidence of tDCS effectiveness beyond those seen with behavioral therapy alone (Elsner et al., 2013; Sandars et al., 2015). Part of the divergence in results is likely due to the mechanism of action of the two methods. TMS directly activates the underlying cortex, inducing action potentials (or preventing action potentials from firing). In contrast, tDCS alters the propensity of neurons to fire, but does not actually cause them to fire directly (Nitsche & Paulus, 2000). For this reason, tDCS must be paired with a behavioral task in order for long-term changes to be observed (e.g., Fritsch et al., 2010). Given the much subtler mechanism of tDCS action, biomarkers that could identify positive changes in brain activation, such as sEEG power or ERP amplitude, would provide researchers with measures to investigate the impact of dosage parameters, while also assessing the engagement of hypothesized brain regions. Currently, it is impossible to determine whether non-significant changes as a result of tDCS are because it truly does not improve rehabilitation outcomes, because inappropriate behavioral assessments are used to measure effects, and/or because the targeted brain region has not been influenced. A handful of studies to date have utilized EEG in this manner in healthy controls, individuals with stroke, and individuals with

traumatic brain injury, to good effect (e.g., Barwood et al., 2011; Boonstra et al., 2016; Ulam et al., 2015).

Conclusion

Millions of people around the world are living with chronic stroke-induced impairments that negatively impact quality of life and life participation. While therapy provided by speech-language pathologists, occupational therapists, and physical therapists allow individuals to regain function following a stroke, recovery can be painstakingly slow and frustrating, and complete restoration of abilities is rare. Advances in neuroimaging techniques offer the promise of elucidating brain function and the neural mechanisms behind observable behaviors. However, critical gaps in our understanding of recovery following stroke persist. Each neuroimaging modality carries with it strengths and weaknesses that limit the inferences we can draw. By combining multiple modalities in research studies, we may be able to offset the technical weaknesses of each, allowing a clearer picture of stroke recovery to emerge. To this end, EEG measures such as those reported here should continue to be investigated and should be combined with other frequently used imaging modalities such as MRI. Deepening our understanding of stroke recovery has the potential to transform the way we provide rehabilitation services, with the ultimate goal of helping more of our clients move even closer to pre-stroke levels of functioning, participation, and life satisfaction.

Appendix A

Table A1. Descriptive statistics for neurologically healthy controls during eyes open rest.

	Mean	SD	Median	Range	Skew	Kurtosis
Delta						
Whole Brain	0.386	0.092	0.392	0.156 - 0.546	-0.617	0.587
Left Hemisphere	0.383	0.095	0.392	0.149 - 0.553	-0.534	0.922
Right Hemisphere	0.382	0.097	0.398	0.158 - 0.553	-0.441	-0.120
Anterior	0.405	0.096	0.395	0.186 - 0.626	-0.210	0.821
Posterior	0.372	0.095	0.387	0.140 - 0.519	-0.675	0.353
LH – Language	0.385	0.097	0.389	0.108 - 0.438	-0.770	1.455
RH – Language	0.372	0.101	0.388	0.165 - 0.557	-0.353	-0.665
Motor	0.395	0.094	0.413	0.140 - 0.627	-0.595	2.377
Cognitive	0.431	0.114	0.427	0.209 - 0.750	0.274	1.720
Clinical	0.380	0.090	0.392	0.153 - 0.515	-0.707	0.352
Theta						
Whole Brain	0.114	0.025	0.119	0.062 - 0.149	-0.489	-0.656
Left Hemisphere	0.112	0.023	0.113	0.065 - 0.143	-0.421	-0.752
Right Hemisphere	0.113	0.027	0.116	0.057 - 0.152	-0.466	-0.801
Anterior	0.116	0.027	0.117	0.064 - 0.170	-0.306	-0.465
Posterior	0.113	0.026	0.112	0.062 - 0.169	-0.133	-0.245
LH – Language	0.105	0.024	0.116	0.055 - 0.152	-0.251	-0.444
RH – Language	0.106	0.028	0.106	0.061 - 0.150	-0.084	-1.129
Motor	0.125	0.033	0.130	0.063 - 0.189	-0.184	-0.130
Cognitive	0.110	0.029	0.113	0.045 - 0.153	-0.481	-0.491
Clinical	0.115	0.024	0.119	0.063 - 0.156	-0.261	-0.587
Alpha						
Whole Brain	0.151	0.054	0.140	0.084 - 0.290	1.324	1.515
Left Hemisphere	0.151	0.055	0.139	0.086 - 0.297	1.332	1.718
Right Hemisphere	0.150	0.053	0.138	0.081 - 0.287	1.239	1.148
Anterior	0.137	0.045	0.127	0.082 - 0.179	1.152	1.076
Posterior	0.169	0.065	0.156	0.083 - 0.351	1.342	1.694
LH – Language	0.150	0.059	0.129	0.071 - 0.304	0.916	0.117
RH – Language	0.150	0.056	0.133	0.075 - 0.271	0.990	0.088
Motor	0.138	0.045	0.128	0.083 - 0.281	1.497	2.740
Cognitive	0.131	0.048	0.113	0.080 - 0.259	1.348	1.074
Clinical	0.154	0.057	0.138	0.082 - 0.293	1.348	1.204
Beta						
Whole Brain	0.285	0.089	0.279	0.102 - 0.461	0.173	-0.476
Left Hemisphere	0.290	0.091	0.305	0.113 - 0.475	0.061	-0.505
Right Hemisphere	0.294	0.097	0.274	0.097 - 0.488	0.338	-0.365
Anterior	0.281	0.095	0.277	0.096 - 0.469	0.299	-0.489
Posterior	0.279	0.092	0.267	0.091 - 0.469	0.334	-0.131
LH – Language	0.295	0.086	0.316	0.145 - 0.333	0.080	-0.436

RH – Language	0.315	0.112	0.298	0.124 - 0.570	0.468	-0.167
Motor	0.278	0.089	0.249	0.074 - 0.506	0.495	0.978
Cognitive	0.271	0.110	0.264	0.069 - 0.557	0.562	0.402
Clinical	0.288	0.090	0.283	0.119 - 0.459	0.236	-0.657
DAR						
Whole Brain	3.236	1.321	3.396	0.701 - 5.503	-0.206	-0.614
Left Hemisphere	3.273	1.392	3.333	0.589 - 6.263	0.066	-0.292
Right Hemisphere	3.209	1.364	3.355	0.852 - 5.531	-0.251	-0.970
Anterior	3.640	1.443	3.845	0.856 - 6.362	-0.176	-0.612
Posterior	2.804	1.301	2.704	0.568 - 5.929	0.278	-0.034
LH – Language	3.378	1.563	3.243	0.498 - 6.482	-0.068	-0.748
RH – Language	3.168	1.485	3.088	0.901 - 6.428	0.131	-0.685
Motor	3.463	1.295	3.573	0.763 - 5.832	-0.371	-0.063
Cognitive	4.046	1.701	4.179	1.011 - 7.817	-0.078	-0.425
Clinical	3.218	1.333	3.340	0.692 - 5.457	-0.216	-0.678
DTABR						
Whole Brain	1.399	0.601	1.338	0.384 - 2.503	0.307	-0.653
Left Hemisphere	1.380	0.633	1.238	0.379 - 2.817	0.651	-0.061
Right Hemisphere	1.364	0.604	1.344	0.381 - 2.453	0.213	-0.897
Anterior	1.531	0.700	1.373	0.447 - 3.316	0.677	0.256
Posterior	1.296	0.573	1.318	0.357 - 2.487	0.237	-0.764
LH – Language	1.353	0.629	1.250	0.345 - 2.851	0.637	-0.215
RH – Language	1.299	0.624	1.251	0.398 - 2.664	0.312	-0.915
Motor	1.481	0.587	1.517	0.328 - 2.737	0.115	0.103
Cognitive	1.675	0.911	1.516	0.504 - 4.763	1.558	3.979
Clinical	1.383	0.592	1.300	0.381 - 2.489	0.268	-0.738
$Q_{slowing}$						
Whole Brain	0.491	0.106	0.510	0.218 - 0.659	-0.684	0.129
Left Hemisphere	0.487	0.105	0.488	0.227 - 0.684	-0.555	0.177
Right Hemisphere	0.485	0.112	0.501	0.198 - 0.654	-0.643	-0.251
Anterior	0.510	0.112	0.523	0.28 - 0.700	-0.585	-0.169
Posterior	0.477	0.109	0.479	0.212 - 0.661	-0.601	-0.042
LH – Language	0.480	0.107	0.493	0.229 - 0.685	-0.367	-0.198
RH – Language	0.478	0.115	0.498	0.182 - 0.662	-0.508	-0.408
Motor	0.512	0.108	0.542	0.216 - 0.692	-1.035	1.114
Cognitive	0.524	0.124	0.535	0.253 - 0.796	-0.453	-0.108
Clinical	0.489	0.106	0.512	0.221 - 0.653	-0.638	-0.011

Table A2. Descriptive statistics for persons with stroke during eyes open rest.

	Mean	SD	Median	Range	Skew	Kurtosis
			Delta			
Whole Brain	0.354	0.115	0.342	0.113 - 0.535	-0.213	-0.431
Left Hemisphere	0.353	0.118	0.340	0.092 - 0.545	-0.289	-0.391
Right Hemisphere	0.353	0.119	0.344	0.129 - 0.550	-0.069	-0.568
Anterior	0.369	0.118	0.363	0.122 - 0.578	-0.191	0.026
Posterior	0.338	0.116	0.338	0.106 - 0.517	-0.059	-0.779
LH – Language	0.357	0.123	0.348	0.091 - 0.549	-0.209	-0.408
RH – Language	0.353	0.128	0.342	0.149 - 0.618	0.386	-0.518
Motor	0.351	0.114	0.366	0.120 - 0.564	-0.371	-0.180
Cognitive	0.399	0.133	0.394	0.119 - 0.634	-0.261	-0.002
Clinical	0.356	0.114	0.351	0.111 - 0.542	-0.366	-0.334
			Theta			
Whole Brain	0.168	0.094	0.142	0.078 - 0.515	2.337	6.847
Left Hemisphere	0.169	0.095	0.138	0.074 - 0.514	2.199	6.221
Right Hemisphere	0.160	0.094	0.130	0.073 - 0.506	2.389	6.849
Anterior	0.163	0.086	0.144	0.067 - 0.464	2.019	5.365
Posterior	0.174	0.105	0.142	0.075 - 0.571	2.496	7.817
LH – Language	0.154	0.090	0.116	0.060 - 0.445	1.867	3.812
RH – Language	0.149	0.090	0.119	0.065 - 0.448	2.041	4.303
Motor	0.182	0.099	0.168	0.078 - 0.519	1.877	4.570
Cognitive	0.146	0.075	0.130	0.059 - 0.407	2.038	5.399
Clinical	0.167	0.094	0.138	0.079 - 0.519	2.479	7.481
			Alpha			
Whole Brain	0.185	0.098	0.164	0.070 - 0.414	1.209	0.543
Left Hemisphere	0.182	0.095	0.165	0.067 - 0.405	1.134	0.460
Right Hemisphere	0.185	0.100	0.154	0.069 - 0.423	1.214	0.550
Anterior	0.162	0.084	0.145	0.069 - 0.361	1.178	0.362
Posterior	0.211	0.118	0.187	0.064 - 0.516	1.313	1.121
LH – Language	0.177	0.087	0.163	0.061 - 0.372	0.720	-0.309
RH – Language	0.178	0.089	0.148	0.049 - 0.377	0.759	-0.216
Motor	0.173	0.093	0.149	0.080 - 0.381	1.243	0.281
Cognitive	0.146	0.076	0.123	0.063 - 0.333	1.192	0.572
Clinical	0.184	0.099	0.162	0.066 - 0.411	1.245	0.558
			Beta			
Whole Brain	0.218	0.098	0.209	0.037 - 0.465	0.315	0.253
Left Hemisphere	0.221	0.102	0.219	0.044 - 0.444	0.063	-0.377
Right Hemisphere	0.229	0.109	0.217	0.032 - 0.508	0.556	0.534
Anterior	0.234	0.120	0.222	0.041 - 0.491	0.529	-0.255
Posterior	0.194	0.093	0.195	0.030 - 0.442	0.586	0.843
LH – Language	0.241	0.122	0.247	0.046 - 0.394	-0.062	-1.116
RH – Language	0.252	0.122	0.236	0.029 - 0.533	0.377	-0.171
Motor	0.223	0.110	0.199	0.040 - 0.470	0.539	-0.251

Cognitive	0.239	0.141	0.227	0.049 - 0.578	0.857	0.256
Clinical	0.219	0.097	0.212	0.039 - 0.456	0.247	0.054
DAR						
Whole Brain	3.050	2.118	2.387	0.310 - 8.700	1.084	0.936
Left Hemisphere	3.068	2.143	2.724	0.263 - 8.651	1.115	1.140
Right Hemisphere	3.117	2.331	2.509	0.352 - 9.518	1.259	1.241
Anterior	3.532	2.379	3.065	0.415 - 8.996	0.879	0.121
Posterior	2.603	2.034	2.002	0.230 - 9.199	1.615	3.261
LH – Language	3.217	2.399	2.479	0.288 - 9.306	1.131	0.842
RH – Language	3.258	2.924	2.364	0.446 - 13.177	1.962	4.473
Motor	2.997	1.909	2.794	0.352 - 7.439	0.691	0.070
Cognitive	4.272	2.975	3.265	0.429 - 10.568	0.812	-0.246
Clinical	3.121	2.139	2.792	0.296 - 9.371	1.160	1.779
DTABR						
Whole Brain	1.897	1.386	1.783	0.267 - 6.720	1.812	4.746
Left Hemisphere	1.926	1.434	1.708	0.222 - 6.275	1.419	2.178
Right Hemisphere	1.815	1.460	1.314	0.299 - 7.297	2.339	7.346
Anterior	1.973	1.412	1.495	0.279 - 6.434	1.506	2.782
Posterior	1.836	1.428	1.681	0.267 - 7.047	2.093	6.184
LH – Language	1.792	1.335	1.326	0.198 - 5.263	1.209	0.881
RH – Language	1.770	1.772	1.148	0.339 - 9.211	3.216	12.689
Motor	1.931	1.431	1.512	0.266 - 6.835	1.740	4.325
Cognitive	2.086	1.453	1.626	0.251 - 5.828	0.993	0.418
Clinical	1.918	1.386	1.736	0.262 - 6.695	1.767	4.504
$Q_{slowing}$						
Whole Brain	0.515	0.141	0.519	0.192 - 0.793	-0.443	-0.228
Left Hemisphere	0.519	0.148	0.525	0.166 - 0.780	-0.438	-0.330
Right Hemisphere	0.501	0.144	0.499	0.209 - 0.811	-0.186	-0.264
Anterior	0.522	0.150	0.526	0.160 - 0.777	-0.539	-0.084
Posterior	0.509	0.138	0.542	0.191 - 0.807	-0.347	-0.387
LH – Language	0.509	0.156	0.493	0.152 - 0.785	-0.185	-0.610
RH – Language	0.492	0.151	0.465	0.219 - 0.845	0.213	-0.477
Motor	0.524	0.151	0.548	0.185 - 0.798	-0.517	-0.439
Cognitive	0.536	0.158	0.565	0.169 - 0.765	-0.734	0.000
Clinical	0.515	0.140	0.517	0.190 - 0.790	-0.503	-0.133

Table A3. Descriptive statistics for neurologically healthy controls during eyes closed rest.

	Mean	SD	Median	Range	Skew	Kurtosis
Delta						
Whole Brain	0.271	0.117	0.245	0.096 - 0.453	0.159	-1.443
Left Hemisphere	0.267	0.113	0.231	0.100 - 0.467	0.190	-1.331
Right Hemisphere	0.271	0.117	0.255	0.092 - 0.459	0.113	-1.465
Anterior	0.243	0.107	0.226	0.079 - 0.415	0.104	-1.557
Posterior	0.314	0.138	0.279	0.113 - 0.522	0.116	-1.401
LH – Language	0.249	0.104	0.250	0.094 - 0.465	0.237	-1.057
RH – Language	0.246	0.097	0.248	0.092 - 0.451	0.207	-0.936
Motor	0.238	0.109	0.207	0.090 - 0.414	0.412	-1.351
Cognitive	0.243	0.106	0.236	0.075 - 0.420	0.077	-1.269
Clinical	0.271	0.116	0.247	0.095 - 0.457	0.157	-1.446
Theta						
Whole Brain	0.104	0.028	0.101	0.057 - 0.181	0.567	0.840
Left Hemisphere	0.105	0.030	0.102	0.058 - 0.191	0.773	1.305
Right Hemisphere	0.100	0.026	0.099	0.054 - 0.164	0.235	0.182
Anterior	0.109	0.025	0.111	0.061 - 0.169	0.362	0.361
Posterior	0.098	0.035	0.089	0.046 - 0.210	1.138	2.536
LH – Language	0.101	0.024	0.105	0.055 - 0.141	-0.185	-0.573
RH – Language	0.102	0.027	0.102	0.054 - 0.159	0.148	-0.151
Motor	0.116	0.033	0.111	0.063 - 0.197	0.577	0.155
Cognitive	0.103	0.026	0.098	0.060 - 0.170	0.838	1.141
Clinical	0.103	0.029	0.104	0.058 - 0.192	0.997	2.470
Alpha						
Whole Brain	0.271	0.117	0.245	0.096 - 0.453	0.159	-1.443
Left Hemisphere	0.267	0.113	0.231	0.100 - 0.467	0.190	-1.331
Right Hemisphere	0.271	0.117	0.255	0.092 - 0.459	0.113	-1.465
Anterior	0.243	0.107	0.226	0.079 - 0.415	0.104	-1.557
Posterior	0.314	0.136	0.279	0.113 - 0.522	0.116	-1.401
LH – Language	0.249	0.104	0.250	0.094 - 0.465	0.237	-1.057
RH – Language	0.246	0.097	0.248	0.092 - 0.451	0.207	-0.936
Motor	0.238	0.109	0.207	0.090 - 0.414	0.412	-1.351
Cognitive	0.243	0.106	0.236	0.075 - 0.420	0.077	-1.269
Clinical	0.271	0.116	0.247	0.095 - 0.457	0.157	-1.446
Beta						
Whole Brain	0.244	0.071	0.246	0.131 - 0.408	0.262	-0.464
Left Hemisphere	0.251	0.073	0.254	0.140 - 0.405	0.193	-0.889
Right Hemisphere	0.244	0.072	0.245	0.130 - 0.407	0.261	-0.489
Anterior	0.230	0.072	0.234	0.127 - 0.409	0.413	-0.171
Posterior	0.248	0.075	0.239	0.136 - 0.391	0.487	-0.698
LH – Language	0.250	0.079	0.245	0.142 - 0.426	0.641	-0.293
RH – Language	0.258	0.082	0.245	0.132 - 0.424	0.369	-0.672

Motor	0.245	0.078	0.240	0.124 - 0.492	1.095	2.797
Cognitive	0.214	0.071	0.224	0.114 - 0.336	0.038	-1.211
Clinical	0.246	0.073	0.250	0.127 - 0.415	0.225	-0.381
			DAR			
Whole Brain	1.863	1.431	1.366	0.357 - 5.771	1.261	1.290
Left Hemisphere	1.837	1.398	1.432	0.357 - 5.424	1.266	1.156
Right Hemisphere	1.913	1.524	1.428	0.343 - 6.428	1.369	1.802
Anterior	2.215	1.763	1.726	0.450 - 7.366	1.549	2.417
Posterior	1.427	1.169	1.037	0.193 - 4.347	1.064	0.246
LH – Language	2.014	1.461	1.537	0.259 - 5.384	1.054	0.370
RH – Language	2.026	1.525	1.524	0.437 - 7.100	1.684	3.606
Motor	2.065	1.504	2.007	0.434 - 6.387	1.229	1.816
Cognitive	2.365	1.971	1.764	0.510 - 8.423	1.728	2.849
Clinical	1.860	1.393	1.535	0.364 - 5.698	1.184	1.016
			DTABR			
Whole Brain	1.044	0.654	0.887	0.294 - 2.896	1.551	2.698
Left Hemisphere	1.036	0.666	0.879	0.271 - 2.978	1.602	2.778
Right Hemisphere	1.045	0.654	0.890	0.271 - 2.928	1.485	2.398
Anterior	1.221	0.753	1.021	0.344 - 3.311	1.659	3.142
Posterior	0.843	0.586	0.680	0.183 - 2.566	1.482	2.157
LH – Language	1.111	0.638	0.986	0.229 - 2.718	1.026	0.619
RH – Language	1.091	0.639	0.922	0.324 - 2.697	1.292	1.371
Motor	1.148	0.686	1.151	0.247 - 3.292	1.444	3.135
Cognitive	1.301	0.830	1.119	0.406 - 3.979	1.904	4.037
Clinical	1.034	0.623	0.923	0.298 - 2.848	1.420	2.308
			$Q_{slowing}$			
Whole Brain	0.420	0.126	0.423	0.206 - 0.672	0.009	-0.265
Left Hemisphere	0.418	0.127	0.419	0.192 - 0.672	0.059	-0.277
Right Hemisphere	0.420	0.126	0.429	0.195 - 0.676	0.048	-0.325
Anterior	0.463	0.119	0.463	0.232 - 0.707	-0.087	-0.008
Posterior	0.373	0.134	0.377	0.157 - 0.655	0.209	-0.527
LH – Language	0.436	0.126	0.440	0.169 - 0.665	-0.096	-0.315
RH – Language	0.432	0.117	0.438	0.218 - 0.665	0.074	-0.188
Motor	0.449	0.131	0.476	0.178 - 0.704	-0.441	-0.199
Cognitive	0.480	0.116	0.488	0.270 - 0.724	0.162	0.052
Clinical	0.418	0.123	0.424	0.210 - 0.665	-0.039	-0.393

Table A4. Descriptive statistics for persons with stroke during eyes closed rest.

	Mean	SD	Median	Range	Skew	Kurtosis
Delta						
Whole Brain	0.284	0.124	0.279	0.087 - 0.604	0.619	0.483
Left Hemisphere	0.275	0.123	0.285	0.098 - 0.552	0.450	-0.382
Right Hemisphere	0.287	0.124	0.271	0.074 - 0.622	0.650	0.902
Anterior	0.251	0.115	0.240	0.082 - 0.538	0.791	0.456
Posterior	0.324	0.138	0.326	0.098 - 0.675	0.370	0.264
LH – Language	0.255	0.108	0.268	0.086 - 0.494	0.487	-0.050
RH – Language	0.265	0.110	0.245	0.063 - 0.575	0.694	1.628
Motor	0.263	0.131	0.229	0.087 - 0.589	1.132	1.173
Cognitive	0.238	0.113	0.210	0.079 - 0.527	0.817	0.538
Clinical	0.281	0.125	0.276	0.083 - 0.596	0.601	0.331
Theta						
Whole Brain	0.171	0.099	0.141	0.054 - 0.509	1.862	4.417
Left Hemisphere	0.175	0.100	0.147	0.055 - 0.510	1.718	3.967
Right Hemisphere	0.161	0.098	0.129	0.052 - 0.491	1.957	4.459
Anterior	0.173	0.094	0.150	0.062 - 0.480	1.638	3.431
Posterior	0.171	0.110	0.137	0.043 - 0.547	1.938	4.567
LH – Language	0.165	0.092	0.143	0.064 - 0.437	1.539	2.305
RH – Language	0.154	0.091	0.131	0.059 - 0.469	2.066	4.939
Motor	0.188	0.093	0.167	0.062 - 0.474	1.241	2.067
Cognitive	0.160	0.097	0.129	0.067 - 0.495	2.006	5.012
Clinical	0.170	0.098	0.139	0.057 - 0.511	1.948	4.927
Alpha						
Whole Brain	0.284	0.124	0.279	0.087 - 0.604	0.619	0.483
Left Hemisphere	0.275	0.123	0.285	0.098 - 0.552	0.450	-0.382
Right Hemisphere	0.287	0.124	0.271	0.074 - 0.622	0.650	0.902
Anterior	0.251	0.115	0.240	0.082 - 0.538	0.791	0.456
Posterior	0.324	0.138	0.326	0.098 - 0.675	0.370	0.264
LH – Language	0.255	0.108	0.268	0.086 - 0.494	0.487	-0.050
RH – Language	0.265	0.110	0.245	0.063 - 0.575	0.694	1.628
Motor	0.263	0.131	0.229	0.087 - 0.589	1.132	1.173
Cognitive	0.238	0.113	0.210	0.079 - 0.527	0.817	0.538
Clinical	0.281	0.125	0.276	0.083 - 0.596	0.601	0.331
Beta						
Whole Brain	0.176	0.066	0.177	0.038 - 0.286	-0.356	-0.502
Left Hemisphere	0.175	0.069	0.192	0.041 - 0.281	-0.497	-0.686
Right Hemisphere	0.186	0.076	0.183	0.036 - 0.337	-0.051	-0.492
Anterior	0.176	0.066	0.177	0.039 - 0.299	-0.248	-0.549
Posterior	0.165	0.078	0.162	0.032 - 0.309	0.204	-0.701
LH – Language	0.193	0.084	0.225	0.046 - 0.301	-0.646	-0.994
RH – Language	0.205	0.086	0.203	0.038 - 0.373	0.101	-0.517
Motor	0.187	0.067	0.182	0.042 - 0.287	-0.316	-0.628

Cognitive	0.167	0.068	0.164	0.046 - 0.285	0.033	-0.920
Clinical	0.178	0.068	0.179	0.039 - 0.286	-0.356	-0.606
DAR						
Whole Brain	2.084	1.824	1.510	0.255 - 7.864	1.725	3.027
Left Hemisphere	2.168	1.742	1.533	0.224 - 6.539	1.260	1.074
Right Hemisphere	2.105	2.146	1.496	0.254 - 9.964	2.375	6.514
Anterior	2.482	2.103	1.840	0.252 - 8.792	1.626	2.342
Posterior	1.683	1.655	1.129	0.182 - 7.009	1.854	3.464
LH – Language	2.319	1.783	1.803	0.260 - 6.833	1.128	0.784
RH – Language	2.431	2.624	1.644	0.364 - 12.294	2.581	7.591
Motor	2.011	1.612	1.608	0.260 - 6.028	1.421	1.587
Cognitive	2.991	2.640	2.390	0.260 - 10.232	1.613	1.911
Clinical	2.139	1.861	1.535	0.265 - 8.457	1.903	4.349
DTABR						
Whole Brain	1.765	1.565	1.143	0.326 - 7.290	2.115	5.439
Left Hemisphere	1.830	1.511	1.240	0.269 - 6.605	1.631	2.886
Right Hemisphere	1.709	1.771	1.126	0.319 - 7.759	2.532	6.587
Anterior	1.959	1.598	1.345	0.302 - 7.022	1.738	3.308
Posterior	1.613	1.694	1.048	0.268 - 8.101	2.582	8.131
LH – Language	1.827	1.535	1.184	0.321 - 6.183	1.531	1.912
RH – Language	1.780	1.951	1.185	0.370 - 9.035	2.785	8.205
Motor	1.709	1.311	1.309	0.338 - 5.703	1.511	2.283
Cognitive	2.202	1.800	1.437	0.258 - 7.502	1.597	2.484
Clinical	1.781	1.591	1.169	0.339 - 7.420	2.149	5.580
$Q_{slowing}$						
Whole Brain	0.488	0.155	0.472	0.220 - 0.803	0.019	-0.507
Left Hemisphere	0.501	0.160	0.498	0.192 - 0.795	-0.090	-0.614
Right Hemisphere	0.474	0.156	0.463	0.216 - 0.810	0.334	-0.126
Anterior	0.525	0.155	0.526	0.215 - 0.804	-0.285	-0.275
Posterior	0.451	0.162	0.458	0.189 - 0.820	0.310	-0.406
LH – Language	0.504	0.157	0.477	0.219 - 0.787	0.042	-0.781
RH – Language	0.484	0.152	0.470	0.246 - 0.842	0.526	0.058
Motor	0.503	0.151	0.507	0.230 - 0.753	-0.226	-0.674
Cognitive	0.549	0.159	0.546	0.196 - 0.817	-0.458	0.023
Clinical	0.490	0.153	0.471	0.225 - 0.803	0.045	-0.524

Appendix B

Table B1. Descriptive statistics during the P3a for neurologically healthy controls in response to novel stimuli.

	Mean	SD	Median	Range	Skew	Kurtosis
Historical						
Fz	3.359	1.756	3.410	-0.259 - 6.230	-0.425	-0.626
Cz	1.661	2.393	1.363	-2.292 - 7.336	0.235	-0.191
Pz	-0.471	1.978	-0.415	-4.945 - 2.830	-0.642	0.103
Expanded						
F3	2.513	1.504	2.172	-0.316 - 5.660	0.328	-0.232
F4	2.471	1.418	2.487	-0.669 - 4.771	-0.462	-0.203
C3	1.117	1.333	0.915	-0.874 - 3.724	0.351	-0.887
C4	0.809	1.433	0.896	-0.762 - 5.071	1.234	1.840
P3	-1.436	1.294	-1.303	-5.217 - 0.500	-1.181	2.056
P4	-1.229	1.753	-0.604	-5.028 - 1.994	-0.367	-0.239

Table B2. Descriptive statistics during the P3a for PWCS in response to novel stimuli.

	Mean	SD	Median	Range	Skew	Kurtosis
Historical						
Fz	2.017	1.850	1.905	-1.887 - 6.360	0.112	0.882
Cz	1.442	1.445	1.534	-1.647 - 5.201	0.335	0.734
Pz	-0.273	1.478	-0.214	-3.117 - 3.794	0.663	0.756
Expanded						
F3	1.588	1.598	1.418	-2.835 - 4.428	-0.395	0.899
F4	1.571	2.132	1.485	-2.755 - 6.221	0.148	0.250
C3	0.539	1.470	0.573	-2.771 - 4.019	0.162	0.911
C4	0.762	1.652	0.747	-4.992 - 3.227	-1.402	4.643
P3	-1.234	1.866	-1.316	-6.315 - 2.792	-0.106	1.669
P4	-0.501	1.207	-0.745	-3.076 - 1.656	0.031	-0.452

Table B3. Descriptive statistics during the P3a for neurologically healthy controls in response to target stimuli.

	Mean	SD	Median	Range	Skew	Kurtosis
Historical						
Fz	2.016	2.211	1.966	-3.106 - 7.497	0.167	0.566
Cz	1.679	2.478	1.802	-3.312 - 8.328	0.315	1.205
Pz	1.734	2.068	1.561	-1.949 - 7.281	0.496	0.951
Expanded						
F3	1.357	1.921	1.562	-3.239 - 4.346	-0.347	-0.368
F4	1.043	1.781	0.920	-1.853 - 4.278	0.158	-1.049
C3	0.700	1.538	0.862	-2.148 - 3.978	0.009	-0.458
C4	0.651	1.218	0.437	-1.128 - 4.751	1.379	3.624
P3	0.596	1.816	0.708	-3.044 - 3.787	-0.293	-0.554
P4	0.704	1.789	0.763	-2.974 - 4.386	-0.030	-0.080

Table B4. Descriptive statistics during the P3a for PWCS in response to target stimuli.

	Mean	SD	Median	Range	Skew	Kurtosis
			Historical			
Fz	1.281	1.552	1.204	-2.365 - 5.891	0.566	2.513
Cz	1.254	1.328	1.279	-1.832 - 3.466	-0.241	-0.150
Pz	0.953	1.378	0.873	-1.084 - 4.043	0.652	0.122
			Expanded			
F3	0.627	1.498	0.547	-1.365 - 3.850	0.303	-1.035
F4	1.199	1.822	1.203	-4.033 - 4.319	-0.729	1.852
C3	0.036	1.237	0.136	-2.807 - 2.365	-0.302	-0.286
C4	0.791	1.312	1.031	-1.924 - 2.954	-0.561	-0.415
P3	-0.407	1.883	-0.232	-4.455 - 3.588	0.039	0.123
P4	0.380	1.108	0.199	-1.189 - 2.671	0.353	-0.967

Table B5. Descriptive statistics during the P3b for neurologically healthy controls in response to novel stimuli.

	Mean	SD	Median	Range	Skew	Kurtosis
Historical						
Fz	2.877	1.492	2.829	-0.584 - 6.101	0.114	0.070
Cz	1.265	1.673	1.388	-1.870 - 4.137	-0.230	-0.553
Pz	0.402	1.885	0.358	-3.948 - 4.192	-0.395	0.243
Expanded						
F3	1.942	1.277	1.681	-0.990 - 4.899	0.372	0.635
F4	1.833	1.321	2.069	-0.576 - 5.203	0.392	0.331
C3	0.789	1.041	0.488	-0.865 - 3.030	0.416	-0.578
C4	0.668	1.242	0.672	-1.374 - 3.355	0.184	-0.460
P3	-0.650	1.524	-0.530	-4.872 - 1.774	-0.891	1.109
P4	-0.403	1.512	-0.100	-3.672 - 2.323	-0.626	0.269

Table B6. Descriptive statistics during the P3b for PWCS in response to novel stimuli.

	Mean	SD	Median	Range	Skew	Kurtosis
Historical						
Fz	1.891	2.215	2.143	-4.408 - 7.199	-0.527	2.283
Cz	1.463	1.869	1.496	-2.642 - 6.743	0.632	1.651
Pz	0.344	1.610	0.417	-3.283 - 3.563	0.044	-0.049
Expanded						
F3	1.606	1.829	1.783	-3.161 - 5.489	-0.243	1.027
F4	1.142	2.325	1.413	-3.875 - 7.081	-0.261	1.568
C3	0.572	1.804	0.847	-4.755 - 4.948	-0.528	2.625
C4	0.658	1.891	0.685	-6.059 - 4.108	-1.484	5.280
P3	-0.987	2.633	-1.028	-10.395 - 3.460	-1.597	5.723
P4	0.018	1.462	0.350	-2.802 - 2.835	-0.159	-0.828

Table B7. Descriptive statistics during the P3b for neurologically healthy controls in response to target stimuli.

	Mean	SD	Median	Range	Skew	Kurtosis
Historical						
Fz	1.334	2.207	1.700	-3.520 - 5.459	-0.425	-0.235
Cz	1.466	1.831	1.289	-1.847 - 4.636	-0.049	-0.915
Pz	2.720	2.068	2.613	-0.716 - 8.854	0.908	1.550
Expanded						
F3	0.794	2.048	1.320	-4.170 - 3.141	-0.975	0.062
F4	0.228	1.912	0.318	-3.175 - 3.707	-0.055	-0.996
C3	0.789	1.115	0.785	-1.197 - 2.576	-0.148	-1.055
C4	0.355	1.026	0.145	-1.388 - 2.714	0.249	-0.482
P3	1.634	1.903	1.862	-2.137 - 5.544	-0.123	-0.009
P4	1.331	1.848	1.650	-1.748 - 5.574	0.344	-0.145

Table B8. Descriptive statistics during the P3b for PWCS in response to target stimuli.

	Mean	SD	Median	Range	Skew	Kurtosis
Historical						
Fz	1.044	1.850	0.740	-3.998 - 6.284	0.289	2.995
Cz	1.240	1.487	0.927	-0.989 - 5.575	1.055	1.797
Pz	1.449	1.809	0.956	-1.347 - 5.612	0.587	-0.656
Expanded						
F3	0.515	1.619	0.531	-2.903 - 3.747	-0.167	-0.319
F4	0.885	1.950	0.921	-5.298 - 4.377	-0.971	2.797
C3	0.323	1.202	0.211	-2.425 - 2.746	-0.004	-0.195
C4	0.869	1.470	0.769	-2.400 - 3.771	-0.055	-0.209
P3	0.135	2.238	0.107	-4.416 - 4.411	0.035	-0.532
P4	0.695	1.120	0.561	-1.026 - 2.743	0.410	-0.924

Table B9. Descriptive statistics during the N150 for neurologically healthy controls during the orthographic task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.459	1.429	-0.579	-3.470 - 2.799	0.020	0.563
Left Posterior	0.164	2.020	0.464	-5.932 - 3.580	-1.192	2.369
Right Anterior	-0.033	1.396	0.044	-3.126 - 4.074	0.639	2.467
Right Posterior	3.226	2.310	3.616	-2.297 - 7.652	-0.252	0.323
Expanded ROIs						
Left Orbito-Frontal	-0.482	1.555	-0.491	-4.116 - 2.930	-0.204	0.913
Left Antero-Medial	-0.278	1.231	-0.440	-2.363 - 2.671	0.519	0.177
Left Antero-Lateral	-0.299	1.007	-0.328	-3.032 - 1.895	-0.475	1.247
Left Postero-Medial	0.065	0.835	0.001	-1.258 - 1.660	0.265	-0.665
Left Postero-Lateral	1.579	1.140	1.688	-0.948 - 3.532	-0.246	-0.305
Left Occipital	0.219	2.364	0.479	-7.283 - 3.607	-1.525	3.539
Right Orbito-Frontal	-0.221	1.591	-0.292	-3.643 - 4.212	0.461	1.461
Right Antero-Medial	-0.182	1.269	-0.400	-2.348 - 3.011	0.852	0.593
Right Antero-Lateral	-0.194	0.973	-0.089	-1.841 - 2.619	0.600	1.423
Right Postero-Medial	0.273	0.681	0.113	-0.492 - 2.668	1.885	5.097
Right Postero-Lateral	0.669	1.584	0.512	-2.049 - 5.173	0.903	1.442
Right Occipital	0.468	3.159	0.727	-9.620 - 7.569	-0.945	3.667

Table B10. Descriptive statistics during the N150 for PWCS during the orthographic task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.128	1.693	-0.229	-2.775 - 3.297	0.361	-0.431
Left Posterior	0.049	1.991	0.040	-5.278 - 5.267	-0.110	2.245
Right Anterior	-0.279	1.427	-0.424	-2.814 - 3.252	0.996	1.502
Right Posterior	3.755	1.837	3.630	-0.211 - 7.907	-0.243	0.292
Expanded ROIs						
Left Orbito-Frontal	-0.357	1.569	-0.446	-3.194 - 3.359	0.497	0.330
Left Antero-Medial	-0.316	1.243	-0.498	-3.683 - 1.522	-0.528	0.391
Left Antero-Lateral	-0.044	1.374	0.039	-2.128 - 3.181	0.337	-0.099
Left Postero-Medial	0.032	1.004	-0.033	-1.991 - 2.304	0.188	-0.127
Left Postero-Lateral	2.223	1.082	2.216	-0.336 - 5.203	0.507	1.926
Left Occipital	0.147	2.545	0.303	-5.586 - 7.435	0.260	1.953
Right Orbito-Frontal	-0.336	1.566	-0.205	-3.406 - 3.221	0.409	0.352
Right Antero-Medial	-0.178	1.417	-0.219	-3.512 - 3.093	-0.028	0.994
Right Antero-Lateral	-0.245	1.128	-0.367	-2.384 - 2.180	0.292	0.048
Right Postero-Medial	0.076	0.781	0.110	-1.252 - 2.243	0.644	0.985
Right Postero-Lateral	0.724	1.459	0.948	-3.116 - 4.125	-0.391	1.022
Right Occipital	0.538	2.517	0.702	-3.734 - 6.462	-0.014	-0.196

Table B11. Descriptive statistics during the N150 for neurologically healthy controls during the phonological task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.517	1.582	-0.347	-4.458 - 2.716	-0.443	0.963
Left Posterior	0.397	1.898	0.538	-5.677 - 3.416	-1.420	3.208
Right Anterior	-0.265	1.627	-0.485	-4.563 - 3.776	0.146	2.193
Right Posterior	3.676	2.256	4.022	-2.435 - 8.041	-0.523	1.008
Expanded ROIs						
Left Orbito-Frontal	-0.606	1.648	-0.680	-5.214 - 3.092	-0.365	1.766
Left Antero-Medial	-0.522	1.148	-0.553	-3.056 - 2.498	0.226	1.017
Left Antero-Lateral	-0.502	0.990	-0.477	-2.891 - 1.792	-0.027	1.476
Left Postero-Medial	0.205	0.841	0.313	-1.177 - 1.872	-0.056	-0.835
Left Postero-Lateral	1.759	1.269	1.661	-1.380 - 4.151	-0.036	0.504
Left Occipital	0.575	2.398	0.859	-7.106 - 4.132	-1.407	3.077
Right Orbito-Frontal	-0.421	1.679	-0.454	-4.524 - 3.990	0.475	2.200
Right Antero-Medial	-0.448	1.096	-0.641	-2.570 - 3.013	1.178	3.115
Right Antero-Lateral	-0.327	1.080	-0.415	-3.153 - 2.720	0.472	3.048
Right Postero-Medial	0.275	0.809	0.275	-1.116 - 2.810	1.042	2.689
Right Postero-Lateral	0.854	1.514	0.443	-1.893 - 4.956	0.871	1.160
Right Occipital	0.901	3.097	1.159	-10.210 - 7.033	-1.616	6.101

Table B12. Descriptive statistics during the N150 for PWCS during the phonological task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.593	1.838	-0.796	-4.630 - 2.317	-0.128	-0.574
Left Posterior	0.565	2.011	0.701	-5.262 - 4.776	-0.739	1.811
Right Anterior	-0.762	1.324	-0.501	-4.737 - 1.578	-1.163	2.653
Right Posterior	4.289	1.775	4.860	0.168 - 7.284	-0.676	-0.167
Expanded ROIs						
Left Orbito-Frontal	-0.842	1.696	-0.684	-4.316 - 2.221	-0.314	-0.590
Left Antero-Medial	-0.512	1.281	-0.716	-3.525 - 2.303	0.126	0.442
Left Antero-Lateral	-0.452	1.392	-0.535	-3.775 - 2.308	-0.263	0.289
Left Postero-Medial	0.231	0.837	0.230	-1.379 - 1.610	0.025	-0.862
Left Postero-Lateral	2.631	1.071	2.311	-0.417 - 4.575	-0.280	1.346
Left Occipital	0.656	2.756	1.196	-5.694 - 6.928	-0.486	1.142
Right Orbito-Frontal	-0.967	1.445	-0.546	-4.562 - 1.537	-0.469	0.206
Right Antero-Medial	-0.441	1.179	-0.540	-2.980 - 2.430	0.439	0.535
Right Antero-Lateral	-0.495	1.126	-0.546	-2.697 - 1.483	-0.300	-0.246
Right Postero-Medial	0.258	0.925	0.162	-1.678 - 2.833	0.696	1.599
Right Postero-Lateral	0.940	1.629	1.341	-3.163 - 4.091	-0.713	0.967
Right Occipital	1.006	2.373	1.573	-3.440 - 5.956	-0.137	-0.559

Table B13. Descriptive statistics during the N150 for neurologically healthy controls during the semantic task.

	Mean	SD	Median	Min	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.760	1.488	-0.585	-4.708 - 2.550	-0.381	1.219
Left Posterior	0.274	1.795	0.504	-4.675 - 3.264	-1.124	1.466
Right Anterior	-0.311	1.332	-0.444	-4.008 - 2.801	-0.294	2.029
Right Posterior	3.642	2.270	3.791	-2.037 - 7.929	-0.504	0.428
Expanded ROIs						
Left Orbito-Frontal	-0.732	1.570	-0.617	-5.622 - 2.907	-0.729	3.298
Left Antero-Medial	-0.578	1.176	-0.606	-3.174 - 2.388	0.268	0.928
Left Antero-Lateral	-0.658	0.978	-0.814	-2.865 - 0.968	-0.415	0.234
Left Postero-Medial	0.221	0.732	0.149	-0.943 - 1.517	0.282	-0.864
Left Postero-Lateral	1.640	1.142	1.777	-1.725 - 3.508	-1.128	2.069
Left Occipital	0.411	2.121	0.375	-6.106 - 4.002	-1.311	2.527
Right Orbito-Frontal	-0.375	1.531	-0.366	-4.794 - 3.572	-0.254	2.855
Right Antero-Medial	-0.265	1.162	-0.426	-2.802 - 3.203	0.836	2.600
Right Antero-Lateral	-0.392	0.961	-0.360	-2.405 - 1.542	-0.158	0.142
Right Postero-Medial	0.423	0.764	0.306	-0.828 - 2.697	0.881	1.777
Right Postero-Lateral	0.926	1.549	0.693	-2.518 - 5.579	0.702	2.760
Right Occipital	0.917	3.065	0.780	-9.999 - 7.257	-1.552	6.065

Table B14. Descriptive statistics during the N150 for PWCS during the semantic task.

	Mean	SD	Median	Min	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.581	2.065	-0.932	-5.171 - 3.253	-0.203	0.092
Left Posterior	0.088	2.189	0.379	-5.804 - 5.162	-0.496	2.066
Right Anterior	-0.451	1.426	-0.625	-3.031 - 3.144	0.716	0.587
Right Posterior	3.847	1.797	3.884	-0.005 - 7.394	-0.331	0.053
Expanded ROIs						
Left Orbito-Frontal	-0.619	1.859	-0.402	-5.521 - 2.134	-0.950	1.242
Left Antero-Medial	-0.227	1.249	0.023	-3.768 - 2.020	-0.957	1.724
Left Antero-Lateral	-0.310	1.708	-0.300	-4.656 - 3.223	-0.174	0.470
Left Postero-Medial	0.030	0.938	0.138	-2.237 - 1.558	-0.560	0.047
Left Postero-Lateral	2.149	1.284	2.010	-0.638 - 4.762	-0.079	0.115
Left Occipital	0.037	2.825	0.186	-7.137 - 7.227	-0.273	1.947
Right Orbito-Frontal	-0.551	1.492	-0.610	-4.197 - 2.568	-0.067	0.791
Right Antero-Medial	0.005	1.515	0.040	-3.522 - 4.142	0.683	2.678
Right Antero-Lateral	-0.109	1.212	-0.556	-2.459 - 2.326	0.697	-0.048
Right Postero-Medial	0.124	1.113	0.012	-2.459 - 2.841	0.517	1.351
Right Postero-Lateral	0.843	1.478	0.686	-2.775 - 4.367	0.170	1.190
Right Occipital	0.511	2.408	0.665	-5.873 - 6.083	-0.357	1.327

Table B15. Descriptive statistics during the N350 for neurologically healthy controls during the orthographic task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.539	1.398	-0.545	-2.998 - 2.308	0.108	-0.500
Left Posterior	0.070	1.286	0.148	-2.525 - 2.412	-0.047	-0.427
Right Anterior	-0.653	1.229	-0.667	-2.900 - 6.200	-0.007	-0.735
Right Posterior	2.992	1.787	3.113	-3.557 - 6.200	-1.939	6.934
Expanded ROIs						
Left Orbito-Frontal	-0.620	1.376	-0.808	-3.863 - 1.744	-0.314	-0.234
Left Antero-Medial	0.008	0.766	0.083	-1.303 - 1.219	-0.102	-1.259
Left Antero-Lateral	0.063	1.043	-0.039	-2.110 - 2.805	0.366	0.782
Left Postero-Medial	0.870	0.767	0.931	-0.528 - 2.277	-0.069	-0.287
Left Postero-Lateral	1.625	0.954	1.711	-1.058 - 3.084	-0.987	1.345
Left Occipital	-0.134	1.672	-0.120	-3.304 - 3.425	0.231	-0.036
Right Orbito-Frontal	-0.773	1.293	-0.812	-3.124 - 1.498	-0.142	-0.727
Right Antero-Medial	-0.135	0.888	-0.194	-1.879 - 1.401	0.053	-0.595
Right Antero-Lateral	-0.252	0.931	-0.193	-2.166 - 1.402	-0.132	-0.559
Right Postero-Medial	0.182	0.591	0.090	-1.005 - 1.334	0.298	-0.219
Right Postero-Lateral	-0.241	0.990	-0.151	-2.543 - 2.216	0.130	0.811
Right Occipital	-0.339	1.692	-0.482	-3.274 - 4.236	0.948	1.165

Table B16. Descriptive statistics during the N350 for PWCS during the orthographic task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.039	1.149	-0.257	-2.108 - 2.640	0.619	0.581
Left Posterior	0.324	1.572	0.092	-3.125 - 4.779	0.538	1.833
Right Anterior	-0.667	1.493	-0.540	-3.870 - 2.242	-0.066	0.293
Right Posterior	3.905	1.167	3.826	1.085 - 6.662	0.003	0.626
Expanded ROIs						
Left Orbito-Frontal	-0.308	1.221	-0.364	-3.315 - 2.982	0.254	1.908
Left Antero-Medial	-0.168	0.895	-0.069	-1.592 - 1.481	-0.065	-1.015
Left Antero-Lateral	0.148	1.136	0.207	-1.446 - 3.709	1.298	2.586
Left Postero-Medial	0.339	0.986	0.308	-1.731 - 3.014	0.088	1.678
Left Postero-Lateral	2.212	1.636	2.117	-0.498 - 6.629	1.050	1.559
Left Occipital	0.411	1.699	0.210	-3.325 - 5.518	0.664	2.444
Right Orbito-Frontal	-0.517	1.533	-0.535	-3.765 - 2.610	0.055	0.128
Right Antero-Medial	-0.371	1.391	-0.181	-4.058 - 1.998	-0.672	0.801
Right Antero-Lateral	-0.444	1.237	-0.501	-3.326 - 2.036	-0.230	0.303
Right Postero-Medial	0.188	0.633	0.281	-1.553 - 1.219	-0.831	1.450
Right Postero-Lateral	0.208	1.200	-0.069	-1.594 - 3.575	1.083	1.339
Right Occipital	0.459	1.641	0.340	-4.266 - 4.351	-0.383	2.103

Table B17. Descriptive statistics during the N350 for neurologically healthy controls during the phonological task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.660	1.154	-0.414	-2.968 - 1.728	-0.295	0.017
Left Posterior	0.240	1.139	0.082	-1.655 - 2.444	0.430	-0.478
Right Anterior	-0.883	1.178	-0.490	-3.268 - 0.616	-0.763	-0.426
Right Posterior	3.380	1.648	3.615	-2.720 - 5.831	-2.195	7.269
Expanded ROIs						
Left Orbito-Frontal	-0.739	1.118	-0.381	-3.433 - 1.009	-0.974	0.372
Left Antero-Medial	-0.225	0.702	-0.208	-1.488 - 1.172	-0.028	-0.559
Left Antero-Lateral	-0.188	0.812	-0.205	-1.630 - 2.010	0.577	1.279
Left Postero-Medial	0.792	0.754	0.612	-0.431 - 2.581	0.798	0.207
Left Postero-Lateral	1.586	0.934	1.447	-1.293 - 3.158	-0.831	2.340
Left Occipital	0.144	1.455	0.139	-2.035 - 3.656	0.529	0.020
Right Orbito-Frontal	-1.023	1.160	-0.579	-3.510 - 0.508	-0.925	-0.195
Right Antero-Medial	-0.238	0.782	-0.145	-1.797 - 1.300	-0.154	-0.612
Right Antero-Lateral	-0.292	0.712	-0.137	-1.661 - 0.790	-0.301	-1.094
Right Postero-Medial	0.192	0.594	0.304	-1.582 - 1.311	-0.853	2.000
Right Postero-Lateral	0.110	0.924	0.202	-2.175 - 2.332	-0.076	1.070
Right Occipital	0.178	1.532	0.106	-2.397 - 3.948	0.552	0.327

Table B18. Descriptive statistics during the N350 for PWCS during the phonological task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	0.200	1.334	0.245	-3.644 - 2.173	-0.907	1.473
Left Posterior	-0.676	2.113	-0.305	-8.261 - 1.724	-1.855	5.361
Right Anterior	0.051	1.105	-0.014	-2.675 - 2.361	-0.286	0.729
Right Posterior	3.275	1.558	3.399	0.095 - 5.771	-0.611	-0.410
Expanded ROIs						
Left Orbito-Frontal	-0.055	1.308	-0.091	-3.457 - 2.528	-0.237	0.720
Left Antero-Medial	0.259	1.169	0.094	-1.646 - 2.696	0.374	-0.426
Left Antero-Lateral	0.316	1.103	0.107	-1.936 - 2.434	0.140	-0.486
Left Postero-Medial	0.185	0.995	0.051	-1.460 - 3.065	0.771	1.303
Left Postero-Lateral	1.785	1.266	1.890	-1.872 - 4.680	-0.499	2.465
Left Occipital	-0.721	2.442	-0.434	-8.318 - 2.867	-1.218	2.459
Right Orbito-Frontal	-0.072	1.155	-0.121	-2.350 - 2.714	0.242	0.564
Right Antero-Medial	0.033	1.220	-0.124	-1.964 - 3.666	1.163	2.379
Right Antero-Lateral	0.122	1.112	0.056	-2.427 - 2.796	0.157	0.699
Right Postero-Medial	0.074	0.795	-0.117	-1.839 - 2.491	0.881	3.229
Right Postero-Lateral	-0.387	1.511	-0.039	-3.383 - 2.153	-0.607	-0.136
Right Occipital	-0.358	2.330	0.204	-7.737 - 2.759	-1.526	2.819

Table B19. Descriptive statistics during the N350 for neurologically healthy controls during the semantic task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.561	0.857	-0.599	-2.196 - 1.481	0.267	0.474
Left Posterior	0.094	1.236	0.105	-2.436 - 2.723	0.326	0.451
Right Anterior	-0.721	0.939	-0.739	-3.132 - 0.645	-0.880	0.448
Right Posterior	3.362	1.691	3.522	-2.738 - 5.805	-2.135	6.699
Expanded ROIs						
Left Orbito-Frontal	-0.580	0.828	-0.572	-2.344 - 1.003	-0.252	0.198
Left Antero-Medial	-0.082	0.837	-0.075	-1.741 - 1.516	-0.118	-0.385
Left Antero-Lateral	-0.077	0.858	-0.124	-2.003 - 2.117	0.308	1.367
Left Postero-Medial	0.669	0.797	0.594	-0.681 - 2.438	0.304	-0.527
Left Postero-Lateral	1.481	1.067	1.409	-1.820 - 3.370	-0.948	2.612
Left Occipital	-0.026	1.572	-0.147	-2.837 - 3.942	0.702	1.115
Right Orbito-Frontal	-0.874	0.922	-0.623	-2.876 - 0.581	-0.467	-0.345
Right Antero-Medial	-0.076	0.851	0.038	-1.709 - 1.430	-0.025	-0.806
Right Antero-Lateral	-0.257	0.771	-0.342	-2.044 - 1.265	-0.169	-0.088
Right Postero-Medial	0.232	0.728	0.272	-1.245 - 1.760	0.105	-0.076
Right Postero-Lateral	0.058	0.966	0.000	-2.816 - 2.180	-0.639	2.348
Right Occipital	0.089	1.548	-0.096	-2.221 - 4.039	0.868	0.863

Table B20. Descriptive statistics during the N350 for PWCS during the semantic task.

	Mean	SD	Median	Range	Skew	Kurtosis
Spironelli & Angrilli ROIs						
Left Anterior	-0.559	1.597	-0.675	-3.324 - 3.795	0.790	1.108
Left Posterior	0.584	1.551	0.264	-2.085 - 5.118	1.280	2.185
Right Anterior	-0.745	1.108	-0.695	-2.844 - 1.263	-0.209	-0.486
Right Posterior	4.122	1.242	3.948	2.004 - 7.320	0.616	0.597
Expanded ROIs						
Left Orbito-Frontal	-0.794	1.410	-0.794	-3.937 - 2.661	0.136	0.709
Left Antero-Medial	-0.343	1.078	-0.178	-2.538 - 1.772	-0.276	-0.278
Left Antero-Lateral	-0.229	1.452	-0.386	-2.053 - 5.604	2.555	9.659
Left Postero-Medial	0.481	0.811	0.280	-1.041 - 2.683	0.789	1.001
Left Postero-Lateral	2.234	1.642	1.903	-0.112 - 6.306	1.065	0.642
Left Occipital	0.617	1.707	0.488	-2.078 - 5.618	1.091	2.018
Right Orbito-Frontal	-0.897	1.219	-0.786	-2.773 - 1.383	0.034	-0.964
Right Antero-Medial	-0.429	1.104	-0.310	-2.637 - 1.599	-0.360	-0.128
Right Antero-Lateral	-0.420	1.105	-0.332	-2.815 - 1.927	-0.212	0.409
Right Postero-Medial	0.238	0.791	0.241	-1.986 - 1.758	-0.516	1.587
Right Postero-Lateral	0.446	1.569	0.178	-1.930 - 4.713	1.314	2.006
Right Occipital	0.723	1.537	0.694	-2.535 - 4.420	0.464	0.989

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