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State Regulation and Executive Function in Traumatic Brain Injury: EEG Correlates of Impairment and Intervention

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Hickey, Melinda A., State Regulation and Executive Function in Traumatic Brain Injury: EEG Correlates of Impairment and Intervention, Doctor of Philosophy thesis, School of Psychology, University of Wollongong, 2020. https://ro.uow.edu.au/theses1/1006

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State Regulation and Executive Function in Traumatic Brain Injury: EEG Correlates of Impairment and Intervention

Melinda A. Hickey, BPsyc (Hons)

Supervisors:

Professor Stuart Johnstone

Dr Jacqueline Rushby

A thesis is presented as part of the requirement for the award of the degree:

Doctor of Philosophy (Clinical Psychology)

This research has been conducted with the support of the Australian Government Research and Training Program Scholarship

The University of Wollongong

School of Psychology

July 2020

Certification

I, Melinda Hickey, declare that this thesis submitted in fulfilment of the requirements for the conferral of the degree Doctor of Philosophy (Clinical Psychology), from the School of Psychology, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.

Melinda Hickey

14th July 2020

Acknowledgments

To Stuart, thank you for your loyalty and persistence in what turned out to be a longer process than I ever imagined. Your patient, calm, and steady support helped ground me in moments of panic, and your trust in me has played a huge part in my development and confidence as a researcher.

To Jacqui, thank you for your creativity, authenticity, and nurturance. Your generous mentorship has been a true gift, and you inspire me not just in the realm of academia but also in life.

To Margaret Musico and Jason Cusack of the Illawarra Brain Injury Service (IBIS), thank you for your expertise, insight, and crucial input in the foundations of this work - for bringing this project to life.

To my colleagues in the PhD and clinical programs, your emotional support and friendship made this process meaningful far beyond its intellectual rewards. A special mention to Sally, Kristy, Carol, Gamze, Frances, Johanna, and Elle. And especially to Emma, my office buddy from start to finish – with you by my side I never felt alone and was never deprived of love and a good laugh.

To my friends and family. Though you could not always understand why I would put myself through this, you trusted me and supported me always. A special thanks to India, Jess, Adam, and Nathan for your advice, understanding, love, and encouragement. To all of you who keep me afloat (and sometimes even flourishing) outside of work.

And finally, to each of the clients of IBIS who participated in this research. For your commitment, perseverance, and enthusiasm. Your resilience and optimism sustained this project (and me) through the most challenging times. Each of your stories brought some necessary humanity to this research. Thank you.

Abstract

Executive dysfunction is a common and persistent consequence of Traumatic Brain Injury (TBI) and has a significant detrimental impact on social, emotional, and occupational functioning. Abnormalities in EEG measures reflecting the energetic state of the brain are also common following TBI, and rehabilitation approaches such as cognitive and neurofeedback training aim to improve executive function (EF) by facilitating changes in brain state and function. However, the field is lacking a parsimonious and clinically applicable theory of the relationship between brain energetic state and cognition in TBI. The Cognitive Energetic Model (CEM; Sanders, 1983) may address this gap. The CEM provides an explanation of how two aspects of energetic state - arousal (baseline energetic state) and activation (mobilisation of arousal in response to processing demands) - interact with computational factors, effort, and evaluative processes to produce efficient cognitive performance. EEG measures of *arousal* (eyes-closed global alpha) and *activation* (changes in delta, theta, alpha, and beta bands between resting or task conditions) provide an empirical basis for investigating the applicability of this model to TBI sequelae and intervention. The aims of this thesis were: 1) to investigate the applicability of the CEM arousal and activation concepts to understanding energetic state abnormalities and their relationship to EF impairment in TBI; and 2) to investigate the effectiveness of a CEM-based neurocognitive training program for improving EF in TBI.

Study 1 investigated EEG measures of arousal and activation recorded during eyes-closed and eyes-open resting conditions. Results showed intact arousal, but impaired activation for the TBI group, compared to healthy controls. The TBI group were characterised by reduced resting theta activation and a trend toward increased resting delta activation. Furthermore, enhanced resting delta and alpha activation and reduced resting theta activation were associated with impaired performance on a response inhibition task across groups. Together, the results suggested that it is not baseline resting state, but rather the ability to mobilise energetic state, that is impaired in TBI, and that this is associated with impaired EF.

Study 2 extended on resting EEG findings by examining the mobilisation of energetic state in response to cognitive processing demands. Task-related activation was operationalised as the change in EEG band amplitudes between an eyes-open resting condition and a response inhibition task condition at three event-rates. Compared to controls, the TBI group showed reduced task-related delta activation, increased theta and beta activation, and a trend toward reduced alpha activation. Furthermore, reduced delta and alpha activation were associated with impaired performance on the response inhibition task across groups. Theta activation was the only measure to show sensitivity to exogenous state modulation via event-rate. A TBI-related enhancement of frontal hemispheric theta activation, specific to the fast (cf. moderate) event-rate task, suggested a potential compensatory effect of exogenous (bottom-up) regulation of energetic state in the more stimulating Fast condition for the TBI group. Overall, the results demonstrated impaired mobilisation of energetic state in response to cognitive demands in TBI, and this was associated with impaired EF.

Study 3 investigated the relationships between arousal and activation measures and self-reported everyday EF behaviour. Across TBI and control groups, increased resting delta activation and reduced resting alpha activation were associated with greater impairments on measures of everyday response inhibition, consistent with relationships observed using the lab-based response inhibition measure in Study 1. In contrast, reduced resting theta and increased beta activation were associated with a broader range of everyday EF measures, reflecting a more generalised role in in both disinhibited and inattentive behaviours. Additionally, resting and task-related theta and beta activation were associated with injury severity and chronicity in the TBI group, however there was no association between arousal and injury variables. This builds on evidence from Study 1 that impaired activation, rather than arousal, characterises energetic state abnormalities in TBI, and highlights a specific role for theta and beta activation in both everyday EF and injury characteristics.

Finally, Study 4 investigated the effectiveness of a CEM-based neurocognitive training (combined cognitive and neurofeedback training) program in a group of adults with TBI. It

addressed key limitations in the literature, utilising a single case experimental design (SCED) to capitalise on the heterogeneity of participants while providing adequate experimental control to infer intervention effects. Study 4 did not establish unequivocal effectiveness of the neurocognitive training program as cognitive, behavioural, and electrophysiological improvements were inconsistent across participants. However, potential predictors of training engagement and benefit were identified, including consistent training rate, younger age, shorter duration of post-traumatic amnesia, longer pre-injury education years, and return to or maintenance of pre-injury occupational functioning.

Overall, the results of this thesis have demonstrated a specific impairment in activation of energetic state (rather than arousal) in TBI, and associations between activation and both cognitive and behavioural manifestations of EF impairment. The present findings replicate prior research using alpha measures of arousal and activation in TBI, and extend evidence to the delta, theta, and beta bands, and to external manipulations of energetic state via event-rate. Associations between activation impairments and cognitive performance, everyday EF, and injury variables, contribute evidence for a role of impaired state regulation in the cognitive and behavioural sequelae of TBI. This highlights the need for interventions that target mobilisation of energetic state in response to changing environmental or processing demands, and the importance of activation measures to assess outcomes. A particular sensitivity of theta activation to exogenous state modulation (via event-rate), EF impairments, and injury variables, along with prior associations of theta activity with top-down attentional control, the anterior cingulate cortex, and cortico-thalamic arousal system, suggests theta activation to be a good candidate measure to index state regulation impairments in TBI, and a potential rehabilitation target. Finally, this thesis demonstrated the SCED to be a suitable methodology for investigating state regulation interventions in TBI, and of value as a much-needed idiographic approach to this heterogeneous condition.

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List of Abbreviations

AD/HD	Attention Deficit/Hyperactivity Disorder
BIS-11	Barratt Impulsiveness Scale 11
BRI	Behavior Regulation Index
BRIEF-A	Behavior Rating Inventory of Executive Function – Adult Version
CEM	Cognitive Energetic Model
CHI	Closed head injury
CPT	Continuous Performance Task
DAI	Diffuse axonal injury
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - 5th Edition
EC	Eyes-closed
EEG	Electroencephalogram
EF	Executive function
EO	Eyes-open
ERP	Event-related potential
GEC	Global Executive Composite
IC	Inhibitory control
LOC	Loss of consciousness
MI	Metacognition Index
mTBI	Mild Traumatic Brain Injury
NF	Neurofeedback
PHI	Penetrating head injury
PTA	Post-traumatic amnesia
RI	Response inhibition
RT	Reaction time

rTMS	Repeated transcranial magnetic stimulation
SART	Sustained Attention to Response Task
SCED	Single case experimental design
SCL	Skin conductance level
TAI	Traumatic axonal injury
TBI	Traumatic Brain Injury
WM	Working memory

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CHAPTER 1: General Introduction

1.1 Traumatic Brain Injury

Traumatic brain injury (TBI) is pathology or alteration in function of the brain caused by an external force, most often sustained as a result of motor vehicle accident, fall, or assault (Menon et al., 2010; Tate et al., 1998). TBI affects over 10 million people worldwide each year (Hyder et al., 2007) and is the leading cause of mortality and disability in high income countries, especially among young adults (Maas et al., 2016; Roozenbeek et al., 2013). The aetiology of TBI depends on such factors as the nature, location, and severity of impact, resulting in heterogeneous outcomes and a range of physical, psychological, and social problems (Koskinen et al., 2011). These problems cause a substantial economic and social burden, making TBI a significant public health concern (Hyder et al., 2007).

The mechanics of TBI lead to a complex and intricate pattern of focal, multi-focal, and/or diffuse damage that typically extends beyond the original site of impact. Damage occurs as a result of both mechanical forces at the time of trauma (i.e. the primary injury) and the consequent physiological and metabolic processes that ensue (i.e. secondary effects) (McCrea, Janecek, Powell, & Hammeke, 2014). A TBI is classified into one of two categories: (1) *penetrating head injury* (PHI), where the skull and dura (the membrane covering the brain) are penetrated by a foreign object; or (2) the more common *closed head injury* (CHI), where blunt impact and/or mechanical forces leave the skull and/or dura intact (Hannay et al., 2004). Given the more variable neurological presentation and the relatively lower prevalence of PHI (Hannay et al., 2004), this thesis will focus on CHIs.

In a CHI, contusional damage to the brain results from direct impact of the head with an external object, or from the differential displacement of the brain relative to the skull. Contusions occur at the site of the impact (coup) and at the side opposite to the impact (contrecoup) as a result of the brain rebounding and colliding within the skull (Ommaya & Gennarelli, 1974). This leads

to heterogeneous effects on the brain, including multifocal damage to the lateral, anterior and ventral surfaces of the frontal and temporal lobes (Bigler, 2007). Rotational forces also result in more diffuse stretching and tearing of white matter fibres, termed diffuse axonal injury[1] (DAI; Gennarelli et al., 1998). This primary shearing of axons initiates a secondary neuropathological process that evolves over the following days to months and involves disruption of axonal transport, axonal swelling, and finally axonal disconnection and generalised degeneration of neighbouring neurons (McGinn & Povlishock, 2016). Axonal injury disrupts neurotransmitter systems involving norepinephrine, serotonin, dopamine, and acetylcholine (Jenkins et al., 2016). Other secondary complications of CHI include ischemia, edema, and increased intracranial pressure (Lezak et al., 2012).

The severity of a CHI is classified according to the immediate functional consequences of the injury, including post-traumatic amnesia (PTA; i.e. disturbance of memory for events that occur immediately following a head injury), duration of loss of consciousness (LOC), and alterations of consciousness (measured using the Glasgow Coma Scale; GCS; Teasdale & Jennett, 1974). See Table 1 for the criteria used in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013).

Table 1.

Severity Classifications of TBI According to DSM-5

Injury characteristic	**Mild TBI**	**Moderate TBI**	**Severe TBI**
Loss of consciousness	< 30 mins	30 mins – 24 hours	> 24 hours
Post-traumatic amnesia	< 24 hours	24 hours – 7 days	> 7 days
Disorientation and confusion at initial assessment (GCS score)	13-15 (not below 13 at 30 mins)	9-12	3-8

[1] Also known as traumatic axonal injury (TAI; McGinn & Povlishock, 2016).

Mild TBI makes up 70 to 90% of all treated injuries (Cassidy et al., 2004). Few patients with mild TBI show structural abnormalities on CT scan, and ongoing dysfunction is thought to reflect DAI that is too microscopic to be visualised through most standard imaging procedures (Mittl et al., 1994). Most mild TBI patients will suffer from acute neurophysiological and neuropsychological deficits including headache, blurred vision, dizziness and imbalance, concentration problems, forgetfulness, slowed thinking, sleep disturbance, and irritability (McCrea et al., 2014). While these acute symptoms tend to resolve within 3-6 months, a subset (approximately 10-15%) of mild TBI patients will exhibit persistent cognitive impairments even after other acute symptoms resolve (Rabinowitz & Levin, 2014).

Moderate-to-severe TBI patients will tend to show a broader range of post-injury symptoms, including structural damage and motor, sensory, or language impairments (Lucas & Addeo, 2006). Cognitive impairments are generally broader and more severe, affecting domains such as self-awareness, reasoning, and visuospatial processing in addition to the typical cognitive impairments seen in milder injuries (Rabinowitz & Levin, 2014). In moderate-to-severe TBI, cognitive impairments tend to persist for decades post-injury (Hoofien et al., 2001), and predict poor psychosocial outcome (Bercaw et al., 2011; Hanks et al., 2008; Sherer et al., 2002; Sigurdardottir et al., 2009; Tate & Broe, 1999). Executive dysfunction in particular is a good predictor of functional outcome in moderate-to-severe TBI, over and above injury severity and demographic (age, pre-injury education) variables (Spitz et al., 2012).

The relationship between cognitive impairment and functional outcome is more complex in mild TBI, with the majority of research suggesting that cognitive variables are not the best predictors of chronic functional disability in this group (Carroll et al., 2004; Ponsford et al., 2000; Sigurdardottir et al., 2009). A range of non-injury and non-cognitive factors have been shown to better predict persistent disability in mild TBI. Such factors include older age at injury (Lingsma et al., 2010; van der Naalt et al., 2017), pre-injury mental health problems (Skandsen et al., 2020; van der Naalt et al., 2017), post-injury emotional distress (van der Naalt et al., 2017; Wäljas et al., 2015), and maladaptive coping strategy use (van der Naalt et al., 2017). A recent study (Skandsen

et al., 2020) found that personal factors (gender, pre-injury underemployment, pre-injury health concerns, and personality characteristics) contributed more strongly to a model predicting functional outcome in mild TBI, than did injury variables (CT abnormalities and PTA). Notably, mild TBI patients who are in litigation or seeking disability compensation self-report worse functional outcome following the typical acute recovery phase (Belanger et al., 2005; Carroll et al., 2004; Hanks et al., 2019; Lange et al., 2010).

While these are general trends in outcomes related to severity of TBI, it is equally important to consider the exceptions that can occur across all levels of severity. For example, injuries classified as mild may result in severe and debilitating dysfunctional outcomes while a severe TBI may lead to surprisingly good outcomes (Hannay et al., 2004; Kennedy & Turkstra, 2006). Regardless of injury severity, significant inter-individual variability in the presence and severity of cognitive deficits has been identified (Goldstein et al., 2001), with proxy markers of cognitive reserve (e.g. premorbid IQ and years of education) shown also to play a role in predicting cognitive outcomes (Mathias & Wheaton, 2015). Nonetheless, the nature of damage that typically occurs as a result of acceleration and deceleration forces means that impairment in some domains of cognition are more common than others.

1.2 Executive function following TBI

Executive function (EF) is an umbrella term referring to high-level cognitive processes that regulate lower level perceptual or motor processes, to facilitate independent, adaptive, and goal-directed behaviour (Lezak, 1995; H. R. Snyder et al., 2015). Current models characterise EF as a number of separable but related components that map onto a common underlying ability (common EF; Baddeley, 1996 common EF;, 2012; Diamond, 2013; Duncan et al., 1997). One such model is the unity/diversity model (Friedman et al., 2008; Miyake et al., 2000; Miyake & Friedman, 2012), which proposes three core components of EF: i) working memory, ii) shifting, and iii) inhibition; that map onto a common EF ability.

EF was historically linked to frontal brain regions due to the executive dysfunction

observed in patients with frontal lobe lesions (Luria, 1969). However, it is now accepted that EF is associated not only with the frontal lobe (Spikman et al., 2000; Stuss, 1992, 2011; Stuss & Benson, 1984) but with a network of regions extending to parietal and subcortical regions (Duncan, 2010; Jurado & Rosselli, 2007; Seeley et al., 2007). Functional neuroimaging studies reflect both the unity and diversity of EF: a large meta-analysis identified a common brain network involving the prefrontal, dorsal anterior cingulate, and parietal cortices, to be active across EF domains (flexibility, inhibition, and working memory), with domain-specific variation in the anterior prefrontal cortex, anterior and mid-cingulate cortex, basal ganglia, and cerebellum (Niendam et al., 2012).

Executive dysfunction is a well-established consequence of TBI (McDonald, Flashman, & Saykin, 2002). This is understandable given the vulnerability of the frontal lobes to damage (Lezak et al., 2012) and the disruption to distributed fronto-parietal networks resulting from DAI (Caeyenberghs et al., 2014). As well as being common, executive dysfunction can be highly persistent with up to 45% of people with a TBI of any severity reporting EF impairments at 10 years post-injury (Ponsford, Downing, et al., 2014). Furthermore, executive dysfunction in TBI is associated with poor psychosocial outcomes, including reduced community integration, reduced life satisfaction, and increased depression (Wood & Rutterford, 2006), as well as poor emotional control (Tate, 1999), reduced social activity and return to work (Vilkki et al., 1994), and loss of social autonomy (Muzaux et al., 1997). Executive dysfunction has been shown to be the best cognitive predictor of functional outcome after TBI; superior to other common TBI-related impairments such as attention and processing speed (Spitz et al., 2012).

The following sub-sections will provide a review of literature on TBI-related impairments in two sub-components of EF, namely inhibitory control and working memory. TBI groups do exhibit impairments on shifting tasks (S. E. Barlow et al., 2018; Da Costa et al., 2015; Osborne-Crowley et al., 2016), however, this thesis focuses predominantly on inhibitory control, and the neurocognitive training program used in Study 4 targets inhibitory control and working memory, so only these two EF sub-components are reviewed in detail here.

1.2.1 Inhibitory control

Inhibitory control (IC) is one component of EF that causes difficulty in the everyday lives of individuals who have sustained a TBI. IC refers to the ability to suppress an intended or activated thought, emotion, or action (Verbruggen & Logan, 2008). Typical behaviours following TBI that suggest impaired IC include social and verbal disinhibition, poor emotion regulation, and impulsivity (McDonald, Hunt, Henry, Dimoska, & Bornhofen, 2010; Rao & Lyketsos, 2000; Rochat, Beni, Annoni, Vuadens, & Van der Linden, 2013; Tate, 1999). IC is not considered to be a unitary construct, but rather consists of a number of sub-processes including response inhibition (RI) and interference control (see Nigg, 2000 for an overview). RI refers to the ability to stop an activated or prepotent motor response and is measured in experimental tasks such as the Go/Nogo task (Nigg, 2000), the sustained-attention-to-response task (SART; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997), or the Continuous Performance Task (CPT ; Conners, 1995) in which participants must, on infrequent trials (<50% probability), inhibit a frequent (or prepotent) motor response. RI can also be measured using the Stop-Signal task (Logan, 1994) which involves the stopping of an already-executed motor response on infrequent trials within a choice reaction time (RT) task.

Interference control refers to the ability to inhibit processing of external or internal stimuli to prevent interference with a primary response or process (Nigg, 2000) and is typically measured by the Flanker (Eriksen & Eriksen, 1974) or Stroop task (Stuss et al., 2001). The Flanker task involves responding to a visually presented central target stimulus that is flanked either side by congruent (e.g. a left pointing arrow surrounded by left pointing arrows), incongruent (e.g. a left pointing arrow surrounded by right pointing arrows), or distractor stimuli (e.g. arrows pointing upwards). The participant must resist the interference of the incongruent/distractor stimuli in order to respond according to the central stimulus. The Stroop task involves a participant reading a list of colour words where the word and ink colour are incongruent (e.g. the word ‘blue’ written in red ink). The participant must inhibit the urge to name the ink colour and instead read the word.

TBI participants at all levels of injury severity consistently show increased RI errors (i.e. failure to inhibit the activated or prepotent response) compared to healthy controls on Go/Nogo, SART, and CPT tasks (Dockree et al., 2004; Draper & Ponsford, 2008; Rochat et al., 2013; Roche et al., 2004). Further, impaired Stop-Signal task performance is associated with impulsive behaviours in this group (Rochat et al., 2013). A meta-analysis reported moderate effect sizes for TBI-related impairments in RI (Dimoska-Di Marco et al., 2011). This same meta-analysis showed only small and non-significant effects for TBI-related impairments in interference control on the Stroop task. The authors also demonstrated that slower response speed across all tasks in the TBI group did not account fully for their RI deficits; a finding corroborated by Dymowski, Owens, Ponsford, & Willmott (2015). Taken together, these results suggest a specific and robust deficit in the ability to inhibit a prepotent motor response in TBI. Therefore, this thesis focuses on RI.

The prefrontal lobe has been reliably associated with effective RI (Ridderinkhof et al., 2004). Imaging studies have shown reduced activation in prefrontal areas during RI tasks in TBI (Fischer et al., 2014; Soeda et al., 2005) for both mild (McAllister et al., 1999, 2001) and moderate-to-severe injuries (Christodoulou, 2001; Perlstein et al., 2004). While prefrontal lesions are common in TBI (Rieger & Gauggel, 2002), effective IC relies on a network of neurons communicating between prefrontal and subcortical thalamic areas (Rubia et al., 2001) and therefore DAI has also been implicated in disrupting the neural networks involved in IC (Felmingham et al., 2004).

1.2.2 Working memory

Another component of EF known to be deficient in individuals with TBI is working memory (WM). WM is the ability to retain information in mind for a short period of time while manipulating that information to perform a task (Baddeley, 1992). Behavioural manifestations of poor WM in adults with TBI include forgetfulness, indecisiveness, and difficulties in multitasking (Johansson & Tornmalm, 2012; Lundqvist et al., 2010).

A range of experimental tasks have been used to elucidate WM deficits in TBI. Poor

performance in TBI groups compared to controls has been reported on dual-task paradigms (McDowell et al., 1997), WM updating tasks (Perlstein et al., 2004; Serino et al., 2006; Slovarp et al., 2012), and tasks requiring simultaneous storage and processing of information (Bublak et al., 2000; Christodoulou, 2001; Vallat-azouvi et al., 2007). WM impairment has been observed in mild (Kumar et al., 2009) and moderate-to-severe injuries (Dunning et al., 2016) and worsens with increasing injury severity (McAllister et al., 2004).

Brain regions considered critical to WM networks are also those that tend to be damaged by TBI, including areas of the bilateral parietal and prefrontal cortical regions, the anterior cingulate, and basal ganglia (McAllister et al., 2001, 2004; Perlstein et al., 2004). Even in the absence of detectable impairment in WM performance, TBI participants have shown abnormal cerebral activation in the dorsolateral prefrontal cortex, a region linked to WM performance in healthy controls (Rodriguez Merzagora et al., 2014).

1.3 Brain electrophysiology and cognition in TBI

Methods for investigating the electrophysiological activity of the brain have long been used to gain insight into human cognition and behaviour, and are particularly relevant to the assessment of cognition and behaviour following TBI given the cortical nature of the injury (Arciniegas, 2011; Dockree & Robertson, 2011; Gaetz & Bernstein, 2001; Thatcher, 2009). While standard neuroanatomical imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) can provide some insight into TBI-related tissue damage, the ability to consistently predict cognitive performance based on volume loss in TBI is limited, most likely due to the diffuse nature of damage (Dockree & Robertson, 2011; Brian Levine et al., 2006). As such, it has been suggested that electrophysiological techniques such as the electroencephalogram (EEG) may be more suitable as they measure the instantaneous electrical and metabolic activity of the neurons damaged by DAI, and can reflect the disruption to communication across distributed neuronal networks involved in cognition rather than localised brain regions (Thatcher, 2009). It has been suggested that EEG may also be sensitive to the more subtle deficits observed after mild

TBI that are not detected by standard imaging methods (Dockree & Robertson, 2011). The following sub-sections will give an overview of electrophysiological measurement of brain activity, associations with state and cognition, and review evidence for electrophysiological abnormalities in TBI.

1.3.1 Measuring brain electrophysiology using the electroencephalogram

The synchronous firing of large networks of neurons in the brain has been described as the critical link between single-neuron activity and behaviour (Buzsáki et al., 2004). As neurons in the cortex co-operate and communicate, synaptic potentials fire at a synchronized rate producing oscillating electrical activity. This activity can be measured non-invasively using the electroencephalogram (EEG), through electrodes placed on the scalp. The oscillations produce characteristic waveforms of differing frequencies which are commonly examined in several frequency bands; delta (0.5-4 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz), and gamma (30-100 Hz) (Rapp et al., 2015). These primary frequency bands may also be examined in narrower sub-frequencies that are known to respond differentially to psychological states and processes, e.g. lower alpha (~6-10 Hz) and upper alpha (~10-12 Hz) (Klimesch, 1999), and beta1 (~12.5-17.5 Hz) and beta 2 (~17.5-25.0) (Valentino et al., 1993).

EEG frequency data are quantified in a number of ways, including: 1) absolute power in each frequency band (measured in microvolts squared, μV^2), 2) relative power (measured as the percentage of power in a particular band compared to total EEG power), 3) coherence (the correlation in the frequency domain of activity between two electrodes), and 4) phase (the correlation in the time domain of activity between two electrodes) (Hughes & John, 1999). EEG activity is typically measured while the participant is at rest, e.g. in eyes-closed (EC) or eyes-open (EO) resting conditions (spontaneous oscillations), or while the participant is active, e.g. completing a cognitive task (induced oscillations). Spontaneous and induced oscillations are recorded over seconds to minutes, and represent the ongoing or tonic 'state' of the brain

(Andreassi, 2007; Herrmann et al., 2005). These can be differentiated from evoked responses (such as event-related potentials; ERPs or event-related synchronisation/desynchronisation; ERS/ERD) which are phasic EEG responses (measured in milliseconds), time-locked to a specific stimulus (Karakaş & Barry, 2017)[2].

1.3.2 Functional interpretations of EEG frequency bands

Distinct patterns of activity in each of the EEG frequency bands have been linked with various psychological states and cognitive processes. Delta activity is maximal over medio-frontal regions (Harmony, 2013), and is dominant during sleep - increasing linearly with deeper sleep stages (stage 3 and 4; Niedermeyer, 2004b). Resting delta activity is more prominent during earlier stages of human development (Clarke et al., 2001; Niedermeyer, 2004a) and in pathological conditions such as schizophrenia (Itoh et al., 2011), Alzheimer's disease (Babiloni et al., 2009), depression (Bjørk et al., 2008), and OCD (Kamaradova et al., 2016). Taken together, the associations of delta activity with sleep, developmental stage, and pathological conditions have led to a functional interpretation of increased delta activity as reflecting a state of diminished 'higher' level brain activity (Harmony, 2013; Knyazev, 2012). However, the behaviour of event-related delta responses in active cognitive tasks suggests a different functional role. Increased event-related delta power has been observed following a Nogo stimulus (Harmony et al., 2009), and when WM is actively engaged (Harmony et al., 1996), with these findings implicating event-related delta in the inhibition of motor responses and the inhibition of interfering cognitive or sensory processing (Harmony, 2013). Increased event-related delta has also been associated with amplitude of the P3 ERP component in a range of cognitive tasks, leading researchers to propose a role for delta oscillations in the response to unexpected or motivationally relevant stimuli (De Blasio & Barry, 2013b; Demiralp et al., 2001; Harper et al., 2014; Karakaş et al., 2000; Knyazev,

[2] This thesis focuses on the measurement of tonic EEG oscillatory activity (spontaneous and induced), however the literature on phasic event-related oscillatory responses (ERS/ERD) is considered here in order to inform functional interpretations.

2012; Schürmann et al., 2001). Knyazev (2012) integrates the seemingly contradictory associations between increased delta in earlier developmental stages, deep sleep, brain pathology, as well as in higher-order cognition, suggesting that delta oscillations reflect evolutionarily old, biologically motivated processes. During sleep, pathology, and early development these processes involve autonomic and metabolic functions, while in the waking, mentally active, adult they reflect attention to motivationally salient stimuli in the environment.

Similar to delta activity, theta activity is more prominent in childhood, reduces with age (Niedermeyer, 2004a), and is associated with drowsiness and the transition to sleep (Schacter, 1977). In the awake adult, theta activity is maximal over frontal midline locations (Iramina et al., 1996; Mitchell et al., 2008). Frontal midline theta (FM-theta) shows event-related synchronisation in a range of cognitive tasks including mental arithmetic (Gartner et al., 2015), working memory (Jensen & Tesche, 2002), episodic memory encoding and retrieval (Chen & Caplan, 2017; Herweg et al., 2020; Klimesch, 1999; Klimesch et al., 2001), cognitive control (Clayton et al., 2015), and during states of meditation (Lagopoulos et al., 2009). The generalised nature of the FM-theta enhancement has led researchers to suggest that it reflects a non-specific function common to these conditions/tasks, such as sustained attention or concentration (Mitchell et al., 2008). Reductions in event-related FM-theta have been associated with mild cognitive impairment (Cummins et al., 2008) and ageing (Cummins & Finnigan, 2007). However, contrary findings are found in resting states, where enhanced frontal theta is associated with AD/HD (Barry et al., 2003), particularly the inattentive sub-type (Clarke et al., 2003), dementia (Grunwald et al., 2002), and is predictive of cognitive decline (Jelic et al., 2000; Prichep et al., 2006). This suggests differential roles of theta oscillations during resting conditions compared to cognitive task conditions. In particular, resting theta has a more diffuse topography, and may reflect a blocking of the ability to encode new information, whereas task-related (phasic) theta reflects enhanced capacity for encoding (Klimesch, 1999; Mitchell et al., 2008). In addition, these contradictory observations have been explained in terms of two distinct forms of theta oscillations – one that indicates healthy cognitive function and one that reflects slowing of the dominant alpha frequency and is associated with cognitive impairment/decline (Finnigan & Robertson, 2011).

Alpha activity is maximal over occipital regions, and is the dominant EEG rhythm in the healthy, awake adult (Klimesch, 2012). It is regarded as an inverse marker of cortical arousal because alpha power is prominent in a relaxed, mentally inactive state (e.g. awake with eyes-closed) and suppressed in more alert states, such as when the subject opens their eyes or engages in mental activity (Barry et al., 2007; Bazanova & Vernon, 2014; Niedermeyer, 2004c). Increased alpha power at rest has been associated with better performance on cognitive tasks (Doppelmayr et al., 2002; Klimesch et al., 2000), whereas pre-stimulus reductions (desynchronisation) of alpha activity are associated with increased cortical activation (Bazanova & Vernon, 2014; Klimesch, Sauseng, & Hanslmayr, 2007; Pfurtscheller & Lopes Da Silva, 1999) and improved cognitive performance (Doppelmayr et al., 2005; Klimesch et al., 1997; Roche et al., 2004). Based on the event-related desynchronisation (ERD) findings, early functional interpretations of alpha suggested that alpha indexed inactivity or 'idling' of the brain (Pfurtscheller et al., 1996a). However, evidence for event-related (post-stimulus) alpha synchronisation in tasks involving RI and over brain regions that are not task-relevant, has led to an inhibitory interpretation of alpha (Klimesch, 2012; Klimesch, Sauseng, & Hanslmayr, 2007). Klimesch et al. (2012; 2007) suggested that during cognitive tasks alpha ERS reflects inhibition of task-irrelevant processing and alpha ERD reflects the release from inhibition for task-relevant processing. Associations between increased alpha activity and tasks involving internal cognitive processing (Cooper et al., 2003; Klimesch et al., 1999; Magosso et al., 2019), mental imagery (Fink & Benedek, 2014), and mind-wandering (Arnau et al., 2020; Compton et al., 2019) have led to interpretations of increased alpha activity reflecting the inhibition of external attention in favour of attention to internal processes.

Beta activity is maximal at fronto-central regions (Kropotov, 2009) and is most prominent in the alert, attentive state (Gola et al., 2012; Kamiński et al., 2012). Beta oscillations have traditionally been linked to somatosensory and motor functions (Pfurtscheller et al., 1996b), and are abnormal in disorders of motor impairment (e.g. Parkinson's disease; Bočková & Rektor, 2019) and impulse control (e.g. AD/HD; Barry & Clarke, 2009; Clarke et al., 2013; and gambling disorder; Lee et al., 2017). Pre-stimulus beta synchronisation has been associated with

anticipatory attention and arousal (De Blasio & Barry, 2013a; Gola et al., 2012; Kamiński et al., 2012) and post-stimulus beta synchronisation with response inhibition (Swann et al., 2009; Wagner et al., 2018). While compared to the other bands the cognitive correlates of beta oscillations are less studied (Engel & Fries, 2010), current functional interpretations include a direct role in inhibitory control (Aron, 2011; Huster et al., 2013) or a more global role in maintenance of motor (and cognitive) set (Engel & Fries, 2010).

1.3.3 EEG abnormalities in TBI

Based on a large literature review, Thatcher (2009) reported the following consistencies in EEG abnormalities following TBI:

1) Reduced amplitude in the higher frequency bands (i.e. 8-40 Hz, covering the alpha, beta, and gamma bands). This effect was linearly related to degree of cortical grey matter injury.
2) Increased amplitude in the lower frequency bands (i.e. 1-4 Hz, in the delta band) in severe TBI. This effect was linearly related to the degree of cerebral white matter injury.
3) Changes in EEG coherence and phase delays in frontal and temporal lobes. These effects were linearly related to the degree of injury to both grey and white matter.

Diminished EEG power is associated with the neuronal loss resulting from DAI. In particular, disruption to the integrity of thalamo-cortical circuits involved in arousal that are typically damaged in TBI results in a shift to lower frequencies recorded at the scalp (Arciniegas, 2011). These lower frequencies likely result not just from altered firing of damaged axons, but from the subsequently disrupted neurotransmitter systems (cholinergic, noradrenergic, and glutamatergic) that would usually suppress low frequency oscillatory activity (Rapp et al., 2015). Phase delays and abnormal coherence are thought to reflect the corresponding disruption of connectivity between proximal and distal EEG generators (Thatcher et al., 1986, 1989).

Note that there have been some contrasting findings, with a review of mild-to-moderate TBI reporting that milder TBI was associated with a reduction in alpha power and an increase in power in the delta, theta, and beta bands (Rapp et al., 2015). Consistent with this, another review of EEG abnormalities in mild TBI reported reduced alpha, and increased delta and theta activity in the acute phase following injury (Ianof & Anghinah, 2017). The authors also noted an acute increase in the theta-to-alpha ratio. EEG abnormalities tended to resolve by three to twelve months post-injury, however in mild TBI patients with persistent (> 1 year) psychiatric, somatic, or cognitive symptoms, EEG was characterised by slow wave abnormalities.

While the majority of TBI studies in the aforementioned reviews have investigated EEG abnormalities in resting conditions, some have also investigated EEG during cognitive tasks. During a memory task, Thornton (2003) reported an increase in relative beta 1 power (13-31 Hz) and beta 2 (32-63 Hz) power mainly in frontal regions, and a decrease in phase and coherence of beta 2, for a mild-TBI group compared to controls. TBI participants have also demonstrated an inability to maintain the expected alpha desynchronisation (Dockree et al., 2004) during sustained attention and RI tasks (Roche et al., 2004) compared to controls. Thatcher et al. (1998) demonstrated that, in a group with moderate-to-severe TBI, EC delta and theta amplitudes were inversely related to performance on neuropsychological tests of attention, WM, and naming, while EC absolute alpha and beta amplitudes were positively related to test performance. Interestingly, Thatcher's line of research also demonstrated that as severity of TBI increases, so too do the abnormalities in resting EEG measures and impairments in neuropsychological test performance (Thatcher, Biver, et al., 2001; Thatcher, Biver, McAlaster, & Salazar, 1998; Thatcher, Biver, McAlaster, Camacho, et al., 1998; Thatcher, North, et al., 2001).

1.3.4 Limitations to understanding the relationship between EEG and cognition in TBI

Though there is a long history of investigating EEG in TBI, the connection between EEG activity and cognition in this population has not been well established. This gap reflects the

broader state of the neuroscience and neuropsychology literature, in which there is still "shockingly little" (Cohen, 2017 p.208) known about the relationship between EEG and cognition. While this relates to the complexity of the brain's dynamic electrical communication, it also reflects a trend in the field toward exploratory and data-driven approaches, such that empirical observations of EEG phenomena abound but conceptual explanation is limited, or so complex that it is of limited practical or clinical value (Cohen, 2017).

In particular, the contribution of *tonic* oscillatory activity to cognitive processes is an under-researched area (Karamacoska et al., 2018; Northoff et al., 2010). Tonic oscillatory EEG activity can be considered a measure of the brain's *energetic state* (Barry et al., 2007; Johnstone & Galletta, 2013). Energetic state refers to the physiological readiness of an organism to respond to stimuli and process information and is associated with concepts such as arousal, activation, and alertness (Hockey et al., 1986; Pribram & McGuinness, 1975; Unsworth & Robison, 2020). In regard to the brain, energetic state is the ongoing pattern of physiological activity in networks of connected neurons that provide the capacity to process information and regulate thinking and behaviour (Gu et al., 2018; Pepperell, 2018; Tang et al., 2012; Unsworth & Robison, 2020). Though there are multiple methods for measuring the energetic qualities of the brain (see Pepperell, 2018), in this thesis, the term 'energetic' will refer to electrophysiological activity measured by the EEG, while the term 'state' will refer to the ongoing or tonic (cf. event-related or phasic) measure of alertness, arousal, or consciousness. TBI often results in damage to arousal-related neural circuitries and related impairments such as coma, LOC, disorientation, and even after good neurological recovery, complaints of brain fog, fatigue, sleep problems, and concentration difficulties (Goldfine & Schiff, 2011; Valko et al., 2016). Thus, the concept of energetic state may be of relevance to understanding EEG abnormalities and their relation to impaired cognition in TBI.

Predominant models of EF have tended to focus purely on cognitive *processes* rather than the *energetic state* that underlies them. Processes such as RI and WM, are inferred from behavioural measures, such as response speed and accuracy (Diamond, 2013; Jurado & Rosselli,

2007; Miyake et al., 2000) and phasic electrophysiological correlates that are thought to reflect discrete information processing steps (e.g. the Nogo N2 ERP component reflects detection of conflicting response options, the Nogo P3a reflects motor response inhibition, and the Nogo P3b reflects response evaluation; see Pires et al., 2014 for a review). Oscillatory EEG activity is known to contribute to the magnitude and timing of ERP components, suggesting a role of the underlying state of the brain in stimulus-response processes (Klimesch, Sauseng, Hanslmayr, et al., 2007). However, the spotlight in prominent EF models remains on information processing stages (and the electrophysiological correlates of these stages) rather than the underlying and ongoing brain state that supports them.

One exception, the Posner attentional network model (Petersen & Posner, 2012; Posner et al., 2019), incorporates a concept of alerting/arousal state into a theory of cognitive functioning. This model proposes three specialised neural networks involved in attention. First, an alerting system that involves achieving and maintaining alertness or vigilance. The alerting system is linked to a network including thalamic, frontal, and parietal areas and the locus coeruleus, and is modulated by norepinephrine (Fan et al., 2005; Petersen & Posner, 2012; Sturm & Willmes, 2001). Second is an orienting system that involves focusing attention on relevant stimuli in the visual field, linked to the superior parietal cortex and inferior frontal gyrus, and modulated by the cholinergic system (Corbetta & Shulman, 2002; Fan et al., 2005; Petersen & Posner, 2012). Third, an executive control system involves controlling behaviour to achieve goals, resolve conflict between competing responses, and inhibit impulsive responding. The executive network includes the anterior cingulate cortex, the basal ganglia, and lateral prefrontal cortex, and is modulated by dopamine (Berger & Posner, 2000; Posner et al., 2019).

Although Posner's alerting system provides a theoretical role for the underlying energetic state of the brain in cognitive functioning, the empirical support for this construct is based on behavioural measures and neuroimaging, rather than oscillatory EEG activity. In Posner's alerting system, level of alertness is inferred from changes in reaction times, e.g. when a target event is preceded by a warning signal (phasic alertness; Petersen & Posner, 2012), at different times of the

day (tonic alertness; Posner, 1975) or over the course of a long and boring task (tonic alertness; Sturm & Willmes, 2001). The neural networks associated with the system are inferred from neuroimaging correlates of these behavioural measures (e.g. Fan et al., 2005). Similar to other EF models, electrophysiological correlates have focused on ERPs (the Contingent Negative Variation or CNV component; Posner, 2008) or ERS/ERD (Fan et al., 2007), rather than the underlying and ongoing, tonic, energetic state.

The Cognitive Energetic Model (CEM; Sanders, 1983) is a model of cognitive functioning that presents both a theoretical account of the role of energetic state in cognition, and established tonic EEG correlates for its energetic state constructs (discussed in detail in the following section). The energetic state concepts of the CEM may provide a unified and clinically relevant link between tonic EEG abnormalities and cognitive impairments in TBI. The CEM has already been shown to be theoretically and clinically applicable to understanding the relationship between energetic state and cognitive impairments in another clinical group: Attention Deficit/Hyperactivity Disorder (AD/HD; Sergeant, 2000, 2005). Empirical validation for the CEM comes from studies suggesting that the cognitive impairments (e.g. WM, inhibitory control, and other executive functions) associated with AD/HD can be partly explained by poor energetic state regulation, measured by the EEG (Johnstone et al., 2010, 2017; Sergeant, 2000, 2005). This research has led to the subsequent design and investigation of a non-pharmacological intervention for children with AD/HD that simultaneously targets both cognitive and energetic state regulation (Johnstone et al., 2017; Johnstone, Roodenrys, et al., 2012). This not only demonstrates the utility of the CEM in a clinical context, but, given the similarities between AD/HD and TBI in terms of a) cognitive impairments in attention and EF (Levin et al., 2007; Mychasiuk, Hehar, & Esser, 2015) and; b) a hypo-arousal EEG profile of increased low frequency and reduced high frequency activity (Barry, Clarke, & Johnstone, 2003; Thornton & Carmody, 2009; Tinius & Tinius, 2000), the CEM may be valuable in understanding and ameliorating cognitive deficits in TBI. The CEM and the measurement of its energetic state concepts are described in detail in the following sections.

1.4 The Cognitive Energetic Model

1.4.1 General principles

The CEM (Sanders, 1983) provides a framework for understanding the link between cognition and EEG measures of brain energetic state. The model was originally conceptualised to explain the impact of stress and arousal on performance in healthy adults. Sanders (1983) proposed that effective information processing results from the interplay of *energetic state* and *computational* factors that are regulated by an *evaluation* mechanism (see **Figure 1.**). In Sanders' model, the *computational* factors represent the linear stages of information processing from stimulus to response (encoding, search, response selection, and motor organisation). The efficiency of this processing relies on basal *state* factors (*arousal* and *activation*) that are coordinated and modulated through *effort*. The *evaluation* mechanism addresses the discrepancy between the individuals current compared to desired energetic state, and through *effort* adjusts arousal and activation according to task demands.

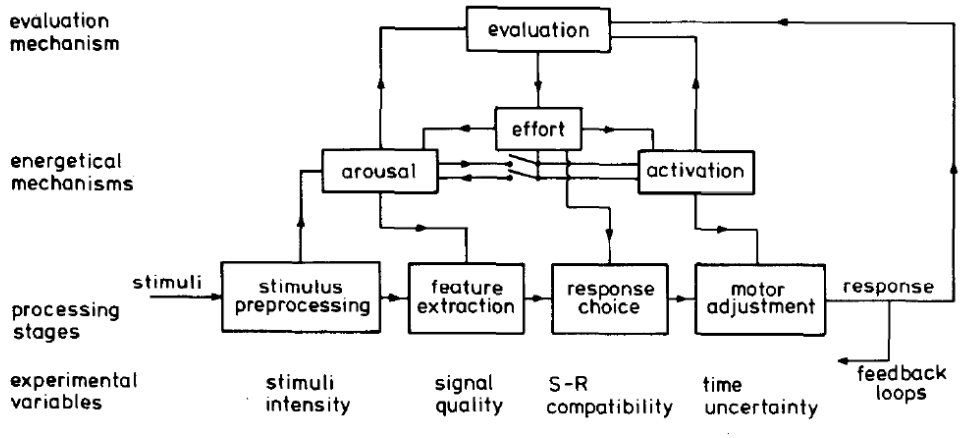
It is important to note that the arousal and activation constructs of the CEM are not in contradiction to the Posner model, nor to other models of EF (e.g. Baddeley, 1996, 2012; Diamond, 2013; Duncan et al., 1997; Miyake et al., 2000; Miyake & Friedman, 2012). The alerting system in the Posner model has overlap with the energetic components of the CEM – they both refer to the physiological energy of the brain as it represents the readiness to process and respond to stimuli (Martella et al., 2020). Likewise, the CEM evaluation mechanism has parallels to the more developed and prominent concepts of 'executive control' (Posner et al., 2019) or 'central executive' (Baddeley, 1996), as well as conflict monitoring accounts of cognitive control (Botvinick et al., 2001). The value of the CEM in the current context is its operationalisation of arousal and activation. If shown to be relevant to TBI, the arousal and activation components (and techniques for measurement) should be considered complementary to, and could be integrated with, other models of EF (as in, for example, Unsworth & Robison, 2020).

Though the CEM was proposed over 30 years ago, its application has previously been

challenging due to a lack of consensus on component definitions, and a lack of methods for directly measuring state factors (Shiels & Hawk, 2010). In particular, the components of arousal and activation have suffered from conceptual confusion (Barry, Clarke, et al., 2005), but have become progressively clearer through the application of psychophysiological measures, including skin conductance and EEG. Since these psychophysiological measures have aided in operationalising the concepts of arousal and activation, they have received considerable attention both in research that directly refers to the CEM and in research that has developed independently alongside it.

Figure 1.

The Cognitive Energetic Model taken from Sanders (1983)



Note. In this thesis the definitions (and thus position in the model) of arousal and activation are reversed, in line with current psychophysiological literature (as discussed in section 1.4.2).

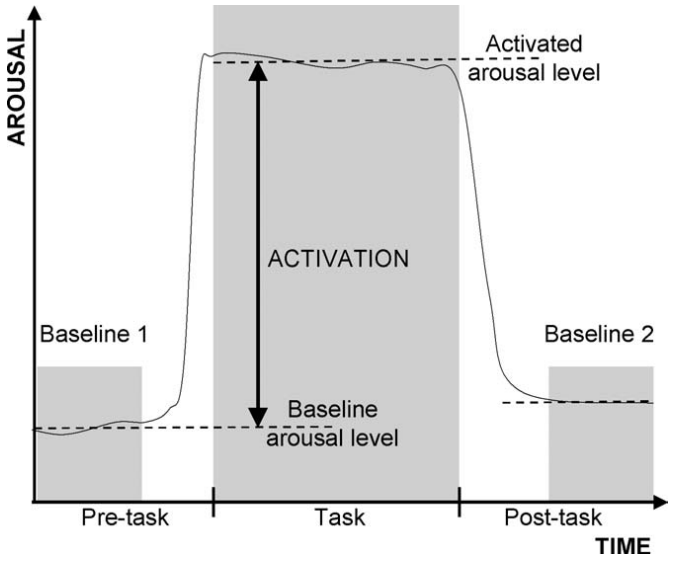
1.4.2 Measurement of CEM state factors: arousal and activation

Pribram & McGuiness (1975, 1992) were the first to differentiate the constructs of activation and arousal, initially defining activation as an individual's tonic energetic state or physiological readiness to respond, and arousal as the task-related mobilization of activation. Sanders (1983) and Sergeant (2000) followed these definitions. However, due to conceptual

inconsistencies in the broader literature, empirical research that provided the physiological evidence for the dissociation of these constructs resulted in a reversal of these definitions (Barry et al., 2007; Barry, Clarke, et al., 2005; Barry & De Blasio, 2017). This line of research defined arousal as the *current energetic state*, and activation as the *task-related mobilisation of arousal*. To maintain consistency with the psychophysiological literature, this thesis will use the latter definitions, as illustrated in **Figure 2.**

Figure 2.

The Distinction Between Arousal and Activation taken from VaezMousavi, Barry, Rushby, & Clarke, 2007a.



Note: Activation is the difference between arousal levels during baseline and task conditions.

A line of research published by Barry, Rushby, and colleagues, has used numerous psychophysiological measures to support the dissociation of the arousal and activation concepts in healthy adults and children. Initial investigations used skin conductance level (SCL), a long-standing and robust physiological measurement of autonomic arousal (Barry et al., 2007). A series of studies in healthy adults and children demonstrated that the phasic physiological response to stimuli during a continuous performance task was predicted by *arousal* (measured by SCL during the task) but not *activation* (measured by difference in SCL between a resting condition and task condition)*;* while errors and RT were predicted by *activation* but not *arousal* (Barry, Clarke, et al., 2005; VaezMousavi et al., 2007b, 2007a). These results support the

conceptualisation of *arousal* and *activation* as two separable state processes involved in energetic state, with dissociable effects on cognitive performance.

Barry and colleagues also demonstrated similar dissociable effects for EEG measures of arousal and activation. A reliable finding in these studies is the inverse relationship between global (i.e. across scalp sites) alpha power and SCL in resting conditions, suggesting that increased alpha power is associated with reduced arousal (Barry et al., 2004, 2008, 2009, 2011; Barry, Rushby, et al., 2005). Further support comes from studies showing reduced global alpha in conditions where arousal was up-regulated either through caffeine ingestion (Barry et al., 2008, 2011; Barry, Rushby, et al., 2005) or through opening the eyes (i.e. EO vs EC resting conditions; Barry et al., 2011, 2007). These studies have established global alpha power as a reliable inverse measure of cortical *arousal*.

The EC resting condition is considered to be the 'baseline' measure of resting EEG state, while the EO resting condition reflects the mobilisation of energetic state in response to visual processing (Northoff et al., 2010). The global reduction in alpha power when moving from an EC to an EO condition is accompanied by topographically specific changes in the other EEG bands (Barry et al., 2007). Specifically, Barry et al. (2007) observed reductions in lateral frontal delta as well as posterior theta and beta, and an increase in frontal beta in the EO compared to EC task. Barry et al. (2007) interpret these focal changes to reflect cortical *activation,* i.e. the mobilisation of energetic state. The EC to EO global alpha reduction, and focal delta, theta, and beta changes have been replicated in healthy and aging adults (Barry & De Blasio, 2017; Karamacoska et al., 2017). Taken together these results support the interpretation of global alpha as an indicator of *arousal* and focal changes in the other EEG bands as reflecting *activation.*

In this thesis, the change in EEG from EC to EO conditions is termed *resting activation*. In resting activation, the change in EEG reflects the additional visual processing requirement of the EO condition, but does not reflect mobilisation of energetic state to facilitate cognitive processing. The EEG changes that occur when a participant moves from a resting condition to a cognitive task condition is here termed *task-related activation,* and reflects mobilisation of

energetic state to meet cognitive processing requirements. Similar to the resting activation findings, studies have shown that task-related activation is reflected in focal EEG changes in the delta, theta, alpha, and beta bands, and that these changes depend on the particular cognitive task being engaged in (Loo et al., 2009; Nazari et al., 2011; Valentino et al., 1993).

1.4.3 Relationships between arousal/activation and cognition

To date, no EEG studies have explicitly examined the CEM concepts of arousal/activation in relation to cognitive performance. However, indirect evidence comes from in studies that have examined EEG *change* between conditions, and linked these changes with behavioural performance and ERP magnitude.[3] For example, in healthy controls, Valentino, Arruda, & Gold (1993) found that higher accuracy in a CPT task was associated with greater task-related activation in global alpha, fronto-temporal beta 2, temporal and temporo-occipital theta, and reduced task-related activation in anterior delta and theta.

Karamacoska et al. (2018) indirectly examined the relationship between arousal, resting activation, and task-related activation, and cognition in an equiprobable Go-Nogo task. They found no associations between arousal (resting global alpha amplitude), nor resting-activation, and performance. Increased task-related activation for fronto-central midline delta was associated with greater Go errors and RT variability. Larger task-related increases in delta and smaller increases in alpha-1 (8-10 Hz) amplitudes were associated with longer RTs. A task-related increase in fronto-central midline theta amplitude was associated with greater Nogo errors. They also observed associations between task-related activation in delta, theta, and beta bands and ERP components that represent cognitive processing stages. It is important to note that Karamacoska et al. (2018) quantified task EEG using the pre- and post-stimulus period, in contrast with Valentino, Arruda, & Gold (1993) who quantified 1-2.5 second epochs across the task duration.

[3] Note: reference to components of the CEM are inferred in this and the following sub-section, not explicitly mentioned in the reviewed studies.

Pre- and post-stimulus EEG reflects phasic EEG responses to stimuli, compared to across task EEG that reflects tonic energetic state and is therefore more in line with the CEM conceptualisation of state factors.

1.4.4 Arousal and activation in TBI

As with the broader literature, research into the relationship between EEG and cognition in TBI has not yet explicitly applied the CEM, nor has it necessarily operationalised arousal and activation according to the CEM definitions. However, a small number of TBI studies have used measures that operationally align with the CEM, and these will be reviewed below.

Two TBI studies have investigated EEG alpha measures that align with the concepts of arousal and activation (Fisher et al., 2015; Rushby et al., 2013). In terms of arousal, both studies showed no difference in resting global alpha power for TBI participants compared to controls, suggesting normal arousal in TBI. In terms of activation, Rushby et al. (2013) found that the EC-to-EO alpha reduction (i.e. resting activation) was attenuated in the TBI group compared to controls. This was supported by Fisher et al. (2015) who found an attenuated alpha reduction when moving from EO to an emotion processing task condition (i.e. task-related activation) in a TBI group, compared to controls. Together, these studies provide evidence of impaired resting- and task-related activation in the alpha EEG band following TBI.

The lack of support for an arousal deficit in Rushby and Fisher et al.'s studies contrasts with reviews that have suggested an overall trend for reduced alpha power (i.e. increased arousal) in TBI compared to controls (Rapp et al., 2015; Thatcher, 2009). Reduced EC alpha has also been associated with poorer neuropsychological performance in TBI (Thatcher, Biver, McAlaster, Camacho, et al., 1998). However, reviews have typically combined EEG data from both resting and cognitive task conditions and at varied scalp locations. When restricted to global alpha in resting conditions, a number of studies have reported no difference in alpha power in TBI compared to controls (Chen, Tao, & Chen, 2006; Dockree et al., 2004; Tebano et al., 1988), consistent with Rushby et al. (2013) and Fisher et al.'s (2015) findings.

In summary, results to date tend to point toward intact arousal following TBI, with an attenuation of resting and task-related activation for alpha power. No studies to date have examined TBI-related activation impairments in delta, theta, and beta bands. While resting or on-task EEG in these bands have shown correlations with cognitive performance, the relationship between CEM-defined resting or task-related activation and cognitive performance in TBI is yet to be explicitly and systematically studied.

1.5 Cognitive rehabilitation of executive functions following TBI

1.5.1 Introduction to cognitive rehabilitation

Due to the significant and persistent impact of cognitive impairments after TBI, cognitive rehabilitation is a crucial part of treatment. Approaches to cognitive rehabilitation are diverse and can be divided broadly into interventions that are *restorative* or *compensatory* (Koehler et al., 2011). Compensatory approaches aim to establish new patterns of cognitive activity through development of either internal strategies such as chunking, pacing, and verbalization (Dirette et al., 1999), or external strategies such as using calendars and alarms (Wehman et al., 1989). In contrast, restorative approaches aim to directly strengthen or restore cognitive function through repeated exercise of targeted cognitive processes, such as through cognitive training (Thornton & Carmody, 2008).

The restorative approach is based on the theory of neuroplasticity; the ability of the nervous system to reorganise its structure and function in response to stimuli during development, or in response to disease, learning, or therapy (Cramer et al., 2011). Neuroplasticity is underpinned by a mechanism in which neurons that repeatedly fire together connect to form functional networks (Munakata & Pfaffly, 2004). Restorative cognitive rehabilitation aims to facilitate neuroplasticity when functional networks are damaged (Mukundan, 2013). The appeal of this approach is that restoring underlying function should theoretically have a positive impact on all activities that involve that function and lead to broad, generalised improvements – this can be compared to compensatory strategies, where one isolated activity must be trained and improved

at a time (Koehler et al., 2011). This thesis will focus specifically on two restorative approaches: cognitive training and neurofeedback (NF) training. The following subsections will define these approaches and review the evidence for their efficacy in TBI.

1.5.2 Cognitive training

There is a great diversity of approaches to cognitive training, and therefore this section will aim to define it for the purpose of this thesis. The most general definition of cognitive training is the repeated *practice* of standardised cognitive tasks targeting specified cognitive processes (Barman et al., 2016; Hallock et al., 2016). However, there are some crucial differences between *practice* (i.e. the repeated performance of a task) and *training*. Cognitive training is differentiated from practice by the presence of: a) an adaptable difficulty level, and b) ongoing performance feedback (Benikos, 2014; Green & Bavelier, 2008; Johnstone et al., 2010; Jolles & Crone, 2012; Klingberg et al., 2002).

Lovden et al. (2010) proposed that it is the prolonged mismatch between existing cognitive resources and environmental demands that drives neuroplasticity. Accordingly, effective cognitive training depends on the training task not only operating at the maximum manageable difficulty level, but also remaining consistently challenging even as performance improves. In support of this, enhanced performance gains have been found on training tasks of higher difficulty (Benikos, 2014; Garcia et al., 2013) and those where the difficulty level adapts in response to performance improvements (Cicerone et al., 2019; Klingberg et al., 2002). Importantly, an adaptive difficulty level has been shown to enhance transfer of training gains to untrained but related tasks (Benikos et al., 2014; Cicerone et al., 2019; Jennings et al., 2005).

It is well-established in fundamental learning literature that performance feedback acts as reinforcement to facilitate learning (Garcia et al., 2013; Green & Bavelier, 2008; Herzog & Fahlet, 1997; Liu et al., 2012). Performance feedback during cognitive tasks leads to activation of brain regions relevant to reward processing (e.g. the caudate nucleus), as well as enhanced activation in task-relevant brain regions (Mattheiss et al., 2018; Tricomi et al., 2006). The ongoing provision of

performance feedback during or immediately after a trained task has been shown to enhance outcomes of cognitive training (Benikos, 2014; Green & Bavelier, 2008; Johnstone, Roodenrys, Blackman, et al., 2012; Klingberg, 2010).

Furthermore, the *processes* targeted in cognitive training (e.g. attention, WM, IC) are differentiated from the higher-order *skills* (e.g. learning, reading, arithmetic, driving) that rely on the complex interplay between multiple cognitive processes (Hallock et al., 2016; Mukundan, 2013). Training programs that target these complex skills are considered 'strategy training' or 'skills training', rather than 'cognitive training' as defined in the literature (Gates & Valenzuela, 2010; Hallock et al., 2016) and in this thesis.

Given that the goal of cognitive training is to improve functioning of individuals in their everyday lives, the importance of generalisation or 'transfer' of training effects beyond trained tasks has been emphasised in recent literature (Cicerone et al., 2019; Sigmundsdottir et al., 2016; van Heugten et al., 2016). *Near-transfer* effects refer to improvements on cognitive tasks that closely resemble the trained tasks and assess the specific processes being trained. *Far-transfer* effects refer to improvements on non-trained tasks that assess cognitive processes that were not explicitly targeted, or improvements in everyday functioning that rely on the targeted processes.

The studies reviewed below include cognitive training that: a) is adaptive, b) provides performance feedback, and, c) targets EF *processes* rather than complex skills or strategies. The evidence for effectiveness of cognitive training will be evaluated in terms of both near- and far-transfer effects, with an emphasis on far-transfer effects as the ultimate goal of training.

1.5.3 Cognitive training in TBI

Systematic reviews and meta-analyses have evaluated the efficacy of cognitive training in TBI, concluding that there is sufficient evidence for the efficacy of training attention *processes* (Cappa et al., 2005; Cicerone et al., 2000, 2011, 2019; Rohling et al., 2009), and EF *skills* (Cicerone et al., 2011, 2019; Tate et al., 2014). Attention process training has been shown to

induce redistribution of the cerebral attention network in TBI, with fMRI studies showing changes in activation of the anterior cingulate cortex, precuneus, and cerebellum (Kim et al., 2009), and the prefrontal and extrastriate cortices (Chen et al., 2011). However, the evidence for transfer of these effects to everyday functioning is limited (Cicerone et al., 2019) and it has been suggested that attention training be combined with strategy and skills training to facilitate generalisability (Cicerone et al., 2011, 2019). In terms of EF, meta-cognitive (self-monitoring and self-regulation) and problem-solving strategy training have shown efficacy in TBI (Cicerone et al., 2011, 2019; Tate et al., 2014) and training gains demonstrated generalisation to everyday functioning (Cicerone et al., 2019; Hallock et al., 2016).

However, reviews of EF skills training do not include studies that target the underlying *processes* involved in EF, such as working memory (WM) and inhibitory control (IC). Instead, WM training has been merged with the attention training literature in a number of reviews in TBI (Cicerone et al., 2000, 2011, 2019; Tate et al., 2014). Furthermore, to date, no studies have investigated the effects of IC training in TBI, despite IC being flagged as an important process to target in this population (Dimoska-Di Marco et al., 2011). Therefore, individual studies of WM and IC training are reviewed in the sub-sections below.

1.5.3.1 Working memory training

Studies of computerised WM training have shown improvements in performance on both near- and far-transfer tasks in children with AD/HD (Klingberg et al., 2002, 2005), pre-school and school-age children (Holmes et al., 2009; Thorell et al., 2009), and young and older adults (Dahlin, Nyberg, Bäckman, & Neely, 2008; Jaeggi, Buschkuehl, Shah, & Jonides, 2014; Lampit, Hallock, & Valenzuela, 2014; Li et al., 2008). WM training has been associated with changes to brain activity in WM networks involving frontal and parietal cortices and the basal ganglia (Klingberg, 2010).

A recent review considers the evidence to be strong enough to recommend WM training be included in TBI rehabilitation (Cicerone et al., 2019). However, it is important to note that this

was a review of studies of ABI (including stroke patients), and not TBI exclusively. The evidence in TBI specifically is limited to a small number of studies. Near-transfer effects for WM training in TBI have been supported by two case series studies (Cicerone, 2002; Vallat-Azouvi et al., 2009), and one study with an active control condition (Serino et al., 2007). All three studies showed that WM training led to far-transfer effects by improving everyday functioning.

Near- and far-transfer effects of WM training are supported more strongly by ABI studies. A randomised controlled study with a mixed ABI sample (7 TBI, 32 stroke, and 6 'other' patients) showed improvements on neuropsychological measures of WM after WM training (Åkerlund et al., 2013). In addition, participants who completed WM training had improvements on measures of general cognitive function (speech and language, orientation, attention/concentration, visuospatial and visual problem-solving, memory, affect and self-awareness), and depression and anxiety symptoms. In an uncontrolled study, an ABI group (5 TBI, 7 stroke, and 6 brain tumour patients) showed improvement on trained tasks and reductions in cognitive problems in daily life after WM training (Johansson & Tornmalm, 2012).

1.5.3.2 Inhibitory control training

While IC has been highlighted as an important target for cognitive training in TBI (Dimoska-Di Marco et al., 2011), no studies to date have assessed its effectiveness in this population. In healthy adults, IC training has led to near-transfer effects with improved performance on trained tasks (e.g. the Go/Nogo task; Benikos et al., 2013) and closely related inhibition tasks (e.g. the Stop-Signal task; Benikos, 2014; Benikos et al., 2014). Far-transfer effects have also been demonstrated in terms of reduced impulsive behaviours including gambling (Verbruggen et al., 2012) and food and alcohol consumption (Houben, 2011; Houben et al., 2011, 2012; Houben & Jansen, 2011) following IC training. Performance improvements are accompanied by training-induced changes to the IC networks of the brain in studies using electrophysiological (Jodo & Inoue, 1990; Manuel et al., 2010; Millner et al., 2012) and imaging methods (Berkman et al., 2014; Kelly et al., 2006).

1.5.4 Neurofeedback training

Neurofeedback (NF) training is a form of biofeedback that aims to normalise dysregulated brain activity by training self-regulation of the EEG. During NF training the participant receives immediate and ongoing feedback and reinforcement for their scalp-recorded EEG. Approaches to NF training are diverse. Training may target any EEG measure, e.g. one or a number of concurrent band power parameters, coherence or symmetry, single or multiple channels. Further, feedback and reinforcement can be provided to the participant in a number of ways, e.g. through integration into a computer game, via a bar graph, or through electrical stimulation (Thomas & Smith, 2015; Thornton & Carmody, 2009). The common element of all NF approaches is the goal of normalising an aspect of the participants' brain energetic state through the process of developing awareness and, subsequently, control of brain activity. A typical protocol addressing cortical under-activation would reward a participant for suppressing slow wave EEG activity and enhancing fast wave EEG activity (Duff, 2004). Randomised controlled studies have shown that NF training is effective at reducing a range of symptoms in clinical populations including AD/HD (Arns et al., 2009; Drechsler et al., 2007), obsessive compulsive disorder (Kopřivová et al., 2013), and chronic PTSD (van der Kolk et al., 2016).

1.5.5 Neurofeedback training in TBI

NF training has been described as a "promising yet unproven" intervention for TBI (May et al., 2013 p. 295). May et al. (2013) reviewed 14 anecdotal or uncontrolled case studies, and eight studies utilising waitlist, treatment as usual (TAU), or healthy adult control group comparisons. The authors suggested that the effectiveness of NF training is 'unproven' due to the absence of randomised, placebo controlled, double blind studies. This conclusion has been corroborated in more recent reviews (Gray, 2017; Thomas & Smith, 2015). However, the approach is promising as the existing research does indicate improvements in attention, impulse control, and processing speed, as well as normalisation of the EEG as a result of NF training in TBI (May et al., 2013). Importantly though, May et al. noted that assessment of improvements in

everyday behaviour and functioning was scarce in the controlled studies.

The earliest literature regarding NF training in TBI were anecdotal reports and case studies. In a clinical case series of 250 TBI cases, Ayres (1987) reported cognitive (attention) and symptomatic (energy, depression, dizziness, and headaches) improvements, and EEG normalisation after 24 sessions of NF training aimed at reducing theta and increasing beta activity. Using a similar protocol, Byers (1995) reported a TBI case study where NF training led to EEG changes, improvement in attention, processing speed, WM, and EF. More recent case studies of NF training for TBI support normalisation of EEG (Nash, 2005; Rutterford, 2012) and improvements in cognitive performance (Nash, 2005; Reddy et al., 2009; Thornton, 2000, 2002), self-reported symptoms (Hammond, 2005; Nash, 2005), and structural and functional connectivity (Munivenkatappa et al., 2014).

Uncontrolled pre-post experimental design studies have also evaluated NF training in TBI. Bounias et al. used individualised NF protocols based on pre-training EEG in 27 ABI participants (21 TBI) and reported normalisation of the targeted EEG bands and improvements on relevant individual clinical symptoms including motor, language, cognitive, psychosocial, pain-related, neuropsychiatric, and metabolic impairments (Bounias et al., 2001, 2002; Laibow et al., 2001, 2002). Studies of EEG coherence training also reported EEG normalisation and improvements in cognitive performance (Walker et al., 2002; Zelek, 2008). A substantial limitation of these studies is the lack of non-treatment or active control groups, without which the influence of confounding variables such as history, maturation, statistical regression, practice, or expectation effects, cannot be ruled out.

There are few controlled studies of NF training for TBI. Keller (2001) reported normalisation of targeted beta activity in TBI participants, as well as enhanced gains on attention tasks in a NF training group (n = 12), compared to a computerised attention training control group (n = 9). Notably, no measure of everyday functioning was included. Schoenberger et al. (2001) evaluated the Flexyx Neurotherapy System (FNS) which provides feedback in the form of subthreshold electromagnetic stimulation based on the dominant EEG amplitude, in a group of 12

adults with mild-to-moderate TBI. Compared to wait-list control, the NF training group showed improved subjective symptoms (e.g. depression and fatigue) and cognitive measures, predominantly WM. Importantly though, FNS removes the role of conscious learning, as the electromagnetic stimulation is not perceptible to the participant, so this study is not directly comparable to the other studies reviewed here. Furthermore, the effect of FNS treatment on EEG measures was not reported, so the proposed mechanism of change (EEG normalisation) cannot be confirmed in this study.

To date, only one study has investigated the combination of NF and cognitive training in TBI (Tinius & Tinius, 2000). In this study a mild TBI group (n = 16) and AD/HD group (n = 13) completed 20 sessions of concurrent NF (individualised power and coherence measures) and cognitive (attention and memory) training. Compared to a non-treatment healthy control group, both treatment groups showed improvements on a sustained attention task and self-reported neuropsychological symptoms after training. A substantial limitation of this study is that training effects on EEG activity were not reported, therefore no interpretation of the role of EEG in cognitive improvements can be made, and significantly, the effect of NF training on its target variable (EEG activity) cannot be confirmed.

1.6 Limitations of the literature

1.6.1 Heterogeneity in group studies

The most common criticism of research examining cognitive rehabilitation for TBI is the lack of double-blind, randomised controlled trials (Cappa et al., 2005; Gray, 2017; May et al., 2013; Rohling et al., 2009). In a recent review only 15% of 96 studies of cognitive rehabilitation in ABI were classified as meeting adequate methodological quality criteria (Sigmundsdottir et al., 2016). Similarly, in a review of NF training for cognitive rehabilitation in ABI, only four of 86 candidate studies were found to meet methodological quality criteria (Ali et al., 2020).

The gold standard RCT emphasises adequate control of confounding variables to ensure

that outcomes can be confidently attributed to the treatment being evaluated. One way the RCT meets this standard is by using strict exclusion criteria to obtain a sample that is *homogenous* on the variable of interest. It has been argued that sample heterogeneity may be the cause of null results in some TBI rehabilitation studies (Maas et al., 2013; Park & Ingles, 2001). It is important to note, however, that homogeneity is not the nature of TBI. Patients typically present with large variations in the cause, site, and severity of injury[4], recovery pattern, cognitive and physical sequelae, personal characteristics, and a high rate of co-morbidities (Maas, 2016; Maas et al., 2010; Saatman et al., 2008). Therefore a notable challenge for research in this area is recruitment of an adequate number of participants for homogenous group comparisons (Hallock et al., 2016; Kennedy & Turkstra, 2006). Even further, it has been argued that the heterogeneity problem means that the RCT may not be the most suitable approach (Thomas & Smith, 2015). Stricter exclusion criteria does not solve the problem, as it reduces the extent to which the sample is representative of the TBI population (Boukrina et al., 2020; Edlund et al., 2004; Seghier & Price, 2018).

Given the inter-individual variation within TBI groups, it has been recommended that intervention studies should investigate the patient characteristics that influence intervention effectiveness (Ali et al., 2020; Cicerone et al., 2019). This recommendation coincides with a recent resurgence in the popularity of the single case experimental design (SCED) in the neuro-rehabilitation literature. The Oxford Centre for Evidence-based Medicine (www.cebm.net) have recently ranked SCED studies as Level 1 evidence, a rank equal to RCTs. The SCED requires more time points of data with fewer participants, and emphasises and explores heterogeneity rather than controlling for it, whilst providing adequate experimental control to infer causal effects of an intervention (Brossart et al., 2018; Evans et al., 2014; Kratochwill et al., 2013; Odom et al.,

[4] While it is common practice to make injury severity the primary homogenous variable, there are a range of classification systems used across studies and symptom heterogeneity within severity categories is still large (Hannay et al., 2004).

2005; Tate et al., 2016).

1.6.2 Outcome measures

Another limitation to the current literature is the nature of outcome measures used to evaluate rehabilitation. The most popular outcome measures are neuropsychological tests or other measures of specific cognitive processes (such as WM, attention, processing speed), and these measures do show consistent training effects (Cicerone et al., 2011; Park & Ingles, 2001; Sigmundsdottir et al., 2016). However, the evidence for generalisation of improved cognitive processes to improved everyday behaviour and functioning is variable and this has been a longstanding criticism of cognitive rehabilitation in general (Cicerone et al., 2011; Lynch, 2002; Park & Ingles, 2001; Sigmundsdottir et al., 2016). There is a lack of everyday functional outcome measures in training studies in TBI (Cicerone et al., 2011; Gordon et al., 2006; Ponsford, Bayley, et al., 2014). The goal of cognitive rehabilitation is not to improve test scores, but rather to improve everyday functioning. Therefore, measures of meaningful functional recovery are necessary to evaluate the effectiveness of treatments.

1.6.3 Theoretical issues and mechanisms of action

There is currently no consistent and coherent theoretical framework on which to base our understanding of the relationship between EEG abnormalities and cognitive impairments in TBI. This is in part due to the complexity of brain dynamics, but also due to a focus on empirical observations, without adequate emphasis on theoretical development in the literature (Cohen, 2017). This lack of conceptual clarity contributes to variability in the choice of outcome measures and interpretation of mechanisms of change in cognitive and NF training studies (Ali et al., 2020; Whyte et al., 2014).

The theory of neuroplasticity is implicit in studies of restorative cognitive rehabilitation in TBI. In these studies, there is an assumption that changes in underlying brain activity are synonymous with changes in cognitive functioning. This assumption is particularly important in

NF training studies, given that the change in brain energetic state is considered the mechanism of cognitive change. However, there is little to no empirical support for this assumption; many studies investigate EEG changes or cognitive or functional changes but not the relationship between them. For example, NF studies have looked at EEG outcomes but not cognitive outcomes (Laibow et al., 2001; Rutterford, 2012; Walker et al., 2002) or cognitive outcomes but not EEG measures (Bounias et al., 2002; Schoenberger et al., 2001; Thornton, 2002). One study combined cognitive and NF training, but only cognitive changes were reported (Tinius & Tinius, 2000). The theoretical connection between neural and cognitive processes has recently been recognised as an important avenue for future research in cognitive rehabilitation for TBI (Ali et al., 2020; Galetto & Sacco, 2017; Hampstead & Bahar-Fuchs, 2020; Sigmundsdottir et al., 2016; Stephens et al., 2015).

Models of EF (e.g. Diamond, 2013; Jurado & Rosselli, 2007; Miyake et al., 2000; Petersen & Posner, 2012) tend to focus on behavioural and phasic electrophysiological correlates of cognitive *processes*, rather than the ongoing energetic *state* that underlies them. Existing research on EEG abnormalities in TBI has focused predominantly on tonic EEG recorded during baseline or resting conditions (for reviews see Rapp et al., 2015; Thatcher, 2009) and these studies provide support for deficiencies in energetic state in TBI. However, the contribution of tonic oscillatory EEG activity (a measure of energetic state) to cognition, is an under-researched area (Karamacoska et al., 2018; Northoff et al., 2010). Furthermore, a single baseline resting measure does not allow investigation of the dynamic *regulation* of energetic state that is crucial to interaction with an unpredictable and changeable environment. The CEM provides a theoretical differentiation of baseline energetic state (arousal), and the regulation of energetic state in response to demands of the environment (activation). In addition, subsequent research has provided measurable EEG indices of these separable constructs - resting global alpha for arousal, and topographical changes in delta, theta, alpha, and beta between conditions for activation (Barry et al., 2007; Barry & De Blasio, 2017; Karamacoska et al., 2017). Thus, the CEM provides a theoretically and empirically valid basis for understanding the relationship between brain energetics and cognition in TBI, and a possible explanation for the mechanism of action in

training these domains, with potential clinical relevance.

1.7 Rationale and general aims

Executive dysfunction frequently persists following neurological recovery from TBI and has a significant impact on an individual's everyday functioning. Impaired EF is accompanied by abnormalities in EEG measures of the energetic state of the brain in TBI, and restorative rehabilitation approaches such as cognitive and neurofeedback training aim to improve functioning by facilitating changes in neuronal connections. As described in detail in Sections 1.3.4 and 1.6.3, the field is lacking a consistent theoretical framework for understanding the relationship between EEG abnormalities and cognitive functioning in TBI, and consequently for designing effective interventions. Unlike other models of EF, the CEM (Sanders, 1983) presents a theoretical account of the role of energetic state in cognition, that may extend understanding of the relationship between EEG oscillations and cognition in TBI. Progress in fundamental EEG research has identified electrophysiological measures of the constructs of *arousal* and *activation*, providing the basis for empirical investigations of the applicability of this model to TBI sequelae and intervention.

The overall aims of this thesis are 1) to investigate the applicability of the CEM arousal and activation concepts in understanding the role of energetic state abnormalities in TBI-related EF impairment; and 2) to investigate the effectiveness of a neurocognitive training program based on CEM principles in improving EF in TBI.

1.7.1 The role of energetic state in TBI-related EF impairment

Much of the research in TBI has used baseline or resting EEG measures in order to establish abnormalities in tonic EEG activity, and this offers support for an interpretation of impaired energetic state. However, the contribution of tonic oscillatory EEG activity (a measure

of energetic state) to cognition, is an under-researched area (Karamacoska et al., 2018; Northoff et al., 2010). Furthermore, this approach neglects the crucial aspect of state 'regulation' that is required to respond flexibly to an unpredictable and ever-changing environment. According to the CEM, efficient cognitive processing involves the interplay of *energetic state* factors (arousal and activation) and *computational* factors (encoding, search, response selection, and motor organisation), that are regulated and coordinated by an *evaluation* mechanism, through conscious *effort*. Energetic state factors are divided into two pools: *arousal*, i.e. tonic energetic state of the organism, and *activation*, i.e. the mobilisation of energetic state in response to environmental demands. While EEG measures of these two distinct pools have been established - global alpha activity reflecting arousal, and topographical changes in delta, theta, alpha, and beta bands as reflecting activation (Barry et al., 2007; Barry & De Blasio, 2017) - they have not yet been investigated in TBI.

Studies 1 and 2 (Chapters 2 and 3 respectively) aim to investigate the presence of impairments of *arousal* and *activation* in a TBI group compared to controls, and to additionally investigate the relationship between these measures and cognitive impairments, specifically RI impairment. The RI task, an auditory Go/Nogo task, was chosen as it has been demonstrated that RI specifically is deficient in TBI, when compared to alternative inhibitory control processes such as interference control (Dimoska-Di Marco et al., 2011). Study 1 investigates the presence of arousal and resting activation impairments in TBI, and their relationship to RI task performance. Arousal is operationalised as EC global alpha[5]. Resting activation is operationalised as the change in EEG activity (in delta, theta, alpha, and beta bands) between EC and EO conditions, reflecting the ability to regulate energetic state in response to the additional visual processing requirements of the EO condition. Study 2 extends on this with a focus on task-related activation, given that

[5] Note that despite the operational definition of arousal as EC 'global' alpha, technical difficulties in the present studies meant that temporo-parietal electrodes had to be excluded from analysis, and so 'global' alpha was derived from fronto-central electrodes only. This is justified as arousal has been shown to differ uniformly across the scalp (Barry et al., 2007) but does not reflect a true 'global' alpha.

this thesis is interested in regulation of energetic state as it relates to cognitive function. Task-related activation is operationalised as the EEG changes between an EO condition and a RI task condition, reflecting the additional cognitive processing requirements of the RI task. Study 2 investigates impairments of task-related activation in TBI, as well as its relationship to RI task performance.

The ultimate goal of cognitive rehabilitation is meaningful improvements in broader everyday functioning, rather than improvements on computerised cognitive tasks. Study 3 (Chapter 4) therefore aims to investigate the relationship between arousal, resting activation, and task-related activation and measures of EF in everyday life. The degree of EEG abnormalities has been associated with injury severity and white matter damage in TBI previously (Thatcher, Biver, et al., 2001; Thatcher, Biver, McAlaster, & Salazar, 1998; Thatcher, Biver, McAlaster, Camacho, et al., 1998; Thatcher, North, et al., 2001). However, these associations have not been investigated in regard to CEM-based state measures. Therefore, Study 3 additionally aims to investigate the relationships between injury variables and the CEM-based measures of energetic state in TBI.

1.7.2 CEM-based neurocognitive training in TBI

Study 4 (Chapter 5) will investigate the effectiveness of a neurocognitive training program based on CEM principles in a group of adults with TBI. Study 4 is designed to address some key limitations in the literature on cognitive rehabilitation for TBI.

Firstly, the CEM provides a theoretical framework that considers the importance of appropriate brain state regulation in cognition and behaviour. It proposes a *reciprocal* interaction between energetic state and cognition/behaviour - such that optimal energetic state facilitates efficient information processing and responding, and responses are monitored and evaluated so that brain activity can be regulated to an appropriate state. At present, cognitive training targets efficient information processing, while neurofeedback targets state regulation, but no approaches that simultaneously target information processing and state regulation exist in TBI rehabilitation. It is likely, according to the CEM, that attempts to target either the information processing or state

regulation domains are impeded by impairments in the other domain. Indeed, baseline EEG activity has been shown to affect the rate and nature of learning in healthy populations (Mukai et al., 2007; Vernon et al., 2003) and is predictive of outcomes of cognitive training (Strangman et al., 2008; Vinogradov et al., 2012). Furthermore, baseline cognitive functioning can impede or enhance response to cognitive rehabilitation (Ben-Yishay et al., 1987; Michel & Mateer, 2006; Sandberg et al., 2016; Wood, 1988).

Study 4 will investigate the effectiveness of the Focus Pocus neurocognitive training program. This program simultaneously targets information processing (through cognitive training of RI and WM) and energetic state regulation (through NF training). The Focus Pocus protocol was initially designed to target executive dysfunction in children with AD/HD who, similar to individuals with TBI, show impairments in RI and WM processes and impairments in EEG measures of energetic state (Barry et al., 2003; Sergeant, 2005). Positive effects of this program have been demonstrated in AD/HD populations (Jiang et al., 2018; Johnstone et al., 2017).

Secondly, the TBI rehabilitation literature has been criticised for its lack of adequately designed, large scale, RCTs (Cappa et al., 2005; Gray, 2017; May et al., 2013; Rohling et al., 2009). This is largely due to the challenges of recruiting large groups with homogeneous characteristics. It has been argued that the inherent heterogeneity of this population not only makes recruitment a practical challenge, but also that large group studies with strict exclusion criteria results in samples that are simply not representative of the population (Ali et al., 2020; Cicerone et al., 2019; Thomas & Smith, 2015). It is recognised that there is an important role of individual differences in intervention response, and that a better understanding of the characteristics that predict training success is needed in order to generalise results to individual patients in the clinical setting (Ali et al., 2020; D. H. Barlow & Nock, 2009; Cicerone et al., 2019; Hampstead & Bahar-Fuchs, 2020).

Therefore, Study 4 utilises the Single Case Experimental Design (SCED), a methodology recently recognised as equal in experimental rigour to the RCT (Oxford Centre for Evidence-based Medicine; www.cebm.net). In a SCED, multiple measurements of the outcome variable/s are

taken during baseline (pre-intervention) and intervention phases, such that an individual participant serves as their own control (Krasny-Pacini & Evans, 2018). Intervention effects are inferred if outcome measures change when the intervention is added or removed, and when this change is replicated either within participants (e.g. in an ABAB design), or between participants (e.g. a multiple-baseline design with multiple participants) (Horner et al., 2005; Kratochwill & Levin, 2010). This means that fewer participants are needed to provide adequate control to establish causal relationships between intervention and outcomes (Kratochwill et al., 2010; Shadish et al., 2002). Another considerable benefit of the SCED in TBI research is that it emphasises intra-individual change (D. H. Barlow et al., 2009), allowing the heterogeneity of this population to be explored rather than screened or averaged out. The use of SCED methodology in Study 4 will facilitate preliminary exploration of individual characteristics with the potential to predict positive response to neurocognitive training.

Finally, outcome measures for the intervention study are informed by limitations of the existing literature. The rehabilitation literature has been limited by a lack of evidence for generalisation of improved performance on laboratory tasks to improvements in everyday functioning (Cicerone et al., 2011; Lynch, 2002; Park & Ingles, 2001; Sigmundsdottir et al., 2016). This is largely due to a lack of relevant functional outcome measures in training studies (Cicerone et al., 2011; Gordon et al., 2006; Ponsford, Bayley, et al., 2014). Study 4 will include measures of everyday EF to evaluate the effect of the intervention on functioning, i.e. meaningful improvements in patients' lives. Additionally, in order to design and enhance effective interventions the mechanisms of change need to be better understood (Ali et al., 2020; Hampstead & Bahar-Fuchs, 2020; Sigmundsdottir et al., 2016; Whyte et al., 2014). Based on the theory of neuroplasticity and the CEM, improvements in state regulation (arousal and activation) should be accompanied by improvements in EF task performance and everyday EF behaviours. Therefore, the effect of neurocognitive training on measures of RI task performance and EEG measures of arousal and activation will also be investigated.

CHAPTER 2:

Study 1: The role of resting state arousal and activation in inhibitory control deficits following TBI.

2.1 Introduction

Impaired executive function (EF) is a well-established long-term consequence of Traumatic Brain Injury (TBI) (McDonald, Flashman, & Saykin, 2002; Ponsford et al., 2014). Response inhibition (RI) is one aspect of EF that is specifically deficient (Dimoska-Di Marco et al., 2011), and associated with impulsive behaviour (Rochat et al., 2013) in this population. Alongside RI impairments, individuals with TBI have abnormalities in the electrophysiological activity of the brain, measured by the electroencephalogram (EEG; Rapp et al., 2015; Thatcher, 2009). As discussed in Chapter 1, despite an implicit assumption in the literature that EEG and cognition are functionally intertwined, there is at present no unified theoretical explanation of how EEG and cognition interact in this population.

The Cognitive Energetic Model (CEM; Sanders, 1983) may offer explanatory and clinical value in this context. According to the CEM, efficient cognitive processing involves the interplay of *energetic state* factors (arousal and activation) and *computational* factors (encoding, search, response selection, and motor organisation), that are regulated by an *evaluation* mechanism, through conscious *effort*. The CEM has shown explanatory and practical utility in AD/HD; another clinical population characterised by executive dysfunction and electrophysiological abnormalities (Sergeant, 2000, 2005). Research in AD/HD has shown that dysregulation of energetic state factors plays an important role in executive dysfunction and is amenable to training in this population (Johnstone et al., 2010, 2017; Sergeant, 2000, 2005).

In the CEM, energetic state factors are divided into two pools: *arousal*, i.e. tonic

energetic state, and *activation*, i.e. the mobilisation of energetic state in response to environmental demands. Barry, Rushby, and colleagues have established EEG measures to operationally define the arousal and activation concepts, by examining changes in EEG during eyes-open (EO) compared to eyes-closed (EC) resting conditions. They established global alpha as a reliable index of arousal (Barry et al., 2004, 2008, 2009, 2011; Barry, Rushby, et al., 2005), and topographically specific EC-to-EO changes in delta, theta, alpha, and beta bands as reflecting activation, in response to the additional visual processing demands of the EO condition (Barry et al., 2007; Barry & De Blasio, 2017).

Though not explicitly referring to the CEM, two recent studies have investigated EEG alpha measures that align with the concepts of arousal and activation, in studies of emotion processing following TBI, demonstrating no evidence of impaired arousal (global alpha power) in the TBI group compared to controls (Fisher et al., 2015; Rushby et al., 2013). Rushby et al. (2013) did however, report an activation impairment for the TBI group, who showed an attenuation of the typical EC-to-EO alpha power suppression. Though reviews have suggested that, compared to controls, a general reduction in alpha power is characteristic of TBI (Rapp et al., 2015; Thatcher, 2009), these reviews have conflated studies recording EEG in both resting and active cognitive task conditions. When focusing on research that measured global alpha in EC resting conditions, a number of studies have reported no group differences (Chen et al., 2006; Dockree et al., 2004; Tebano et al., 1988). Together, the literature points to intact arousal, and impaired activation in the alpha EEG band following TBI. Importantly, no studies have yet investigated activation in the delta, theta, and beta bands in TBI, nor the relationship between activation measures and RI in TBI. The current study aims to investigate arousal and activation measured by EEG in resting tasks to determine a) where TBI-related impairments exist; and b) whether these impairments are related to deficient RI in this group.

A Go/Nogo task with three different stimulus presentation rates is used in this study, as event-rate has been shown to act as an external modulator of energetic state (Sanders, 1983; Van Der Meere & Stemerdink, 1999). Sanders (1983) proposed that fast event-rates induce a hyper-

activated[6] state and slow event-rates induce a hypo-activated state compared to an optimal medium event-rate. This results in impaired inhibitory control performance in the fast and slow event-rates, compared to the medium. Event-rate effects have been used to support interpretations of impaired state regulation in AD/HD, child development, and healthy control studies (Benikos & Johnstone, 2009; Johnstone & Galletta, 2013; Sergeant, 2000; Van Der Meere & Stemerdink, 1999). The current study is interested in how resting arousal and activation are related to performance when energetic state is externally regulated by event-rate in TBI.

In the current study, it is expected that the TBI group will show no difference in global alpha power in the EC condition, compared to controls, reflecting intact arousal (hypothesis one). In regard to activation, it is expected that the TBI group will show smaller changes in focal delta, theta, alpha, and beta between EC and EO conditions, compared to controls, reflecting attenuated activation (hypothesis two). Further, it is expected that activation measures will be related to Go/Nogo task performance, such that larger EC-to-EO changes in delta, theta, alpha, and beta will be associated with higher accuracy and faster and less variable RTs (hypothesis three). While it is expected that these associations will be present in both groups, the group difference in these associations will also be explored. In regard to the effect of event-rate, it is expected that TBI-related performance deficits will be more apparent in the slow and fast event-rate tasks (compared to medium), given the additional activation requirements of these tasks (hypothesis four).

2.2 Method

2.2.1 Participants

Twenty six adults (14 males) with a mean age of 46.0 years (*SD* = 11.78, range 22 - 63) who had sustained a TBI were recruited from a local brain injury service. The mean length of

[6] Studies of event-rate effects have used the terms hyper/hypo-arousal and hyper/hypo-activation to describe the modulation of energetic state. Given that these studies involve the comparison between tasks of different processing requirements we suggest that this is more indicative of activation. This is supported by Johnstone & Galletta (Johnstone & Galletta, 2013) who showed that event-rate differences in pre-stimulus alpha were more in line with activation than arousal.

post-traumatic amnesia (PTA) was 25.19 days (*SD* = 30.04, range 0 - 93 days). According to PTA, LOC, and GCS scores, seven participants met criteria for *mild* TBI, six met criteria for *moderate* TBI, eleven met criteria for *severe* TBI, and two participants did not have sufficient clinical information to assess severity. The mean time since injury was 5.62 years (*SD* = 7.46, range 4 months – 26 years). TBI participants had a mean education of 13.65 years (*SD* = 3.05, range 10 – 21 years). **Table 2** shows the clinical features of the participants.

Thirteen of 20[7] TBI participants showed impairment (> 1.5 SD below normative mean) on at least one standardised neuropsychological measure: Coding (WAIS-IV; Wechsler, 2008), Trail Making Test Parts A and B (Hannay et al., 2004). Premorbid IQ for the TBI group ($n = 20$) was estimated from the National Adult Reading Test (Nelson & Willison, 1991) at a mean of 98.7 (*SD* = 13.05, range 74 - 116).

The control group included 33 adults (4 male) with no history of brain injury. They were recruited through the University research participation scheme. The control group had a mean age of 30.52 years (*SD* = 11.28, range 18 – 52 years) and a mean of 14.52 years of education (*SD* = 2.15, range 11 – 21 years).

All participants completed a screening questionnaire and were excluded if they had uncorrected hearing or vision loss or a severe psychiatric illness. For the final sample, there was no significant difference between the groups for years of education (t (57) = 1.22, $p = .228$). However, the distributions of gender and age differed significantly, with the TBI group having more males ($\chi^2 = 11.46$, $p = .001$) and being significantly older (t (57) = -5.12, $p < .001$).

[7] Neuropsychological test data was collected for only 20 of the 26 participants in the TBI group.

Table 2.

Injury Characteristics of Participants with TBI (n = 26)

#	Age	Education (years)	Gender	Time post-injury	PTA (days)	Cause of injury	Site of injury/initial scan
1[e]	37	16	M	4 m	5	Assault	Right frontal and temporoparietal lobe haemorrhages; right thalamic microhaemorrhage; right lateral ventricle haemorrhage at occipital horn, DAI.
2[e]	40	13	F	11 m	unk	Fall	Streaks of blood found over left frontal lobe and left sylvanian fissure.
3[e]	60	11	M	1y 1m	6 hours	Fall	No pathology.
4[e]	45	13	F	10 m	11	MVA	Subarachnoid haemorrhage; possible shearing; edema in superior cerebellum and medial temporal lobe.
5[e]	62	20	F	6 m	1	MVA-Ped	Left extra dural haematomas, associated midline shift, undisplaced temporal and parietal bone fractures. Craniotomy.
6[e]	44	12	M	1 y 6 m	57	MBA	6cm area of intraparenchymal haemorrhage in right frontoparietal region with associated cerebral oedema and masse effect; subcutaneous soft tissue over left frontal region.
7	63	11	F	7 m	unk	Fall and hypoxia	CT - no pathology. MRI - multifocal ischemic infarction, diffusion restriction in the temporal-parietal and parafalcine frontal lobes bilaterally, high signal within the caudate heads and white matter hyperintensities.
8	50	13	M	5 y 5 m	7	MBA	No pathology.
9	52	12	M	5y 10m	14	MBA	Widespread hemosiderin deposition in the grey/white interface of corpus callosum.
10[a]	55	16	M	1 y 8 m	5	Fall	Bifrontal contusion with extensive fracture through anterior cranial fossa.
11[a,c]	37	11	M	4y 11m	21	Fall	Left occipital extradural haematoma and subdural haematoma. Craniotomy and external ventricular drain followed by cranioplasty.

Note. PTA is based on information from medical records. Injury details are based on initial CT or MRI scan.
MBA = motorbike accident; MVA = motor vehicle accident (driver or passenger); Ped = pedestrian; unk = unknown.
[a] Performance >2 S.D. below mean for age and education for Trails A or B, [b] Performance >1.5 S.D. below mean for age and education for Trails A or B, [c] Performance >2 S.D. below mean for age for digit symbol coding, [d] Performance >1.5 S.D. below mean for age for digit symbol coding, [e] No neuropsychological data available

#	Age	Education (years)	Gender	Time post-injury	PTA (days)	Cause of injury	Site of injury/initial scan
12	43	21	M	25 y	1	MVA	Frontal/occipital coup contra coup x2.
13[a]	43	12	M	5y 4m	14	Fall	Right subdural haematoma, skull fracture, skull infection - craniotomy, left subarachnoid haemorrhage; bilateral frontal and temporal contusions, right occipital contusion.
14[a]	50	12	M	2y 2m	6 hours	MVA-Ped	Left frontal gliosis.
15[a,d]	54	13	M	2y	unk	Assault/ Fall	No pathology.
16	27	18	F	3y 2m	9	MVA	Left frontal, parietal, and temporal injury, midline shift and subsequent left craniotomy.
17[a,c]	30	11	M	6y 10 m	93	MVA	Axonal injury w/ haemorrhage in the pons, midbrain, left frontal lobe and intraventricular haemorrhage; cranial nerve IV palsy.
18[a]	45	12	F	1y 5 m	0	Fall	Left parietal skull fracture; small epidural haematoma left parasagittal; small bilateral subdural haematoma.
19[a]	55	17	M	5y 3m	72	MVA-Ped	Posterior left thalamic acute haemorrhage; haemorrhagic contusion left frontal lobe; subdural hygroma in both frontal regions; CSF leak ear and nose.
20	22	16	F	10m	12 hours	MVA	Right extradural haematoma; temporal contusions.
21[a,c]	22	10	M	5y 7m	unk	Assault	No records.
22[a]	46	11	M	1y 0m	unk	Fall	Cerebral swelling.
23[a,c]	52	10	M	3y 6m	6	MBA	Haemorrhagic contusions to both frontal lobes and left temporal lobe, DAI.
24	56	12	M	12y 1m	29	MVA	No pathology.
25[a,c]	42	16	M	22y 5m	45	MVA-Ped	No records.
26[a]	63	16	F	26 y	unk	MVA	No records.

Note. PTA is based on information from medical records. Injury details are based on initial CT or MRI scan.
MBA = motorbike accident; MVA = motor vehicle accident (driver or passenger); Ped = pedestrian; unk = unknown.
[a] Performance >2 S.D. below mean for age and education for Trails A or B, [b] Performance >1.5 S.D. below mean for age and education for Trails A or B, [c] Performance >2 S.D. below mean for age for digit symbol coding, [d] Performance >1.5 S.D. below mean for age for digit symbol coding, [e] No neuropsychological data available

2.2.2 Measures

2.2.2.1 Resting EEG conditions

Participants had EEG recorded during two resting conditions (recording procedure described below). Participants sat in front of a laptop computer; in the eyes-open (EO) condition they were instructed to direct their eyes at a white fixation cross presented in the centre of the black computer screen for 2 minutes; in the eyes-closed (EC) condition they were instructed to sit still with their eyes-closed for 2 minutes. They were given no other instruction.

2.2.2.2 Auditory Go/Nogo tasks

In the Go/Nogo tasks participants were delivered 150 auditory tones of 50 ms duration, presented via earphones at 70 dB. Tones were either 1000 Hz (presented 70% of the time; the Go tone) or 1500 Hz (presented 30% of the time; the Nogo tone). Participants were instructed to press a button on the keyboard to the Go tone, and not to press to the Nogo tone. They were instructed to respond as quickly and accurately as possible. If the participant's response was incorrect or too slow, a central fixation cross following that trial would turn red, providing feedback to the participant on their performance.

Participants complete three versions of the Go/Nogo task at three difference event-rates. In the fast event rate trials were presented with an inter-stimulus interval (ISI) of 1250 ms and response window of 500 ms. The Medium event task rate had an ISI of 2000 ms and response deadline of 1000 ms. The Slow event rate task had an ISI of 4000 ms and response deadline of 1750 ms.

2.2.3 Procedure

Ethics approval for the project was obtained from the Illawarra Shoalhaven Local Health District and the Human Research Ethics Committee of the University of Wollongong prior to the start of the study.

Each participant attended a two hour testing session where they read an information sheet, provided written consent, and completed a screening and clinical information questionnaire. The TBI group also provided written consent to allow the researchers access to clinical information regarding their injury from hospital records. Participants then completed the Coding and Trail Making Test Parts A and B, and the National Adult Reading Test (NART; Nelson & Willison, 1991).

EEG was recorded using the Emotiv EPOC portable EEG device (described below). Once the headset was fitted, the participant was seated approximately 60 cm from the laptop computer. Participants first had continuous EEG recorded during the resting conditions where the order of EC and EO was counterbalanced between participants to account for order effects. Participants then had EEG recorded during two 1-minute 'active' EEG conditions where they were instructed to 'focus' or 'relax' (order of focus and relax counterbalanced between participants). They then had EEG recorded while they completed an auditory Oddball (not reported here) and the Go/Nogo tasks (the order of cognitive tasks was randomised for each participant). EEG results from the active and cognitive task conditions are not reported in the present study. Participants then completed a 15 min CogState computerised test battery and the Behavior Rating Inventory of Executive Function - Adult and the Barratt Impulsiveness Scale-11 questionnaires (not reported here).

2.2.4 Electrophysiological recording

EEG was recorded using an Emotiv EPOC© wireless EEG headset. The EPOC EEG system was modified using a purpose-built transmitter module to allow stimulus markers to be recorded in the EEG trace. This modified system has been validated against research-grade EEG equipment (Badcock et al., 2013; Badcock et al., 2015). EEG was recorded from 12 scalp electrode sites (AF3, F7, F3, FC5, T7, P7, P8, T8, FC6, F4, F8, AF4) at 128 Hz. One electrode located on the mastoid (M1) acted as a ground reference point. The other mastoid electrode (M2) acted as a feed-forward reference to reduce external electrical interference.

2.2.5 Data extraction

EEG was processed offline using the Neuroscan Scan (v 4.5.1) software package. Each EEG channel was bandpass filtered from 0.5 and 30 Hz and divided into two second epochs. Epochs were baseline corrected across their duration. Epochs with amplitude values ± 100 Hz were automatically rejected. Remaining epochs affected by eye movement, muscle artifact, or noisy channels were identified via visual inspection and removed from further processing. **Table 3** summarises the mean number of epochs that were accepted following the automatic and manual artifact rejection for each group and condition.

A Fourier transformation using a 10% Welch window was applied to the accepted 2 second epochs, resulting in a power value (μV^2) for each 0.5 Hz iteration. Absolute EEG power (μV^2) in four frequency bands was derived as the sum of the power in the frequency bins in the following ranges: delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-25.0 Hz). Band power at each electrode was subject to a square root transformation, resulting in an amplitude measure (μV). Amplitude was used as it has been shown to be less skewed than power measures which often need a logarithmic transformation (Barry et al., 2011; Barry & De Blasio, 2017). Relative amplitude for each band was calculated by dividing the amplitude in each band by the summed amplitude across the 0.5-25.0 Hz range.

Following an integrity check of the data, due to technical difficulties with recording, it was deemed that the data recorded from the temporo-parietal electrodes (T7, T8, P7, P8) were not reliable and so were excluded from analysis. Fronto-central electrodes were divided into three topographical regions by averaging EEG amplitude at electrodes: Left (F7, FC5), Medial (AF3, F3, F4, AF4), and Right (F8, FC6). A global 'frontal' measure was taken as the mean of all fronto-central electrodes.

Table 3

Mean Number of Accepted Epochs. SD in Brackets.

	EC	EO
Control	47.32 *(8.00)*	37.68 *(11.76)*
TBI	53.00 *(7.97)*	47.12 *(10.32)*
Mean	49.91 *(8.43)*	42.22 *(11.97)*

2.2.6 Statistical analyses

In order to address significant group differences in age, Pearson's two tailed bivariate correlations tested the relationship between Age and EEG and performance variables. There were significant relationships between age and EC right relative theta and beta, EO right relative theta and beta, and EO frontal relative beta. There were also significant relationships between age and Go/Nogo Medium Go accuracy and Go/Nogo Medium RT. Therefore, age was included as a covariate for analyses involving these variables.

Group differences in Go/Nogo task performance were analysed with one-way ANOVAs for each performance variable (Go accuracy, Nogo accuracy, RT, and RT variability). Task (Fast, Medium, Slow) was a within-subjects repeated factor and Group (TBI, Control) was a between-subjects factor. Planned contrasts compared the Fast and Slow tasks to the Medium task.

Group differences in relative EEG amplitude were analysed with separate ANOVAs for each band. ANOVAs were three-way mixed design with Condition (EO, EC) and Region (Left, Medial, Right) as within-subjects repeated-measures factors and Group (TBI, control) as a between-subjects factor. The Region factor included planned contrasts comparing amplitude in the left hemisphere (L) with the right hemisphere (R), and the medial region (M) with the mean of the hemispheres (L/R). As all contrasts were planned independently and there were no more of them than the degrees of freedom for effect, Bonferroni-type adjustments of α were not required (Tabachnick & Fidell, 2013). Greenhouse-Geisser correction was not necessary because single

degree of freedom contrasts are not affected by the violations of sphericity assumptions common in repeated-measures analyses of physiological data (O'Brien & Kaiser, 1985). Unless otherwise stated F tests for performance have (1,36) degrees of freedom, and for EEG variables (1,50). Effects approaching significance ($.05 \leq p < .10$) are reported but interpreted with caution.

EEG *activation* measures were derived by subtracting EC amplitude from EO amplitude for each band and region (as per Karamacoska et al., 2018), with a negative value indicating an amplitude reduction in the EO compared to EC condition.

The relationship between EEG activation and cognitive performance measures were tested using Spearman's rank order correlation (Spearman's Rho) for the whole sample. This non-parametric procedure was chosen as visual inspection of the scatterplots identified some multivariate outliers, which were confirmed using Mahalanobis Distance analyses (Tabachnick & Fidell, 2013). Spearman's correlation is robust against the influence of extreme values (Field, 2009). Correlations including theta, beta, and Go/Nogo Medium performance variables were tested with Spearman's partial correlation, controlling for age.

Significant correlations found for the whole sample were examined for between group differences using the Fisher r-to-z transformation. A positive z-score denotes a correlation coefficient that was larger for the Control group compared to the TBI group, and a negative score denotes a larger coefficient for the TBI group. A significant p-value ($p < .05$) for this test suggests there is a difference between the correlation coefficients for each group.

2.3 Results

2.3.1 Group comparisons

2.3.1.1 Go/Nogo performance

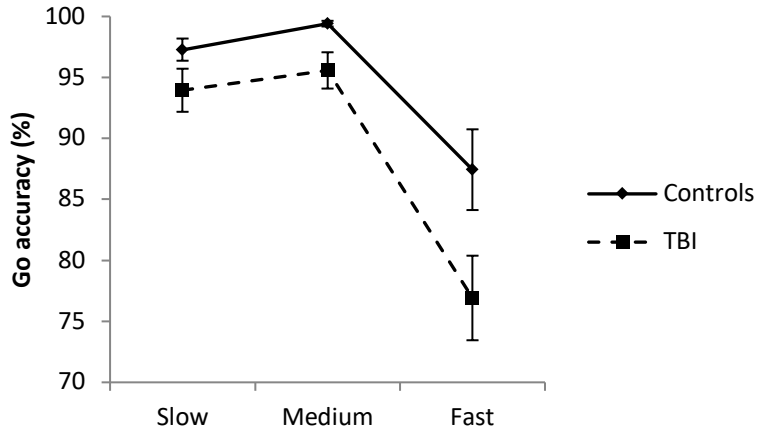
Table 4 shows group means for performance measures in each Task.

Go accuracy: As shown in **Figure 3**, across Task, the TBI group had lower Go accuracy

than controls (F (1,35) = 7.77 (1,35), p = .009, η_p^2 = 0.18). Go accuracy was lower in the Fast compared to Medium task (F (1,35) = 7.50 p = .010, η_p^2 = 0.18). There was no difference between the Slow and Medium task. Contrasts revealed no significant interactions between Group and Task.

Figure 3.

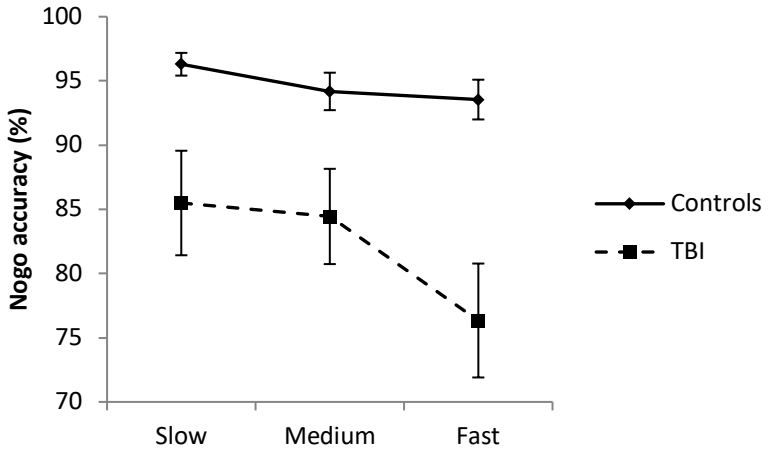
Mean Go Accuracy (%) and Standard Error for Each Group



Nogo accuracy: Across Task, the TBI group showed lower Nogo accuracy than controls (F (1,36) = 15.05, p < .001, η_p^2 = 0.30; see **Figure 4**). Planned contrasts revealed a tendency for Nogo accuracy to be lower in the Fast compared to Medium task which approached significance only (F (1,36) = 3.87, p = .057, η_p^2 = 0.10). There was no difference between Slow and Medium Nogo accuracy, nor any interactions with Group.

Figure 4.

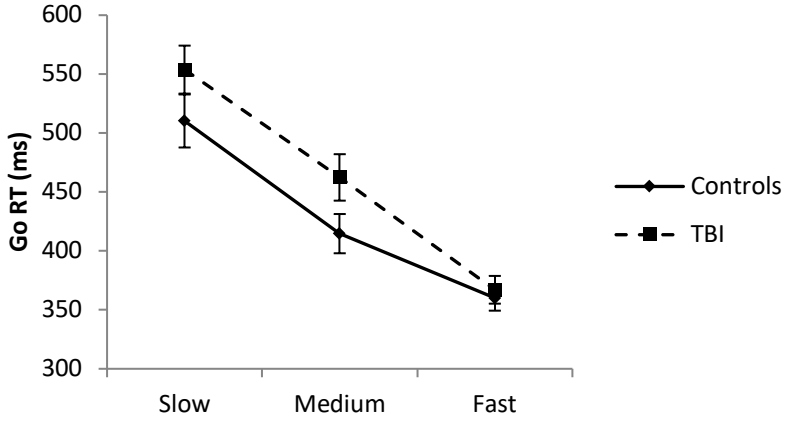
Mean Nogo Accuracy (%) and Standard Error for Each Group



Go RT: There was no main effect of Group on Go RT. RT was significantly slower in the Slow compared to Medium task (F (1,36) = 10.97, p = .002, η_p^2 = 0.23) with no difference between Fast and Medium tasks (see **Figure 5**). Task effects did not interact with Group.

Figure 5.

Mean Go RT (ms) and Standard Error for Each Group



RT variability: Across Task, the TBI group showed greater RT variability than controls (F (1,37) = 10.57, p = .002, η_p^2 = 0.22). As seen in **Figure 6**, contrasts revealed significantly larger variability in the Slow task, and significantly reduced variability in the Fast task, compared to Medium (S > M: F (1,37) = 25.52, p < .001, η_p^2 = 0.41; F < M: F (1,37) = 12.50, p = .001, η_p^2 =

0.25). The F < M effect was larger in the TBI group compared to controls (F (1,37) = 4.93, p = .033, η_p^2 = 0.12).

Figure 6.

Mean Go RT Variability (ms) and Standard Error for Each Group

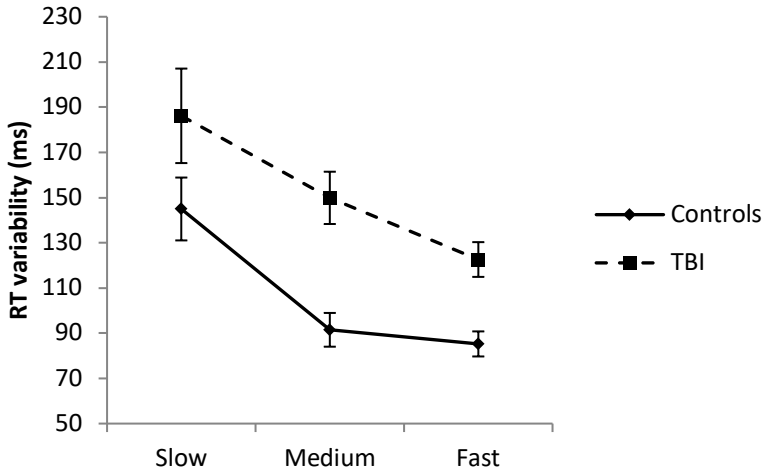


Table 4.

Mean Performance for Each Task by Group. SD in Brackets.

	Go/Nogo Slow		Go/Nogo Medium		Go/Nogo Fast	
	Control	**TBI**	**Control**	**TBI**	**Control**	**TBI**
Go Acc (%)	97.27 (3.98)	94.49 (7.06)	99.02 (1.83)	93.60 (10.28)	89.25 (13.20)	76.19 (17.20)
Nogo Acc (%)	96.23 (4.10)	86.67 (16.21)	93.82 (6.86)	83.46 (15.42)	91.76 (8.69)	77.00 (17.90)
RT (ms)	511.44 (103.22)	552.63 (81.60)	415.89 (72.56)	474.10 (93.26)	359.04 (46.12)	366.04 (46.23)
RT Var (ms)	145.85 (61.07)	179.62 (87.13)	95.17 (31.30)	149.87 (49.08)	84.60 (25.39)	117.89 (34.29)

Note: Acc = accuracy, RT = reaction time, Var = variability.

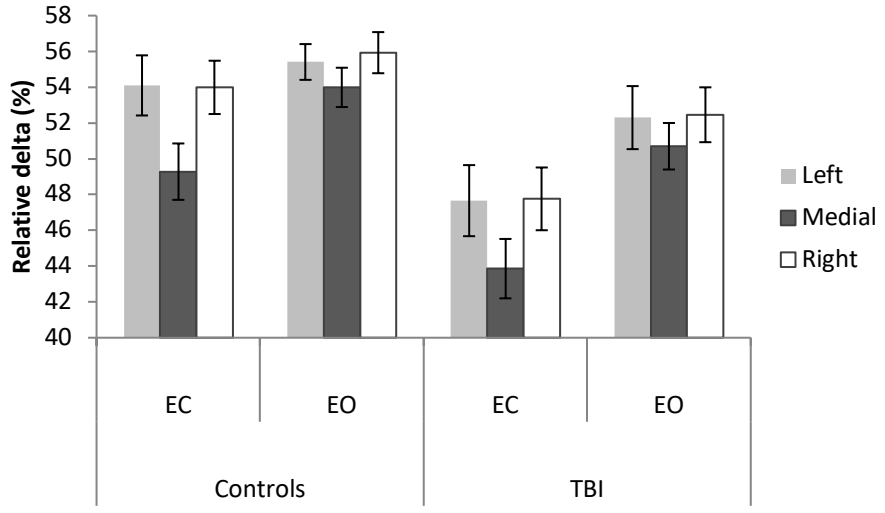
2.3.1.2 Relative EEG amplitude

Table 5 shows group means for relative amplitude (%) for each EEG band in EO and EC conditions.

Delta: Across Region and Condition, relative delta was reduced in the TBI group compared to controls (Control > TBI: F (1,50) = 6.33, p = .015, η_p^2 = 0.11). Across Region and Group, relative delta was increased in the EO compared to EC condition (EC < EO: F (1,50) = 27.81, p < .001, η_p^2 = 0.36). Across Group and Condition, relative delta was larger in the hemispheres compared to the medial region (M < L/R: F (1,50) = 35.76, p < .001, η_p^2 = 0.42). As shown in **Figure 7**, the EC < EO effect was larger in the medial region compared to the hemispheres (EC < EO x M > L/R: F (1,50) = .16.65, p < .001, η_p^2 = 0.25). A Group x Condition interaction which approached significance only, indicated a tendency for the EC < EO effect to be larger in the TBI group than controls (TBI > Control x EC < EO: F (1,50) = 3.22, p = .079, η_p^2 = 0.06).

Figure 7.

Relative Delta (%) in EC and EO for Each Region and Group.

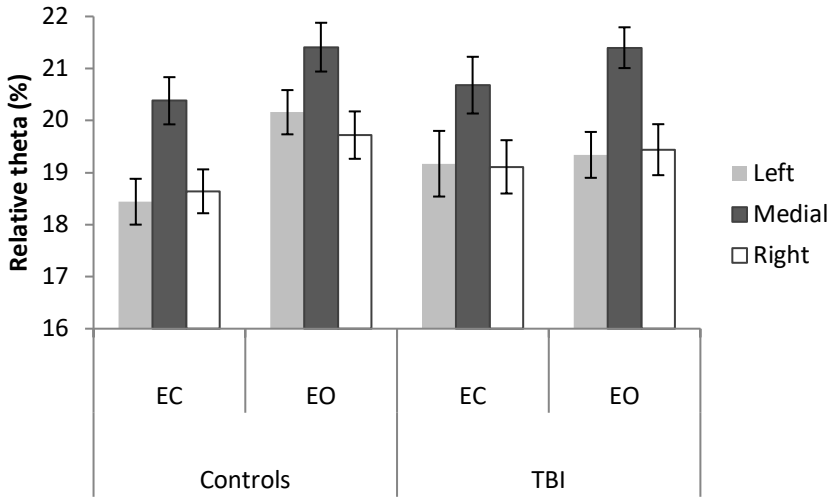


Theta: **Figure 8** shows relative theta amplitude. A Group x Condition interaction for relative theta indicated that the TBI group had a reduced EC < EO effect compared to controls

(TBI < Control x EC < EO: (F (1,49) = 4.12, p = .048, η_p^2 = 0.08). A Condition x Region interaction which approached significance only, indicated a tendency for the EC < EO effect to be larger in the hemispheres than medial region across groups (EC < EO x M < L/R: F (1,49) = 3.67, p = .061, η_p^2 = 0.07).

Figure 8.

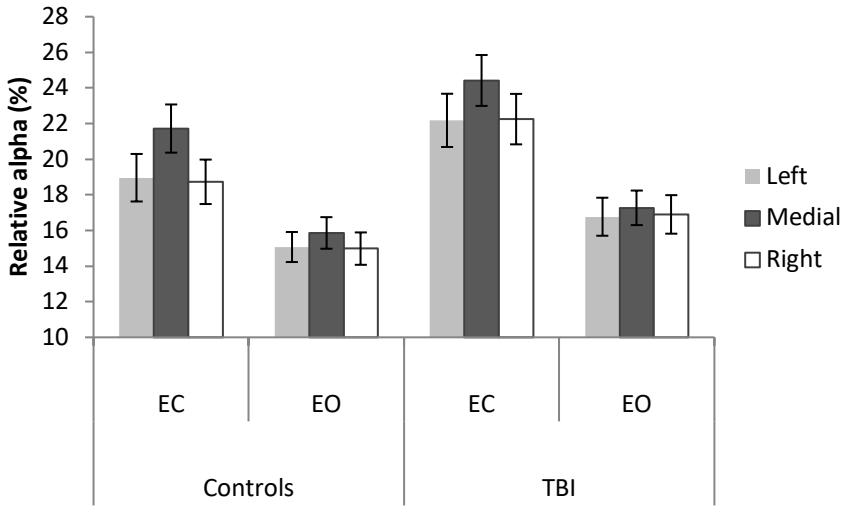
Relative Theta (%) in EC and EO for Each Region and Group



Alpha: Across Group and Region, relative alpha was reduced in the EO compared to EC condition (EC > EO: F (1,50) = 66.23, p < .001, η_p^2 = 0.57). Across Condition and Group, relative alpha was larger in the medial region than the hemispheres (M > L/R: F (1,50) = 39.32, p < .001, η_p^2 = 0.44). As shown in **Figure 9**, the EC > EO effect was enhanced in the medial region (EC > EO x M > L/R: F (1,50) = 36.76, p < .001, η_p^2 = 0.42). There were no effects of or interactions with Group.

Figure 9.

Relative Alpha (%) in EC and EO for Each Region and Group



Beta: Across Region and Condition, the TBI group showed increased relative beta compared to controls (TBI > Controls: F (1,49) = 11.06, p = .002, η_p^2 = 0.18; see **Figure 10**). Relative beta did not differ significantly between Region nor Condition.

Figure 10.

Relative Beta (%) in EC and EO for Each Region and Group

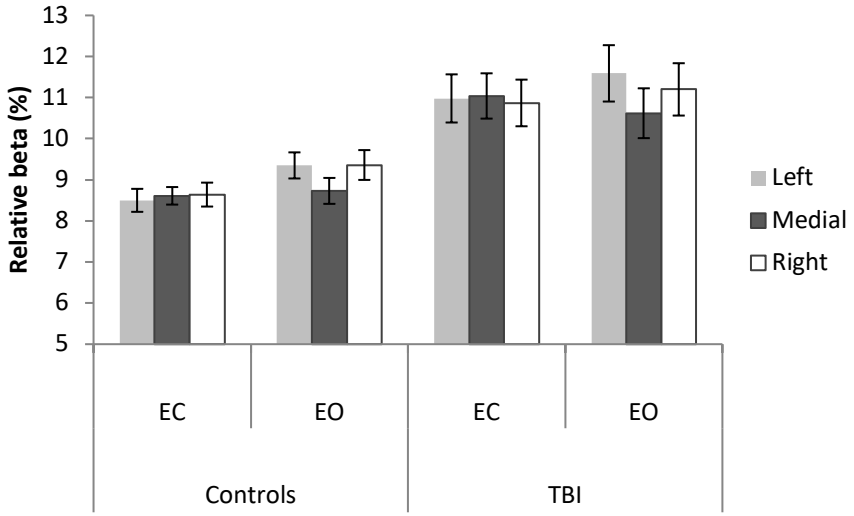


Table 5.

Mean Relative Amplitude (%) for Each Band in EO and EC Conditions by Group. SD in Brackets.

		EC		EO	
		Control	**TBI**	**Control**	**TBI**
Delta	**Left**	54.10 (8.89)	47.66 (9.73)	55.41 (5.29)	52.30 (8.63)
	Medial	49.28 (8.34)	43.86 (8.13)	53.99 (5.81)	50.70 (6.37)
	Right	53.99 (7.88)	47.76 (8.59)	55.93 (6.08)	52.46 (7.51)
Theta	**Left**	18.44 (2.33)	19.17 (3.09)	20.16 (2.25)	19.34 (2.16)
	Medial	20.38 (2.40)	20.68 (2.67)	21.41 (2.48)	21.40 (1.92)
	Right	18.64 (2.23)	19.11 (2.51)	19.72 (2.41)	19.44 (2.40)
Alpha	**Left**	18.96 (7.06)	22.18 (7.32)	15.07 (4.46)	16.77 (5.23)
	Medial	21.72 (7.16)	24.42 (7.00)	15.86 (4.69)	17.27 (4.75)
	Right	18.73 (6.60)	22.25 (6.94)	14.98 (4.81)	16.90 (5.30)
Beta	**Left**	8.50 (1.48)	10.98 (2.87)	9.35 (1.68)	11.59 (3.36)
	Medial	8.61 (1.13)	11.04 (2.70)	8.73 (1.67)	10.62 (2.97)
	Right	8.64 (1.54)	10.87 (2.78)	9.36 (1.92)	11.20 (3.12)

2.3.2 Activation and performance relationships

As there were no Group x Region interactions, activation scores for delta, theta, alpha, and beta were taken as the mean of all frontal electrodes. **Table 6** displays the coefficients (r) for correlations between activation and performance variables for the whole sample. Where correlations were significant for the overall sample, the groups were compared using the Fisher r-to-z transformation and the z-scores are shown in brackets in **Table 6**. Correlation coefficients for each group are displayed in Appendix A (**Table S1.**).

Delta: Frontal delta activation was inversely related to Nogo accuracy in the Slow, Medium and Fast tasks (see **Figure 11**), and to Go accuracy in the Medium task. Frontal delta

activation was positively related to RT variability in the Medium and Fast tasks (see **Figure 11**). Generally, this suggests that greater delta activation was associated with poorer accuracy and more variable response times. Results of the Fisher r-to-z analyses showed no significant differences in the correlation coefficients between groups (z-scores are presented in brackets in **Table 6**).

Theta: Frontal theta activation was positively related to Nogo accuracy in the Slow condition, such that larger theta activation was associated with better accuracy. This correlation did not differ between groups.

Alpha: Frontal alpha activation was positively related to Nogo accuracy and inversely related to RT variability in the Fast condition (**Figure 12).** Given that alpha activation reflected a *reduction* in amplitude in EO cf. EC, and a lower rank reflects a more negative value, Figure 12 shows that a greater EC-to-EO alpha amplitude reduction was associated with lower accuracy and more variable RTs. These correlations did not differ significantly between groups.

Beta: Frontal beta activation did not show any significant relationships with performance measures.

Table 6.

Correlation Coefficients (r) for Relationships between EEG Activation and Go/Nogo Task Performance Variables for the Whole Sample. Z Scores Derived from Fisher r-to-z in Brackets.

		Slow				Medium				Fast			
Band	Region	Go Acc	Nogo Acc	RT	RT Var	Go Acc	Nogo Acc	RT	RT Var	Go Acc	Nogo Acc	RT	RT Var
Delta	Frontal	-.235	-.454** (-0.37)	.103	.142	-.306* (1.76)	-.303* (-0.85)	.214	.317* (-0.89)	-.215	-.301* (0.88)	-.149	.314* (-0.95)
Theta	Frontal	.256	.378* (0.05)	-.017	-.129	.236	.156	-.233	-.196	-.023	.031	-.023	-.007
Alpha	Frontal	.203	.248	-.158	-.132	.167	.190	-.183	-.230	.207	.316* (-0.32)	.160	-.325* (-0.05)
Beta	Frontal	-.030	.119	.085	.041	.282	.130	-.052	-.239	.098	.122	.159	-.083

Note: Acc = accuracy, RT = reaction time, Var = variability; ** $p < .01$, * $p < .05$

Figure 11.

Significant Relationships between Frontal Delta Activation and Nogo Accuracy for Each Task

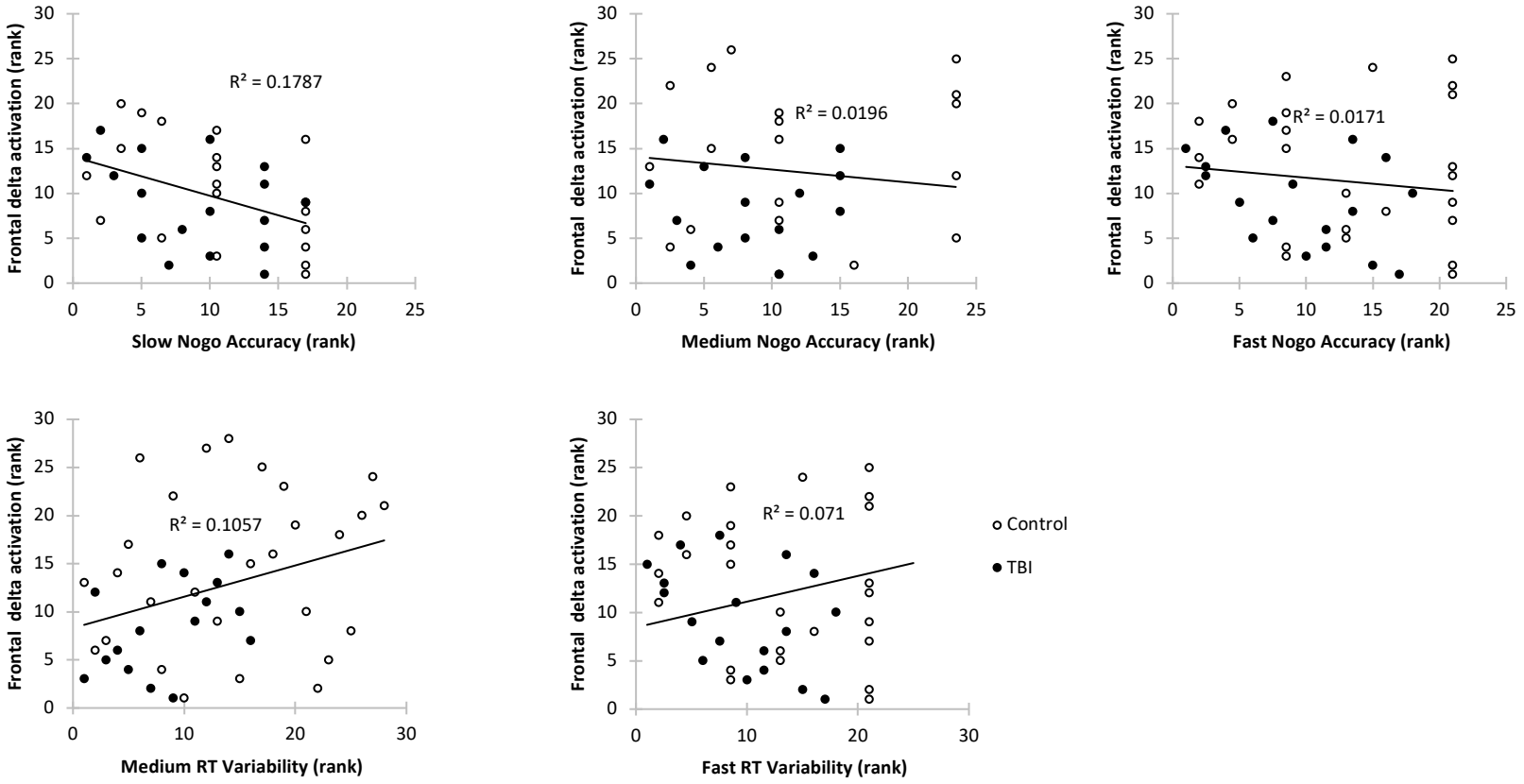
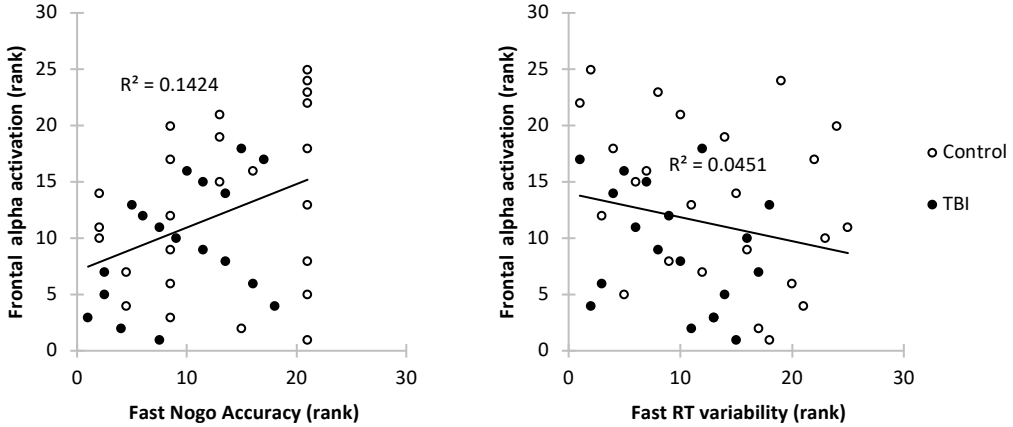


Figure 12.

Relationships between Frontal Alpha Activation and Performance Variables in the Fast Task



2.4 Discussion

The aim of the current study was to investigate arousal and activation measured by EEG in resting tasks to determine a) where TBI-related impairments exist; and b) whether these impairments are related to deficient RI in this group.

2.4.1 Arousal and activation impairments

The first hypothesis - that the TBI group would show intact arousal - was supported. The TBI group did not differ from controls in EC frontal alpha amplitude. This is consistent with previous research showing no difference between TBI and controls for resting global alpha (Dockree et al., 2004; Fisher et al., 2015; Rushby et al., 2013; Tebano et al., 1988). The second hypothesis - that the TBI group would show attenuated activation - was partially supported, with evidence for reduced theta activation and a trend toward increased delta activation for the TBI group, but no group differences for alpha or beta activation.

Across groups, opening the eyes resulted in a) an increase in frontal delta, enhanced in the medial region; b) an increase in frontal theta in the hemispheres; c) a reduction in frontal alpha, enhanced in the medial region; and d) no change in beta activity. Though these findings contrast with previous studies of absolute EEG amplitude and power (i.e. an overall reduction in EO for delta, theta, alpha, and beta bands; Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Barry & De Blasio, 2017; Karamacoska, Barry, Steiner, Coleman, & Wilson, 2018), they are consistent with a previous study examining relative power. Johnstone et al. (2012) observed an increase in relative frontal delta, theta, and beta, and a reduction in relative frontal alpha in EO compared to EC in healthy adults. In the same study they replicated the increased theta and reduced alpha effects in healthy children. This is consistent with the across groups delta, theta, and alpha findings in the present study.

Compared to controls, the TBI group had reduced relative delta across EC and EO

conditions. In relation to the second hypothesis, there was a trend toward greater delta activation in the TBI group, such that they had a larger (cf. controls) increase in delta on opening the eyes. This may reflect a compensatory mechanism to adjust for lower EC delta in the TBI group. However, even with the larger EC-to-EO delta activation for the TBI participants, their EO delta amplitudes were still reduced compared to controls. The across conditions (average of EC and EO) delta amplitude reduction in TBI (cf. controls) is not operationalised by the CEM, and thus not related to the present hypotheses, however it was an unusual and unexpected result. It contradicts commonly observed associations between TBI and increased resting delta activity (Ianof & Anghinah, 2017; Rapp et al., 2015; Thatcher, 2009), and that increased relative delta power is generally considered a good indicator of brain pathophysiology (Claassen et al., 2004; Finnigan et al., 2016; Foreman & Claassen, 2012).

Results from studies of relative delta in TBI have been mixed, with Tebano et al. (1988) finding a reduction and Korn et al. (2005) finding an increase in delta compared to controls. Apart from differences in injury severity, electrode locations, and EEG quantification (Rapp et al., 2015), mixed findings might also reflect differences in non-injury characteristics of the samples. Reduced resting delta power has been observed in a group of mild TBI patients with comorbid Post-Traumatic Stress Disorder (PTSD; Franke et al., 2016). This reduction was in comparison to both healthy controls and to mild TBI patients without PTSD, and the authors attributed the effect to the over-arousal symptomatic of PTSD. Given the traumatic nature of injury, it is unsurprising that PTSD prevalence is high in TBI populations (Van Praag et al., 2019). Four TBI participants in the present study reported a prior diagnosis of PTSD, and the majority of the group reported current symptoms of anxiety, stress, and other emotional difficulties, all of which have been associated with heightened arousal (Meerwijk et al., 2013, 2014; Pruneti et al., 2010; Ziegler, 2004). Psychological symptoms (related or unrelated to TBI) may be variables on which the present TBI sample differs from previous studies and may account for the unexpected delta finding. Another potential confounding variable is age. Reduced resting delta activity has been observed in older (cf. younger) adults (Barry & De Blasio, 2017) and the current TBI sample was significantly older than the controls. The correlation analysis revealed no significant relationship

between age and resting delta amplitude in the present study. Nonetheless, the unexpected finding of reduced resting delta (averaged across EC and EO) in the TBI group needs replication in age-matched groups, and with control for, or investigation of, PTSD and other psychological symptoms.

Across EC and EO conditions, the TBI group showed no difference in theta amplitude compared to controls, consistent with previous studies of EC relative theta in TBI (Chen et al., 2006; Tebano et al., 1988). However, in the current study the EC-to-EO increase in theta was smaller in the TBI group compared to controls, reflecting reduced theta activation. No functional interpretation of the EC-to-EO theta change exists in the current literature, and studies investigating this change measure in healthy adults found no association with behavioural performance or ERPs in a Go/Nogo task (Barry et al., 2019; Karamacoska et al., 2018). A functional interpretation of the present findings can be inferred from studies using event-related or at rest measures of theta, however, this should be considered cautiously since these measures differ from the *activation* measure used here. Event-related enhancement of FM-theta has been associated with improved cognitive performance in a range of tasks (e.g. working memory, episodic memory, cognitive control) and is thought to reflect a generalised function common to all of these tasks, such as sustained attention or concentration (Mitchell et al., 2008). Functional interpretations of resting theta are less well-established, but enhanced resting theta has been suggested to reflect blocking of the encoding of new information (Klimesch, 1999; Mitchell et al., 2008) and healthy neurocognitive function in general (Finnigan & Robertson, 2011). Compared to EC, the EO condition is known to activate visual and attentional brain networks (Hüfner et al., 2009; Marx et al., 2003; Xu et al., 2014). The larger theta activation (i.e. larger EC-to-EO increase in amplitude) in controls in the present study might reflect the role of theta in healthy neurocognitive function, and in particular, sustained visual attention to the central fixation cross on the computer screen in the EO condition. Accordingly, the reduced theta activation (i.e. smaller EC-to-EO increase) in TBI may reflect impaired or attenuated visual attention.

The typical reduction in alpha amplitude in the EO compared to EC condition was

observed, however this effect did not differ between groups. This is inconsistent with a previous finding of attenuated alpha activation in TBI (Rushby et al., 2013). This inconsistency may reflect differences in methodology. In particular, only fronto-central electrode sites were examined in the current study. Rushby et al., (2013) and others (Barry & De Blasio, 2017; Karamacoska et al., 2018) have found the EC-to-EO alpha reduction to be maximal at parietal regions.

Across conditions, relative beta was increased in the TBI group compared to controls. This contrasts with previous findings from studies of relative beta in resting tasks, such as Tebano et al. (1988) and Chen et al. (2006) who reported no difference between mild TBI and controls. The inconsistency may be due to topographical differences, as Tebano et al. report only temporo-occipital sites and Chen et al. the average of 16 channels across the scalp. Notably in the present study, beta amplitude did not differ between EC and EO conditions, nor was the difference affected by group. This suggests no evidence of impaired beta activation in TBI.

The findings of reduced delta and increased beta amplitudes for the TBI group across the EO and EC conditions are not interpretable based on the CEM operationalisation of arousal (EC global alpha) nor activation (EC-to-EO *differences* in amplitude of each of the frequency bands) constructs (Barry et al., 2007). However, increased resting delta activity has been associated with a state of diminished higher-level brain activity (Knyazev, 2012), and increased resting beta activity has been associated with alertness (Laufs et al., 2006). Accordingly, the larger delta amplitudes and smaller beta amplitudes for controls in the present study reflect a mentally inactive or low alertness state (appropriate for a resting condition). Reduced delta amplitudes for the TBI group reflects an inappropriately over-active or alert state for the resting condition. Non-injury characteristics such as psychological symptoms and ageing have been proposed above as potential explanations for this finding. However, the over-active/alert state for the present TBI sample may reflect the heterogeneous consequences of TBI. TBI groups have been shown to be separable based on disorders of *control*, e.g. impulsivity, aggression, emotional lability; or disorders of *drive*, e.g. amotivation, apathy, cognitive inflexibility, the presence of which are dependent on the localised neuropathology of the individual's injury (McDonald, Rushby, Kelly, & de Sousa, 2014;

Tate, 1987, 1999). The present sample shows an over-active/alert resting state and so may be representative of the portion of TBI patients who struggle with disorders of *control*. Using electrophysiological methods to investigate the differences between disorders of control and drive in TBI would be an interesting avenue for future research and may inform individualised treatment targets.

2.4.2 Activation-cognition relationships

The third hypothesis was that increased activation would be associated with better performance on the Go/Nogo task. This hypothesis was supported for alpha and theta activation, however the opposite effect was observed for delta (i.e. increased delta activation was associated with poorer performance). There were no group differences in the correlation coefficients suggesting these relationships were universal and independent of TBI status.

Increased delta activation (i.e. amplitude increase from EC-to-EO) was associated with poorer Nogo accuracy in all three event-rates, supporting a relationship with RI. Additional associations between increased delta activation and reduced Go accuracy in the Medium task, and greater RT variability in Medium and Fast tasks, also support a broader role of delta activation in general attention and cognitive processes. Enhanced event-related delta activity has been associated with Nogo stimuli (Harmony et al., 2009) and with the amplitude of the P3 ERP component (Harper et al., 2014), suggesting a role in inhibitory processes and in response to unexpected and motivationally salient stimuli during cognitive task conditions (De Blasio & Barry, 2013b; Demiralp et al., 2001; Karakaş et al., 2000; Knyazev, 2012; Schürmann et al., 2001). However, associations between resting delta and cognitive processes are less established and the present relationship between delta *activation* and Go/Nogo performance is a novel finding. Reduced EC delta amplitude has been associated with longer RTs in a Go/Nogo task in healthy controls (Karamacoska et al., 2019). In the present study, the trend-level increase in delta activation in the TBI group might have reflected compensation for lower EC delta (cf. controls), and thus the delta-performance relationships may have been driven by EC delta rather than delta

activation per se. This would be in line with Karamacoska et al.'s (2019) findings. However, the relationship between EC delta and cognitive performance was not analysed in the present study, so this needs further clarification.

Greater theta activation (i.e. EC-to-EO increase in theta amplitude) was associated with higher Nogo accuracy in the Slow task only. This association was in the predicted direction and accompanied reduced theta activation in the TBI group. Increased resting theta has been associated with better performance on sustained attention and EF tasks (Finnigan & Robertson, 2011) and increased on-task theta power has been associated with sustained attention and WM (Mitchell et al., 2008). This may explain the specificity of theta associations in the Slow task, as the slower event-rate places greater demands on sustained attention and WM than the faster tasks.

In contrast, resting alpha activation was associated with performance (Nogo accuracy and RT variability) in the Fast task condition only. In the current study, greater EC-to-EO alpha suppression was associated with reduced accuracy and greater RT variability in the Go/Nogo Fast task. This was unexpected based on the cortical activation interpretation of alpha suppression (Barry et al., 2007; Bazanova & Vernon, 2014). A potential explanation for this finding is similar to the unexpected direction of the delta-performance activation relationship here. That is, a larger reduction in alpha amplitude in the EO (cf. to EC) might be a compensatory reaction driven by larger EC alpha amplitude (and therefore lower baseline arousal). This explanation is supported by evidence that increased upper alpha power (10-12 Hz) at rest is associated with better performance on cognitive tasks (Doppelmayr et al., 2002; Klimesch et al., 2000). The relative contributions of EC alpha (baseline arousal) versus compensatory alpha suppression (activation) to deficient RI performance needs to be clarified in future research.

Two prior studies investigated the relationship between EC-to-EO change scores and Go/Nogo performance in healthy controls and did not find any significant associations (Karamacoska et al., 2018, 2019). However, there were a number of differences compared to the current study. Firstly, larger variation in both performance and EEG measures would be expected

with the inclusion of the TBI group in the current study, making relationships stronger than if performance and activation were at the optimal level expected of controls. Secondly, Karamacoska et al. used an equiprobable Go/Nogo task. The most consistent relationships in the current study were between activation and Nogo accuracy, so the effects of activation may be stronger on the more difficult inhibitory control process required by the 30% Nogo probability task. Finally, Karamacoska et al. examined absolute EEG amplitudes and prior studies have consistently reported differences when absolute vs. relative EEG measures are used (for a review see Klimesch, 1999). Relative amplitude was examined here to reduce the effect of inter-individual variation (Nuwer, 1988), particularly important given the EEG variability seen in TBI groups (Roche et al., 2004; Rushby et al., 2013; Williams et al., 2008).

2.4.3 Performance and event-rate

Overall, the TBI group showed lower Go and Nogo accuracy and greater RT variability than the controls, but no difference for mean RT. Hypothesis four predicted that TBI-related performance deficits would be more apparent in the Slow and Fast event-rate tasks, given the additional activation requirement of these tasks compared to the Medium event-rate. This hypothesis was not supported. The modulation of Go and Nogo accuracy and RT by event-rate did not differ by group, suggesting that on these measures the TBI group were able to regulate performance in response to changing task demands in the same way as controls.

The only significant Group x Task interaction was for RT variability in the Fast compared to Medium task. An impairment specific to the Fast event rate theoretically reflects a problem with over-activated energetic state (Raymaekers et al., 2004; Sergeant, 2000). However, the TBI group actually showed a relative (cf. controls) improvement in RT variability in the Fast task, and the effect instead reflected a TBI-related impairment in the Medium condition (see **Figure 6**). This is an unexpected finding and suggests that the TBI group were more impaired in the condition designed to induce 'optimal' activation levels for performance. A possible explanation is that this indicates a problem with top-down compared to bottom-up state regulation.

The Fast event-rate induces regulation of activation through external task demands, i.e. bottom-up regulation. The TBI group were less impaired on this externally demanding task than in the Medium task where the external regulation requirement is lesser, and a more top-down or internally driven regulatory process is required. This is in line with interpretations of RT variability as an index of top-down attentional control, both in general (Bellgrove et al., 2004; Ramchurn et al., 2014), and in TBI specifically (Stuss et al., 1989, 2003; Vasquez et al., 2018).

It is also consistent with evidence that exogenous (bottom-up) stimulation can improve attentional control and goal directed behaviour in TBI (Fish et al., 2007; Manly et al., 2004). Further, impaired functional connectivity of the sustained attention network in TBI has been shown to normalise with the addition of an alerting cue to the SART (Richard et al., 2018). This suggests that impaired top-down control in TBI can be compensated for with bottom-up modulation of attention. It is possible that the Fast event-rate provided a more effective level of exogenous stimulation for the TBI group than the Slow and Medium event-rates. According to the CEM (Sanders, 1983), difficulty engaging top-down regulation might reflect the CEM *effort* pool or *evaluation* mechanism. The evaluation mechanism monitors performance and exerts top-down control of the arousal and activation pools through effort. Effort is required to inhibit activation when stimuli are presented in quick succession, and to excite activation when event-rate is slow. The relationship between perceived effort and performance should be investigated to clarify this conjecture.

In line with the top-down regulation interpretation, associations between delta activation and performance were broadest in the Medium condition – significant associations were found for Medium Go and Nogo accuracy and RT variability. Delta activation was not associated with Go accuracy in the Fast or Slow tasks, nor with RT variability in the Slow task. This may also suggest that external regulation of delta activation compensated for Go accuracy and RT variability, reflective of general attention and processing speed, but did not compensate for Nogo accuracy, reflective of the more complex cognitive requirements of inhibitory control.

Though resting EEG findings suggest an over-active/alert resting state (reduced delta and increased beta) for the TBI group, the performance results do not support an over-activation interpretation. Rather, there was an overall performance deficit across event-rates for the TBI group, and a specific RT variability deficit in the condition expected to induce 'optimal' state of activation. Further investigation of EEG measured during the Go/Nogo tasks (i.e. task-related activation) would clarify whether this reflects an issue with top-down regulation of energetic state that in turn mediates performance.

2.4.4 Limitations

EEG data was analysed from fronto-central regions only due to technical issues with the recordings from parietal and occipital sites. This is a limitation, especially for the investigation of alpha and beta activation, as EO-to-EC changes are typically largest in posterior regions (e.g. Barry & De Blasio, 2017). Fronto-temporal regions of the brain are the most vulnerable to damage in TBI (Rieger & Gauggel, 2002) and are crucially involved in EF (Ridderinkhof et al., 2004), justifying the frontal focus of the current study. However, not all participants in the current sample had evidence of frontal damage. Some participants had exclusively parietal or sub-cortical damage, and some had no visible pathology. Nonetheless, acceleration and deceleration forces cause DAI that can disrupt the distributed fronto-parietal and fronto-subcortical networks involved in EF (Niendam et al., 2012), and this is not always visualised by conventional neuroimaging (Ma et al., 2016). The lack of posterior data does not preclude drawing conclusions about arousal, as arousal has been shown to differ uniformly across the scalp (Barry et al., 2007). Thus, the fronto-central data provide a useful starting point for understanding how arousal and activation are differentially impacted by TBI, but require replication with broader topography.

The nature of relative EEG is that band amplitudes are interdependent, and therefore an activation-performance relationship for one band could drive or be driven by relationships in the other bands. It is important to note that all EEG bands are present in the raw EEG at any given time and it is the relative proportion of each band that determines the state of the brain (relative

EEG measures tap into this). Therefore, a focus on relative contributions of all bands, rather than on individual bands, should be taken into account when interpreting the results.

Though interpretations of event-rate effects were based on existing literature suggesting that fast event-rates elicit hyper-activation and slow event-rates elicit hypo-activation, in the present study, energetic state during the Go/Nogo tasks was not measured and so state effects of the event-rate manipulation cannot be confirmed. The expected inverted-U pattern (Slow < Medium > Fast) for performance was not observed here. Ceiling effects for accuracy in the Slow and Medium tasks, particularly in controls, may suggest that these tasks did not induce the expected modulation of energetic state. The next step is to measure patterns of task-related activation induced by the changing event-rate to clarify these issues.

There are limitations to the use of Spearman's correlation in this study. As the analysis is performed on ranked values, the approach does not take into account individual differences in the *direction* of EEG amplitude changes between conditions. Interpretation of the relationships were based on the direction of amplitude changes in the group averages, i.e. if on average there was an amplitude increase then larger ranks were associated with larger increases, conversely if there was on average an amplitude reduction then smaller ranks were associated with larger reductions. Nonetheless, it is plausible that some individuals would exhibit EO-related increases in a certain band while others would exhibit a reduction in the same band and this is not visualised by the ranked data. This would be an interesting avenue for future research.

Individual differences are particularly relevant given the heterogeneity of TBI samples (Maas, 2016; Maas et al., 2010; Saatman et al., 2008). Given the limitations of the local TBI recruitment pool the TBI group in this study was highly heterogeneous in terms of both injury severity and cognitive impairment. Though all participants had subjective cognitive complaints, only 13 of 26 TBI participants had cognitive impairments in the clinical range according to neuropsychological measures (but note that 6 participants had no neuropsychological measures completed). Sample heterogeneity is a well-known challenge in the TBI literature (Ali et al.,

2020; Boukrina et al., 2020; Kennedy & Turkstra, 2006). However, in addition, the sample size was relatively small and therefore analyses (especially correlation and Fisher r-to-z) may have been underpowered. The effects observed here should be replicated in larger and/or more homogenous samples.

Another challenge posed by the available recruitment pool was the significant age difference between the groups. Both cognitive and EEG variables are known to be affected by ageing (Hashemi et al., 2016; Hedden & Gabrieli, 2004), and in the current study correlation analyses confirmed a relationship between age and both EEG (theta and beta amplitudes) and cognitive (Go/Nogo Medium Go accuracy and RT) variables. In an attempt to mitigate a confounding effect, age was included as a covariate in group comparison analyses. Though this approach is commonly used in published neuropsychological literature (Bate et al., 2001; Rike et al., 2014; Spikman et al., 2000), when there are pre-existing group differences on the covariate this procedure is statistically limited (Adams et al., 1985; Miller & Chapman, 2001). Therefore, results of the current study may not adequately separate the effects of TBI from the effects of age. Replication in age-matched groups is needed to confirm the effects observed here.

2.4.5 Conclusion

The aim of the current study was to investigate arousal and activation measured by EEG in resting tasks to examine energetic state impairments in TBI, and how these relate to deficient RI in this group. Overall, results supported the hypothesis of intact resting arousal (no group difference in EC alpha amplitude) and abnormal resting activation (greater EC-to-EO delta amplitude increase and smaller theta amplitude increase) in TBI. Activation measures were associated with RI performance deficits. Specifically, a larger EC-to-EO increase in the delta band, a smaller EC-to-EO increase in the theta band, and larger EC-to-EO reduction in the alpha band, were associated with poorer RI performance.

Though the TBI group showed broad deficits in RI performance (cf. controls) at all three

event-rates, they also showed an additional deficit in regulating responding (RT variability) in the Medium (cf. Fast) event-rate task. This may suggest an additional and specific deficit in top-down regulation of energetic state in TBI, that can be ameliorated somewhat by exogenous (bottom-up) regulation. However future research should clarify this with task-related activation measures.

Overall, the results of this study support the applicability of the activation construct of the CEM to understanding energetic state impairments and executive dysfunction in TBI. Specifically, increased delta and reduced theta activation differentiated TBI participants from controls, and increased delta and alpha, and reduced theta activation were associated with deficient RI performance. These results may have implications for rehabilitation of EF in this population because, according to the CEM, activation impairments could impede the recovery of EF processes. Thus, intervention aimed at improving dynamic regulation of energetic state (i.e. activation), rather than baseline arousal, may improve outcomes of cognitive rehabilitation.

CHAPTER 3:

Study 2: The role of task-related activation in inhibitory control deficits following TBI.

3.1 Introduction

Study 1 demonstrated that TBI is associated with intact arousal but increased delta and reduced theta activation in resting conditions, compared to controls. Additionally, Study 1 revealed that increased resting delta activation (i.e. greater EC-to-EO increase in amplitude), reduced resting theta activation (i.e. smaller EC-to-EO increase) and increased resting alpha activation (i.e. greater EC-to-EO reduction) were associated with deficits in performance on a Go/Nogo task. These findings suggest that the brain's ability to activate appropriately in response to environmental or processing demands is impacted following a TBI, and that this is associated with deficient RI.

Study 1 focused on *resting activation*, i.e. the change in EEG band amplitude when the participant moves from an eyes-closed (EC) to an eyes-open (EO) condition. This reflects an adjustment of energetic state in response to visual processing demands, but not necessarily the ability to regulate state in response to cognitive demands. Study 2 will examine activation that occurs when cognitive processing demands are added, i.e. *task-related activation* (the difference in EEG amplitude between an EO resting and a Go/Nogo task condition). This study aims to examine whether task-related activation is impaired in TBI, and whether this is associated with impaired performance in the Go/Nogo task.

In Study 1, Go RT variability deficits for the TBI group were larger at a Medium event-rate compared to a Fast event-rate. Further, delta activation was associated with broader performance impairments at the Medium event-rate compared to the Fast and Slow event-rates.

Impairments at the Fast or Slow event-rates would suggest a problem with over- or under-activation, respectively (Raymaekers et al., 2004; Sergeant, 2000). However, greater impairment in the Medium event-rate, observed in Study 1, suggests difficulty regulating state when external task demands are at the optimal level for performance. This may reflect a specific deficit in top-down or internally regulated activation in TBI (necessary for performance at slow and moderate event-rates), alongside an intact response to external task demands (induced by the fast event-rate). This interpretation is consistent with evidence that in TBI patients with impaired sustained attention, the provision of exogenous (bottom-up) stimulation (e.g. alerting tones) can improve maintenance of attentional control and goal-directed behaviour (Fish et al., 2007; Manly et al., 2004) and increase functional connectivity of the sustained attention neural network (Richard et al., 2018). According to the Cognitive Energetic Model (CEM; Sanders, 1983), this top-down regulation deficit may reflect problems with the *evaluation* mechanism and/or *effort* pool, which together have the role of modulating energetic state based on performance monitoring. The current study aims to investigate the impaired top-down regulation hypothesis by measuring task-related activation at each event-rate.

Broadly, it is expected that task-related activation will be impaired in the TBI group compared to controls, and that task-related activation will be associated with RI performance for both groups. Though TBI-related impairments were specific to increased delta and reduced theta activation in Study 1, it should be noted that resting and task-related activation reflect different processes and so the same pattern is not necessarily expected in the current study. Therefore, group differences in task-related activation for the delta, theta, alpha, and beta bands will be explored. Likewise, in the current study delta, theta, alpha, and beta activation measures will all be examined for relationships with performance. Following greater TBI-related performance deficits found in the Medium condition (compared to Fast and Slow) in Study 1, it is expected that group differences in task-related activation will also be largest in the Medium condition, reflecting TBI-related impairment in top-down state regulation, with intact externally or task driven regulation.

3.2 Method

3.2.1 Participants

Sixteen adults (12 male) with a mean age of 43.56 years (SD = 12.72, range = 22 - 63) who had sustained a TBI were recruited from a local brain injury service. The mean length of post-traumatic amnesia (PTA) was 24.65 days (SD = 30.45, range = 0-93 days), and the mean time since injury was 6.63 years (SD = 5.56, range = 10 months - 26 years). According to PTA, LOC, and GCS scores, four participants met criteria for *mild* TBI, three met criteria for *moderate* TBI, eight met criteria for *severe* TBI, and one participant did not have sufficient clinical information to assess severity. TBI participants had a mean education of 13.50 years (SD = 2.56, range = 10-20 years). Table 7 summarises the clinical features of the participants. Eleven TBI participants showed impairment (> 1.5 SDs below the normative mean) on at least one standardised neuropsychological measure: Coding (WAIS-IV; Wechsler, 2008), Trail Making Test Parts A and B (Hannay et al., 2004). Premorbid IQ for the TBI group was estimated from the National Adult Reading Test (Nelson & Willison, 1991) at a mean of 98.44 (*SD* = 12.50, range = 69-116).

The control group included 19 adults (two male) with no history of brain injury. They were recruited through the University research participation scheme. The control group had a mean age of 31.47 (*SD* = 11.79, range = 18-52) and a mean of 14.42 years of education (*SD* = 1.74, range = 13–20).

All participants completed a screening questionnaire and were excluded if they had uncorrected hearing or vision loss or a current psychiatric condition. There was no significant difference between the groups for years of education (t (33) = 1.26, p = .216). However, the distributions of gender and age differed significantly, with the TBI group having more males (χ^2 = 8.43, p = .004) and being significantly older (t (33) = -2.92, p = .006). Participants in this study were a subset of those who participated in Study 1.

Table 7.

Injury Characteristics of Participants with TBI (n = 16)

#	Age	Education (years)	Gender	Time post-injury	PTA (days)	Cause of injury	Site of injury/initial scan
8	50	13	M	5y 5m	7	MBA	No pathology.
10[a]	55	16	M	1y 8m	5	Fall	Bifrontal contusion with extensive fracture through anterior cranial fossa.
11[a,c]	37	11	M	4y 11m	21	Fall	Left occipital extradural haematoma and subdural haematoma. Craniotomy and external ventricular drain followed by cranioplasty.
13[a]	43	12	M	5y 4m	14	Fall	Right subdural haematoma, skull fracture, skull infection - craniotomy, left subarachnoid haemorrhage; bilateral frontal and temporal contusions, right occipital contusion.
14[a]	50	12	M	2y 2m	6 hours	MVA-Ped	Left frontal gliosis.
15[a,d]	54	13	M	2y	unk	Assault/Fall	No pathology.
16	27	18	F	3y 2m	9	MVA	Left frontal, parietal, and temporal injury, midline shift and subsequent left craniotomy.
17[a,c]	30	11	M	6y 10 m	93	MVA	Axonal injury w/ haemorrhage in the pons, midbrain, left frontal lobe and intraventricular haemorrhage; cranial nerve IV palsy.
18[a]	45	12	F	1y 5m	0	Fall	Left parietal skull fracture; small epidural haematoma Left parasagittal; small bilateral subdural haematoma.
19[a]	55	17	M	5y 3m	72	MVA-Ped	Posterior left thalamic acute haemorrhage; haemorrhagic contusion left frontal lobe; subdural hygroma in both frontal regions; CSF leak ear and nose.
20	22	16	F	10m	12 hours	MVA	Right extradural haematoma; temporal contusions.
21[a,c]	22	10	M	5y 7m	unk	Assault	No records.
22[a]	46	11	M	1y 0m	unk	Fall	Cerebral swelling.
24	56	12	M	12y 1m	29	MVA	No pathology.
25[a,c]	42	16	M	22y 5m	45	MVA-Ped	No records.
26[a]	63	16	F	26y	unk	MVA	No records.

Note. PTA is based on information from medical records. Injury details are based on initial CT or MRI scan.
MBA = motorbike accident; MVA = motor vehicle accident (driver or passenger); Ped = pedestrian; unk = unknown.
[a] Performance >2 S.D. below mean for age and education for Trails A or , [b] Performance >1.5 S.D. below mean for age and education for Trails A or B, [c] Performance >2 S.D. below mean for age for digit symbol coding, [d] Performance >1.5 S.D. below mean for age for digit symbol codi

3.2.2 Procedure and measures

See sub-section 2.2.3 for description of the overall procedure. In this study EEG data recorded during the EO resting condition and auditory Go/Nogo tasks (Fast, Medium, Slow event-rates) were analysed. See sub-sections 2.2.2.1 and 2.2.2.2 for description of these recording conditions.

3.2.3 Electrophysiological recording and data extraction

EEG was recorded using the Emotiv EPOC© wireless EEG headset, which had been modified with a purpose-built transmitter module to allow recording of event markers. This modified system has been validated against research-grade EEG equipment (Badcock et al., 2013; Badcock et al., 2015). EEG was recorded from 12 scalp electrode sites (AF3, F7, F3, FC5, T7, P7, P8, T8, FC6, F4, F8, AF4) at 128 Hz. A ground reference electrode was located on the mastoid (M1) and another mastoid electrode (M2) acted as a feed-forward reference for external electrical interference.

EEG was processed offline using the Neuroscan Scan (v 4.5.1) software package. Processing procedures were identical for the resting and task conditions. A bandpass filter from 0.5 to 30 Hz was applied to each EEG channel. Two second epochs were extracted from the continuous EEG across the total duration of each condition (EO = 2 min, Go/Nogo Slow = 10 min, Medium = 5 min, Fast = 3 min). For the Go/Nogo task conditions this included segments of EEG data recorded during Go and Nogo stimuli presentation, and correct and incorrect responses, but which were not time-locked to stimulus presentation or responses. The epochs were baseline corrected across their duration and those with amplitude values exceeding ± 100 Hz were automatically rejected. Remaining epochs were visually inspected for eye movement, muscle artifact, and noisy channels and if identified were rejected manually. **Table 8** summarises the mean number of epochs that were accepted following automatic and manual artifact removal for

each group and condition.

Accepted epochs were then Fourier transformed using a 10% Welch window, resulting in frequency bins of 0.5 Hz resolution. Absolute EEG power (μV^2) in four frequency bands was derived from the sum of the power in the 0.5 Hz frequency bins in the following ranges: delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), and beta (12.5-25.0 Hz). An amplitude measure (μV) for each frequency band was calculated by a square root transformation of band power at each electrode. Amplitude was used as it reduces the characteristic skew of power measures (Barry et al., 2011; Barry & De Blasio, 2017). A relative amplitude measure for each band was obtained by dividing the amplitude in each band by the summed amplitude across the 0.5-25 Hz range. As per the data integrity check outlined in Chapter 2 (section 2.2.5) temporo-parietal electrodes (T7, T8, P7, P8) were excluded from analysis. Remaining electrodes were divided into three fronto-central topographical regions by averaging EEG amplitude at electrodes: Left (F7, FC5), Medial (AF3, F3, F4, AF4), and Right (F8, FC6). A global 'frontal' measure was taken as the mean of all fronto-central electrodes.

Table 8

Mean Number of Accepted Epochs. SD in Brackets.

	EO	**Go/Nogo Slow**	**Go/Nogo Medium**	**Go/Nogo Fast**
Control	37.90 *(11.67)*	205.68 *(76.51)*	63.83 *(36.94)*	25.18 *(9.29)*
TBI	47.11 (*11.01)*	188.12 *(74.36)*	117.19 *(29.97)*	44.24 *(25.26)*
Mean	42.26 *(12.14)*	197.39 *(74.95)*	88.94 *(42.30)*	34.71 *(21.09)*

3.2.4 Statistical analyses

Given the significant difference between groups, Age was included as a covariate for all analyses. Group differences in Go/Nogo task performance were analysed with separate one-way

ANOVAs for each performance variable (Go accuracy, Nogo accuracy, Go RT, RT variability) separately. Planned contrasts compared the Fast and Slow tasks to the Medium task.

Task-related activation measures for each task (Fast, Medium, Slow) were derived by subtracting EO EEG amplitude from Task EEG amplitude for each band and region (as per Karamacoska et al., 2018), with a negative score indicating an amplitude reduction in the Task compared to EO condition. Group differences in EEG activation scores were analysed with separate ANOVAs for each band (delta, theta, alpha, and beta). ANOVAs were three-way mixed design with Task (Fast, Medium, Slow) and Region (Left, Medial, Right) as repeated-measures factors and Group (TBI, control) as the between-subjects factor. Within the Region factor a planned polynomial contrast compared activity in the left hemisphere (L) with the right hemisphere (R), and the medial region (M) with the mean of the hemispheres (L/R). Within Task, planned contrasts compared the Fast and Slow tasks with the Medium task. As all contrasts were planned independently and there were no more of them than the degrees of freedom for effect, Bonferroni-type adjustments of α were not required (Tabachnick & Fidell, 2013). Greenhouse-Geisser correction was not necessary because single degree of freedom contrasts are not affected by the violations of sphericity assumptions common in repeated-measures analyses of physiological data (O'Brien & Kaiser, 1985). F tests for performance have (1,30) degrees of freedom, and for EEG variables (1,32). Effects approaching significance (i.e. *p* between .05 and .10) are reported but interpreted with caution.

The relationship between EEG activation measures and cognitive performance were tested using Spearman's rank order correlation (Spearman's Rho) for the whole sample. The non-parametric procedure was used as visual inspection of the scatterplots identified some multivariate outliers, which were confirmed using Mahalanobis Distance analyses (Tabachnick & Fidell, 2013). Spearman's correlation is robust against the influence of extreme values (Field, 2009). Where there were significant Group x Region interactions in the group comparisons, activation was assessed at each region for the correlations. Otherwise, the Frontal activation measure (mean of all electrodes) was used.

Significant correlations found for the whole sample were examined for between group differences using the Fisher r-to-z transformation. A positive z-score denotes a correlation coefficient that was larger for the Control group compared to the TBI group, and a negative score denotes a larger coefficient for the TBI group.

3.3 Results

3.3.1 Group comparisons

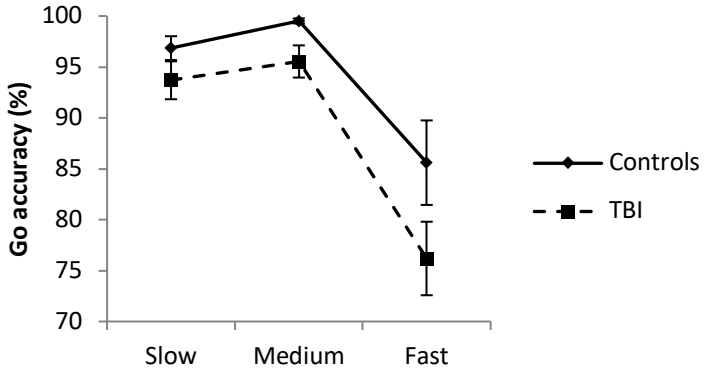
3.3.1.1 Go/Nogo performance

Table 9 displays group means for performance variables at each event-rate.

Go accuracy: As shown in **Figure 13**, the TBI group had significantly reduced accuracy compared to controls across Task (TBI < Control: $F = 5.18$, $p = .030$, $\eta_p^2 = 0.15$). Go accuracy was significantly reduced in the Fast compared to the Medium ($F = 7.06$, $p = .013$, $\eta_p^2 = 0.19$) event-rate, with no significant difference between the Slow and Medium event-rates. There was no significant Group x Task interaction.

Figure 13.

Mean Go Accuracy (%) and Standard Error for Each Group and Event-Rate

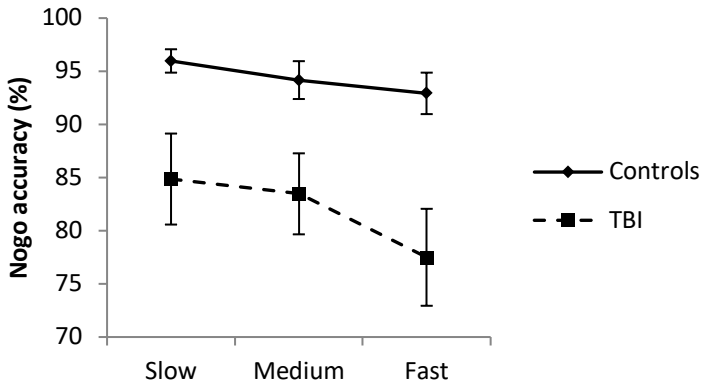


Nogo accuracy: The TBI group had significantly reduced Nogo accuracy compared to controls across Task (TBI < Control: $F = 14.47$, $p = .001$, $\eta_p^2 = 0.33$); see **Figure 14**. Nogo

accuracy tended to be higher at the Slow compared to Medium event-rate, but the effect approached significance only ($F = 3.53$, $p = .070$, $\eta_p^2 = 0.12$). Nogo accuracy did not differ between Fast and Medium event-rates. There was no Group x Task interaction.

Figure 14.

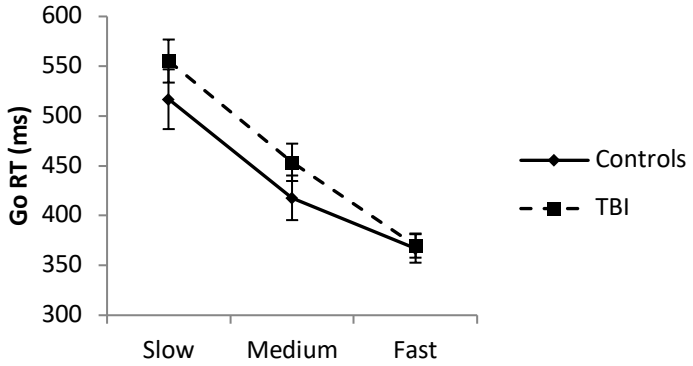
Mean Nogo Accuracy (%) and Standard Error for Each Group



Go RT: Go RT is illustrated in **Figure 15**. Go RT did not differ between groups. RT was significantly longer at the Slow compared to Medium event-rate ($F = 9.84$, $p = .004$, $\eta_p^2 = 0.19$), with no difference between the Fast and Medium event-rates. There was no significant Group x Task interaction.

Figure 15.

Mean Go RT (ms) and Standard Error for Each Group



RT variability: As shown in **Figure 16**, RT variability was increased in the TBI group

compared to controls across Task ($F = 7.37$, $p = .011$, $\eta_p^2 = 0.20$). A Group x Task interaction approached significance for the Fast vs Medium event-rate comparison, due to the tendency for the TBI group to have a greater reduction in RT variability in the Fast compared to Medium event-rate, compared to controls (TBI > Controls x Fast < Medium: $F = 3.25$, $p = .082$, $\eta_p^2 = 0.10$).

Figure 16.

Mean Go RT Variability (ms) and Standard Error for Each Group

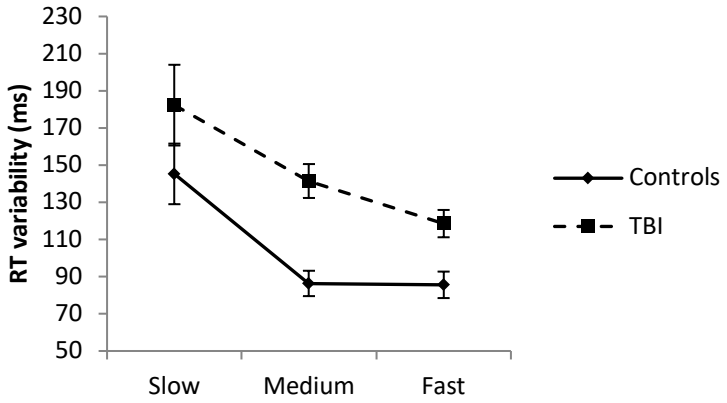


Table 9.

Mean Performance for Each Event-Rate by Group. SD in Brackets.

	Go/Nogo Slow		**Go/Nogo Medium**		**Go/Nogo Fast**	
	Control	**TBI**	**Control**	**TBI**	**Control**	**TBI**
Go Acc (%)	96.85 (4.66)	93.69 (7.44)	99.52 (0.98)	95.54 (6.33)	85.60 (16.59)	76.19 (14.43)
Nogo Acc (%)	95.97 (4.39)	84.86 (17.12)	94.17 (7.11)	83.47 (15.24)	92.92 (7.79)	77.5 (18.23)
RT (ms)	516.90 (119.99)	555.21 (86.46)	417.91 (89.57)	453.55 (75.06)	367.06 (57.22)	369.93 (48.54)
RT Var (ms)	145.29 (65.23)	182.29 (86.84)	86.35 (27.28)	141.46 (36.50)	85.60 (28.49)	118.54 (29.43)

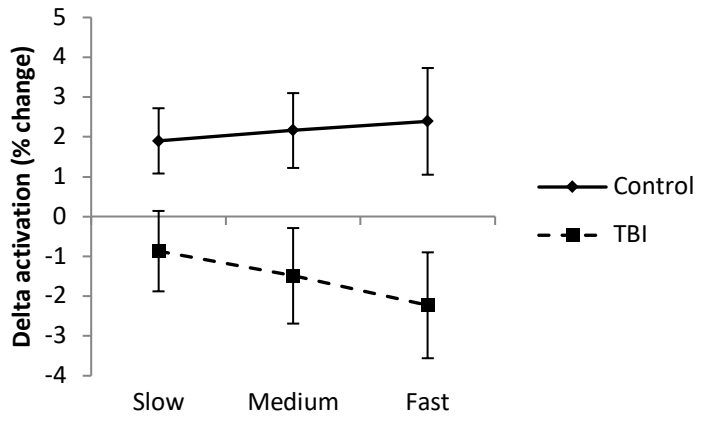
Note: Acc = accuracy, RT = reaction time, Var = variability.

3.3.1.2 Relative EEG activation

Delta: As shown in **Figure 17**, a Group main effect was present; the TBI group showed a task-related reduction in delta, and the control group showed a task-related increase in delta (F = 8.04, p = .008, η_p^2 = 0.20). A tendency for delta activation to be increased at the Slow compared to Medium event-rate approached significance (F = 3.99, p = .054, η_p^2 = 0.11). There were no Group x Task interactions, nor any interactions with Region.

Figure 17.

Mean Relative Delta Activation (% Change From EO to Task) and Standard Error at Each Event-Rate for Each Group



Theta: Mean relative theta activation data is plotted in **Figure 18**. There was no main effect of Group for theta activation. A Task main effect (F = 5.32, p = .007, η_p^2 = 0.14) and planned contrasts revealed a significant reduction in theta activation at the Slow compared to Medium event-rate (F = 7.64, p = .009, η_p^2 = 0.19).

Significant Group x Task x Region interactions revealed different patterns of theta activation between groups. A significant quadratic effect within Region for the Fast vs Medium comparison (quadratic: F = 4.35, p = .045, η_p^2 = 0.12) is illustrated in **Figure 19**A. For controls there was a M > L/R effect for the Fast task, and a M < L/R for the Medium task. The TBI

showed similar topographic patterns, but a reduced M > L/R effect for the Fast task, and reduced M < L/R effect for the Medium task, compared to controls. The linear effect within Region was also statistically significant (linear: $F = 4.55$, $p = .041$, $\eta_p^2 = 0.12$) and is illustrated in **Figure 19**B. For controls relative theta activation showed a L = R effect for the Medium task, but a L > R effect for the Fast task. The TBI group showed a different topographic pattern, with a L > R effect for the Medium task, and a R > L effect for the Fast task. There was a significant linear effect within Region for the Medium vs Slow comparison (linear: $F = 6.25$, $p = .018$, $\eta_p^2 = 0.16$). This effect is illustrated in **Figure 19**C. Controls showed a substantially reduced L > R effect in the Medium compared to the Slow task, while the TBI group showed a larger L > R effect in the Medium compared to the Slow task.

Figure 18.

Mean Relative Theta Activation (% Change From EO to Task) and Standard Error at Each Event-Rate And Region for Each Group

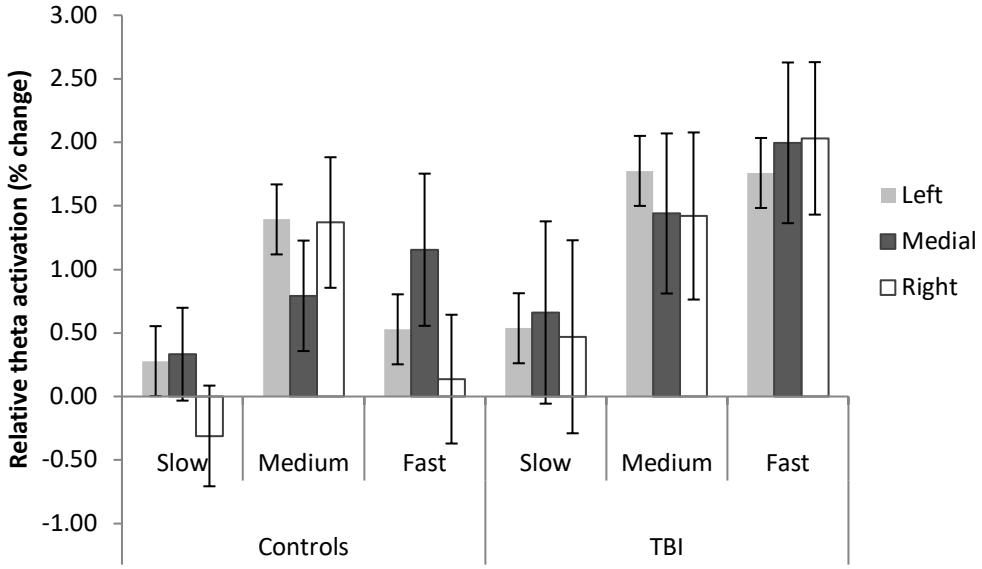
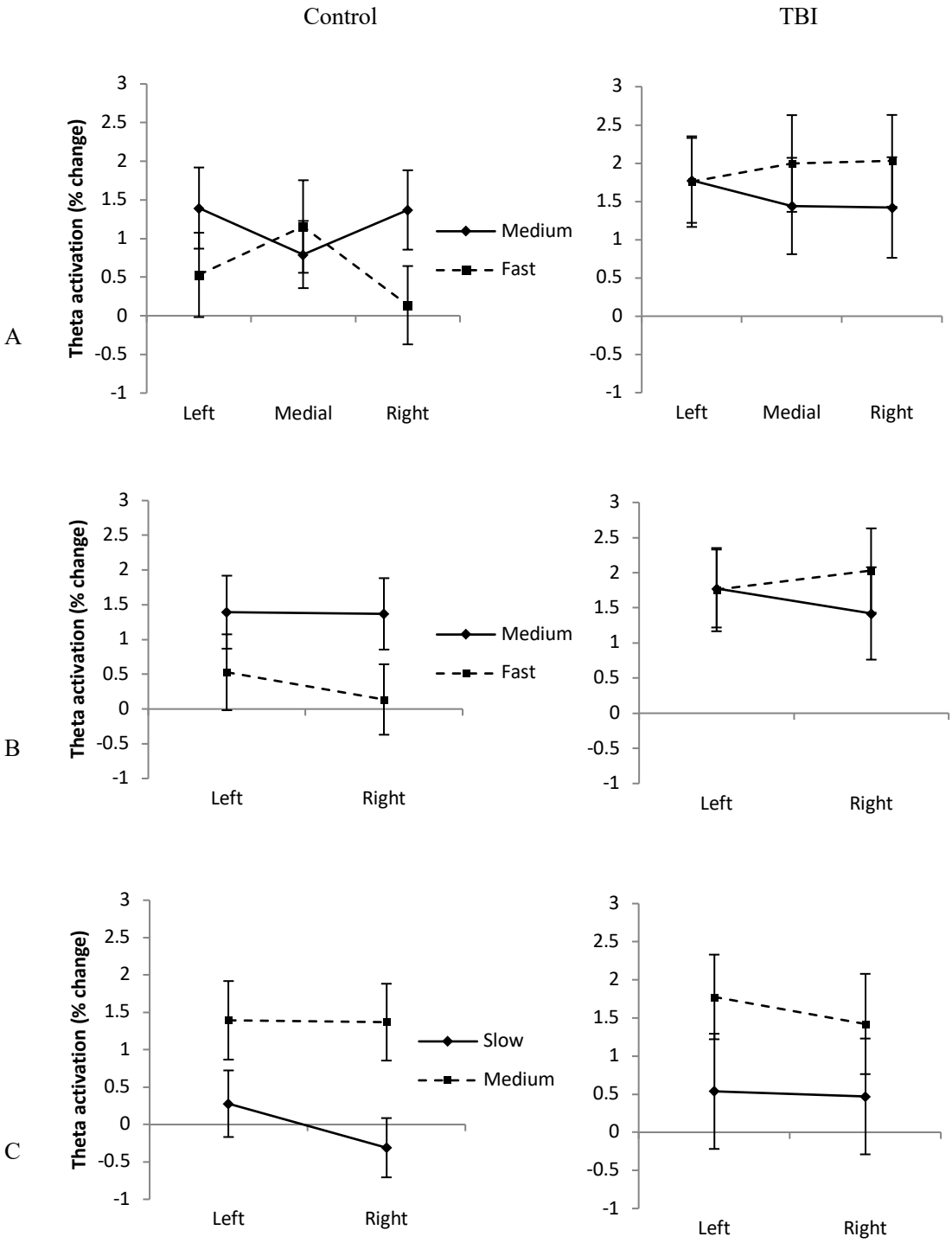


Figure 19.

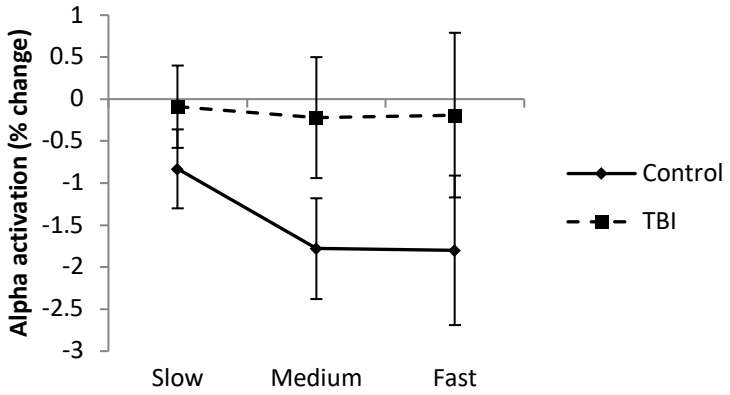
Significant Interaction Effects for Mean Relative Theta Activation (% Change From EO to Task) and Standard Error for Each Group



Alpha: As shown in **Figure 20**, the TBI group tended to have a reduced task-related reduction in alpha compared to controls; an effect that approached significance (F (1,32) = 3.63, p = .066, η_p^2 = 0.10). There was no Group x Task interaction effect, nor any interactions with Region for alpha activation.

Figure 20.

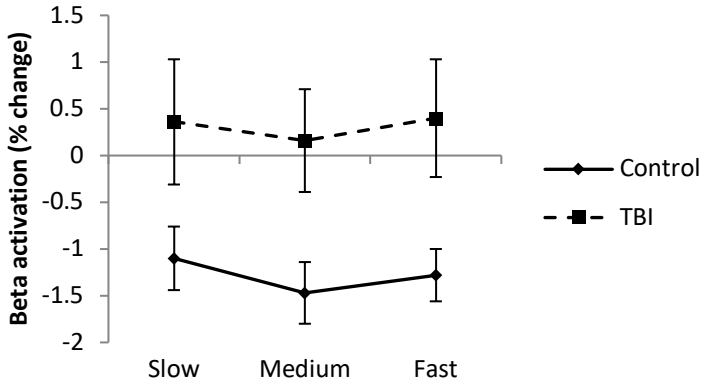
Mean Relative Alpha Activation (% Change From EO to Task) and Standard Error at Each Event-Rate for Each Group



Beta: A main effect of Group showed that the TBI group had a slight task-related increase in beta, while the control group showed a task-related reduction (F (1,32) = 6.40, p = .017, η_p^2 = 0.17); see **Figure 21**. There was no Group x Task interaction effect, nor any interactions with Region for beta activation.

Figure 21.

Mean Relative Beta Activation (% Change From EO to Task) and Standard Error at Each Event-Rate for Each Group



3.3.2 Activation and performance relationships

There were no significant Group x Region interactions for delta, alpha, or beta activation scores; consequently, the Frontal mean was used in correlations for these bands. There was a significant interaction with Region for theta, so Left, Midline, and Right regional theta activation was assessed in addition to the overall Frontal mean.

Table 10 displays the coefficients (*r*) for correlations between activation and performance variables for the whole sample. For significant correlations for the whole sample, the groups were compared using the Fisher r-to-z transformation and the z-scores are shown in brackets in **Table 10.** Correlation coefficients for each group are displayed in Appendix B (**Table S2.**). **Table 11** displays group means for relative EEG amplitude (%) for each band at each event-rate. **Figure 22** and **Figure 23** illustrate the relationships between activation and performance variables for the significant correlations.

Delta: Delta activation (see **Figure 22**) showed a significant positive relationship with Go accuracy and an inverse relationship with Go RT in the Slow task. In the Medium task, delta activation was positively related to Go accuracy, and inversely related to RT variability. Group comparisons showed a dissociable task-related effect with a task-related increase in amplitude for

controls (reflected in larger rank values), and a task-related reduction in the TBI group (reflected in smaller rank values). Therefore, larger task-related increases in delta were associated with higher Go accuracy and faster and less variable response times, whereas larger task-related reductions in delta were associated with lower Go accuracy and longer and more variable response times. There was no association between delta activation and performance in the Fast task. Relationships did not differ significantly between the groups.

Theta: There were no significant correlations between regional or frontal theta activation scores and performance.

Alpha: Alpha activation (see **Figure 23**) showed a significant inverse relationship with Go accuracy and a significant positive relationship with RT in the Slow task. In the Medium task, alpha activation was inversely related to Go accuracy, and positively related to RT variability. Given that alpha activation reflected a task-related *reduction* in amplitude, and a lower rank reflects a more negative value, **Figure 23** shows that a larger task-related reduction in alpha was associated with higher Go accuracy and with faster and less variable RTs. Relationships did not differ significantly between the groups.

Beta: There were no significant correlations between beta activation scores and performance.

Table 10.

Correlation Coefficients (r) for Relationships between EEG Activation and Go/Nogo Task Performance Variables for the Whole Sample. Z Scores Derived from Fisher r-to-z in Brackets.

		Slow				Medium				Fast			
Band	Region	Go Acc	Nogo Acc	RT	RT Var	Go Acc	Nogo Acc	RT	RT Var	Go Acc	Nogo Acc	RT	RT Var
Delta	Frontal	.357* (-0.45)	.249	-.382* (0.00)	-.318	474** (-0.24)	.200	-.168	-.351* (-0.60)	.180	-.058	-.098	-.158
Theta	Left	-.042	.170	-.001	.058	-.017	-.051	.093	.106	.067	.021	-.247	.014
	Medial	-.041	.040	.155	.177	.065	.100	-.013	-.023	.133	.119	-.165	-.037
	Right	-.097	.083	.221	.183	.121	.306	.177	-.131	-.078	-.264	-.204	.244
	Frontal	-.104	.115	.189	.203	.113	.145	.045	-.047	.098	.017	-.238	.027
Alpha	Frontal	- .377* (0.64)	-.339	.460** (-0.52)	.315	-.501** (0.98)	-.240	.242	.438* (0.76.)	-.301	.124	.308	.203
Beta	Frontal	-.162	-.224	.112	.065	-.336	-.284	.008	.290	-.120	-.037	-.051	.130

Note: Acc = accuracy, RT = reaction time, Var = variability. ** $p < .01$, * $p < .05$

Figure 22.

Correlations between Activation and Performance Variables for Go/Nogo Slow Task

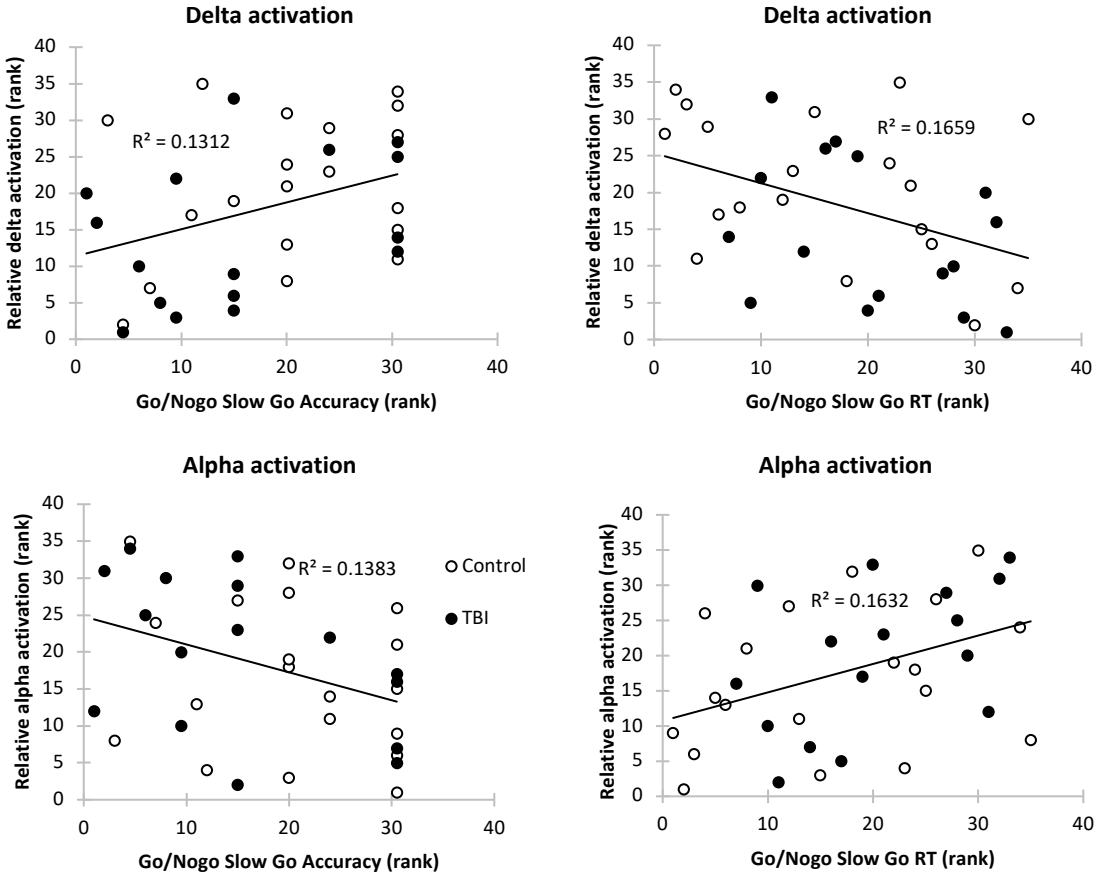


Figure 23.

Correlations between Activation and Performance Variables for Go/Nogo Medium Task

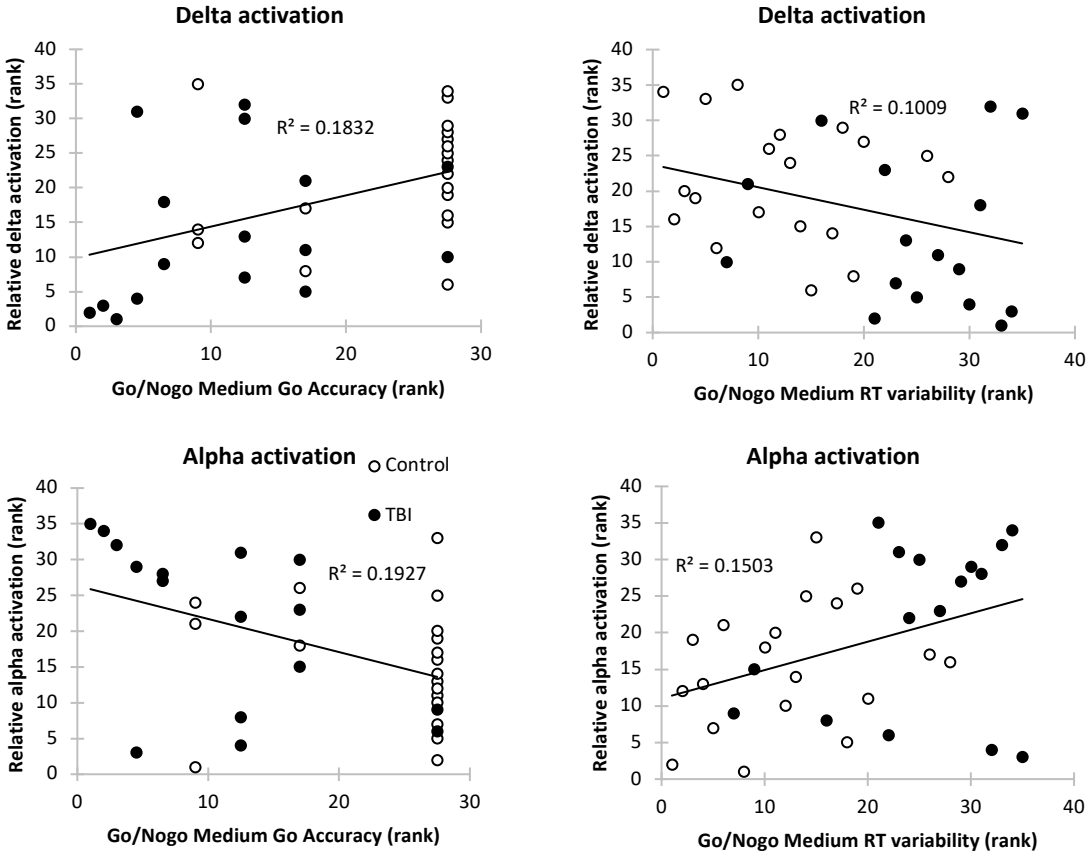


Table 11.

Mean Relative Amplitude (%) for Each Band at Each Event-Rate by Group. SD in Brackets.

	Go/Nogo Slow		Go/Nogo Medium		Go/Nogo Fast		EO	
	Control	**TBI**	**Control**	**TBI**	**Control**	**TBI**	**Control**	**TBI**
Delta								
Left	58.06	51.30	57.64	50.00	59.07	49.98	55.85	52.23
	(5.89)	(5.72)	(5.32)	(5.52)	(6.00)	(6.62)	(5.04)	(9.66)
Medial	54.12	49.97	55.58	49.93	54.69	48.93	53.51	50.83
	(4.79)	(6.28)	(4.05)	(4.76)	(5.08)	(5.62)	(4.68)	(8.14)
Right	58.59	51.41	57.60	50.48	58.99	49.71	55.37	52.20
	(6.17)	(5.88)	(4.05)	(6.12)	(5.05)	(6.11)	(6.53)	(8.49)
Theta								
Left	20.14	19.67	21.25	20.91	20.39	20.89	19.86	19.13
	(1.83)	(3.00)	(2.71)	(2.49)	(2.67)	(2.35)	(2.34)	(2.07)
Medial	21.94	21.24	22.40	21.98	22.27	22.57	21.61	20.58
	(1.83)	(2.85)	(2.56)	(2.52)	(2.96)	(2.54)	(2.04)	(2.03)
Right	19.47	19.51	21.15	20.46	19.91	21.08	19.78	19.04
	(1.86)	(3.03)	(2.56)	(2.75)	(2.45)	(2.56)	(2.50)	(2.18)
Alpha								
Left	14.19	16.63	13.54	16.73	13.05	16.63	15.12	16.92
	(5.57)	(4.46)	(4.55)	(3.94)	(3.80)	(4.04)	(4.52)	(5.96)
Medial	15.98	17.41	14.54	17.07	14.86	17.27	16.18	17.44
	(6.00)	(4.87)	(3.70)	(3.62)	(3.29)	(3.71)	(4.68)	(5.55)
Right	14.01	16.83	13.58	16.81	13.19	16.61	15.49	17.04
	(5.23)	(4.91)	(3.75)	(3.79)	(3.00)	(3.57)	(5.42)	(6.15)
Beta								
Left	7.61	12.40	6.64	12.36	7.48	12.50	9.17	11.72
	(1.67)	(2.64)	(1.91)	(3.16)	(1.71)	(3.69)	(1.95)	(3.60)
Medial	7.96	11.36	7.47	11.02	7.68	11.24	8.71	11.15
	(1.49)	(3.05)	(1.54)	(2.86)	(1.59)	(3.19)	(1.76)	(3.25)
Right	7.93	12.24	7.67	12.24	7.91	12.59	9.36	11.72
	(2.21)	(2.18)	(1.66)	(3.04)	(1.94)	(3.06)	(2.19)	(3.19)

3.4 Discussion

The current study extended on findings from Study 1, which showed: a) TBI-related impairments in delta and theta activation during resting conditions, and b) associations between resting delta, theta, and alpha activation and performance on a Go/Nogo task. Specifically, the current study aimed to investigate impairments in task-related activation in TBI, and associations between these measures and Go/Nogo task performance. It additionally aimed to corroborate the TBI-related performance impairments in top-down or internally-driven state regulation found in Study 1, with task-related activation measured at three event-rates for the Go/Nogo task.

3.4.1 Task-related activation impairments

The present study aimed to investigate the electrophysiological correlates of energetic state across the duration of the Go/Nogo task. According to the CEM, the change in amplitude between EO resting and task conditions reflects the *activation* of energetic state to meet the requirements of the cognitive task, and the present results will be interpreted in terms of energetic state. However, tonic oscillatory activity measured during the task occurred in the context of ongoing sensory, cognitive, and behavioural processes, and so the literature regarding event-related EEG measures will be discussed briefly. These interpretations are tentative, given that event-related EEG was not quantified, analysed, nor hypothesised about in the present study.

As expected, the TBI group showed impaired task-related delta activation. While the control group showed a task-related increase in relative delta, the TBI group showed a task-related reduction. The task-related increase for controls is consistent with the existing literature. Functional interpretations of an increase in task-related delta vary, but generally include a role in the detection of motivationally salient stimuli in the environment (Başar et al., 2001; Knyazev, 2012; Lakatos et al., 2008), inhibitory control (Huster et al., 2013; Kamarajan et al., 2004), and inhibition of interfering cognitive or sensory processing (Harmony, 2013). One clinical study that used comparable methodology to the current study reported reduced delta in a CPT task (cf. to an

EO condition) in children with AD/HD, but not in controls (Nazari et al 2011). The delta reduction in their study was proposed to reflect attention to external distractors that impeded cognitive performance of the prescribed task. This is consistent with evidence of reduced event-related delta during a task involving processing of external stimuli, compared to a task involving internal mental concentration (Harmony et al., 1996). The task-related increase in delta for controls is also consistent with the increase in delta in EO compared to EC in Study 1. Those findings, combined with the current results, suggest incremental amplitude increases in conditions from least activating (EC) to most activating (cognitive task) for controls. This would align with the interpretation of delta reflecting the inhibition of unnecessary neural processes (Harmony, 2013), or of interfering stimuli (Nazari et al., 2011), with little need for inhibition of interference in the EC condition, a slightly higher need due to visual attention in EO, and the greatest need during performance of the cognitive task.

In contrast, the TBI group showed an increase in delta from EC to EO in Study 1, but a reduction in delta in the cognitive task (cf. EO) in the current study. Though the TBI group had a tendency for greater resting delta activation than controls, this was in the context of lower delta amplitude for the TBI group in the resting tasks overall (average of EC and EO), which suggests an over-active/alert resting state (Knyazev, 2012). Taken together the results of Study 1 and 2 suggest that the TBI group exhibited delta over-activation in resting conditions, and delta under-activation in the cognitive task. A comprehensive review has concluded that delta activity originating in frontal brain regions during tasks demanding attention acts to modulate neural networks that are distant from the frontal lobes, in order to inhibit interference from neural processes that are unnecessary to the task at hand (Harmony, 2013). In the current study, the lack of task-related recruitment of frontal delta in the TBI group may reflect a deficiency in long-range neural communication due to DAI, and a subsequent failure to inhibit brain activity that interfered with attention to the task.

Both groups showed a task-related increase in relative theta. The effect of event-rate on theta activation differed between groups, particularly in the hemispheric regions. In the

hemispheres, controls showed an inverted-U pattern, with greater theta activation in the Medium task (compared to Fast and Slow), while the TBI group showed incrementally larger activation as event-rate was increased. Event-related enhancement of FM-theta has been associated with increasing task difficulty or cognitive load (Jensen & Tesche, 2002; Sauseng et al., 2007) and this is in line with the present observation that in the medial region frontal theta activation increased linearly with increasing event-rate for both groups. The event-related FM-theta enhancement is thought to reflect generalised cognitive processes such as sustained attention or concentration (Mitchell et al., 2008), and has been associated with the cognitive control of attention more specifically (Cavanagh & Frank, 2014; Clayton et al., 2015). The group differences observed, particularly in the Fast task, suggests that the TBI group may have found the faster event-rate comparatively more demanding on cognitive or attentional control processes than did the controls. However, the TBI group did not exhibit a relative performance deficit in the Fast task, so increased theta activation may reflect a compensating effect, where greater cognitive or attentional control was employed in order to maintain performance.

The TBI group had reduced resting theta activation (i.e. smaller EC-to-EO increase) in Study 1, but increased task-related theta activation (especially in the Fast task) in the current study, suggesting theta under-activation at rest and over-activation in the cognitive task. Reduced resting theta activation in Study 1 was interpreted to reflect reduced visual attention in the TBI group (Hüfner et al., 2009; Marx et al., 2003; Xu et al., 2014). Taken together, the results of the two studies suggest that with exogenous modulation (i.e. increasing speed of event-rate), the TBI group can up-regulate energetic state (indexed by theta amplitude), but without exogenous modulation (i.e. in the absence of ongoing external stimulation in the EO condition) they cannot. Interestingly, theta was the only frequency band differentially modulated by event-rate. More detailed discussion of event-rate and exogenous modulation of theta is provided below in section 3.4.3.

Though the effect only approached significance, the TBI group showed a tendency toward reduced task-related alpha activation (i.e. a smaller reduction in alpha from EO to Task),

compared to controls. Post-stimulus increases (ERS) in alpha power are thought to reflect the inhibition of task-irrelevant processing (Klimesch, 2012; Klimesch, Sauseng, & Hanslmayr, 2007). However pre-stimulus reductions (ERD) of alpha activity are associated with increased cortical arousal (Bazanova & Vernon, 2014; Klimesch, Sauseng, & Hanslmayr, 2007; Pfurtscheller & Lopes Da Silva, 1999) and improved cognitive performance (Doppelmayr et al., 2005; Klimesch et al., 1997; Roche et al., 2004). The present study quantified the tonic level of alpha amplitude across the task, not the event-related alpha response, however present results are in line with pre-stimulus alpha ERD. That is, compared to EO, the cognitive task induced a desynchronisation of alpha, reflecting increased cortical arousal, that was somewhat diminished in the TBI group. Diminished task-related alpha activation in the TBI group is consistent with a prior report of a smaller alpha suppression in TBI (cf. controls) in an emotion processing task (cf. EC) – also interpreted as deficient regulation of arousal (Fisher et al., 2015). In Study 1 of this thesis, there was no evidence for reduced resting alpha activation for the TBI group, despite a previous report of this effect (Rushby et al., 2013). The focus on fronto-central regions in the current study, and/or the known heterogeneity in the TBI population, may account for differences with this prior study. Therefore, the nature of alpha activation impairment in TBI still needs to be clarified.

The TBI group showed a task-related increase in beta, while controls showed a reduction, suggesting abnormal task-related beta activation in TBI. In Study 1, there was no evidence of abnormal beta activation at rest for the TBI group, although they did have greater beta amplitude than controls overall (average of EC and EO), suggestive of an over- active/alert resting state. Functional interpretations of beta activity during cognitive tasks include a direct role in inhibitory control (Aron, 2011; Huster et al., 2013), or a more global role in maintenance of cognitive and motor set (Engel & Fries, 2010). In line with this interpretation, pathological enhancement of event-related beta activity has been interpreted as a failure to flexibly modify behavioural and cognitive set (Engel & Fries, 2010). Accordingly, increased beta activation in the TBI group in the present study may reflect a greater demand for inhibitory control on Nogo trials due to a more rigid maintenance of motor set (i.e. more automated Go responding; Dockree et al., 2006).

3.4.2 Task-related activation-cognition relationships

Greater task-related delta activation (i.e. task-related increase in amplitude) was associated with better performance on the Go/Nogo task. Specifically, associations were found between increased delta activation and increased Go accuracy and reduced RT at the Slow event-rate, and increased Go accuracy and reduced RT variability in the Medium event-rate task. Conversely, task-related reductions in delta amplitude were associated with poorer Go accuracy and longer and more variable response time. This is consistent with group comparisons revealing a task-related reduction in delta for the TBI group, compared to controls who showed a task-related increase. This suggests that impaired delta activation in TBI (i.e. a task-related reduction in delta amplitude cf. a task-related increase for controls) is associated with poorer RI task performance.

The present findings contradict the results of Karamacoska et al. (2018) who reported that increased task-related delta activation in a Go/Nogo task predicted reduced Go accuracy and increased RT variability in controls. However, their study used the mean of amplitudes in EO and EC conditions to operationalise a resting baseline, and pre-stimulus delta to operationalise task-related activation, which may explain the different results in the current study. Findings of the current study do align with the broader event-related delta literature. Increased delta in frontal regions has been associated with a broad range of cognitive processes, and as such is thought to play a role in the allocation of attention and inhibition of interfering cognitive or sensory processing (Harmony, 2013). Supporting this, delta activity has been shown to contribute to the P300 event-related potential component, which occurs in response to infrequent, unexpected, or salient stimuli (Knyazev, 2007, 2012). Notably, delta activation in the current study was associated with Go accuracy and RTs, but not Nogo accuracy, and this supports evidence for a role of delta activation in more general cognitive processing and attention, rather than in inhibitory control per se. This more generalised role aligns with evidence that pre-stimulus delta contributes to both endogenous and exogenous ERP components and that this contribution does not differ between Go and Nogo stimuli (De Blasio & Barry, 2013b). It is also in line with functional

interpretations of delta activity as reflecting the inhibition of interfering cognitive or sensory processing (Harmony, 2013) in order to detect motivationally salient stimuli (Knyazev, 2012).

Enhanced task-related alpha activation (i.e. a larger reduction in alpha) was associated with better performance (i.e. higher Go accuracy, shorter RTs in the Slow task, and higher Go accuracy and less variable RTs in the Medium task). This was expected given that task-related alpha suppression has been associated with improved performance on RI (Karamacoska et al., 2018; Loo et al., 2009; Roche et al., 2004), vigilance (Valentino et al., 1993), and memory tasks (Backer et al., 2015; Klimesch, 1999). Similar to the delta relationships, alpha activation was associated with Go performance measures (Go accuracy, RT, and RT variability) and not with Nogo performance, also suggesting a cognitive role that is non-specific to RI. This is in line with cortical arousal/activation interpretations of task-related alpha, such that up-regulation of cortical arousal (i.e. activation) improves cognitive processes (Bazanova & Vernon, 2014; Klimesch, Sauseng, & Hanslmayr, 2007; Loo et al., 2009; Pfurtscheller & Lopes Da Silva, 1999). Alternatively, the relationship between alpha and Go processes, might reflect the role of alpha ERD in selective attention (Foxe & Snyder, 2011; Weisz et al., 2011), anticipatory attention (Klimesch, 2012), or attentional control (Mathewson et al., 2009; Roche et al., 2004) during the task. Attention-related and arousal-related alpha have been proposed to reflect different functional mechanisms and have different neural generators; cortico-cortical (frontal and parietal) and thalamo-cortical for attention-related, and the thalamic for arousal-related alpha (Foxe & Snyder, 2011). The present findings are more in line with arousal-related alpha given its association with the tonic (compared to event-related) alpha measure used here. However, since event-related measures were not quantified, and topographical analyses were limited, the relative contributions of attention vs. arousal-related alpha to the recording cannot be determined here. Attenuated task-related alpha activation (i.e. a smaller task-related reduction in alpha amplitude) for the TBI group (cf. to controls) did not reach significance in the current study, and the activation- performance relationships did not differ by group, so there is not strong evidence to suggest that the relationship between alpha activation and performance is impaired in TBI.

Though the TBI group showed impaired theta and beta activation, these measures did not correlate with performance. The lack of relationship for theta is surprising, given its association with general mechanisms of cognition such as attention (Başar et al., 2001; Klimesch, 1999; Mitchell et al., 2008), and it's modulation by group and by event-rate in the present study. Likewise, beta has been previously associated with motor responding (Engel & Fries, 2010) and inhibitory control (Aron, 2011; Güntekin et al., 2013; Huster et al., 2013). Importantly though, the vast majority of research into EEG and cognition relationships has focused on the on-task, pre-stimulus activity, rather than activation measures, and so is not directly comparable to the current study.

3.4.3 Event-rate and state regulation

The effect of the Fast event-rate on hemispheric theta activation in the TBI group aligns with the interpretation of a compensatory effect of exogenous (bottom-up) state regulation outlined in Study 1. In Study 1 it was suggested that an attenuated RT variability deficit for the TBI group (cf. controls) in the Fast condition (cf. Medium) might reflect impaired top-down regulation of energetic state in the Medium condition, and a potential compensatory effect of exogenous (bottom-up) regulation on task performance in the Fast condition. That is, for the TBI group the Fast event-rate presented external task demands that were sufficiently activating to enhance consistency of performance. In the present study, hemispheric theta activation mirrored this effect, i.e. it was enhanced in the TBI group at the Fast event-rate. Taken together this suggests that increased exogenous stimulation of the Fast task was sufficient to sustain RT variability in the TBI group, through the modulation of theta activation. According to the CEM, this modulation involves the evaluation mechanism, which monitors performance and exerts top-down control of energetic state through the effort pool (Sanders, 1983).

Supporting this interpretation are links between top-down attentional control and both RT variability and FM-theta activity. Reduced RT variability has been shown to index top-down attentional control generally (Bellgrove et al., 2004; Ramchurn et al., 2014) and in TBI (Stuss et

al., 1989, 2003; Vasquez et al., 2018). FM-theta activity has been linked specifically with the monitoring and control of sustained attention (Clayton et al., 2015), with increasing FM-theta activity associated with increasing need for cognitive control (Cavanagh & Frank, 2014; Clayton et al., 2015) and with brain regions associated with cognitive control, particularly the dorsomedial prefrontal cortex (DLPFC; Oehrn et al., 2014) and the anterior cingulate cortex (ACC; Raghavachari et al., 2001; Sauseng et al., 2007; Wang et al., 2005). Note though that these associations are observed for theta in frontal midline areas, whereas the present results are enhanced in the frontal hemispheric regions, suggesting a more diffuse frontal theta in the Fast task for the TBI group. Evidence that exogenous stimulation can activate attentional control mechanisms comes from studies showing normalised performance and neural networks in TBI when an exogenous cue is added to attention and EF tasks (Fish et al., 2007; Manly et al., 2004; Richard et al., 2018). Notably though, in the present study, the tendency for the TBI group to show a reduced RT variability decrement (cf. controls) in the Fast (cf. Medium) task, was approaching significance only. This may be due to a lack of statistical power in this relatively smaller sample.

The sensitivity of hemispheric theta activation to the event-rate manipulation was also supported by its quadratic pattern in controls (largest theta activation in the Medium event-rate cf. Slow/Fast). Performance measures however, did not show the expected quadratic pattern. The Slow and Medium event-rates were likely affected by ceiling effects for accuracy, especially in controls, and therefore differences in activation between Slow and Medium tasks may not have been induced as the tasks were not distinct enough in terms of cognitive demands. The ISI for the Slow condition (4 seconds) in the present study was slightly faster than the reported event-rates in a meta-analysis in AD/HD (ranging 4.25 – 8.30 seconds; Metin et al., 2012). Thus, the lack of quadratic trend and the lack of group differences may reflect that this task was not slow enough to induce hypo-arousal. As a result, conclusions about bottom-up and top-down regulation must be cautious, and future research should aim to optimise the event-rate manipulation to adequately address this question.

3.4.4 Limitations and future directions

Functional interpretations of EEG bands from the literature have been based almost exclusively on studies investigating on-task or pre-stimulus EEG – not activation as it has been operationalised here. These probably reflect distinct phenomena. The investigation of activation measures in RI tasks is novel, and thus requires replication, especially in regard to patterns in healthy controls.

As mentioned in Study 1, due to unforeseen technical issues EEG data was analysed from fronto-central regions only. This is justified in the current study since it is predominantly the pre-frontal regions (Ridderinkhof et al., 2004) that have been implicated in RI processes, and the fronto-temporal regions are most vulnerable to damage in TBI (Rieger & Gauggel, 2002). However, effective cognitive performance depends on neuronal networks that span throughout the brain, including frontal-parietal cortical connections involved in attention (Petersen & Posner, 2012), and prefrontal and subcortical thalamic connections in inhibitory control (Rubia et al., 2001). Given that the current sample had varied sites of focal damage, and that TBI also leads to DAI that damages these distributed networks (Felmingham et al., 2004), future research should aim to clarify the topography of TBI-related impairments in activation more broadly.

The groups showed some dissociation of the task-related amplitude changes (e.g. the TBI group showed a task-related reduction in delta amplitude, while controls showed a task-related increase). Correlations between EEG activation and cognitive performance were interpreted in light of these dissociable group effects. However, Spearman's correlations transform EEG activation data to ranked values. Though the directions of amplitude changes are still interpretable (i.e. lower ranks = increasingly negative changes, higher ranks = increasingly positive), the ranked data scatterplots do not explicitly visualise individual differences in the direction of task-related EEG amplitude changes and their associations with performance. Given the dissociation of activation effects between the groups observed here, along with the known heterogeneity within TBI groups, this would be an interesting avenue for future research. Another limitation is the

significant age difference between the groups. This was addressed statistically with the addition of age as a covariate in the group comparison analyses. However, the use of covariance analysis has been shown to be statistically limited when there is a pre-existing group difference (Adams et al., 1985; Miller & Chapman, 2001). Therefore, the results of the current study require replication in age-matched samples to separate TBI- and age-related effects.

Laboratory-based cognitive measures do not necessarily correlate with measures of everyday functioning in TBI (Chaytor & Schmitter-Edgecombe, 2003; Donovan et al., 2011; Sbordone, 2001). It is possible that TBI-related impairments were attenuated in the current study as certain factors (e.g. instructions from the experimenter, structured nature of the task, and absence of distractions) might impact effort and energetic state in the laboratory setting. For these results to be meaningful for individuals with TBI, and to guide rehabilitation, it is imperative to investigate whether the observed state regulation impairments relate to their functioning in everyday life.

3.4.5 Conclusion

The aim of the current study was to investigate impairments in task-related activation in TBI, and to identify associations between task-related activation and Go/Nogo task performance. Compared to controls, the TBI group showed significant abnormalities in activation in the delta, theta, and beta bands, and a trend toward abnormal alpha activation. Controls showed a task-related increase in delta and reduction in beta, while conversely, the TBI group showed a task-related reduction in delta and increase in beta amplitudes. Both groups showed a task-related increase in theta amplitudes, however this effect was larger in the TBI group, particularly in the hemispheric regions, and particularly in the Fast task. Enhanced delta activation (a greater task-related increase) and alpha activation (a greater task-related reduction) were associated with enhanced Go responses in the Go/Nogo task, suggesting a role in attention rather than inhibitory processes per se.

The TBI-related enhancement of frontal hemispheric theta activation, specific to the Fast event-rate task, suggests a potential compensatory effect of exogenous (bottom-up) regulation of energetic state in the more stimulating Fast condition, and may reflect enhanced attentional control. However, the trend for event-rate to modulate RT variability differentially in TBI was approaching significance only, and so the role of top-down vs. bottom-up state regulation in TBI-related cognitive deficits remains to be clarified. Broadly, the current study demonstrates that abnormalities in regulation of energetic state in response to cognitive task demands in TBI are associated with impaired cognitive performance. These findings have implications for cognitive rehabilitation in TBI, suggesting that targeting the task-related regulation of energetic state may be of benefit to improving cognitive function following TBI.

CHAPTER 4:

Study 3: The role of arousal and activation in everyday executive function following TBI.

4.1 Introduction

According to the Cognitive Energetic Model (CEM), abnormalities in energetic state underlie impairments in cognitive performance. In Studies 1 and 2, the TBI group showed abnormalities in resting and task-related activation compared to controls. Furthermore, activation measures were associated with performance on a response inhibition (RI) task. The lack of group differences in arousal in these studies suggested that TBI has specific effects on the ability to modulate or activate energetic state in response to visual or cognitive processing demands, rather than baseline energetic state. Overall, these results suggest a role for energetic state abnormalities in cognitive impairment after TBI, and provide a theoretical underpinning for incorporating state regulation interventions into cognitive rehabilitation for this population.

Studies 1 and 2 measured executive function (EF) through a computerised, auditory Go/Nogo task. However, the impact of executive dysfunction after TBI is pervasive and ubiquitous in patients' everyday lives, extending far beyond poor performance on laboratory tasks. Patients complain of social and verbal disinhibition, emotion dysregulation, impulsivity, poor planning and decision making (Rochat et al., 2013; Schiehser et al., 2011). These issues negatively impact quality of life, occupational outcomes, and relationships (Tate, 1999; Vilkki et al., 1994; Wood & Rutterford, 2006). Consequently, the goal of EF rehabilitation for patients is not improvement on neuropsychological tests or computerised cognitive tasks, but rather the ability to function better in everyday life.

Neuropsychological and laboratory-based measures of EF have been criticised for

lacking ecological validity as they demonstrate only modest correlations with everyday functioning (Chaytor & Schmitter-Edgecombe, 2003; Gioia & Isquith, 2004; Sbordone, 2008). Inconsistent or absent correlations between EF tests and everyday functioning have been demonstrated in children (Anderson et al., 2002; Mangeot et al., 2002), older adults (Rabin et al., 2006), neurological disorders (Burgess et al., 1998; Chaytor et al., 2006), and brain injury patients (Schiehser et al., 2011; Wood & Liossi, 2006; Wood & Rutterford, 2004). Self-report scales of everyday EF behaviours have demonstrated better power in predicting functional and occupational outcomes than neuropsychological assessments (Barkley & Fischer, 2011). By testing the component processes of EF in a highly structured and artificial environment, traditional neuropsychological tests may neglect the complexity and multiplicity of processes involved in effective EF in daily life, as well as other motivational, emotional, and environmental demand characteristics that interact to result in behaviour (Barkley & Fischer, 2011; Chaytor et al., 2006; Sbordone, 2008).

Therefore, to understand the meaning of state regulation impairments for individuals with TBI, it is important to clarify the role of deficient energetic state regulation beyond its impact on the computerised Go/Nogo task used in Studies 1 and 2. The current study aims to examine whether the activation measures associated with task performance in Studies 1 and 2 also impact everyday EF behaviours and trait impulsivity as measured by the Behaviour Rating Inventory of Executive Function – Adult (BRIEF-A) and the Barratt Impulsiveness Scale (BIS-11), respectively. The BRIEF-A is a self-report measure of everyday behaviours related to components of EF, such as the ability to inhibit actions and emotions, self-monitor behaviour, and plan and organise tasks. In TBI, BRIEF-A scores are elevated (Finnanger et al., 2015; Lovstad et al., 2012) and correlated with ratings of competence in daily life (García-Molina et al., 2012). The BIS-11 measures three components of impulsivity (motor, attentional, and non-planning) and individuals with TBI have shown elevated scores compared to controls in each domain (Travis Seidl et al., 2015). Furthermore, elevated BIS-11 scores have been associated with problematic alcohol use (Travis Seidl et al., 2015), aggression (Greve et al., 2001, 2002), and poor decision making (McHugh & Wood, 2008) in TBI groups.

Degree of injury severity has been associated with the degree of EEG abnormalities in previous studies of TBI (Thatcher, Biver, et al., 2001; Thatcher, Biver, McAlaster, & Salazar, 1998; Thatcher, Biver, McAlaster, Camacho, et al., 1998; Thatcher, North, et al., 2001), however these relationships are yet to be investigated in terms of arousal and activation measures. Therefore, a secondary aim of the present study is to investigate the relationship between arousal and activation and injury characteristics, namely severity and chronicity.

It is expected that the TBI group will demonstrate deficits on measures of everyday EF compared to healthy controls. In Studies 1 and 2 impaired performance on a computerised RI task was associated with increased resting delta and reduced resting theta activation, as well as reduced task-related delta and increased task-related alpha and beta activation. In the current study, it is expected that these same activation measures will be correlated with everyday EF scores. The relationships between injury severity and chronicity and energetic state measures will also be explored.

4.2 Method

4.2.1 Participants

Participants in this study had participated in Study 2. See section 2.2.1 for description of participants.

To account for the potential impact of mental health symptoms on EEG, cognitive, and behavioural measures, participants completed the Depression, Anxiety, and Stress scale (DASS-21; Lovibond & Lovibond, 1995). The DASS-21 is a self-report measure of the frequency of symptoms of depression, anxiety, and stress over the past week. As there were no significant differences between the groups on DASS-21 scores (M_{Dep} = 4.16, SD = 4.23; M_{Anx} = 4.05, SD = 4.50; M_{Str} = 7.29, SD = 5.00) these scores were not considered in subsequent analyses.

4.2.2 Measures

4.2.2.1 EEG conditions

See sub-sections 2.2.2.1 and 2.2.2.2 for descriptions of EEG conditions used to measure arousal (EC), resting activation (EC and EO), and task-related activation (EO and the Go/Nogo Medium event-rate task) in the present study.

4.2.2.2 Behaviour Rating Scale of Executive Function – Adult Version

The BRIEF-A (Roth et al., 2005) is a standardised questionnaire consisting of 75 items measuring aspects of EF in everyday life over the past 4 weeks. These items make up nine clinical scales: Inhibit, Self-Monitor, Plan/Organise, Shift, Initiate, Task Monitor, Emotional Control, Working Memory, and Organisation of Materials. From these scales three summary indices are derived. The Behavioural Regulation Index (BRI) reflects an individual's ability to maintain appropriate control of their behaviour and emotional responses. The Metacognition Index (MI) reflects the ability to initiate activity, sustain working memory, organise one's external environment, and plan, organise and monitor problem solving. The Global Executive Composite (GEC) is a summary score that combines all of the clinical scales and reflects overall functioning. T-scores are derived by comparison of raw scares to an age equivalent normative sample, with higher T-scores indicating higher frequency of dysfunctional behaviours. The BRIEF-A includes a self-report questionnaire and an equivalent informant-report questionnaire. The self-report questionnaire was used in the current study. It required approximately 10 minutes to complete.

4.2.2.3 Barratt Impulsiveness Scale - 11

The BIS-11 (Patton, Stanford, & Barratt, 1995; Stanford et al., 2009) is a 30 item self-report questionnaire that measures the personality/behavioural construct of impulsiveness. Sub-scales include six first-order factors (Attention, Cognitive Instability, Motor, Perseverance, Self-

control, and Cognitive Complexity), three second-order factors (Attention, Motor, Non-planning), and a Total score. The Attention factor measures the inability to focus attention or concentrate; the Motor factor measures tendency to act without thinking; and the Non-planning factor measures a lack of "futuring" or forethought. The questionnaire required less than 10 minutes to complete.

4.2.3 Procedure

See section 2.2.3 for description of the testing procedure.

4.2.4 Electrophysiological recording and data extraction

See sections 2.2.4 and 2.2.5 for description of electrophysiological recording and data extraction methods for the resting conditions. See section 3.2.3 for the Go/Nogo condition. **Table 12** summarises the mean number of epochs of EEG data that were accepted following automatic and manual artifact removal for each group and condition.

Table 12

Mean Number of Accepted Epochs. SD in Brackets.

	EC	EO	Go/Nogo Medium
Control	48.35 *(8.75)*	37.90 *(11.67)*	63.83 *(36.94)*
TBI	53.05 *(7.92)*	46.68 *(10.86)*	117.19 *(27.97)*
Mean	50.64 *(8.58)*	42.18 *(11.99)*	88.94 *(42.30)*

4.2.5 Statistical analyses

To address significant group differences in age, Pearson's two tailed bivariate correlations tested the relationship between age and EEG variables. There were significant relationships between age and EC right relative theta and beta, EO right relative theta and beta, and EO frontal relative beta. Therefore, Age was included as a covariate for analyses involving

theta and beta. Group differences in BRIEF-A subscale and composite scores and BIS-11 second-order subscale and total scores were analysed with separate one-way ANOVAs for each score.

A measure of *arousal* was derived by taking the mean Frontal alpha amplitude in EC condition. *Resting activation* was derived by subtracting EC amplitude from EO amplitude for each band and region, so that a negative score indicates an amplitude reduction in the EO condition compared to EC. *Task-related activation* was derived by subtracting Task amplitude from EO amplitude for each band and region so that a negative score indicates an amplitude reduction in the Task condition compared to EO. A measure of injury severity was derived by calculating number of days in PTA. A measure of injury chronicity was derived by calculating the time (in months) since injury.

The relationships between EEG measures (arousal, resting activation, and task-related activation) and everyday EF measures (BRIEF-A subscale and composite scores, and BIS-11 second-order subscale and total scores) were tested using Spearman's rank order correlation (Spearman's Rho) for the whole sample. Relationships between EEG and injury measures (PTA, time-since-injury) were tested in the same way within the TBI group only. The non-parametric procedure was chosen as visual inspection of the scatterplots identified some multivariate outliers, which were confirmed using Mahalanobis Distance analyses (Tabachnick & Fidell, 2013). Spearman's correlation is robust against the influence of extreme values (Field, 2009). Spearman's partial correlations controlling for age were conducted for analyses involving theta and beta variables (given the observed associations in this study) and analyses involving time-since-injury (given the logical association with age).

Significant correlations found for the whole sample were examined for between group differences using the Fisher r-to-z transformation. A positive z-score denotes a correlation coefficient that was larger for the Control group compared to the TBI group, and a negative score denotes a larger coefficient for the TBI group.

4.3 Results

4.3.1 Group differences

Table 13. and Table 14. show descriptive statistics and results of analyses for group comparisons of the BRIEF-A and BIS-11 measures, respectively. **Table 13.** also displays the number of participants in each group that had a BRIEF-A T-score in the clinical range (i.e. T-score ≥ 65) for each scale and summary score.

BRIEF-A. T-scores were significantly higher in the TBI group compared to controls for all subscales except for the Emotional Control, Plan/Organise and Organisation of Materials subscales. The TBI group also scored significantly higher on both the Behaviour Regulation and Metacognition Indices, and on the Global Executive Composite score.

BIS-11: The TBI group had significantly higher scores than controls on the Motor subscale and Total score of the BIS-11. A trend for the TBI group to score higher on the Non-Planning subscale was approaching significance, and there was no significant difference between groups for the Attentional subscale.

Table 13.
Descriptive Statistics and Results of ANOVA for BRIEF-A T-Scores.

	Control *M (SD)*	TBI *M (SD)*	Control clinical	TBI clinical	*F*	*p*	η_p^2
Inhibit	51.81 (11.29)	58.26 (12.48)	5	8	4.33	.042*	0.07
Shift	52.94 (10.02)	61.00 (15.32)	5	11	5.93	.018*	0.09
Emotional control	53.91 (13.09)	59.35 (11.66)	6	8	2.76	.102	0.05
Self-monitor	48.79 (10.24)	56.23 (12.90)	1	5	6.11	.016*	0.10
Behavior Regulation Index	52.82 (10.64)	61.08 (12.81)	5	10	7.32	.009**	0.11
Initiate	51.85 (10.42)	59.04 (14.50)	4	7	4.91	.031*	0.08
Working memory	58.45 (10.42)	59.04 (14.50)	11	16	16.28	< .001**	0.22
Plan/Organise	53.85 (10.98)	61.08 (14.88)	4	9	2.42	.125	0.04
Task monitor	53.70 (9.32)	61.08 (14.88)	7	11	4.61	.036*	0.08
Organisation of materials	50.61 (8.74)	53.42 (13.69)	3	8	0.92	.341	0.02
Metacognition Index	54.70 (10.24)	62.54 (16.72)	6	9	4.93	.030*	0.08
Global Executive Composite	53.85 (9.11)	62.62 (15.35)	3	9	7.46	.008**	0.12

Note: Clinical scores = number of participants with T-scores over the clinical cut-off (≥ 65), ** $p < .01$, * $p < .05$. $df = (1, 52)$

Table 14.

Descriptive Statistics and Results of ANOVA for BIS-11 Scores.

	Control	TBI	*F*	*p*	η_p^2
	M (SD)	*M (SD)*			
Attentional	16.42 (4.80)	17.60 (5.98)	0.62	.434	0.01
Motor	21.55 (3.99)	24.70 (5.20)	6.18	.016*	0.11
Nonplanning	22.55 (4.09)	25.30 (7.00)	3.29	.076	0.06
Total	60.52 (9.61)	67.60 (14.78)	4.49	.039*	0.08

Note: ** $p < .01$, * $p < .05$. $df = (1, 52)$

4.3.2 Correlations between arousal/activation and everyday EF

4.3.2.1 Arousal relationships

Table 15 and **Table 16** show the correlation coefficients for relationships between arousal and BRIEF-A and BIS-11 scores. Where correlations were significant for the overall sample, the group difference in coefficients was tested using the Fisher r-to-z transformation (z-scores are shown in brackets in the tables). Correlation coefficients for each group are displayed in Appendix C (**Tables S3. and S4.**). Scatterplots for significant correlations are presented in **Figure 24**.

BRIEF-A: There was a positive relationship between EC frontal alpha and the Self-monitor subscale, such that the greater alpha amplitude in EC was associated with a higher T-score (higher frequency of dysfunctional behaviours). Though the correlation was larger in controls compared to the TBI group, this difference did not differ significantly. There were no other significant relationships.

BIS-11: There were positive relationships between EC frontal alpha and the Motor

subscale and Total BIS-11 score, such that greater alpha amplitudes were associated with higher Motor and Total scores (i.e. higher frequency of impulsive behaviours). These correlations were larger in controls compared to the TBI group but the differences did not reach statistical significance.

Table 15.

Correlation Coefficients (r) for Relationships between Resting Arousal and BRIEF-A Subscale T-Scores for the Whole Sample. Z Scores Derived from Fisher r-to-z in Brackets.

		BRIEF-A subscale											
Task/ band	**Region**	**Inhibit**	**Shift**	**Emotional control**	**Self-monitor**	**BRI**	**Initiate**	**Working memory**	**Plan/ Organise**	**Task monitor**	**Organise materials**	**MI**	**GEC**
EC/ alpha	**Frontal**	.162	.098	.023	.277* (0.96)	.112	.074	.105	-.016	.072	-.007	.060	.062

Note: EC = eyes-closed, BRI = Behaviour Regulation Index, MI = Metacognition Index, GEC = Global Executive Composite, * $p < .05$. $df = 52$

Table 16.

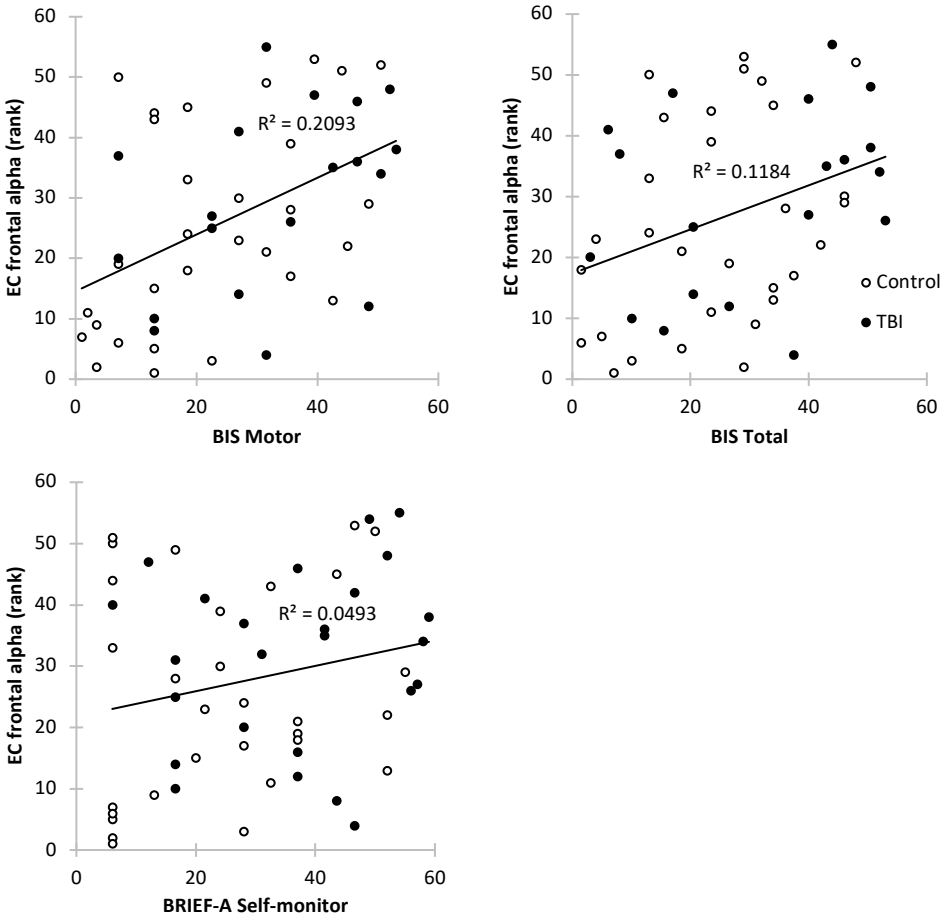
Correlation Coefficients (r) for Relationships between Resting Arousal and BIS-11 Subscale Scores for the Whole Sample. Z Scores Derived from Fisher r-to-z Analysis in Brackets.

		BIS-11 subscale			
Task/band	**Region**	**Attentional**	**Motor**	**Nonplanning**	**Total**
EC/alpha	**Frontal**	.119	.523** (0.82)	.231	.347* (0.31)

Note: EC = eyes-closed, ** $p < .01$, * $p < .05$. $df = 46$

Figure 24.

Relationships between Arousal and BRIEF and BIS-11 Scores



4.3.2.2 Resting activation relationships

Table 17 and **Table 18** show the correlation coefficients for relationships between resting activation measures and BRIEF-A and BIS-11 scores. Where correlations were significant for the overall sample, the group difference in coefficients was tested using the Fisher r-to-z transformation (z-scores are shown in brackets in the tables). Correlation coefficients for each group are displayed in Appendix C (**Tables S5. and S6.**). Significant correlations are presented in **Figure 25** through to **Figure 27**.

BRIEF-A:

Delta: Frontal delta activation did not show any significant relationships with BRIEF-A scores.

Theta: Frontal theta showed significant inverse relationships with the Inhibit, Emotional Control, and Initiate subscales, the Behaviour Regulation Index, and the Global Executive Composite. As shown in **Figure 25.**, larger EC-to-EO increases in theta were associated with lower T-scores (i.e. lower frequency of dysfunctional behaviours) on these scales. The correlation coefficients were larger in the TBI group compared to controls, however the differences were not statistically significant.

Alpha: There were no significant relationships between alpha activation and BRIEF-A scores.

Beta: Frontal beta activation showed significant positive relationships with the Inhibit and Emotional Control subscales, and the Behaviour Regulation Index. As shown in **Figure 26.** greater EC-to-EO increases in beta were associated with higher T-scores (i.e. higher frequency of dysfunctional behaviours) on these scales. The correlation coefficients were larger in the TBI group compared to controls, however the differences were not statistically significant.

BIS-11:

Delta: There was a significant positive relationship between frontal delta activation and the Motor subscale. A larger EC-to-EO delta increase was correlated with higher frequency of impulsive behaviour on this scale (see **Figure 27.**). This relationship was stronger in the TBI group, compared to controls, but the difference was not significant.

Theta: There were significant inverse relationships between frontal theta activation and the Attention and Non-Planning subscales, as well as the BIS-11 Total score. This suggests that larger EC-to-EO increases in theta were associated with lower frequency of impulsive behaviours

on these scales (see **Figure 27.**). Though the correlations were stronger in the TBI group compared to controls, the differences were not significant.

Alpha: There was a significant inverse relationship between frontal alpha activation and the Motor subscale. Larger EC-to-EO reductions in alpha activation were associated with higher frequency of impulsive behaviours on this scale (see **Figure 27.**). This correlation was larger in controls compared to TBI group, but the difference did not reach significance.

Beta: There was a significant positive relationship between frontal beta activation and Attention subscale. Larger EC-to-EO beta increases were associated with higher frequency of impulsive behaviours on this scale (see **Figure 27.**). This correlation was larger in the TBI group compared to controls, but this difference was not significant.

Table 17.

Correlation Coefficients (r) for Relationships between Resting Activation and BRIEF-A Subscale T Scores for the Whole Sample. Z Scores Derived from Fisher r-to-z in Brackets.

		BRIEF-A subscale											
Task/ band	**Region**	**Inhibit**	**Shift**	**Emotional control**	**Self-monitor**	**BRI**	**Initiate**	**Working memory**	**Plan/ Organise**	**Task monitor**	**Organise materials**	**MI**	**GEC**
Delta	**Frontal**	.076	.072	-.059	.223	.034	.040	.090	-.072	.032	.077	.055	.024
Theta	**Frontal**	-.367** (1.82)	-.240	-.337* (0.34)	-.231	-.366** (1.22)	-.303* (1.50)	-.161	-.142	-.142	-.068	-.197	-.285* (0.66)
Alpha	**Frontal**	-.108	-.051	.076	-.224	-.026	-.028	-.073	.096	-.035	-.097	-.038	-.005
Beta	**Frontal**	.372** (-0.75)	.148	.398** (-0.54)	.359	.359** (-0.02)	.145	.069	.052	.079	.002	.059	.190

Note: BRI = Behaviour Regulation Index, MI = Metacognition Index, GEC = Global Executive Composite, ** $p < .01$, * $p < .05$. *df* (delta, alpha) = 50, *df* (theta, beta) = 49

Table 18.

Correlation Coefficients (r) for Relationships between Resting Activation and BIS-11 Subscale Scores for the Whole Sample. Z Scores Derived from Fisher r-to-z in Brackets.

		BIS-11 subscale			
Band	**Region**	**Attentional**	**Motor**	**Non-planning**	**Total**
Delta	**Frontal**	-.025	.303* (-0.26)	.244	.188
Theta	**Frontal**	-.403** (1.64)	-.246	-.380* (0.45)	-.392** (1.35)
Alpha	**Frontal**	.045	-.355* (-0.37)	-.173	-.175
Beta	**Frontal**	.342* (-0.92)	.253	.027	.261

Note: ** $p < .01$, * $p < .05$. *df* (delta, alpha) = 44, *df* (theta, beta) = 43

Figure 25.

Relationships between Resting Theta Activation and BRIEF-A T-Scores

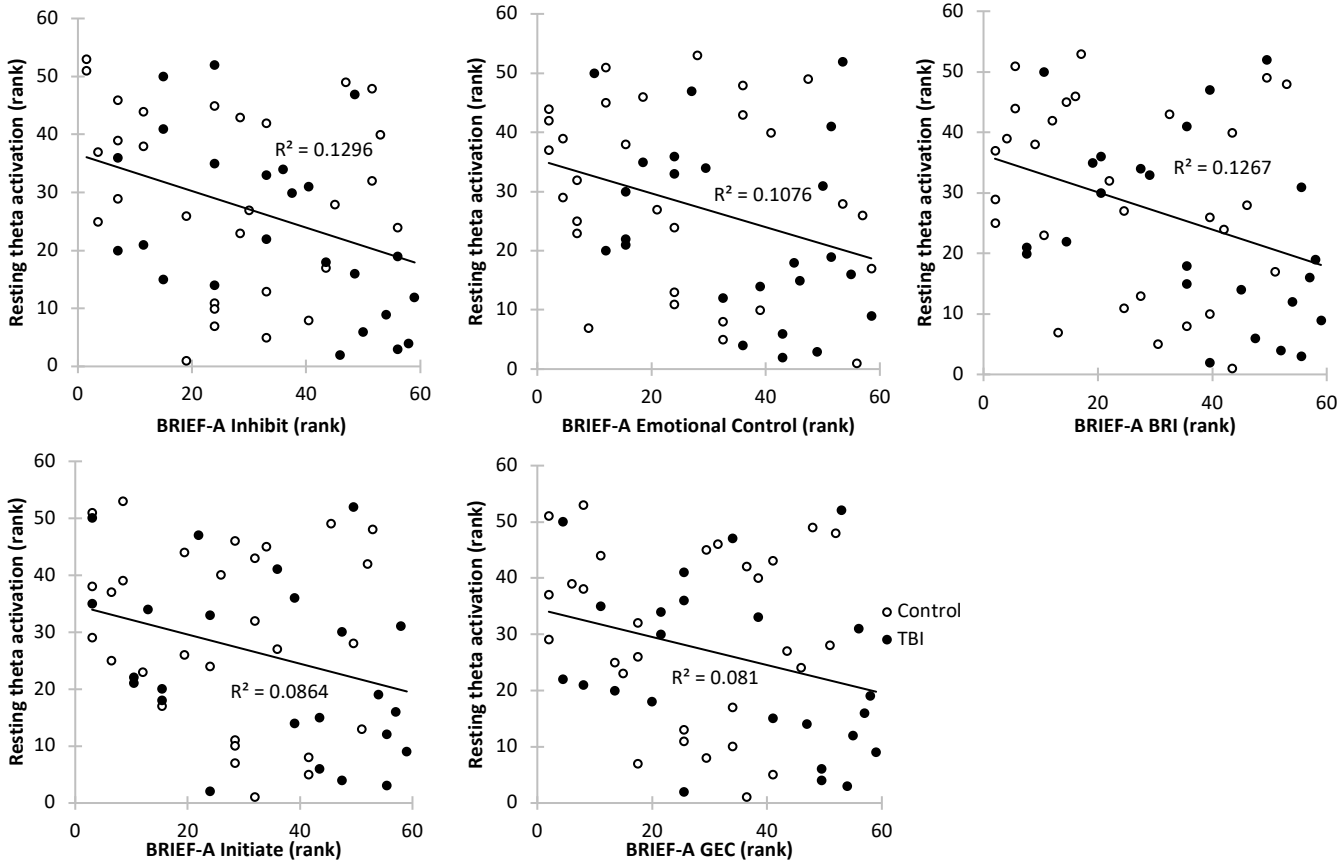


Figure 26.

Relationships between Resting Beta Activation and BRIEF-A T-Scores

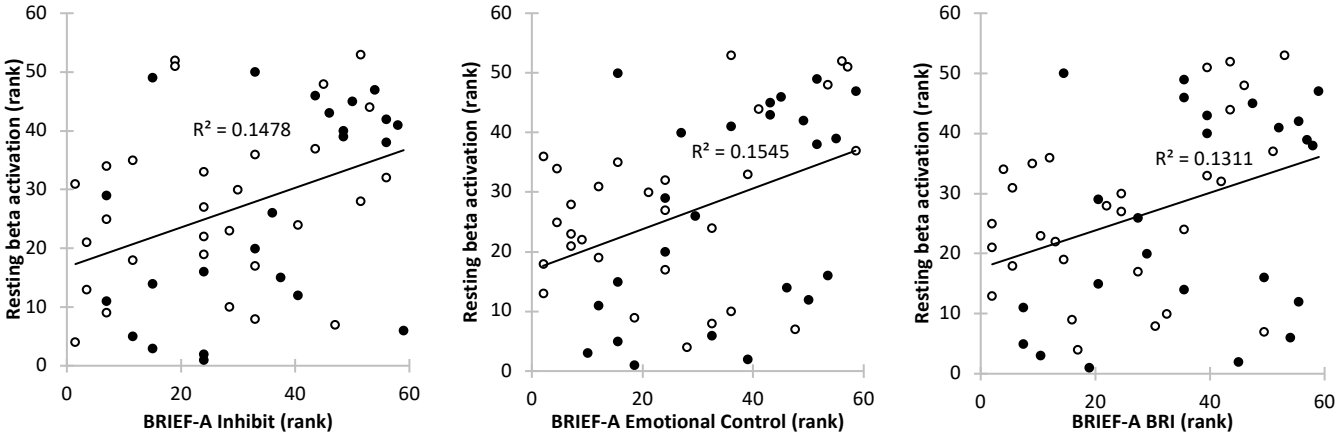
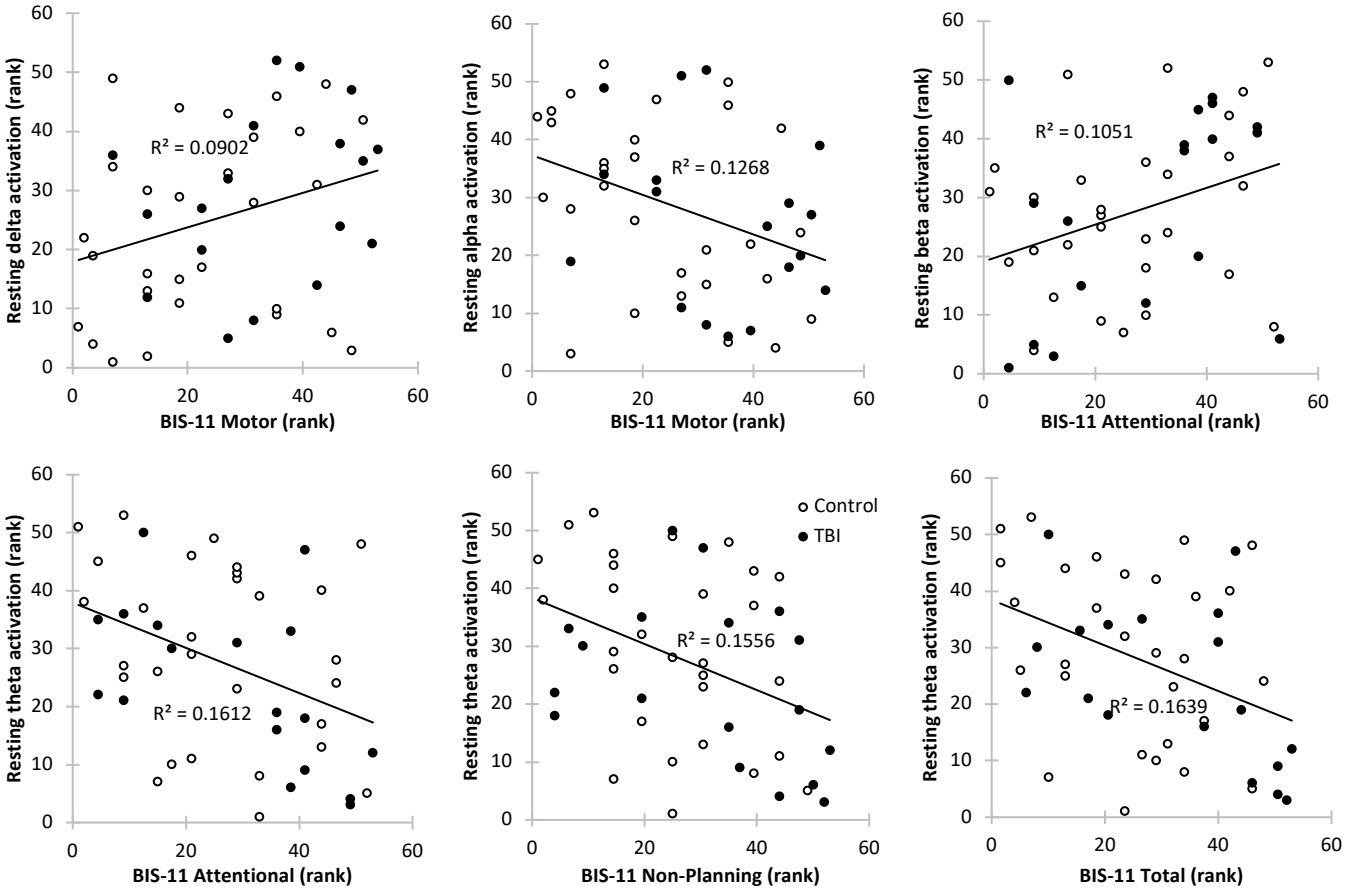


Figure 27.

Relationships between Resting Activation and BIS-11 Scores



4.3.2.3 Task-related activation relationships

There were no significant relationships between task-related activation measures and BRIEF-A or BIS-11 scores.

4.3.3 Correlations between arousal/activation and injury severity and chronicity

Table 19 shows the correlation coefficients for relationships between EEG arousal, resting activation, and task-related activation variables and injury severity and chronicity for the TBI group.

4.3.3.1 Arousal relationships

There were no significant relationships between arousal (EC alpha) and PTA or time-since-injury.

4.3.3.2 Resting activation relationships

There was a positive relationship between frontal theta activation and PTA, and an inverse relationship between frontal beta activation and PTA. See **Figure 28** for scatterplots of these relationships. There were no significant relationships between resting activation measures and time-since-injury.

4.3.3.3 Task-related activation relationships

There was a positive relationship between frontal beta activation and PTA and time-since-injury (see **Figure 28**). There were no relationships between task-related activation and PTA or time-since-injury for the other EEG bands.

Table 19.

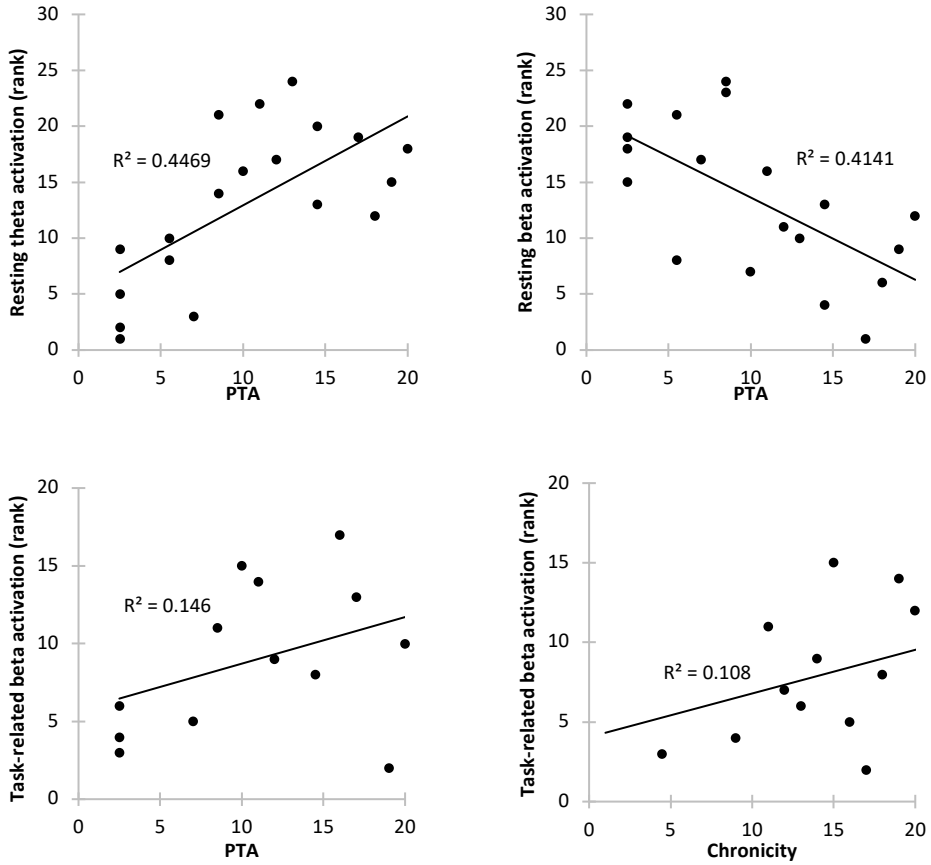
Correlation Coefficients (r) for Relationships between EEG Arousal and Activation and Injury Severity and Chronicity for the TBI Group.

Measure	Band	Region	PTA	Time-since-injury
Arousal	**Alpha**	**Frontal**	-.063	-.336
Resting activation	**Delta**	**Frontal**	.092	-.180
	Theta	**Frontal**	.650**	.225
	Alpha	**Frontal**	-.124	.203
	Beta	**Frontal**	-.658**	-.313
Task-related activation	**Delta**	**Frontal**	-.190	.013
	Theta	**Frontal**	-.147	-.222
	Alpha	**Frontal**	-.104	-.173
	Beta	**Frontal**	.845**	.781*

Note: ** $p < .01$, * $p < .05$. *df* (arousal) = 17 *df* (resting delta, alpha) = 17, *df* (resting theta, beta) = 16 *df* (task-related delta, alpha) = 8, *df* (task-related theta, beta) = 7

Figure 28.

Relationships between Resting and Task-Related Activation and Injury Variables



4.4 Discussion

The aim of the present study was to investigate the relationship between impaired energetic state (arousal and activation), everyday EF behaviours, and injury characteristics in TBI. In line with hypotheses, relationships between resting activation measures and everyday EF behaviours were observed. Significant relationships between arousal and everyday EF were unexpected. Also unexpected were no associations between task-related activation and everyday EF. However, there were significant associations between both resting and task-related activation and injury severity/chronicity. These key findings will be discussed in detail below.

4.4.1 Group differences in everyday EF

Compared to controls, the TBI group had elevated (i.e. more impaired) scores on sub-scales of the BRIEF-A including Inhibition, Self-Monitor, Shift, Initiate, Task Monitor, and Working Memory. The TBI group did not show any difference to controls on the Plan/Organise or Organisation of Materials subscales. Previous studies have shown both elevated (Lovstad et al., 2012), and non-elevated (Finnanger et al., 2015), scores on the Plan/Organise and Organisation of Materials sub-scales in TBI groups compared to controls. This result suggests that the present sample had intact planning and organising skills, and this may reflect the use of compensatory strategies to buffer the impact of their other EF impairments.

It is surprising that the TBI group did not show any difference to controls on scores for the BRIEF-A Emotional Control sub-scale as emotion dysregulation is a common consequence of TBI (Engberg & Teasdale, 2004), and this sub-scale has been reported to be elevated in TBI groups compared to controls (Finnanger et al., 2015; Lovstad et al., 2012). Emotion dysregulation can be, in part, a result of a lack of self-awareness and as a result is often under-reported by individuals with TBI (Fleming & Strong, 1999). Interestingly, factor analysis of the BRIEF-A in both healthy controls (Roth et al., 2013) and TBI (Donders & Strong, 2016) have shown that an 'Emotion Regulation' factor was distinct from a 'Behavioural Regulation' factor, suggesting that these are discrete constructs and so may be differentially affected by TBI. Consistent with this, differential engagement of frontal neural networks has been observed in neuroimaging studies of cognitive/behavioural control, compared to emotional control (Kompus et al., 2009). Given that we did not observe group differences in mental health measured by the DASS-21, it is possible that the present TBI sample reflects a group with intact emotion regulation, but impaired behavioural control.

The TBI group showed higher impulsivity on the Motor subscale and Total score of the BIS-11 but no difference on the Non-planning and Attentional subscales, compared to controls. The Motor subscale reflects the tendency to act without thinking (Patton et al., 1995; Stanford et

al., 2009) and together the BIS-11 results suggest that the present TBI sample may be better characterised by impulsive behaviour rather than inattention or planning difficulties. The lack of group difference for the Non-Planning subscale is consistent with the Plan/Organise and Organisation of Materials subscale scores of the BRIEF-A. However, the lack of group difference in the Attentional sub-scale is somewhat surprising, given that scores on the BRIEF-A reflecting attentional constructs were elevated for the TBI group.

4.4.2 Relationships between arousal/activation and everyday EF

Reduced arousal in EC was associated with more dysfunctional behaviours on the Self-Monitor scale of the BRIEF-A, and on the Motor and Total BIS-11 scores in the overall sample. The Self-Monitor subscale reflects impulsivity in social interactions such as talking without thinking or at inappropriate times, acting before thinking, and lack of awareness of the impact on others (Roth et al., 2005). The BIS-11 Motor subscale similarly reflects acting without thinking but in broader contexts, e.g. spending too much money. This result is consistent with hypo-arousal models of AD/HD that suggest that impulsive and disinhibited behaviour is a compensatory effort to up-regulate less than optimal arousal levels (Clarke et al., 2002; Lubar, 1991; Satterfield & Cantwell, 1974). Zhang et al. (2018) found that reduced arousal in children with AD/HD had an indirect effect on everyday EF and EF task performance through resting alpha and delta activation, respectively. Their results suggest that those with lower baseline arousal over-activate and thus perform poorly. This indirect effect may explain present findings, although mediation and moderation analyses are needed to confirm this.

In line with hypotheses, greater resting delta activation (i.e. larger EC-to-EO increase in amplitude) was associated with higher scores on the BIS-11 Motor subscale. This is consistent with results from Study 1 showing that increased resting delta activation was associated with poorer Nogo accuracy in the Go/Nogo task. This supports a specific association between delta activation and RI, measured both by cognitive task performance (specifically Nogo errors), and

everyday behaviour (BIS-11 Motor sub-scale). The Inhibit scale of the BRIEF-A did not show significant associations with delta activation, and this is surprising given that it similarly measures the ability to inhibit impulsive responding in everyday life. In a study of children with AD/HD, increased resting delta activation in frontal regions was predictive of better EF task performance, but not of everyday EF measured by the BRIEF-A (Zhang et al., 2018). This is consistent with prior research showing little or no correlation between EF task performance and everyday EF. Nonetheless, the present association of delta activation with the BIS-11 Motor subscale, combined with abnormal delta activation for the TBI group in studies 1 and 2, suggests a role for impaired delta activation in cognitive and behavioural manifestation of impaired RI in TBI.

As expected, reduced resting theta activation (i.e. smaller EC-to-EO increase in theta amplitude) was associated with higher scores on the BRIEF-A Inhibit, Emotional Control, and Initiate subscales, as well as the Behaviour Regulation Index and the Global Executive Composite score. On the BIS-11, reduced resting theta activation was associated with the Attention and Non-Planning subscales, as well as the Total score. Together these results suggest that reduced theta activation was associated both with difficulties inhibiting impulsive or reactive behaviours and forethought, and also with concentration and initiating actions. This is consistent with associations between FM-theta and a range of attention, memory, and EF tasks (Y. Y. Chen & Caplan, 2017; Clayton et al., 2015; Finnigan & Robertson, 2011; Herweg et al., 2020; Jensen & Tesche, 2002; Klimesch, 1999), suggesting a more generalised role in cognition and behaviour, such as sustained attention and concentration (Klimesch, 1999; Mitchell et al., 2008; Sauseng et al., 2007). Therefore, it is quite likely that the associations between theta activation and everyday EF here reflect the underlying attentional mechanisms required for flexible cognitive and behavioural control (Hanif et al., 2012; Mackie et al., 2013).

Corroborating evidence for the role of theta activation in attention comes from source localization studies identifying the ACC is one of the key generators of FM-theta (Raghavachari et al., 2001; Sauseng et al., 2007; Wang et al., 2005). The ACC has been implicated in neural networks facilitating sustained attention and attentional control (Bush et al., 2000; Posner et al.,

2019). Specifically, a proposed functional role of the ACC in attention is as a central modulator of intrinsic alertness (Mottaghy et al., 2006) or arousal (Aston-Jones & Cohen, 2005; Paus, 2001). It is proposed to assert a top-down effect on the thalamus and brainstem (including the locus-coeruleus-norepinephrine system) in order to regulate arousal in response to environmental demands and to have a specific role in intrinsic, endogenous (in contrast with external, stimulus-driven) control of attention (Aston-Jones & Cohen, 2005; Mottaghy et al., 2006). The present association of resting (but not task-related) theta activation with behaviour supports this intrinsic role. The ACC and its thalamic connections are particularly vulnerable to diffuse axonal injury and degeneration in TBI (Stamatakis et al., 2002; Zhou et al., 2013), and are associated with TBI-related attentional deficits (Hu et al., 2013; Kim et al., 2009; Richard et al., 2018). A recent study demonstrated that increased FM-theta indexed improved executive attention performance, likely via increased attentional effort, in TBI (Shah et al., 2017). The authors proposed that FM-theta reflects the engagement of the frontal-thalamocortical system involve in arousal regulation. Overall, the present findings suggest that reduced resting theta activation plays a role in attentional and executive problems in TBI, and indexes impaired state regulation involving the ACC and frontal-thalamocortical arousal system, which underlies attention and subsequent behavioural control.

Enhanced resting alpha activation (i.e. larger EC-to-EO reduction in alpha amplitude) was associated with more impulsive behaviours on the BIS-11 Motor sub-scale. This is in line with associations between enhanced resting alpha activation and lower Go and Nogo accuracy and increased RT variability in Study 1. Like delta activation, this suggests a role of alpha activation in RI task performance and everyday RI specifically. The specificity of this relationship is in accordance with an inhibitory control interpretation of alpha activity – where alpha indexes not only the inhibition of task-irrelevant neural processes, but also the inhibition of motor responses (Knyazev, 2007; Klimesch, 2007). However, this interpretation stems predominantly from evidence of alpha ERS in RI tasks, and task-related alpha activation was not associated with EF in the present study. The resting activation-EF association is more difficult to interpret. Given the inverse relationship between resting alpha and cortical arousal/activation (Barry et al., 2007;

Bazanova & Vernon, 2014), the direction of the alpha activation-EF relationships were in the unexpected direction. This might be explained by an indirect effect of baseline resting arousal (as seen in Zhang et al. (2018), described above) such that larger EC alpha (reflecting hypo-arousal) drives greater EO alpha suppression (activation) in a compensatory response. This is consistent with some evidence that increased resting alpha (hypo-arousal) correlates with deficient RI in healthy controls (Schiller et al., 2014), and with hypo-arousal models of impulsivity (Clarke et al., 2002; Lubar, 1991; Satterfield & Cantwell, 1974). The relative contributions of EC alpha (arousal) versus compensatory EO alpha suppression (activation) to impulsivity remain to be clarified.

Increased resting beta activation (i.e. larger EC-to-EO increase in beta amplitude) was associated with higher scores on the BRIEF-A Inhibit, Emotional Control, and Behaviour Regulation Index scales. This is in line with associations between excessive beta power and impaired motor (Bočková & Rektor, 2019), impulse (Barry & Clarke, 2009; Clarke et al., 2013; Lee et al., 2017), and emotional (Li et al., 2019) control. It has been suggested that enhanced beta reflects the maintenance of motor (and cognitive) set and that its association with impaired behavioural control reflects an overly rigid adherence to an automatic response mode, to the detriment of flexible and adaptive responding (Engel & Fries, 2010). The tendency for a TBI group to adopt a more rigid and automated response mode during an RI task has been observed previously (Dockree et al., 2006). However, task-related (rather than resting) beta activation would be more relevant to this interpretation, and no associations were observed presently.

In addition, increased resting beta activation was also associated with the BIS-11 Attention subscale. Similar to the role of theta activation, this suggests beta activation is associated with both inhibitory control and attention-related behaviours. This is in line with the Shah et al. (2017) study in which both enhanced theta and reduced beta were associated with attentional effort in TBI, and purported to reflect engagement of the fronto-thalamocortical arousal system. Though Shah et al. (2017) propose that beta suppression indexes state regulation in the same way as the theta enhancement, in this thesis the link between beta activity and regulation of

energetic state in TBI is less clear. There was no impairment of beta activation in the TBI group observed in study 1. However, the TBI group did show overall increased beta averaged across the resting tasks, when compared to controls. Excessive beta power has been observed in a sub-type of children with AD/HD (Clarke et al., 2013), and mirrors the developmental trajectory of impulsivity and hyperactivity in AD/HD (Barry & Clarke, 2009). An association between increased beta power and the BRIEF-A Emotional Control sub-scale has also been reported in adults with AD/HD (Li et al., 2019). Therefore, there may be a role for beta in TBI-related EF impairments, however it is not beta *activation* per se that is impaired. This may be due to increased beta in the EC condition for the TBI group, diminishing the EC-to-EO difference.

Given the opposing directions of the theta and beta effects here, the extensive evidence for associations between larger theta/beta ratio and deficient attention and inhibition in the AD/HD literature (Barry et al., 2003; S. M. Snyder & Hall, 2006; Zhang et al., 2019) must be mentioned. However, the opposite effect was observed in the current study, i.e. reduced theta and increased beta activation were associated with poorer behavioural outcomes, suggesting that the direction of these effects might be distinctive to TBI. Interestingly though, many of the sub-scales that were associated with resting theta and beta activation (BRIEF-A Emotional Control, BIS Attentional, and BIS Non-Planning) were not elevated in the TBI group. This may suggest a more general association for these activation measures across the population. However, these measures have shown impairment in other TBI samples (Finnanger et al., 2015; Lovstad et al., 2012; Travis Seidl et al., 2015), so these findings require replication in independent and larger samples.

4.4.3 Relationships between arousal/activation and injury variables

Greater injury severity was associated with increased resting theta activation (i.e. larger EC-to-EO increase in amplitude) and reduced resting beta activation (i.e. smaller EC-to-EO increase in amplitude). Both severity and chronicity were associated with increased task-related beta activation (i.e. larger EC-to-EO increase in amplitude). Interestingly, although delta and

alpha activation were associated with cognitive and behavioural deficits in TBI previously in this thesis, they were not associated with injury variables. Arousal was not associated with injury variables, further supporting that arousal deficits are not characteristic of TBI.

The degree of injury severity has been associated with degree of EEG abnormalities in TBI previously (Thatcher, Biver, et al., 2001; Thatcher, Biver, McAlaster, & Salazar, 1998; Thatcher, Biver, McAlaster, Camacho, et al., 1998; Thatcher, North, et al., 2001). MRI studies have shown increased delta and theta, and reduced alpha and beta power in EC to be associated with longer T2 relaxation times, a marker of grey and white matter integrity, in TBI (Thatcher, Biver, McAlaster, Camacho, et al., 1998; Thatcher, North, et al., 2001). Though the use of *activation* here is not directly comparable to Thatcher's relative power measure, the present results are in line with increased low frequency activity, and reduced high frequency activity being associated with more severe injury.

Given previous studies demonstrating associations between injury severity and degree of cognitive impairment (Thatcher, Biver, McAlaster, & Salazar, 1998; Thatcher, Biver, McAlaster, Camacho, et al., 1998), it is surprising that the activation measures that were characteristic of more severe injuries (i.e. increased resting theta, reduced resting beta, and increased task-related beta activation) were not associated with greater behavioural impairment. Contrarily, increased resting theta and reduced resting beta activation were associated with less behavioural impairment in the combined (TBI and control) sample. This pattern of dissociation has been observed in fMRI studies previously. Increased brain activation (measured by blood oxygen level-dependent signal) has been associated both with increasing injury severity, and enhanced cognitive control task performance (Scheibel et al., 2007, 2009) and less impaired everyday EF (measured by the BRIEF-A; Olsen et al., 2015). The authors have interpreted increased activation as a compensatory mechanism, which reflects the allocation of more extensive neural resources in order to maintain adequate task performance, or behavioural control, in the more severe injuries. Imaging studies have shown topographical differences in BOLD signal activation in TBI (cf. to controls) in WM and cognitive control tasks, further supporting a compensatory interpretation,

where re-organisation of networks after injury results in different neural resources being employed to perform the same task (Newsome et al., 2007; Scheibel et al., 2007, 2009). Hyperconnectivity of the ACC to other cortical regions, as measured by the BOLD fMRI signal, has also been linked to a greater need for top-down attentional control in TBI (Mayer et al., 2011; Sheth et al., 2021) and this has relevance to the theta and beta findings here, given the proposed modulatory role of the ACC for these frequency bands (Shah et al., 2017). Accordingly, increased theta and reduced beta activation might be explained by a greater need for top-down state regulation and/or more extensive neural resource employment in the more severe injuries. The heterogeneity of activation patterns *within* TBI groups has also been identified as a potential confounding factor (Newsome et al., 2007), highlighting the complexity of mapping neural activity and function in TBI.

4.4.4 Overall patterns

Greater resting delta (EC-to-EO increase) and alpha (EC-to-EO reduction) activation were associated specifically with deficient everyday RI, and this aligns with a role of resting delta and alpha activation in RI task performance observed in Study 1. This is an important finding given the inconsistent or lacking correlations between laboratory-based EF measures and everyday functioning typically observed (Chaytor & Schmitter-Edgecombe, 2003; Gioia & Isquith, 2004; Sbordone, 2008), and provides a strong case for the role of delta and alpha activation in disinhibited cognition and behaviour following TBI.

Reduced resting theta activation (smaller EC-to-EO increase) and increased resting beta activation (larger EC-to-EO increase) were associated more broadly with EF and inattentive behaviours, and injury severity and chronicity. This is in line with a recent study demonstrating that increased frontal midline theta and reduced frontal midline beta power indexed executive attention in TBI (Shah et al., 2017). The authors linked the theta and beta power findings to the engagement of fronto-thalamocortical systems that facilitate executive attention through arousal regulation. This interpretation is well supported by source localisation of FM-theta to the ACC (Raghavachari et al., 2001; Sauseng et al., 2007; Wang et al., 2005), and implications of a central

role of the ACC in modulating the arousal system in response to environmental demands (Aston-Jones & Cohen, 2005; Mottaghy et al., 2006; Paus, 2001). Given its broad associations with both attentive and EF behaviours here, FM-theta activation presents a good candidate for measuring impaired regulation of energetic state, and its association with executive and attention dysfunction, in TBI. Unexpectedly, the theta and beta activation measures associated with more impaired everyday EF were associated with reduced injury severity. This might suggest a greater need for top-down regulation (Mayer et al., 2011; Sheth et al., 2021) and/or allocation of more extensive neural resources (Olsen et al., 2015; Scheibel et al., 2007, 2009) in the more severe injuries. The results of the current study point to a role of theta and beta activity in EF behaviour generally, and in injury severity in TBI, however the nature of these relationships need clarification.

Lower arousal (increased EC alpha) was associated with poor self-monitoring and impulsive behaviours in the overall sample. In Study 1 there were no group differences in resting arousal between controls and the TBI group, consistent with previous research (Fisher et al., 2015; Rushby et al., 2013). In the current study, injury severity and chronicity were associated with activation measures (resting and task-related) but not with arousal. Taken together, these results suggest that though baseline arousal does have a role in everyday EF in the general population, TBI-related EF impairment is not attributable to a baseline arousal deficit. Results of the first three studies of this thesis converge to suggest that it is the intrinsic (cf. externally modulated) *regulation* of arousal that is impaired and related to executive dysfunction in TBI, and that this might be best indexed by theta (and perhaps also beta) activation.

4.4.5 Limitations and future directions

As noted in Study 2, the functional interpretations of EEG bands adopted here reflect literature that predominantly uses on-task or event-related EEG rather than tonic activation measures, and these likely represent distinct phenomena. The EEG data was analysed from fronto-central brain regions only, and though this is justifiable given the localisation of EF and vulnerability of the frontal lobe to TBI-related damage, it does limit the topographical

interpretations that may be important in understanding activation (Barry et al., 2007). Relatedly, not all participants had frontal damage: some had exclusively parietal and/or sub-cortical damage, or no visible pathology on scans.

Though there were no statistically significant group differences in the correlations, there was a tendency for the TBI group to have stronger correlations (cf. to controls) between delta, alpha, and beta activation, and behavioural measures, while controls had stronger correlations (cf. TBI group) between arousal, theta activation, and behavioural measures. Furthermore, the relationship between theta and beta activation and injury variables in the TBI group was in the opposite direction expected based on activation relationships with behavioural impairment in the combined sample. This may reflect dissociable compensatory mechanisms for TBI and control groups. These are points for further research that may be clarified with replication in a more highly powered sample. Relatedly, many correlation analyses were conducted in the present study, which increases the chance of Type I error. It was considered however, that these analyses were exploratory and statistical correction for multiple comparisons would exclude findings that should be investigated further in future studies (Althouse, 2016; Bender & Lange, 2001). Interpretations of the present findings should be taken with the appropriate caution and emphasis on the need for replication.

In the previous studies of this thesis activation in some EEG bands was differentially modulated by group, such that one group had a condition-related increase in EEG amplitude, and the other group a condition-related reduction. Spearman's correlation transforms EEG activation data to ranked values and therefore the ranked data scatterplots presented here do not explicitly visualise the differences in direction of task-related EEG amplitude changes, because all ranks are positive values. Though the directions of amplitude changes are interpretable (i.e. lower rank values = increasingly negative changes, higher rank values = increasingly positive) and based on results from group comparisons in the previous studies of this thesis, the ranked data plots do limit visualisation of the differences in direction of amplitude changes and their relation to behavioural and injury variables.

Given the heterogeneity of TBI (Maas, 2016; Maas et al., 2010; Saatman et al., 2008), group comparisons may obscure inter-individual differences within the TBI group (Hallock et al., 2016; Kennedy & Turkstra, 2006). Furthermore, it is possible that problems with either control or drive processes (elaborated in subsection 2.4.1), and underlying over- or under-activation, respectively, may be the basis for dysfunctional behaviours measured in this study. In this case, the linear model may not adequately represent these individual differences, and future research should clarify with more sophisticated models.

Lack of insight is a common feature of TBI and can lead to underreporting of impairments. As such, it is a limitation that the present study relies on self-report measures of everyday EF and impulsivity. Previous research has shown no significant differences in BRIEF-A scores reported by TBI participants compared to their significant others (Garcia et al., 2013; Lovstad et al., 2012). Nonetheless, future research would benefit from replicating the role of arousal and activation relationships with other-reports of everyday EF.

4.4.6 Conclusion

This study demonstrates relationships between measures of energetic state and impaired everyday EF in TBI. Greater resting delta and alpha activation were associated specifically with deficient everyday RI, aligning with relationships between resting delta and alpha activation and RI task performance observed in Study 1. Reduced resting theta activation and increased resting beta activation were associated more broadly with EF and inattentive behaviours, and with injury severity and chronicity. Though arousal was associated with everyday EF in the overall sample, it was not associated with injury variables. This adds further support to evidence from Study 1, that TBI is not best characterised by a baseline arousal impairment but rather by impairment to the top-down intrinsic *regulation* of energetic state, and that this underlies executive dysfunction. Given the association between theta activity and the ACC and cortico-thalamic arousal system in prior literature, and the sensitivity of theta activation to energetic state modulation, EF impairments, and injury variables in this thesis, theta activation appears to be a good index of impaired intrinsic state regulation that underlies executive dysfunction in TBI.

CHAPTER 5:

Study 4: Neurocognitive training in TBI: A single case experimental design study

5.1 Introduction

A range of abnormalities have been reported in the EEG of individuals who have sustained a TBI (e.g. Rapp et al., 2015; Thatcher, 2009). According to the Cognitive Energetic Model (CEM; Sanders, 1983), EEG abnormalities reflect impaired energetic state of the brain and this underlies cognitive and behavioural dysregulation. Study 1 showed that *activation* rather than *arousal* measures of energetic state under resting conditions differentiated a TBI group from controls. This reflects a deficiency in the ability to mobilise and regulate energetic state in response to environmental demands, rather than abnormal resting baseline activity in TBI. Study 2 showed that deficits in energetic state regulation in TBI were also present when moving from a resting condition to a cognitive task condition (eyes-open cf. Go/Nogo task, *task-related activation)*, suggesting that deficient state regulation is present in multiple contexts.

Impaired state regulation was also shown to relate to cognitive and behavioural measures of EF. In Study 1, resting delta, theta, and alpha activation were associated with performance on a Go/Nogo task in TBI and control groups. In Study 2, greater task-related delta activation and reduced task-related alpha activation were associated with improved Go accuracy and reduced RT variability. Study 3 showed that state regulation impairments were related to behavioural dysregulation in TBI. Delta and alpha activation were associated specifically with everyday RI behaviour, while theta and beta activation were associated with broad everyday EF and inattentive behaviours.

Both cognitive training and neurofeedback (NF) training (in which certain frequencies of

the EEG are reinforced in real-time) have been used to address cognitive and behavioural functioning in TBI with mixed results (Gray, 2017; Hallock et al., 2016; Sigmundsdottir et al., 2016; Thornton & Carmody, 2008). A potential reason for the inconsistent evidence for efficacy of these approaches may be related to the association between impaired state and impaired cognition and behaviour. The ability to regulate energetic state in a way that allows learning and engagement is a necessity to participate in and benefit from cognitive rehabilitation. Indeed, studies have shown that intrinsic neural dynamics can affect the rate and nature of learning in healthy controls (Mukai et al., 2007; Vernon et al., 2003) and can predict success with cognitive training (Strangman et al., 2008; Vinogradov et al., 2012). Similarly, response to cognitive rehabilitation can be impeded or enhanced by pre-intervention cognitive functioning (Ben-Yishay et al., 1987; Michel & Mateer, 2006; Sandberg et al., 2016; Wood, 1988). Therefore, a training protocol that simultaneously targets energetic state and cognitive factors may improve outcomes of cognitive rehabilitation for TBI, and also address the time and financial costs of sequential cognitive rehabilitation.

The Focus Pocus neurocognitive training program uses NF principles to train state regulation (with exercises targeted at attention and relaxation, and the simultaneous combination of these states), along with cognitive training tasks targeting the processes of RI and WM. The program was developed for use in children with AD/HD as an alternative to pharmacological treatment (Johnstone, 2013) and has shown good outcomes in this population (Jiang et al., 2018; Johnstone et al., 2017). Similar to TBI, AD/HD is characterised by an inability to regulate impulsive behaviour and this has been linked to impaired state regulation (Barry et al., 2003; Sergeant, 2005). The Focus Pocus program was designed to target state regulation issues, specifically increased slow wave and reduced fast wave EEG activity (Barry et al., 2003), as well as inhibitory control and WM deficits in AD/HD (Sergeant, 2005). Though the pattern of EEG abnormalities is not as well established in TBI as it in AD/HD, the Focus Pocus program targets both increases in fast wave (in 'focus' tasks) and increases in slower wave (in 'relax' tasks), and is suitable for targeting state regulation broadly.

The evidence for efficacy of NF and cognitive training in patients with TBI has been criticised for being based predominantly on uncontrolled and case studies (Gray, 2017; Hallock et al., 2016; May et al., 2013; Sigmundsdottir et al., 2016; Thomas & Smith, 2015). This predominance of case studies makes sense in the context of a population characterised by enormous heterogeneity of injury cause, location, and severity, as well as pattern of recovery, and personal characteristics (Maas, 2016; Maas et al., 2010; Saatman et al., 2008). It is therefore difficult to recruit participants in adequate numbers to form homogenous groups for comparison in RCTs (Hallock et al., 2016; Kennedy & Turkstra, 2006). Though RCTs have long been emphasised as the gold standard of treatment efficacy studies, recently the Oxford Centre for Evidence-based Medicine (http://www.cebm.net) have ranked single case experimental design (SCED) studies as Level 1 evidence, alongside RCTs. The SCED overcomes challenges of clinical research in TBI by requiring fewer participants, whilst providing adequate experimental control to infer intervention effects (Brossart et al., 2018; Odom et al., 2005). For each participant in the SCED, outcome variables are measured repeatedly and systematically in baseline (pre-intervention) and intervention phases, allowing individuals to serve as their own control (Krasny-Pacini & Evans, 2018). As such, the SCED study can provide a robust basis for establishing a causal relationship between intervention and outcome (Kratochwill et al., 2010; Shadish et al., 2002). Intervention effects are inferred if outcome variables change when, and only when, the intervention is provided or removed, and when there is replication of the effect within participants (e.g. in an ABAB design), or between participants (e.g. in a multiple-baseline design with three or more participants) (Horner et al., 2005; Kratochwill & Levin, 2010).

Another feature that distinguishes the SCED from the RCT is emphasis on intra-individual change rather than change in a group average (D. H. Barlow et al., 2009). Given the challenge of heterogeneity and mixed outcomes for cognitive training in TBI, it has been suggested that the patient characteristics that influence intervention effectiveness should be the target of future research (Cicerone et al., 2019). In the current study, the use of the SCED was also justified by an interest in individual characteristics relevant to intervention response; factors that would otherwise be screened or averaged out in group comparisons (D. H. Barlow & Nock,

2009; Horner et al., 2005). The multiple-baseline (AB) design is recommended when the dependent variable is unlikely to 'reverse' back to baseline levels on withdrawal of the intervention (Dallery et al., 2013; Kratochwill et al., 2010; Smith, 2012; Tate et al., 2013). The aim of NF and cognitive training is to improve cognition and neural activity in a way that leads to functional improvements that are sustained (not reversed) after the treatment is complete (Ali et al., 2020; Sigmundsdottir et al., 2016; Willis & Schaie, 2009). Therefore, the multiple-baseline (AB) design was most appropriate to assess the effect of neurocognitive training.

The current study aims to investigate the effects of neurocognitive training on state regulation, RI performance, and everyday EF behaviour in individuals with TBI. Intervention effects will be demonstrated through changes in EEG, task performance, and self- and other-reported behaviour between baseline and intervention phases. Given the broad approach of the training program, broad improvements in state regulation, cognitive measures, and transfer to behaviour are expected. Based on results from Studies 1 and 2, it is expected that any improvement in resting and task-related delta activation, and task-related alpha activation, will be accompanied by improvements in RI task performance. Based on the results of Study 3, it is expected that any improvements in resting theta and beta activation will be accompanied by improvements in BRIEF-A scores. A case study approach will supplement quantitative analyses to explore individual injury and demographic factors related to intervention response.

5.2 Method

5.2.1 Participants

Seven participants were referred by clinical psychologists at a local brain injury service and recruited for the study. Criteria for inclusion were brain injury caused by trauma; cognitive complaints in the domain of attention, EF, and/or memory; no uncorrected hearing or vision loss; and no psychiatric illness or situational factors that would impede their ability to participate in the training program. All participants had participated in Studies 1, 2, and 3 of this thesis prior to their participation in the current study.

Table 20 shows the demographic and clinical characteristics of each participant. The mean age was 42.57 years (*SD* = 13.85; range 22-56), with mean years of education at 13.57 years (*SD* = 2.51; range 11-18). There were 5 male and 2 female participants. The mean length of post-traumatic amnesia (PTA) was 13.42 days (*SD* = 10.27, range 0.5-29). The average time since injury was 4.89 years (*SD* = 3.67; range 0.8-12). Four participants were unemployed at the time of the study, one was engaged in casual work, one in full-time work, and one in full-time study.

Table 20.

Injury Characteristics of Participants

Case	Gender	Age	Education (years)	Pre-morbid IQ	Time post-injury	PTA (days)	Cause of injury	Site of injury/initial scan	Employment status pre-injury	Employment status current
R002	M	50	13	110	5y 5 m	7	MBA	No pathology.	Full-time	Full-time
R003	M	52	12	98	5y 10m	14	MBA	Widespread haemosiderin deposition in the grey/white interface of corpus callosum.	Full-time	Casual work
R005	M	37	11	91	4y 11m	21	Fall	Left occipital extradural and subdural haematoma. Craniotomy and external ventricular drain followed by cranioplasty.	Full-time	Unemployed
R009	M	54	13	87	2y	unk.	Assault/ Fall	No pathology.	Full-time	Unemployed
R010	F	27	18	105	3y 2m	9	MVA	Left frontal, parietal, and temporal injury, midline shift and subsequent left craniotomy.	Full-time student	Full-time student
R014	F	22	16	92	10m	7	MVA	Right extradural haematoma; temporal contusions.	Full-time	Part-time
R018	M	56	12	110	12y 1m	29	MVA	No pathology.	Full-time	Unemployed

Note. PTA is based on information from medical records. Injury details are based on initial CT or MRI scan.
MBA = motorbike accident; MVA = motor vehicle accident (driver or passenger); unk. = unknown.

Table 21 presents the cognitive and neuropsychological difficulties participants experienced as a result of TBI. This information was collected from demographic questionnaires, as well as neuropsychological assessment reports provided, with participant consent, by the brain injury service. The most frequent difficulties reported were in domains of attention, EF, and memory.

Table 22 presents relevant psychological and medical conditions and treatments for each participant prior to their injury and at the time of enrolment to the study. These were collected from demographic questionnaires and neuropsychological assessment reports. Five of the seven participants had psychological and emotional difficulties at enrolment to the study. These difficulties were assessed by clinical psychologists at the brain injury service and considered to be stable and managed well enough to not impede the participants' ability to engage in the neurocognitive training procedure. Participant R014 was taking regular anti-depressant medication throughout the study. Five of the seven participants were currently or previously engaged with psychological therapy to address psychological or emotional issues related to TBI.

Table 21.

Cognitive and Neuropsychological Difficulties

Case	Attention	Executive function	Learning	Memory	Perceptual -motor	Social cognition
R002	x					x
R003	x	x		x		
R005[a,c]	x	x		x		
R009[a,d]	x	x	x	x	x	
R010	x	x		x		
R014	x	x	x	x		
R018	x	x	x	x	x	

Note: [a] Performance >2 S.D. below mean for age and education for Trails A or B, [b] Performance >1.5 S.D. below mean for age and education for Trails A or B, [c] Performance >2 S.D. below mean for age for digit symbol coding, [d] Performance >1.5 S.D. below mean for age for digit symbol coding.

Table 22.

Current and Previous Conditions and Treatments

Case	Current conditions	Current treatments	Pre-injury conditions	Previous treatment
R002	Nil.	Psychological therapy.	Nil.	Nil.
R003	Emotional dysregulation; low mood; sleep problems.	Nil.	Nil.	Nil.
R005	Depressive and anxiety symptoms; substance use.	Disulfiram; psychological therapy.	Nil.	Nil.
R009	Depressive and anxiety symptoms; headaches; neck, shoulder, and back pain; sleep problems.	Nil.	Nil.	Nil.
R010	Mild anxiety and stress.	Psychological therapy.	Mild anxiety.	Nil.
R014	Depressive symptoms, migraine, fatigue, vertigo.	Escitolopram (20mg/daily); psychological therapy.	Nil.	Nil.
R018	Nil.	Nil.	Nil.	Psychological therapy.

5.2.2 Measures

See subsection 2.2.2 for description of resting and Go/Nogo Fast EEG conditions. For descriptions of the electrophysiological recording and data extraction methods for resting conditions (EC and EO) see sections 2.2.4 and 2.2.5, and for the Go/Nogo task see section 3.2.3. **Table 23** summarises the average number of epochs of EEG data that were accepted following automatic and manual artifact removal for each participant in each condition, across week. EEG measures of arousal and resting activation are outlined in Section 2.2.6, and EEG measures of task-related activation are outlined in section 3.2.4.

Table 23.

Mean Number of Accepted epochs. SD in Brackets.

	EC	EO	Go/Nogo Task
R002	55.00 *(5.08)*	49.50 *(5.62)*	23.80 *(3.58)*
R003	56.00 *(3.95)*	49.82 *(4.38)*	28.80 *(1.75)*
R005	52.30 *(6.11)*	42.30 *(13.22)*	26.89 *(5.42)*
R009	48.80 *(8.09)*	40.50 *(8.71)*	21.30 *(5.40)*
R010	53.08 *(4.27)*	48.58 *(10.05)*	27.17 *(3.61)*
R014	51.85 *(4.43)*	39.31 *(11.69)*	24.58 *(2.97)*
R018	45.45 *(7.38)*	39.50 *(10.78)*	24.00 *(5.31)*
Mean	51.78 *(6.43)*	44.22 *(10.39)*	25.22 *(4.61)*

A short and modified version of the BRIEF-A (Roth et al., 2005) was used (see subsection 4.2.2.2 for description of the full BRIEF-A questionnaire). The shortened version consisted of items from the Shift, Inhibition, and Working Memory subscales only, chosen based on the three components of the unity/diversity model of EF (Friedman et al., 2008; Miyake et al., 2000; Miyake & Friedman, 2012). The modified version asked participants to rate their behaviours over the past *week* rather than the past month.

5.2.3 Design

A non-concurrent multiple baseline SCED was conducted to investigate training effects. The non-concurrent design was chosen so that participants could begin the baseline phase at the time of enrolment into the study, rather than wait for all participants to be recruited. Each participant completed a baseline phase followed by an intervention phase. Participants were randomly allocated a baseline phase of 4, 5, or 6 weeks, in line with recommendations of at least 3 data points in each phase (Kratochwill et al., 2010). One participant (R018) was allocated a 4 week baseline, however technical difficulties with their internet connection meant that this phase was extended to 6 weeks. The length of the intervention phase was a minimum of 5 weeks, dependent on the number of weeks taken to complete at least 20 neurocognitive training sessions.

5.2.4 Procedure

Ethics approval for the project was obtained from the Illawarra Shoalhaven Local Health District and the Human Research Ethics Committee of the University of Wollongong prior to the start of the study.

During both the baseline and intervention phases, participants attended weekly assessment sessions at the University of Wollongong. Each assessment session involved recording of EEG during EO and EC conditions and a Go/Nogo task, and the modified BRIEF-A self-report questionnaire. Each session lasted approximately 45-60 mins. Participants were also given a modified BRIEF-A informant report questionnaire to be completed on the same day by a significant other (e.g. friend or relative) and returned the following week. In the final session participant were given a reply-paid envelope to return the final informant report. In the first session, participants read a Participant Information Sheet and signed a consent form, which included consent to the researcher using clinical and demographic information and neuropsychological test scores collected in a previous study. They were advised of the length of their baseline phase. In the final assessment session of the baseline phase, participants were given

an iPad and Neurosky EEG headset for use during the training phase, as well as written instructions on the use of the headset and the Focus Pocus program, and a demonstration of the Focus Pocus software. Participants were instructed to complete 3-5 training sessions per week (a minimum of 20 and maximum of 25 sessions in total) in their own home at a time that suited them. They were encouraged to schedule regular training sessions into their weekly routine and to set reminders (e.g. on their mobile phone calendar).

5.2.5 Training program

Participants used the Focus Pocus (version 2) neurocognitive training software on an iPad device. Focus Pocus was developed by NeuroCog Solutions Pty Ltd, incorporating intellectual property licensed from the University of Wollongong. Focus Pocus consists of a series of computerised mini-games targeting inhibitory control (IC), working memory (WM), and state regulation. During use of the software, participants wore a wireless, dry-sensor EEG headset; the NeuroSky MindWave Mobile. The headset recorded EEG from a single, dry sensor resting on the forehead (located at the medial pre-frontal area) and referenced to an electrode clipped to the left earlobe. The MindWave device has been shown to validly discriminate psychological states comparative to research-grade EEG hardware (Johnstone, Blackman, et al., 2012). The EEG recorded from the MindWave has been shown to be stable within sessions (Rieiro et al., 2019), and has good test re-test reliability at daily, weekly, and monthly intervals (Rogers et al., 2016). It has discriminative and prognostic value in stroke populations (Aminov et al., 2017; Rogers et al., 2019), and has been used for intervention with children with AD/HD (Jiang et al., 2018; Johnstone et al., 2017; Johnstone, Roodenrys, et al., 2012) and anxiety (Wijnhoven et al., 2015; Wols et al., 2018). The MindWave device consistently monitored electrode impedance and if sub-standard impedance occurred (e.g. device was removed, or there was substantial head movement), the game play was paused until acceptable impedance was once again achieved.

The IC games in Focus Pocus were based on the Go/Nogo paradigm and similar adaptive inhibitory control tasks (Benikos et al., 2013), and the WM games were based on a spatial

working memory paradigm (e.g. Morris et al., 1988). The state regulation games were based on NF principles, and aimed to reinforce and inhibit EEG activity in three brain states; '*relaxation'* (operationalised by increases in the alpha band and reductions in delta, theta, and beta bands), '*attention'* (operationalised by increases in the beta band, and reductions in the other bands); and '*zen'* (operationalised predominantly by increases in alpha *and* beta activity). The real-time EEG activity was used to actively control elements of the game. For example, in a game featuring a broomstick race, the player's broomstick speed was linked directly to their live attention level, with higher attention level results in faster broomstick speed. During the IC and WM games, EEG was also recorded and the average attention level during the game was categorised as low, medium, high, or very-high, and used as a multiplier for game points (x1, x2, x3, x4, respectively). The game difficulty level adapted continuously based on performance on the previous game to ensure that games were challenging but not too difficult. Participants received on-screen feedback about performance following each game in the form of a star rating (i.e. 0 to 5 stars) and additional feedback on accuracy for IC and WM games, and average and highest power level for state regulation games. Each training sessions consisted of 14 games (4 IC, 4 WM, and 6 state regulation) presented in random order, and taking approximately 20 minutes to complete in total.

5.2.6 Data analysis

Visual analysis of the graphical display of data is the standard approach to interpreting the results of a SCED study (Kratochwill et al., 2010; Lane & Gast, 2014). Visual analysis allows firstly for interpretation of specific features of the data *within* a phase including: 1) level – the mean score, 2) trend – the slope of the line of best fit, and 3) variability – the range or standard deviation. Secondly, it allows interpretation of differences *between* phases including: 4) immediacy – the change in level between the last 3 data points in one phase, and the first 3 data points in the subsequent phase, 5) overlap – the proportion of data points in one phase that overlap with data points in another phase, and 6) consistency – the consistency of data across phases. Where differences between phases are evident, an effect can be interpreted to be a result of the independent variable (e.g. the intervention). Importantly, experimental control is demonstrated

when there are three demonstrations of this effect[8]. The *three demonstration* criterion can be met by within-case replication (i.e. the experimental effect is shown at three points in time within a single participant/case) or inter-case replication (i.e. the effect is shown at three points in time across participants/cases; Horner et al., 2005; Kratochwill et al., 2010).

There are also a number of statistical methods being validated for use in SCED analysis, motivated by the notable limitations of visual inspection. These limitations include an inability to account for trends in baseline phases or high variability in data, low inter-rater agreement, insensitivity to small changes, no reliable method for estimating effect-sizes, and a lack of consistent decision-making guidelines (Harrington & Velicer, 2015). One statistical method shown to address these limitations is the Tau-U method (Brossart et al., 2018; Parker et al., 2011). Tau-U is a non-parametric statistic that combines non-overlap and trend analysis. The non-overlap component is based on the rationale that data in the baseline and intervention phases should show little-to-no overlap if there is an effect of the intervention. The Tau-U method also measures trend within and across phases, and, most importantly, can control for baseline trend by correcting for this in the phase comparison.

Current expert consensus suggests that a combination of visual and statistical analysis should be used to evaluate SCED outcomes, as statistical methods can provide limited information about clinical significance or contextual factors (Brossart et al., 2014, 2018; Shadish et al., 2015). In the current study, Tau-U was used to detect intervention effects on outcome measures, while controlling for baseline trend. Where differences between phases were detected statistically, visual analysis (Kratochwill et al., 2010) was then used to assess level (to confirm Tau-U results) and immediacy (to determine timing of the effect). The conclusion that the intervention showed an effect on an outcome measure was drawn only when the effect was replicated in at least 3 cases

[8] There is no formal basis for the 'three demonstrations' criterion at present. Rather it is a conceptual recommendation that has been adopted as the norm in published research (Kratochwill et al., 2013; Kratochwill & Levin, 2010)

(the *three demonstrations* criteria).

5.3 Results

5.3.1 Training completion and progression

Each participant completed the recommended minimum of 20 training sessions. Four of 7 participants completed the maximum of 25 training sessions. The number of training sessions completed each week ranged from 0-9. When sessions per week were averaged across the intervention phase, 5 of the 7 participants completed the recommended 3-5 sessions per week, however on a week to week basis this was inconsistent. **Table 24** displays the number of training sessions per week for each participant.

Table 24.

Number of Training Sessions Completed Per Week during the Intervention Phase

Case	Week									Total	Mean
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		
R002	4	2	2	0	0	2	3	6	1	20	2.22
R003	5	5	4	3	8					25	5
R005	4	2	5	5	3	1				20	3.33
R009	7	7	7	2	2					25	5
R010	2	4	3	1	3	5	4	3		25	3.13
R014	2	1	1	3	3	1	2	4	4	21	2.33
R018	1	2	6	9	5	2				25	4.17

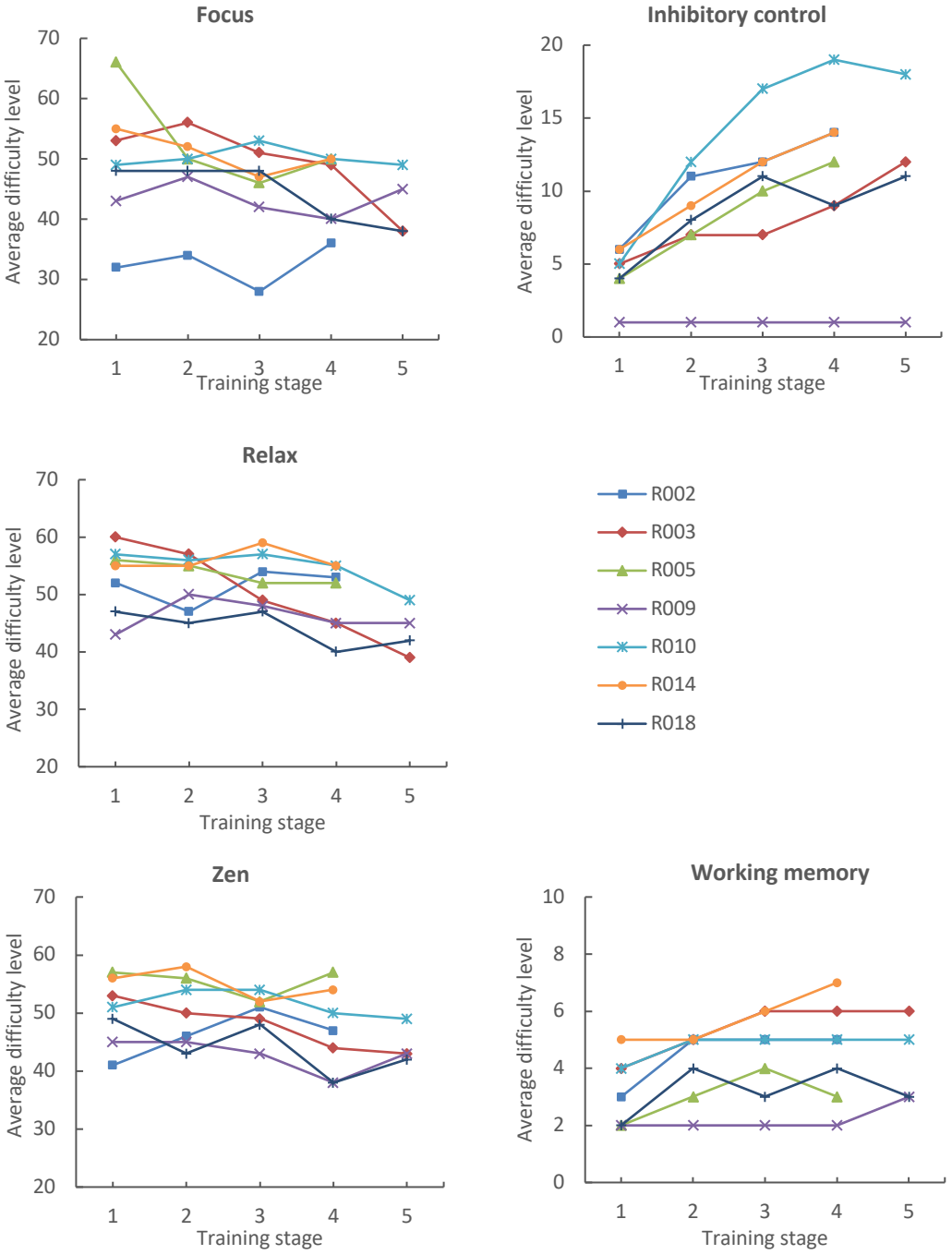
Figure 29 displays the average difficulty level for each training component at each stage of training for each participant. Each stage consists of the average of five training sessions, so that the 25 sessions are divided into five stages. Difficulty level for the IC tasks showed a consistent

increasing trend for 6 of 7 participants. Participant R009 did not progress through difficulty levels on the IC tasks, but rather stayed at the same level throughout. This lack of progression is also evident in the WM games for this participant, except for an increase in level at the final stage. All participants showed a progression from lower to higher difficulty levels in the WM games.

The trend for progression to higher levels in the state regulation games was not evident. Most participants showed a decrease in difficulty level in state regulation tasks in final compared to initial stages (as seen in **Figure 29**), with some exceptions. R002 showed an increase in levels in all state regulation games in the final compared to first training stage. R009 showed an increase in level in both the Focus and Relax games. R010 showed no change in Focus level, R014 no change in Relax level, and R005 no change in Zen level.

Figure 29.

Average Difficulty Level at Each Stage of Training for Each Participant. Each Stage Consists of Five Training Sessions. The Left Column Shows State Regulation Training Tasks. The Right Column Shows Cognitive Training Tasks



5.3.2 Intervention effects on everyday EF behavior

Table 25 and **Table 26** display Tau-U results for the BRIEF-A self- and informant-reports. **Figure 30** displays the raw data. Tau-U analyses demonstrated that R014 had a reduction on the Inhibit scale, reflecting reduced dysfunctional behaviours, and R018 an increase on the Inhibit scale, in the intervention compared to baseline phase. Visual analysis of Inhibit scores (see **Figure 30**) confirmed that $mean_B$ was higher than $mean_I$ for R014 ($mean_B$ = 73.60 vs. $mean_I$ = 55.44) with the opposite effect for R018 ($mean_B$ = 56.17 vs. $mean_I$ = 63.00). For both participants, as the intervention was introduced, Inhibit scores were changed without delay. R014 had a reduction of 6.00 points between the end of baseline and beginning of intervention phases, and R018 had a 4.67 point increase. R010 showed a trend for a reduction on the Inhibit scale that was approaching significance. However, based only on results reaching statistical significance, the inter-case *three demonstration* criterion was not met.

Tau-U analyses demonstrated that R003 and R014 showed a reduction in Shift scale scores in the intervention compared to baseline phase, reflecting a reduction in dysfunctional behaviours. The other participants showed no significant changes. Visual analysis of Shift scores (see **Figure 30**) confirmed that $mean_B$ was higher than $mean_I$ for R003 ($mean_B$ = 51.00 vs. $mean_I$ = 44.00) and R014 ($mean_B$ = 60.80 vs. $mean_I$ = 49.33). For both participants this effect was immediate with a reduction of 7.60 points for R003 and a reduction of 3.00 points for R014 at the start of intervention compared to end of baseline. The inter-case *three demonstration* criterion was not met.

Tau-U analyses demonstrated that R003 showed a reduction on WM scale scores in the intervention phase, indicating a reduction in dysfunctional behaviours, while R018 showed increased WM scores in the intervention compared to baseline phase. Visual analysis confirmed a reduction in WM scores (see **Figure 30**) in the intervention phase for R003 ($mean_B$ = 77.67 vs. $mean_I$ = 67.60) and an increase for R018 ($mean_B$ = 48.83 vs. $mean_I$ = 57.67). For both participants the effect was immediate with a reduction of 15.67 scores for R003 and an increase of 6.33 scores

for R018. R002 and R014 had reductions on the WM scale that were approaching significance. However, according strictly to results reaching statistical significance, the inter-case *three demonstration* criterion was not met.

Table 25.

Tau-U Analysis of Intervention Effects on BRIEF-A Self-Report

Measure	Case	Tau	SD_{Tau}	*z*	*p*
Inhibit	R002	0.100	0.365	0.274	0.784
	R003	0.000	0.365	0.000	1.000
	R005	-0.292	0.391	-0.746	0.456
	R009	0.440	0.383	1.149	0.251
	R010	-0.667	0.347	-1.922	0.055
	R014	-0.800	0.333	-2.400	0.016*
	R018	0.667	0.333	2.000	0.046*
Shift	R002	0.040	0.383	0.104	0.917
	R003	-1.000	0.365	-2.739	0.006**
	R005	-0.292	0.391	-0.746	0.456
	R009	0.120	0.383	0.313	0.754
	R010	-0.583	0.347	-1.681	0.093
	R014	-0.711	0.333	-2.133	0.033*
	R018	0.404	0.333	1.214	0.225
WM	R002	-0.720	0.383	-1.880	0.060
	R003	-0.967	0.365	-2.647	0.008**
	R005	-0.500	0.391	-1.278	0.201
	R009	0.400	0.383	1.045	0.296
	R010	-0.611	0.347	-1.761	0.078
	R014	-0.644	0.333	-1.933	0.053
	R018	0.667	0.333	2.000	0.046*

Note: WM = working memory, ** $p < .01$, * $p < .05$.

In regard to BRIEF-A informant's reports, it should be noted that participant R004 did not have a suitable "significant other" to complete the report. R003 did not return enough informant reports to meet the 3 data points per phase requirement. Tau-U analyses demonstrated that R009 showed an increase in Shift and WM scores in the intervention compared to baseline phase, suggesting an increase in dysfunctional behaviours. No other participants showed significant intervention effects for the informant report scales. Visual analysis (see **Figure 30**) confirmed a reduction in Shift ($mean_B$ = 65.80 vs. $mean_I$ = 66.00) and WM scores ($mean_B$ = 69.40 vs. $mean_I$ = 70.00) for R009. The effect was immediate in both cases with a 4 point increase for Shift and 3 point increase for WM scores at start of intervention compared to end of baseline. The inter-case *three demonstration* criterion was not met.

Table 26.

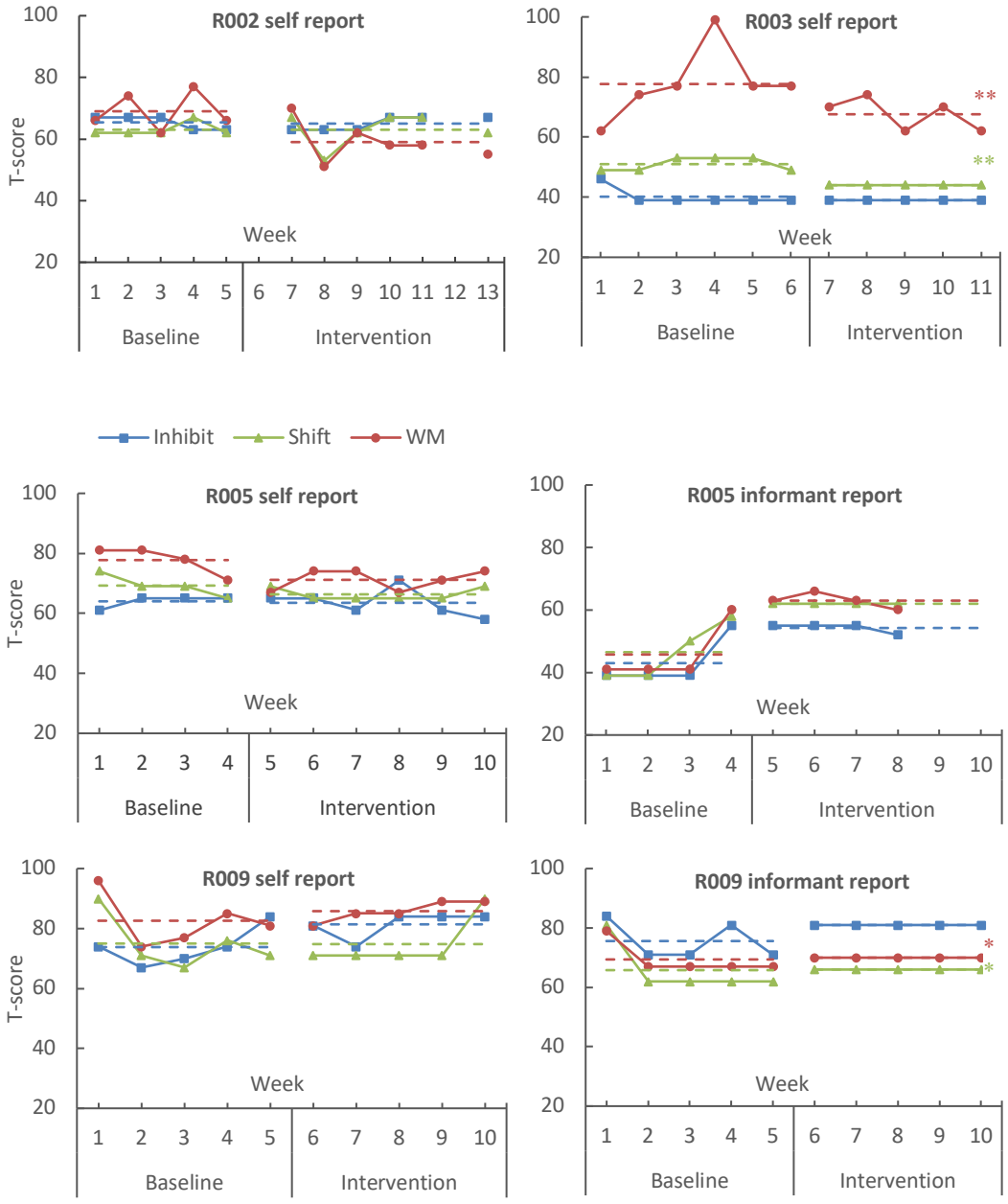
Tau-U Analysis of Intervention Effects on BRIEF-A Informant-Report

Measure	Case	Tau	SD_{Tau}	*z*	*p*
Inhibit	R005	0.500	0.433	1.155	0.248
	R009	0.400	0.383	1.045	0.296
	R010	-0.583	0.391	-1.492	0.136
	R014	0.133	0.333	0.400	0.689
	R018	0.139	0.347	0.400	0.689
Shift	R005	0.688	0.433	1.588	0.112
	R009	0.760	0.383	1.985	0.047*
	R010	0.500	0.391	1.279	0.201
	R014	0.156	0.333	0.467	0.641
	R018	0.083	0.347	0.240	0.810
WM	R005	0.750	0.433	1.732	0.083
	R009	0.760	0.383	1.985	0.047*
	R010	0.667	0.391	1.706	0.088
	R014	-0.378	0.333	-1.133	0.257
	R018	0.278	0.347	0.801	0.423

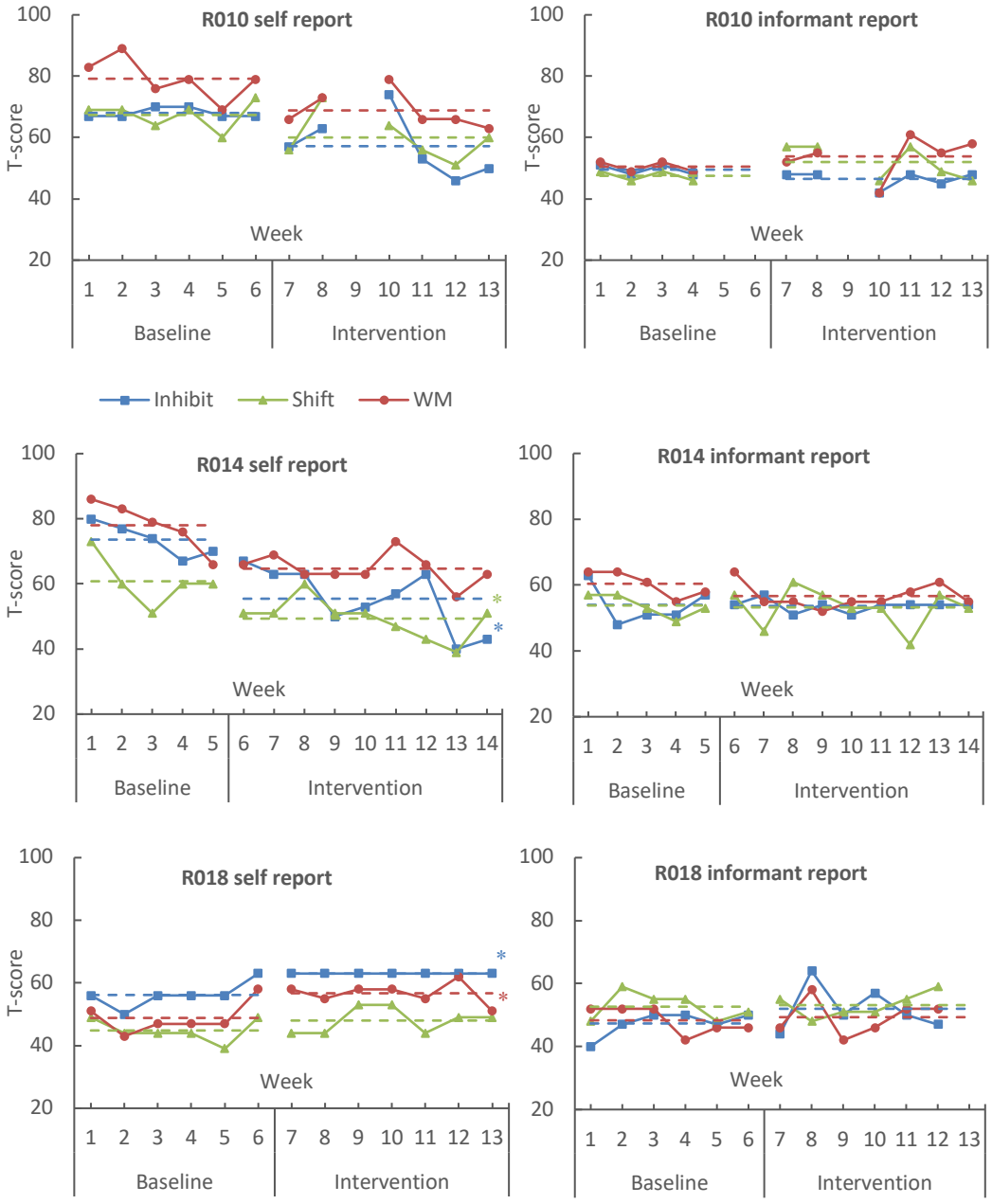
Note: WM = working memory, ** $p < .01$, * $p < .05$.

Figure 30.

T-Scores on the BRIEF-A Self- and Informant-Reports during Baseline and Intervention Phase. The Dashed Lines Represents the Level (Mean Score) for Each Phase.



Note: * = scores with significant differences between phases, ** p < .01, * p < .05.
Informant reports were not available for R002 and R003.



Note: * = scores with significant differences between phases, ** $p < .01$, * $p < .05$.
Informant reports were not available for R002 and R003.

5.3.3 Intervention effects on cognitive performance

Table 27 displays Tau-U results for Go/Nogo task performance. **Figure 31** displays the raw data. Tau-U analyses demonstrated that R010 showed a reduction in Go accuracy in the intervention phase. The other participants showed no significant changes for Go accuracy. Visual analysis of graphs in **Figure 31** confirmed the reduction in Go accuracy for R010 ($mean_B$ = 97.78% vs. $mean_I$ = 95.71%) and this was an immediate effect with a reduction of 4.29% at start of intervention compared to the end of baseline. This did not meet the inter-case *three demonstration* criterion.

Tau-U analyses demonstrated that R002 and R009 had a significant reduction in Go RT in the intervention phase. Visual analysis (**Figure 31**) confirmed the RT reduction for R002 ($mean_B$ = 363.99 ms vs. $mean_I$ = 324.94 ms) and R009 ($mean_B$ = 355.56 ms vs. $mean_I$ = 308.25 ms). This effect was immediate for R009 (initial reduction of 55.99 ms) but delayed for R002 (initial reduction of 5.87 ms). R005 showed a reduction in Go RT in the intervention phase, that was approaching significance. However, according only to statistically significant effects, this effect did not meet the inter-case *three demonstration* criterion.

Table 27.

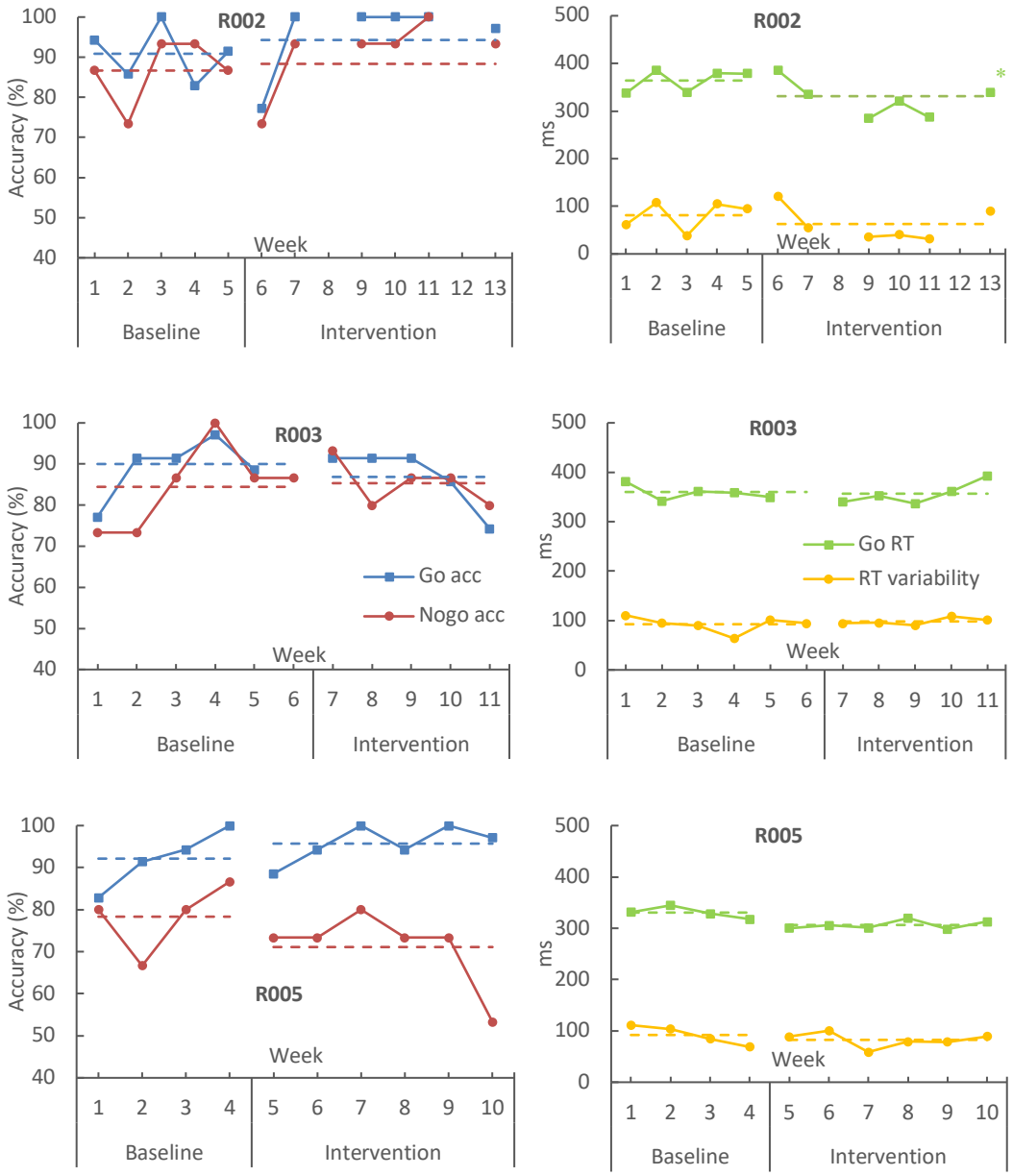
Tau-U Analysis of Intervention Effects on Go/Nogo Performance

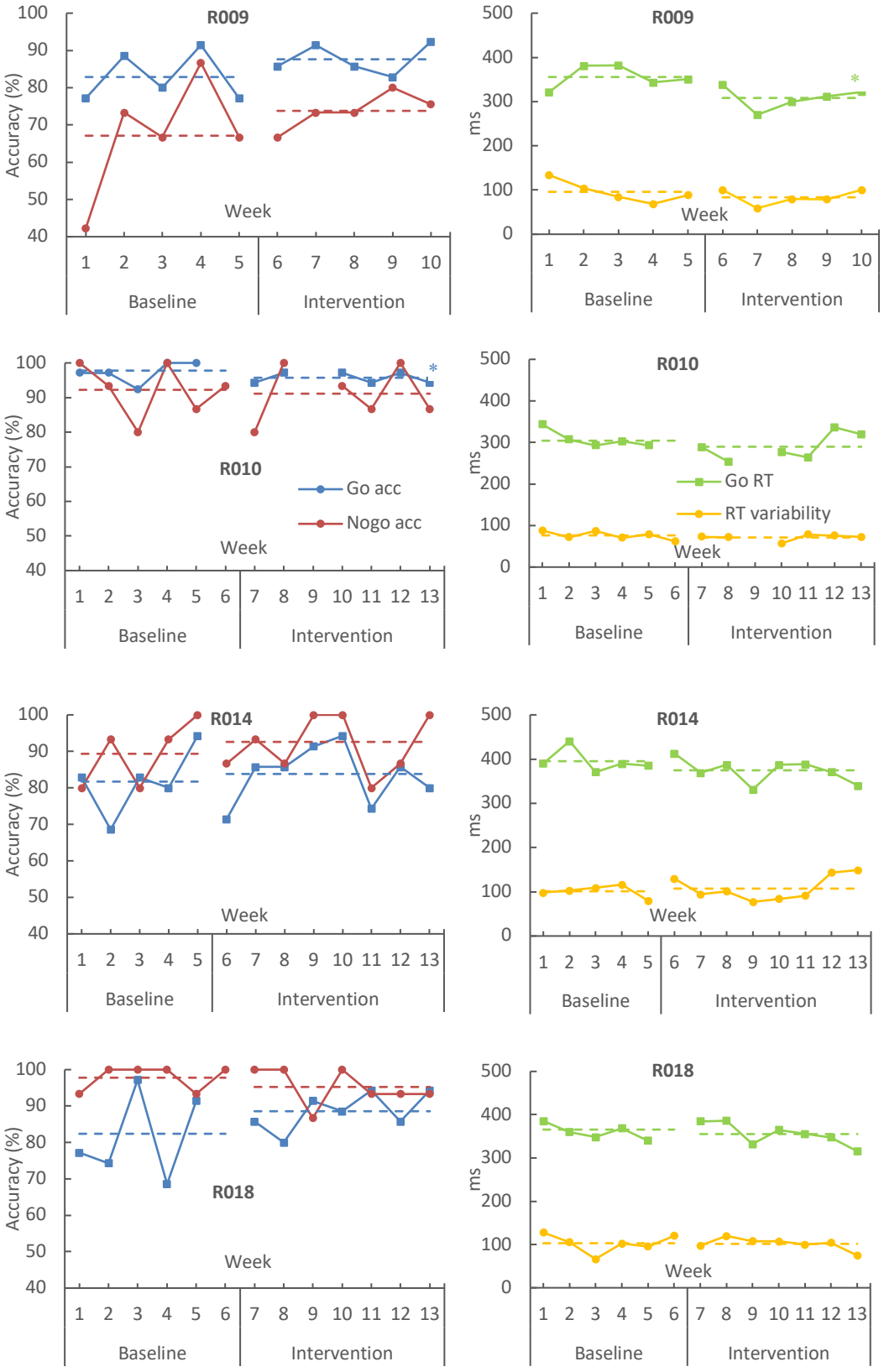
Measure	Case	Tau	SD_{Tau}	*z*	*p*
Go Accuracy	R002	0.533	0.365	1.461	0.144
	R003	-0.533	0.365	-1.461	0.144
	R005	0.083	0.391	0.213	0.831
	R009	0.480	0.383	1.253	0.210
	R010	-0.694	0.347	-2.002	0.045*
	R014	0.178	0.333	0.533	0.594
	R018	0.357	0.333	1.071	0.284
Nogo Accuracy	R002	0.367	0.365	1.004	0.315
	R003	-0.167	0.365	-0.456	0.648
	R005	-0.625	0.391	-1.599	0.110
	R009	0.240	0.383	0.627	0.531
	R010	0.000	0.347	0.000	1.000
	R014	0.111	0.333	0.333	0.739
	R018	-0.286	0.333	-0.857	0.391
Go RT	R002	-0.733	0.365	-2.008	0.045*
	R003	-0.267	0.365	-0.730	0.465
	R005	-0.750	0.391	-1.919	0.055
	R009	-0.920	0.383	-2.402	0.016*
	R010	-0.028	0.347	-0.080	0.936
	R014	-0.333	0.333	-1.000	0.317
	R018	-0.286	0.333	-0.857	0.391
RT variability	R002	-0.400	0.365	-1.095	0.273
	R003	0.433	0.365	1.187	0.235
	R005	-0.083	0.391	-0.213	0.831
	R009	-0.120	0.383	-0.313	0.754
	R010	0.028	0.347	0.080	0.936
	R014	-0.111	0.333	-0.333	0.739
	R018	0.024	0.333	0.071	0.943

Note: ** $p < .01$, * $p < .05$.

Figure 31.

Cognitive Performance Outcomes during Baseline and Intervention Phases for All Participants. The Dashed Lines Represent the Level (Mean) for Each Phase.





Note: * = scores with significant differences between phases, ** $p < .01$, * $p < .05$.

5.3.4 Intervention effects on arousal

Table 28 displays Tau-U results for EC relative frontal alpha amplitude. **Figure 32** displays the raw data. Tau-U analyses revealed no significant intervention effects on EC frontal alpha.

Table 28.

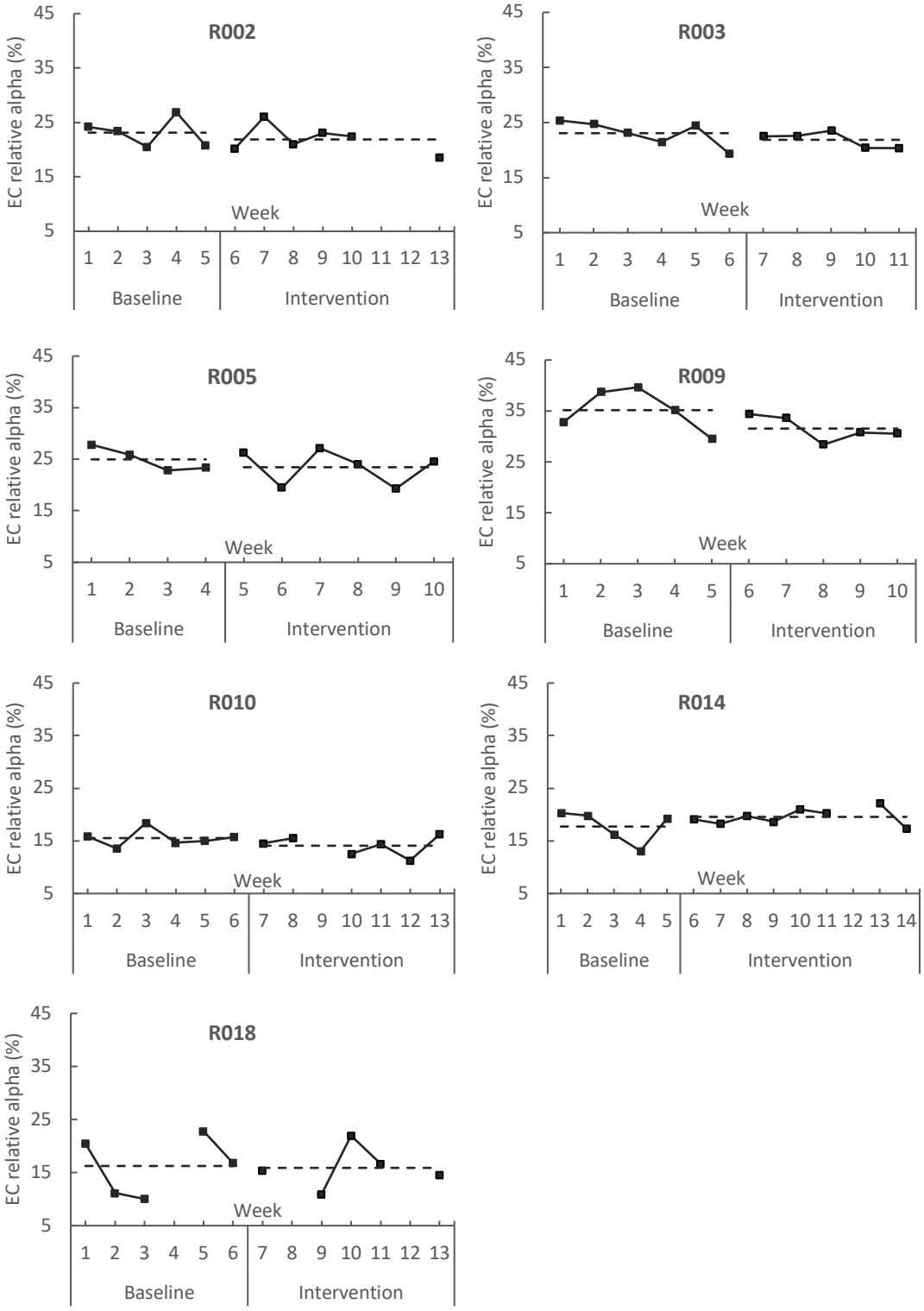
Tau-U Analysis of Intervention Effects on Arousal (EC Relative Alpha Amplitude)

Measure	Case	Tau	SD_{Tau}	*z*	*p*
EC Frontal alpha	R002	-0.267	0.365	-0.730	0.465
	R003	-0.033	0.365	-0.091	0.927
	R005	0.000	0.391	0.000	1.000
	R009	-0.440	0.383	-1.149	0.251
	R010	-0.444	0.347	-1.281	0.200
	R014	0.400	0.342	1.171	0.242
	R018	-0.120	0.383	-0.313	0.754

Note: EC = eyes-closed, ** $p < .01$, * $p < .05$.

Figure 32.

EC Relative Alpha during Baseline and Intervention Phases for All Participants. The Dashed Lines Represent the Level (Mean) for Each Phase.



5.3.5 Intervention effects on resting activation

Table 29 displays Tau-U results for resting activation outcomes. **Figure 33** displays the raw data. Tau-U analyses demonstrated a reduction in resting theta activation for participant R018, however there were no intervention effects for the other participants. Visual analysis of **Figure 33** confirmed that mean theta activation for R018 was larger in the baseline than intervention phase for R018 ($mean_B = 2.16$ vs. $mean_I = 0.40$). This effect was immediate with a reduction of 3.17 at the start of intervention phase compared to end of baseline phase. R005 showed a trend toward an increase in resting delta activation that was approaching significance only. Intervention effects on resting activation did not meet the inter-case *three demonstrations* criterion.

Table 29.

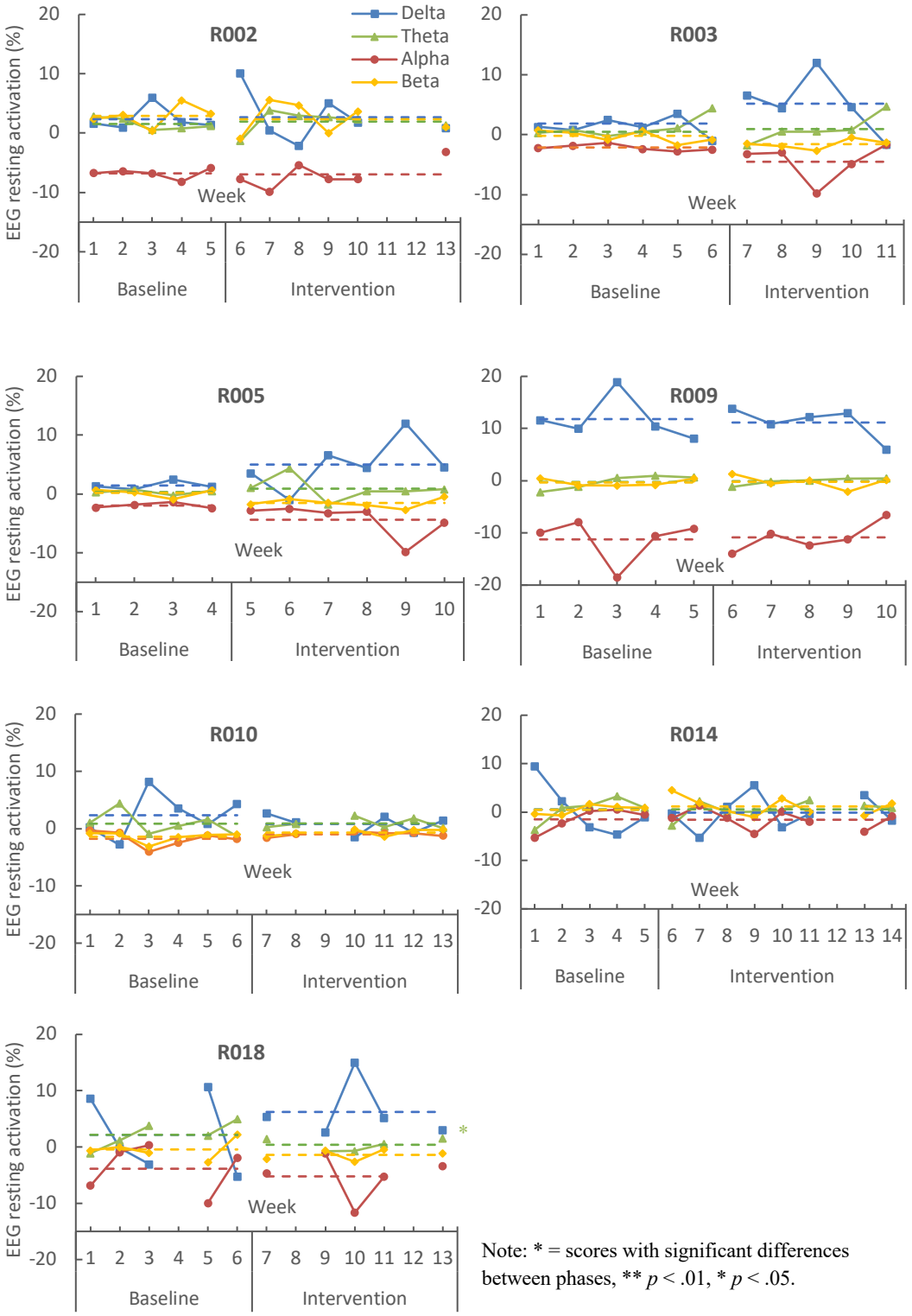
Tau-U Analysis of Intervention Effects on Resting Activation for Delta, Theta, Alpha, and Beta Bands

Measure	Case	Tau	SD_{Tau}	*z*	*p*
Resting delta activation	R002	-0.200	0.365	-0.548	0.584
	R003	0.600	0.365	1.643	0.100
	R005	-0.750	0.391	-1.919	0.055
	R009	0.360	0.383	0.940	0.347
	R010	-0.361	0.347	-1.041	0.298
	R014	-0.200	0.365	-0.548	0.584
	R018	0.600	0.365	1.643	0.100
Resting theta activation	R002	0.467	0.365	1.278	0.201
	R003	-0.367	0.365	-1.004	0.315
	R005	0.500	0.391	1.279	0.201
	R009	-0.600	0.383	-1.567	0.117
	R010	0.194	0.347	0.560	0.575
	R014	-0.275	0.342	-0.805	0.421
	R018	-0.760	0.383	-1.985	0.047*
Resting alpha activation	R002	-0.133	0.365	-0.365	0.715
	R003	-0.433	0.365	-1.187	0.235
	R005	0.500	0.391	1.279	0.201
	R009	-0.200	0.383	-0.522	0.602
	R010	0.417	0.347	1.201	0.230
	R014	-0.250	0.342	-0.732	0.464
	R018	-0.280	0.383	-0.731	0.465
Resting beta activation	R002	-0.200	0.365	-0.548	0.584
	R003	-0.433	0.365	-1.187	0.235
	R005	0.583	0.391	1.492	0.136
	R009	0.120	0.383	0.313	0.754
	R010	0.444	0.347	1.281	0.200
	R014	0.150	0.342	0.439	0.661
	R018	-0.360	0.383	-0.940	0.347

Note: ** $p < .01$, * $p < .05$.

Figure 33.

Resting Activation (Change in Relative Amplitude between EO and EC Conditions) During Baseline and Intervention Phases. The Dashed Line Represents the Level (Mean) for Each Phase.



Note: * = scores with significant differences between phases, ** $p < .01$, * $p < .05$.

5.3.6 Intervention effects on task-related activation

Table 30 displays Tau-U results for task-related activation outcomes. **Figure 34** displays the raw data. Tau-U analyses demonstrated a significant increase in task-related delta activation for participant R018. This was confirmed with visual analysis ($mean_B = 0.27$ vs. $mean_I = 9.63$) and found to be an immediate effect (increase of 11.62 at start of intervention compared to end of baseline). There were no intervention effects on task-related delta activation for the other participants.

Tau-U analyses showed that R018 had a significant change in task-related theta activation in the intervention phase. Visual analysis (see **Figure 34**) confirmed this ($mean_B = -0.06$ vs. $mean_I = -4.11$), suggesting that relative theta showed a task-related reduction during the baseline phase, and this reduction was larger in the intervention phase for R018. This was an immediate reduction of 6.79 at the beginning of the intervention phase compared to end of the baseline phase. There were no intervention effects on task-related theta activation for the other participants.

Tau-U analysis indicated that participants R010 and R014 showed a change in task-related alpha activation in the intervention phase. Visual analysis (see **Figure 34**) confirmed this (R010: $mean_B = -0.79$ vs. $mean_I = 0.47$; R014: $mean_B = -0.68$ vs. $mean_I = 1.59$) suggesting a shift from a task-related alpha reduction in the baseline phase, to a task related alpha increase in the intervention phase for both participants. The effect was immediate with an increase of 1.43 and 1.47 for R010 and R014, respectively. There were no intervention effects on task-related alpha activation for the other participants.

Tau-U analysis demonstrated that R009 and R018 had a significant change in task-related beta activation in the intervention compared to baseline phase. Visual analysis (see **Figure 34**) confirmed this (R009: $mean_B = -1.37$ vs. $mean_I = -0.29$; R018: $mean_B = 0.37$ vs. $mean_I = -3.82$). This suggests an average task-related reduction in beta during baseline phase was reduced for

R009 in the intervention phase, and an average task-related increase in beta for R018 in the baseline phase was reversed to a task-related reduction in the intervention phase. The effects were immediate with R009 showing an increase of 2.63 and R018 showing a reduction of 2.32 at the beginning of the intervention phase, compared to end of baseline phase. There were no intervention effects on task-related beta activation for the other participants. The *three demonstrations* criterion was not met for any task-related activation measure.

Table 30.

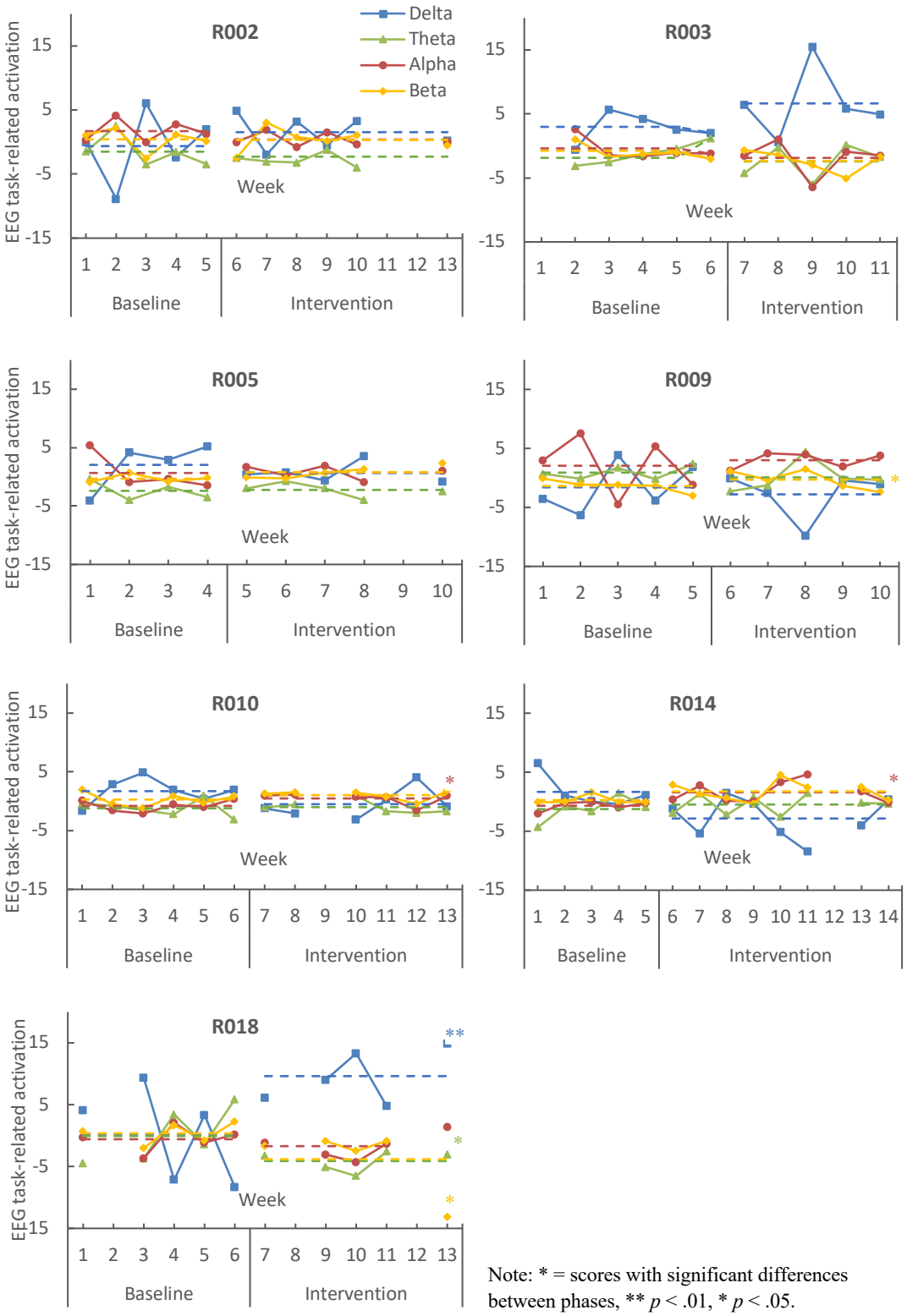
Tau-U Analysis of Intervention Effects on Task-Related Activation for Delta, Theta, Alpha, and Beta Bands

Measure	Case	Tau	SD_{Tau}	*z*	*p*
Task-related delta activation	R002	0.200	0.365	0.548	0.584
	R003	0.680	0.383	1.776	0.076
	R005	-0.600	0.408	-1.470	0.142
	R009	-0.120	0.383	-0.313	0.754
	R010	-0.556	0.347	-1.601	0.109
	R014	-0.550	0.342	-1.610	0.107
	R018	1.000	0.383	2.611	0.009**
Task-related theta activation	R002	0.067	0.365	0.183	0.855
	R003	-0.600	0.383	-1.567	0.117
	R005	0.000	0.408	0.000	1.000
	R009	-0.600	0.383	-1.567	0.117
	R010	0.250	0.347	0.721	0.471
	R014	0.050	0.342	0.146	0.884
	R018	-0.840	0.383	-2.193	0.028*
Task-related alpha activation	R002	-0.467	0.365	-1.278	0.201
	R003	-0.120	0.383	-0.313	0.754
	R005	0.600	0.408	1.470	0.142
	R009	0.120	0.383	0.313	0.754
	R010	0.694	0.347	2.002	0.045*
	R014	0.775	0.342	2.269	0.023*
	R018	-0.520	0.383	-1.358	0.175
Task-related beta activation	R002	-0.133	0.365	-0.365	0.715
	R003	-0.200	0.383	-0.522	0.602
	R005	0.500	0.408	1.225	0.221
	R009	0.760	0.383	1.985	0.047*
	R010	0.333	0.347	0.961	0.337
	R014	0.600	0.342	1.757	0.079
	R018	-0.920	0.383	-2.402	0.016*

Note: ** $p < .01$, * $p < .05$.

Figure 34.

Task-Related Activation (Change in Relative Amplitude between EO and Task Conditions) During Baseline and Intervention Phases. The Dashed Line Represents the Level (Mean) for Each Phase.



Note: * = scores with significant differences between phases, ** $p < .01$, * $p < .05$.

5.3.7 Case studies

R002 was a 50 year old male, who sustained a TBI in a motorbike accident five years and 5 months prior to the study. PTA lasted seven days classifying his injury as 'severe' (Teasdale, 1995), however it was noted that this estimate may have been confounded by medication administered in the hospital and the neuropsychologist assessed resulting impairments as 'mild'. Initial scans were unable to visualise any pathology. R002 had completed 13 years of schooling, and prior to his injury was engaged in full-time work running his own business. He had returned to this role and to an active lifestyle at the time of participation in the study. His cognitive impairments were mild, involving difficulties with attention and social cognition. He was receiving psychological treatment for interpersonal difficulties. R002 had an inconsistent training rate. He completed an average of two training sessions per week over 9 weeks. However, he completed no sessions during weeks four and five due to competing work engagements. Visual inspection showed that he progressed to higher levels in both the state regulation and cognitive training games, suggesting he was able to improve his performance over time. R002 showed an improvement on the WM scale of the BRIEF-A self-report was approaching significance. However, he did not show any statistically significant improvements on outcome measures.

R003 was a 52 year old male who sustained a TBI in a motorbike accident five years and 10 months prior to the study. PTA lasted 14 days classifying his injury as 'very severe'. No initial scans were available but scans one year post-injury showed widespread hemosiderin deposition in the gray/white interface of the corpus callosum. R003 had completed 12 years of schooling. Prior to his injury he was employed full-time running his own business and managing contractors. At the time of the study he had been unable to return to his prior employment and was supported financially by limited casual employment and disability support pension. He had cognitive impairments in attention, EF, and memory. He was experiencing some low mood, emotion dysregulation, and sleep difficulties at the time of the study, for which he was not engaged in any treatment. R003 completed the training program in the minimum timeframe of five weeks. Training rate for the first four weeks was consistent (ranging 3-5 sessions/week),

however he completed the final eight sessions during week five, which is a higher rate than was recommended. R003 progressed through the levels on the IC and WM games, however his performance on the state regulation games showed a decrement over the training stages. This suggests he engaged well with the cognitive training games, but not with the state regulation games. In terms of outcomes R003 showed significant improvements on the Shift and WM scales of the BRIEF-A self-report. However, he showed no significant improvements on cognitive or EEG outcome measures.

R005 was a 37 year old male who had sustained a TBI as the result of a fall four years and 11 months prior to the study. PTA lasted 21 days classifying his injury as 'very severe'. Initial scans showed left occipital extradural and subdural haematoma and he underwent craniotomy, external ventricular drain, and subsequent cranioplasty. R005 had completed 12 years of schooling and was in full-time employment prior to his injury. At the time of the study he was unemployed and receiving disability support pension. His had cognitive impairments in complex attention, EF, and memory. At the time of the study he was engaging in psychological and pharmacological therapy for substance use and anxiety. R005 trained consistently averaging three training sessions per week over six weeks. He progressed to higher levels in the IC and WM games during the intervention phase, however he showed a decrement on the Focus and Relax games, and no change in Zen games. R005 showed no significant improvements on outcome measures in the intervention phase. However, he did show reductions in Go RT and increased resting delta activation (i.e. larger EC-to-EO increase in amplitude) that were both approaching significance.

R009 was a 54 year old male, who sustained a TBI from an assault and fall two years prior to the study. Initial scans did not detect any pathology and PTA was unknown. R009 had undertaken diploma level qualification prior to his injury and was working full-time. He was unable to maintain his employment post-injury and was unemployed at the time of the study. His cognitive impairments were broad across attention, EF, learning, memory, and perceptual-motor domains. At the time of the study he reported some depressive and anxiety symptoms, sleep

difficulties, and pain, but was not engaged in any treatment. R009 completed the training sessions in five weeks. Training rate was inconsistent. He completed seven sessions (higher than the recommended rate) per week for the first three weeks, and then two per week for the final weeks. Generally he did not appear to progress through the levels on any of the games, except for slight increases in the Focus and WM games in the final training stage. For the IC games he showed baseline performance throughout, suggesting that he did not engage at all. In terms of outcomes R009 showed improvements on the WM scale of the BRIEF-A self-report and in Go RT in the intervention phase, compared to baseline. He also showed a significant change in task-related beta activation (i.e. smaller task-related reduction) in the intervention phase.

R010 was a 27 year old female, who sustained a TBI in a motor vehicle accident three years and two months prior to the study. PTA lasted nine days classifying her injury as 'very severe'. Initial scans showed injury to left frontal, parietal, and temporal areas, as well as midline shift, and she underwent a left craniotomy. This participant was a full-time university student prior to her injury, and upon participating in the study she had returned to full-time study. At the time of the study she was engaged in psychological treatment for mild anxiety and stress. She had impaired WM, and was finding verbal memory and attention taxing as reported by her neuropsychology assessment. R010 trained at a consistent rate over eight weeks. Though some weeks she completed fewer than the recommended sessions, she maintained the recommended average of 3 sessions/week. During training R010 showed the largest increase in level for the IC games of all the participants. She showed a smaller improvement on WM games. She maintained her difficulty level for the Focus and Zen games, with a slight decrement in the Relax games. In terms of outcomes, R010 showed a significant change in task-related alpha activation, i.e. shifting from a task-related alpha amplitude reduction in the baseline phase to a task-related alpha increase in the intervention phase. She also showed a reduction in Go accuracy in the intervention phase. Her self-report scores on the Inhibit scale of the BRIEF-A trended toward a reduction in the intervention phase, though this was approaching significance only.

R014 was a 22 year old female, who sustained a TBI in a motor vehicle accident 10

months prior to the study. PTA lasted seven days which classifies her injury as 'severe'. Initial scans showed a right extradural haematoma and temporal contusions. Prior to her injury she had completed an undergraduate university degree and was employed full-time in the health care field. At the time of her participation in the study she had returned to work on reduced duties. She was receiving anti-depressant and psychological treatment for depressive symptoms. Her cognitive impairments according to the neuropsychological assessment were broad, spanning complex attention, memory, EF, and learning. R014 trained quite consistently over nine weeks. She tended to training at below the recommended rate. During training R014 showed progression through the difficulty levels on IC and WM games, a very slight decrement in Focus and Zen games, and no change in the Relax games. R014 showed significantly improved self-report scores on the Inhibit and Shift scales of the BRIEF-A in the intervention phase, and a trend for improved scores on the WM scale that was approaching significance. She also demonstrated a significant change in task-related alpha activation, i.e. shifting from a task-related alpha amplitude reduction in the baseline phase to a task-related alpha increase in the intervention phase.

R018 was a 56 year old male who sustained a TBI in a motor vehicle accident 12 years and 10 months prior to the study. PTA was 29 days classifying his injury as 'very severe'. No pathology was detected on initial scans. R018 had completed 12 years of schooling and was self-employed in a full-time capacity prior to the study. He had been unable to return to work after his injury and remained unemployed at the time of the study. He had cognitive impairments across attention, EF, learning, memory, and perceptual-motor domains. He reported no psychological difficulties at the time of the study. R018 had an inconsistent training rate. Due to unreliable internet connection in his home he was only able to complete three sessions in total over the first two weeks. In weeks three and four he completed more sessions than recommended (six and nine sessions, respectively) and then slowed down to five and two sessions for weeks five and six respectively. During training he progressed through the difficulty levels for the IC and WM games, however he showed a decrement on the state regulation games. In terms of outcomes R018 showed a decrement in Inhibit and WM scale scores for the BRIEF-A self-report in the intervention phase, compared to baseline. He showed reduced resting theta activation (i.e. a

smaller EC-to-EO increase in theta amplitude) in the intervention (cf. baseline) phase. He showed a significantly larger task-related delta amplitude increase, and larger task-related theta amplitude reduction in the intervention phase (cf. baseline). He shifted from a task-related beta amplitude increase in the baseline phase, to a task-related beta reduction in the intervention phase.

5.4 Discussion

The current study aimed to investigate whether a neurocognitive training program that simultaneously targeted state regulation and cognitive impairments could improve functioning in seven individuals with TBI. It was hypothesised that the program would lead to changes in EEG activation measures, and improvements on cognitive and behavioural measures of executive dysfunction. The SCED methodology was utilised to emphasise the inter-individual heterogeneity of this population and a supplementary case study analysis was carried out to investigate clinically relevant factors related to outcomes. According to the inter-case replication (three-demonstration) criterion, the hypothesis that the neurocognitive training program would consistently improve energetic state, cognitive, and behavioural measures across participants was not supported. Furthermore, the expected relationships between activation measures and cognitive/behavioural measures (based on Studies 1-3) were not observed. However, the case studies revealed some consistencies in training engagement, outcomes, and clinical characteristics for individual participants that may help to clarify potential predictors of success with this training approach. Explanations for the lack of inter-case replication of intervention effects as well as clinically relevant individual factors to consider for future research and practice are discussed below.

During the training program participants R010 and R014 showed the greatest progress through difficulty levels in the IC and WM games of all participants, suggesting superior engagement. Their training rate was similar; showing a more consistent rate across a longer period of time than the other participants. Interestingly, research with healthy adults has shown that cognitive training that exceeds three sessions/week can neutralise efficacy, potentially due to cognitive fatigue (Lampit et al., 2014), and so R010 and R014 may have trained at a more optimal

rate than the others.

The reasons for superior training engagement for R010 and R014 may lie in a number of demographic similarities. Both were females aged in their 20's. Younger age is predictive of current technology aid use in ABI (Jamieson et al., 2017), and therefore these participants may have been more comfortable independently using the touchscreen tablet and wireless headset. R010 and R014 had the highest number of years of education of all participants and were the only participants who had engaged in university level study. They also showed continued good educational/occupational functioning following their injuries, and this may reflect retained motivation and self-management abilities that were not present for the participants who were unable to return to work. Both younger age and higher education have been shown to predict neuropsychological improvement following cognitive rehabilitation in brain tumour and schizophrenia patients (Gehring et al., 2011; Ramsay et al., 2018). Participant R005 was relatively younger (37 years old compared to the other four participants who were in their 50's) and was the only other participant who showed a consistent training rate and good progression through the training levels. This further supports the notion that younger age was associated with better engagement with the program.

The role of age could also be related to the theory of cognitive reserve. Cognitive reserve refers to individual differences in the brain that enhance resilience to damage, such as greater synaptic density, number of neurons, and ability to use alternative neural networks (Kaneko & Keshavan, 2012), all of which reduce with age (Charlton et al., 2006; Gordon et al., 2008). Cognitive reserve improves the outcome of brain injury, plays a role in functional restoration and reorganisation during recovery post-TBI (Fraser et al., 2019; Green et al., 2008), and predicts successful outcomes in cognitive rehabilitation generally (Barlati et al., 2019). Cognitive reserve may explain why the youngest participants had better capacity to engage in the training program.

According to PTA duration, R010 and R014 had milder injuries relative to the other participants. While R002 also had a relatively short PTA duration and was also high-functioning,

he was older (50 years) and did not train consistently. Domains of cognitive impairment for R010 and R014 did not differ from the other participants, however they were both engaged in current psychological treatment for anxiety/stress and depressive symptoms respectively and R014 was on anti-depressant medication. Outcomes could be confounded by the alternative treatment, however two other participants (R002 and R005) were also engaged in psychological treatment, and concurrent cognitive and psychological rehabilitation is common in clinical practice.

In terms of outcomes, participants R010 and R014 both showed a change in task-related alpha activation in the intervention phase, compared to baseline. Both participants shifted from a task-related reduction in alpha amplitude in the baseline phase to a task-related alpha increase in the intervention phase. The direction of this effect is unexpected based on prior research that suggests increased task-related alpha activation (i.e. larger task-related reduction in alpha power) is associated with improved cognitive performance (Karamacoska et al., 2018; Valentino et al., 1993). Similarly, in Study 2, increased task-related alpha activation (i.e. larger amplitude reduction) was correlated with better performance on a Go/Nogo task. It must be noted that though the TAU analysis showed a statistically significant effect, the actual magnitude of alpha amplitude change between phases were small - only 0.68% and 1.91% (for R010 and R014 respectively). For R014 state regulation changes occurred alongside improvements in everyday behaviours related to inhibition and attention shifting (and a trend-level improvement in WM behaviours). These changes were large (i.e. a reduction of 11.47 T-scores for Shift scale, and a reduction of 18.16 T-scores for Inhibit scale; equivalent to a 1-to-2 standard deviation change) and, for the Inhibit scale, clinically relevant (i.e. progressing from a clinically elevated T-score at baseline into the normal range in the intervention phase). R010 showed an improvement on the BRIEF-A scale measuring inhibition behaviour, though this effect was approaching significance only. Contrary to expectations, R014 showed no cognitive improvements, and R010 showed a significant decrement in Go accuracy in the intervention phase. However, the decrement for R010 was small (2% change in accuracy) and may reflect a ceiling effect in the baseline phase. It is important to consider that none of these effects met the three-demonstration criteria, and must therefore be interpreted with the necessary caution.

In summary, the participants who showed the greatest training engagement were those who had higher educational/occupational functioning post-injury, longer pre-injury education years, shorter PTA, were of younger age (potentially related to greater familiarity with technology, and cognitive reserve), and those who maintained a more consistent training rate over a longer period of time, compared to other participants. The other participant who was higher-functioning and had shorter duration PTA did progress through the levels, however he did not train consistently and did not have any improvements on outcome measures, so both age and consistency appear to be important. Participants who did not engage as well with the training program were older (in their 50's), had longer PTA duration, and had been unable to return to their usual work post-injury. This suggests that a training program of this type (independent, home-based) is likely only suitable for individuals with less severe injuries and/or impairments. Unfortunately, this study did not recruit enough participants with these characteristics (i.e. at least three to meet the three demonstration criteria) to demonstrate effectiveness for this sub-group of the TBI population.

There are common difficulties within the TBI population that may account for the inconsistencies in training engagement and outcomes in the current study. TBI is characterised by difficulties with apathy, motivation, initiation, and planning (Jamieson et al., 2020; Worthington & Wood, 2018), all of which are necessary to independently initiate and persevere with a consistent training routine. Consistency in training rate is an important factor in cognitive rehabilitation outcomes (Vinogradov et al., 2012). The variability in training rate between participants, and lack of progression through difficulty levels (especially for WM and state regulation games) observed for some participants may reflect a failure to engage adequately in the training program. Future research could address this by assessing the subjective experience of participants, and developing strategies for increasing compliance with the protocol, such as providing instructions to a significant other to help them support the participant to complete the training as recommended. Including a significant other would also leverage the developmental and psychosocial factors that support learning and neuroplasticity. From a developmental perspective cognitive, behavioural, and state regulation ability matures with the co-regulation

from significant attachment figures (Davidson & McEwen, 2012; Walsh et al., 2019). Re-wiring of the injured brain may benefit from the same approach.

Rates of learning and response to cognitive rehabilitation can be affected by the presence of certain pre-intervention cognitive impairments (Ben-Yishay et al., 1987; Michel & Mateer, 2006; Wood, 1988) and intrinsic neural dynamics (Strangman et al., 2008; Vinogradov et al., 2012). The heterogeneity of injury mechanism, consequences, severity, cognitive deficits, process of recovery, and co-existing conditions in TBI is well-established (Kennedy & Turkstra, 2006). Therefore, not only did participants likely begin the intervention phase with differing cognitive deficits and potentials for neuroplasticity, but these inter-individual differences may have impeded their ability to engage adequately in the training (Vinogradov et al., 2012). Furthermore, intra-individual variability in neuropsychological performance is a hallmark feature of TBI (Hill et al., 2013; Rapp et al., 2013). Results may have been confounded not only by high variability in performance on outcome measures week-to-week, but also by highly variable cognitive engagement in each training session.

Personality factors, related or unrelated to TBI, may have accounted for the differential response to training between participants. Inadequate effort allocation to cognitive tasks can be both a neurological consequence of TBI (Seel et al., 2015) and also related to personality style (Stulemeijer et al., 2007). Motivation for treatment, baseline work habits, and attitude toward intelligence are also individual factors that predict engagement and successful outcomes in cognitive rehabilitation (Jaeggi et al., 2014; Medalia & Richardson, 2005).

5.4.1 Limitations and future directions

Engagement may have been impacted detrimentally by the limitations of this particular training protocol in this population. The inconsistent training rate may have been influenced by hardware and software issues, including technical limitations such as poor internet connection, and/or a lack of technological literacy, familiarity, or comfortability, particularly in the older

participants. Such technical limitations were identified in a study using the same training program in children with AD/HD (Zhang, 2018).

The Focus Pocus program was initially designed for and evaluated in children with AD/HD. Previous studies have included parent or caregiver involvement in structuring and reinforcing engagement in the program (Johnstone et al., 2017; Zhang, 2018) which is an important future consideration. Though the principles of the program are relevant to adult populations, the game-based interface was aimed at children (wizard-themed) and so may be less intrinsically enjoyable and reinforcing to adults. Furthermore, the specific EEG frequency bands reinforced and inhibited in the Focus Pocus program, were based on the increased slow wave and reduced fast wave activity observed in AD/HD (Barry et al., 2003). While a similar pattern of EEG was identified in review of the broad TBI literature (Thatcher, 2009), justifying the choice of this particular neurofeedback protocol, Studies 1-3 in this thesis identified some differences between the populations, including a stronger role for delta and theta activation measures in TBI. Overall, the results suggest that this specific NF protocol is not well-suited nor beneficial to the adult TBI population. A NF component tailored to TBI-specific EEG abnormalities would likely be of more benefit. Furthermore, identifying the specific state regulation difficulties that may impede the ability to stay attentive and engaged in the training protocol would be useful for assessing who is likely to benefit.

There was no active control condition used in the current study. Participants were aware that they were receiving no intervention in the baseline phase, and so expectation effects need to be considered. The experimenter was also not blinded to condition. However, as expectation effects are considered to be a result of beliefs this would be more relevant to subjective self-report measures (e.g. BRIEF-A) than more objective measures such as cognitive task performance and EEG measures. The impact of simple practice effects was controlled for with the baseline trend correction used in the Tau-U method. Nonetheless, future studies would benefit from an active control condition involving non-adaptive EF games and sham NF. The BRIEF-A used in the current study was modified to assess behaviours in the past week, rather than in the past 6 months

as in the standard version. It was also restricted to three sub-scales in the current study, and did not assess composite scores which are known to have better psychometric properties (Roth et al., 2005). This modified version is yet to be psychometrically validated and it is unclear how sensitive this measure is to short-term changes. Furthermore, no longer-term follow up of training effects beyond the training phase was conducted. Given the slow, gradual nature of neuroplastic change, enduring effects would be of interest.

The use of SCED methodology in this study aimed to overcome a number of the typical challenges to research in TBI populations, such as recruitment difficulties, small sample sizes, and sample heterogeneity. However, there were limitations to the design of the study that need to be addressed in future research. Though the inter-case three-demonstration criterion is considered best practice within multiple-baseline SCED studies (Kratochwill et al., 2010; Smith, 2012), this is a professional convention and has no specific formal basis (Kratochwill et al., 2013; Kratochwill & Levin, 2010). Given the heterogeneity of TBI presentations, intra-case replication may be more suitable. However, the intra-case three demonstration criterion is limited to ABAB designs (A = no treatment, B = treatment) where the withdrawal of the treatment can also demonstrate effects. The outcomes of neurocognitive training were not expected to reverse back to pre-treatment levels once the intervention was complete, and therefore an ABAB design was not appropriate (Dallery et al., 2013; Kratochwill et al., 2010; Smith, 2012; Tate et al., 2013). A potential future direction for assessing intra-case effects in the multiple-baseline design with more confidence would be to conduct an initial comparison between each individual and a normative sample on relevant outcome measures. Improvement on the individual's most deficient outcome score in at least three cases would reflect intervention effects though the outcomes of interest may differ between participants.

5.4.2 Conclusion

Studies 1 to 3 showed correlations between state regulation measures and cognitive/behavioural outcomes, and supported deficits in each of these domains for individuals

with TBI. Therefore, it is a logical and important to question whether interventions that simultaneously target state regulation and cognitive processes can have a positive impact on the functioning of individuals who have sustained a TBI. The results of this study did not meet the inter-case replication criteria to support the effectiveness of this intervention. However, this study presents a first investigation using the SCED to determine intervention effects on EEG state measures in TBI. This experimental approach is very novel in the EEG literature, and this study shows the utility, feasibility, and sensitivity of this approach in TBI. Furthermore, this methodology allows for a more detailed and clinically relevant picture of the real-world application and challenges involved in administering neurocognitive training in TBI, than do studies based on averaging heterogeneous groups. Based on the results of this study an independently administered neurocognitive training program may be more appropriate for individuals of younger age, shorter PTA, longer pre-injury education years, and those who have maintained or returned to pre-injury educational/occupational functioning. Future SCED studies should aim to confirm these predictive factors by including at least three cases matched on these injury and demographic variables.

CHAPTER 6: General Discussion

Executive dysfunction is a prominent and persistent consequence of TBI. EF rehabilitation aims to ameliorate dysfunction by training cognitive processes and/or the underlying electrophysiological activity of the brain. However, at present the field is lacking a practical framework for understanding the relationship between brain activity and cognitive functioning in TBI. Unlike other models of EF, the Cognitive-Energetic Model (CEM; Sanders, 1983) provides a theoretical explanation of the role of energetic state in cognition, and has established EEG measures of its energetic state constructs (arousal and activation). These energetic state constructs may extend our understanding of the link between EEG abnormalities and cognitive impairments in TBI, with potential implications for cognitive intervention. In this context, the overall aims of this thesis were to investigate: 1) the applicability of the CEM arousal and activation constructs to understanding TBI-related energetic state abnormalities and their relation to EF impairment; and 2) the effectiveness of a CEM-based neurocognitive training program for improving EF in TBI.

A summary of the main findings of the thesis follows, with consideration of how these findings add to understanding of the role of energetic state abnormalities in EF impairment and intervention in TBI. Also discussed are overall implications, limitations, and future directions for integrating energetic state abnormalities into our knowledge of EF impairment and intervention in TBI.

6.1 The role of energetic state in TBI-related EF impairment

6.1.1 Resting activation

Study 1 investigated EEG measures of arousal and activation recorded during resting conditions to determine whether these were impaired in TBI and related to impaired EF. Arousal

was operationalised as global[9] alpha amplitude in the EC condition, with resting activation operationalised as the change in delta, theta, alpha, and beta band amplitudes between EC and EO conditions (as per Barry et al., 2007; Barry & De Blasio, 2017). EF was measured using the Go/Nogo task, as RI has been identified as a specific and robust deficit in TBI (Dimoska-Di Marco et al., 2011). As hypothesised, the TBI group showed intact resting arousal, replicating results from prior research showing no TBI-related abnormality in EC global alpha (Dockree et al., 2004; Fisher et al., 2015; Rushby et al., 2013; Tebano et al., 1988). When compared to controls, the TBI group in Study 1 were characterised instead by reduced resting theta activation (i.e. a smaller EC-to-EO increase in amplitude) and a trend toward increased resting delta activation (i.e. larger EC-to-EO increase in amplitude).

The EC-to-EO increase in theta (i.e. resting theta activation) was diminished in the TBI group (cf. controls) as expected. In line with functional interpretations of FM-theta involvement in sustained attention (Mitchell et al., 2008), this was interpreted to reflect TBI-related attenuation of sustained visual attention to the fixation cross in the EO condition. A trend toward a larger EC-to-EO increase in delta (i.e. resting delta activation) in the TBI group was unexpected, and might have been driven by the lower EC delta for the TBI group (cf. controls). Lower delta amplitudes averaged across the EC and EO conditions in the TBI group (cf. controls) were also unexpected, given that increased resting delta is typically associated with brain pathophysiology (Claassen et al., 2004; Finnigan et al., 2016; Foreman & Claassen, 2012), including TBI (Ianof & Anghinah, 2017; Rapp et al., 2015; Thatcher, 2009). The diminished resting delta in the present TBI sample suggested an over-active/alert state at rest for this group (Franke et al., 2016; Knyazev, 2012), and this interpretation was further supported by the larger beta amplitudes (across EC and EO) in the TBI group (cf. controls) (Laufs et al., 2006). The over-active/alert resting state might be due to

[9] Note that technical difficulties resulted in a 'global' measure that was derived from fronto-central electrodes only. As arousal should differ uniformly across the scalp (Barry et al., 2007) this approach is justifiable, but still does not reflect a true 'global' alpha.

psychological/emotional symptoms associated with heightened arousal in this TBI sample (Franke et al., 2016), or age differences between the groups (Barry & De Blasio, 2017), although this remains to be clarified.

Increased resting delta activation (i.e. larger EC-to-EO amplitude increase), reduced resting theta (i.e. smaller EC-to-EO increase), and increased alpha activation (i.e. larger EC-to-EO reduction) were associated with impaired RI performance. Delta and alpha activation were associated broadly with both Go and Nogo processes (accuracy and RT variability) suggesting roles in general cognitive processing, rather than inhibition per se. Theta activation was associated only with Nogo accuracy, which may suggest a specific role in inhibition. However, this association was evident only at the Slow event-rate, which places comparatively greater demands on sustained attention, and given the established associations between theta and sustained attention (Mitchell et al., 2008), it was proposed that an attention deficit might underlie the poorer Nogo performance. There were no group differences in the activation-cognition associations, indicating universal rather than TBI-specific relationships. Overall, the results of Study 1 suggested that the brain's ability to activate in response to environmental or processing demands (i.e. activation), rather than the brain's baseline resting state (i.e. arousal), is impaired following a TBI and that this impairment is associated with deficient RI task performance.

6.1.2 Task-related activation

Study 1 provided evidence for impaired activation in resting conditions, which reflects the mobilisation of energetic state in response to visual processing demands, but not in response to cognitive demands. Study 2 investigated the presence and associations of task-related activation impairments in TBI by examining EEG amplitude changes between an EO resting condition and an auditory Go/Nogo task condition. In Study 2, the TBI group showed a task-related reduction in delta amplitude (cf. a task-related increase for the controls), and a task-related increase in beta amplitude (cf. a task-related reduction for controls). The TBI group also showed an enhancement of the task-related increase in theta amplitude, and a trend-level attenuation of the task-related

reduction in alpha amplitude, compared to controls.

The present operationalisation of activation as the EEG amplitude change between EO and cognitive task conditions, demonstrated effects in line with evidence from event-related EEG measures. The absence of a task-related increase in delta activation for the TBI group was consistent with associations between delta ERS and the inhibition of task irrelevant processes and distracting stimuli (Harmony, 2013; Nazari et al., 2011), suggesting that the TBI group did/could not employ this inhibitory process in the same manner as controls. The association between attenuated or absent task-related delta activation and reduced Go accuracy, and longer and more variable RTs, suggested that the failure to inhibit interference detrimentally affected task performance. The tendency for the TBI group to have reduced task-related alpha suppression (cf. controls) is consistent with prior research in TBI (Fisher et al., 2015). It is also in line with cortical arousal interpretations of alpha ERD (Bazanova & Vernon, 2014; Klimesch, Sauseng, & Hanslmayr, 2007; Loo et al., 2009; Pfurtscheller & Lopes Da Silva, 1999), suggesting an attenuation of the typical task-related increase in cortical arousal in the TBI group. Reduced alpha suppression was associated with reduced Go accuracy, and longer and more variable RTs, supporting a role for regulation of cortical arousal in supporting cognitive performance. Notably, associations between delta and alpha activation and performance were present for Go processes only (accuracy, RT, and RT variability), suggesting a role in attention, rather than inhibition (i.e. Nogo accuracy). The task-related increase in beta amplitude, exclusive to the TBI group, was consistent with associations between beta ERS and inhibitory control (Aron, 2011; Huster et al., 2013) and/or failure to flexibly modify behavioural set (Engel & Fries, 2010). This might suggest that the TBI group performed the task with a more rigid maintenance of motor set (i.e. more automated responding; Dockree et al., 2006), potentially resulting in a greater demand for or more difficult inhibitory control. However, task-related beta activation was not associated with performance in Study 2, and thus the direct role of beta activation in motor inhibition and response processes was not supported here.

Theta activation was the only EEG measure to be modulated by event-rate. A task-

related increase in frontal hemispheric theta was enhanced in the TBI group (cf. controls), in the Fast event-rate (cf. Medium). Since event-related frontal theta enhancement is associated with enhanced sustained attention (Mitchell et al., 2008) and top-down attentional control (Cavanagh & Frank, 2014; Clayton et al., 2015), this effect likely reflected that with greater exogenous stimulation (via fast event-rate), a TBI-related deficit in top-down modulation of theta activity at the slower/less stimulating event-rates could be ameliorated. In studies 1 and 2, RT variability was the only performance variable to be modulated by event-rate (in the Fast task), and it too is associated with top-down attentional control in general (Bellgrove et al., 2004; Ramchurn et al., 2014) and in TBI specifically (Stuss et al., 1989, 2003; Vasquez et al., 2018). However, no direct association between theta activation and RT variability was observed in this thesis. The implications of the event-rate modulation of theta activation and RT variability are discussed in more detail below (section 6.1.3).

6.1.3 External modulation of energetic state via event rate

One approach to investigating state regulation is to externally modulate energetic state by manipulating the stimulus presentation rate in a cognitive task. Sanders (1983) and others (Raymaekers et al., 2004; Van Der Meere & Stemerdink, 1999) propose that a fast event-rate induces a hyper-activated state (resulting in fast, impulsive responding) and that a slow event-rate induces a hypo-activated state (resulting in slow, inattentive responding). Theoretically then, healthy performance should show a quadratic or inverted-U effect with optimal performance at the Medium compared to Fast/Slow event rates. In Studies 1 and 2, the TBI group showed broad deficits in Go/Nogo performance (cf. controls) that did not differ between the Fast, Medium, and Slow event-rate versions of the task. However, in Study 1 the TBI group showed an additional deficit in regulating response speed (RT variability) in the Medium condition (c.f. Fast). An impairment specific to the Medium event-rate reflects neither hyper- nor hypo-activation, but instead reflects difficulty regulating state when the external demand is lesser, and a more top-down or internally driven regulatory process is required. The results of Study 1 led to the conjecture that the relatively reduced performance deficit for the TBI group (cf. controls) in the

Fast condition (cf. Medium), might reflect impaired top-down modulation of activation, which was ameliorated by exogenous (bottom-up) state modulation in the Fast condition. This interpretation is consistent with evidence that in TBI patients with impaired sustained attention, the provision of exogenous (bottom-up) stimulation can improve maintenance of attentional control and goal-directed behaviour (Fish et al., 2007; Manly et al., 2004). Furthermore, an exogenous alerting cue can increase functional connectivity of the sustained attention network in adults with TBI, to a level that is comparable with controls (Richard et al., 2018). Studies of event-rate in AD/HD have also shown improvement or normalisation of RT variability at a fast (compared to slow or moderate) event-rate, interpreted as effective up-regulation of energetic state induced by the relatively heightened stimulation of the fast event-rate (Andreou et al., 2007; Börger & Van Der Meere, 2000; van der Meere et al., 1995).

In order to confirm that the Fast event-rate differentially modulated energetic state in TBI, Study 2 quantified task-related EEG activation at each of the event-rates of the Go/Nogo task. In Study 2, the Fast (cf. Medium) task induced a relative improvement in RT variability in the TBI group (cf. controls), in line with Study 1 (though this was only a trend-level effect, likely due to reduced statistical power in the smaller sample subset). However, event-rate did differentially modulate task-related hemispheric theta activation between the groups. The TBI group showed a relative enhancement of hemispheric theta activation (cf. controls) that was specific to the Fast (cf. Medium) event-rate. Taken together the findings from Study 1 and 2 suggest that, for the TBI group, the exogenous demands of the fast event-rate were sufficient to improve RT variability, through enhancement of hemispheric theta activation. This is supported by the literature associating both RT variability and theta activity with top-down attentional control (Bellgrove et al., 2004; Cavanagh & Frank, 2014; Clayton et al., 2015; Ramchurn et al., 2014). According to the Cognitive Energetic Model (CEM; Sanders, 1983), (CEM; Sanders, 1983), the impaired top-down regulation of RT variability and theta activation in the Medium and Slow tasks for the TBI group, could reflect problems with the *effort* pool or *evaluation* mechanism, given that these mechanisms are responsible for the top-down, conscious modulation of energetic state based on performance monitoring.

In controls, task-related hemispheric theta activation was the only measure to show the expected quadratic pattern induced by event-rate (i.e. larger in the Medium than Fast/Slow), suggesting a possible sensitivity of frontal hemispheric theta activation to modulation through event-rate. Note that this effect was different for frontal medial theta which showed a linear increase with event-rate for both groups, in line with previous associations between FM-theta and task difficulty (Mitchell et al., 2008). The expected quadratic effect was not observed in any performance or other activation measures in the present studies, suggesting that the parameters for event-rate manipulation used here may not have been ideal for modulating energetic state. In Study 1, the Fast task induced the expected reductions in Go and Nogo accuracy across groups. However, the expected effect of the Slow event-rate on accuracy was not observed. The ISI for Fast and Slow event-rates in the current studies were within the bounds of existing research (Curtindale, 2020; Metin et al., 2012). However, the ISI for the Slow condition (4 seconds) in the present studies was slightly faster than the reported event-rates in a meta-analysis in AD/HD (Metin et al., 2012). The authors reported an ISI range of 4.25 – 8.30 seconds (M = 6.90) as constituting a 'slow' event-rate. This may explain the lack of accuracy effects in the Slow (cf. Medium) condition, and the lack of group differences on performance measures in the Slow condition in the present studies. That is, the ISI may not have been slow enough to induce hypo-arousal. Most of the research on event-rate has been conducted in children with AD/HD with varying ISI's and results (Epstein et al., 2012; Metin et al., 2012). As such, the optimal ISI ranges for effective manipulation of energetic state need clarification, especially in TBI (this is the first event-rate study in TBI to the author's knowledge). Therefore, further research is necessary to optimise the event-rate parameters to investigate the 'top-down deficit' hypothesis presented in this thesis. This may also clarify the role of the CEM *evaluation* and *effort* mechanisms in state regulation in TBI.

6.1.4 Everyday EF

The impact of executive dysfunction on the lives of individuals extends far beyond performance on computerised, laboratory tasks. It is the everyday manifestations of EF

impairments that negatively impact quality of life, occupational outcomes, and relationships for those with TBI (Tate, 1999; Vilkki et al., 1994; Wood & Rutterford, 2006). Therefore, Study 3 aimed to understand the meaning of state regulation impairments for individuals with TBI by investigating relationships with everyday EF behaviours (measured by BRIEF-A and BIS-11 questionnaires).

Study 3 showed that reduced arousal was associated with impaired everyday behaviours related to RI specifically (the BRIEF-A Self-Monitor subscale, and BIS-11 Motor subscale). This association is consistent with arousal models of AD/HD which propose that disinhibited behaviour is an effort to up-regulate sub-optimal arousal levels (Clarke et al., 2002; Lubar, 1991; Satterfield & Cantwell, 1974). It is proposed in this thesis that hypo-arousal may have an indirect impact on disinhibited behaviour by eliciting compensatory over-activation in response to environmental demands. This indirect relationship has been demonstrated in children with AD/HD (Zhang et al., 2018) but was not explicitly tested here and therefore requires further investigation.

In Study 3, enhanced resting delta activation (i.e. larger EC-to-EO increase in amplitude) and enhanced resting alpha activation (i.e. larger EC-to-EO reduction in alpha amplitude) were associated with impaired everyday EF; specifically for a subscale measuring everyday RI (i.e. the BIS-11 Motor subscale). The direction of these relationships were consistent with observations in Study 1, where increased resting delta and alpha activation were associated with impaired RI task performance. This was an interesting finding given the inconsistent or non-existent relationships typically observed between laboratory-based and everyday EF measures (Chaytor & Schmitter-Edgecombe, 2003; Gioia & Isquith, 2004; Sbordone, 2008). The results presented here indicated the specificity of resting delta and alpha activation to the cognitive and behavioural processes involved in RI.

While reduced resting theta (i.e. smaller EC-to-EO increase) and increased resting beta activation (i.e. larger EC-to-EO increase) were associated with worse everyday EF and inattentive behaviours in Study 3, they showed no consistent relationship with RI task performance in Study

1. This suggests that resting theta and beta activation do not have an association with RI specifically, but rather a broader relationship with attention and EF generally. These broad associations likely reflect the role of theta in cognitive processes such as sustained attention (Mitchell et al., 2008), and top-down attentional control (Cavanagh & Frank, 2014; Clayton et al., 2015). Further, theta activity has been implicated in the arousal-regulation network, involving the ACC, thalamus, locus-coeruleus, and norepinephrine system (Aston-Jones & Cohen, 2005; Shah et al., 2017). Beta activity has similarly been linked with attentional control and the fronto-thalamocortical arousal network in TBI (Shah et al., 2017), however the functional interpretation of resting beta activity is less well-established (Engel & Fries, 2010), and overall findings for beta in the present thesis were less consistent, compared to those for theta. Compared to task-related activation, resting activation reflects more intrinsic, endogenous energetic state regulation, since there is no external cognitive demands in the resting conditions. That resting but not task-related activation was associated with everyday attention and EF, points to the importance of intrinsic, endogenous state regulation in impaired everyday behaviour in the present sample. This result also indicates an ameliorating effect of external stimulation (through task demands and increasing event-rate) on performance and state regulation measures in the present TBI sample, in line with previous research in TBI groups (Fish et al., 2007; Manly et al., 2004; Richard et al., 2018). Overall, the results are proposed to support a role for reduced resting theta activation and increased resting beta activation in everyday attention impairments in TBI, resulting from deficient state regulation by the frontal-thalamocortical arousal system, which underlies subsequent behavioural dysregulation in everyday life.

6.1.5 Injury variables

The degree of EEG abnormality in TBI has been associated with both the degree of injury severity and the degree of white matter damage (Thatcher, Biver, et al., 2001; Thatcher, Biver, McAlaster, & Salazar, 1998; Thatcher, Biver, McAlaster, Camacho, et al., 1998; Thatcher, North, et al., 2001). However, these relationships had not previously been investigated in regard to CEM-based state measures. Study 3 also investigated associations of arousal and activation with

measures of injury severity and chronicity in the TBI group.

Arousal was not associated with injury variables, building on evidence from Studies 1 and 2 that arousal is not a useful indicator of energetic state abnormalities in TBI. However, significant associations between activation and injury characteristics were observed. Greater injury severity was associated with increased resting theta activation (i.e. larger EC-to-EO increase in amplitude) and reduced resting beta activation (i.e. smaller EC-to-EO increase in amplitude), and greater severity and chronicity were associated with increased task-related beta activation (i.e. larger EC-to-EO increase in amplitude). Given the typical association between degree of severity and degree of impairment (Thatcher, Biver, McAlaster, & Salazar, 1998; Thatcher, Biver, McAlaster, Camacho, et al., 1998), the direction of these effects was somewhat surprising, as increased resting theta and reduced resting beta activation were associated with less impairment on everyday EF measures in the whole sample (including controls). This is consistent with evidence for the complexity of relationships between injury severity, white matter integrity, and cognitive and behavioural function in TBI (Kinnunen et al., 2011; Newsome et al., 2007; Olsen et al., 2015). Functional MRI studies have observed similar dissociations whereby increased activation was associated with increased injury severity, but better performance on a cognitive control task (Scheibel et al., 2007, 2009) and less impaired everyday EF (measured by the BRIEF-A; Olsen et al., 2015). This has been interpreted as possibly reflecting a compensatory effect, with increases in activation indicating greater or more distributed cognitive and energetic resources employed to perform the task and to regulate everyday behaviour (Olsen et al., 2015; Scheibel et al., 2007, 2009).

6.2 CEM-based neurocognitive training in TBI

Study 4 aimed to investigate the efficacy of simultaneously training energetic state regulation and cognitive processes in TBI. Based on TBI-related abnormalities in state regulation (activation) and associations between energetic state and cognition and behaviour observed in Studies 1-to-3, energetic state is a logical target for EF rehabilitation. Furthermore, consistent

with the CEM and empirical evidence for the effect of baseline EEG activity on the rate and nature of learning (Mukai et al., 2007; Vernon et al., 2003) and on cognitive training outcomes (Strangman et al., 2008; Vinogradov et al., 2012), the ability to regulate energetic state in a way that facilitates learning is necessary for engagement in and benefit from cognitive training.

The Focus Pocus neurocognitive training program uses NF to train state regulation (with exercises targeted at attention and relaxation, and the simultaneous combination of these states), and cognitive training targeting RI and WM processes. This particular program offered an alternative to traditional, time and finance intensive sequential cognitive rehabilitation and allowed participants to independently train state and cognitive processes simultaneously, using commercially available software and hardware. A SCED with seven participants was utilised to overcome challenges of larger scale clinical research in TBI, by requiring fewer participants while still providing adequate experimental control to infer intervention effects.

According to the inter-case replication criteria, the results of Study 4 did not provide evidence that the neurocognitive training program resulted in hypothesised improvements in state regulation, cognition, nor behaviour, across participants. Notably, there was considerable between-subject variability in the rate of training and the progression through difficulty levels, which suggested that some participants did not adequately engage in the training program. In general, there are a number of characteristic difficulties in TBI that may serve as barriers to training engagement, including difficulties with apathy, motivation, initiation, and planning (Jamieson et al., 2020; Worthington & Wood, 2018). Pre-intervention cognitive impairments, cognitive reserve, and potential for neuroplasticity are also factors that can enhance or impede engagement in cognitive rehabilitation (Ben-Yishay et al., 1987; Michel & Mateer, 2006; Strangman et al., 2008; Vinogradov et al., 2012; Wood, 1988). These factors were not measured in the study and are presented as avenues for necessary future investigation.

However, a supplementary case series identified some important consistencies in training engagement, outcomes, and clinical characteristics for individual participants, shedding light on

potential predictors of success with neurocognitive training. Two participants had consistent training rates and progressed well through difficulty levels. Accordingly, it was proposed that the neurocognitive training program may be more appropriate for individuals of younger age, shorter PTA, longer pre-injury education years, and who had returned to or maintained their pre-injury educational/occupational functioning. These factors are in line with the theory of cognitive reserve, which explains the enhanced plasticity and resilience to injury of a younger brain. Furthermore, younger age in adults is predictive of technology aid use in ABI (Jamieson et al., 2017), and so familiarity with training technology may have had a role in superior engagement in the program for these participants.

The two participants who demonstrated superior training engagement also showed consistencies in state regulation outcomes, specifically a change in task-related alpha activation in the intervention phase, compared to baseline. However, these changes were small and in the unexpected direction based on prior research (Karamacoska et al., 2018; Valentino et al., 1993) and the results of Study 2. One of these participants showed large and clinically relevant training-related improvements in inhibition and attention shifting behaviours; however, these behavioural improvements were not evident in the other participant. These small and/or inconsistent effects do not provide support for the generalised effectiveness of the program in improving everyday functioning, nor do they provide support for improved state regulation as the mechanism of functional improvements. However, neural changes have been shown to precede behavioural changes (Atienza et al., 2002; Lampit et al., 2015), and so it is possible that functional transfer may follow state regulation changes after some time. A follow-up evaluation would be needed to test this hypothesis.

6.3 Implications

6.3.1 Cognitive-energetic model in TBI

The extant literature in TBI has focused on baseline or resting EEG measures in order to establish deficiencies in energetic state (for reviews see Rapp et al., 2015; Thatcher, 2009).

However, this approach neglects the crucial aspect of state 'regulation' that is required to respond dynamically to an unpredictable and ever-changing environment. The CEM accounts for the role of regulation by differentiating between baseline energetic state (arousal) and the dynamic mobilisation of energetic state in response to the environment or processing demands (activation). This thesis has established the presence of TBI-related deficits in activation, and thus in the ability of individuals with TBI to regulate their energetic state, in comparison to their healthy counterparts. The absence of observed abnormalities in arousal supports a distinct role of deficient state *regulation* rather than baseline resting state in TBI-related impairments. The absence of arousal deficits, and presence of activation deficits, replicate prior findings using resting and task-related alpha measures in TBI (Fisher et al., 2015; Rushby et al., 2013). This thesis has extended evidence for activation impairments to the delta, theta, and beta EEG bands, and to external manipulations of energetic state via event-rate. Furthermore, it has also contributed evidence for associations between activation and cognitive performance, everyday EF, and injury variables, suggesting a role for impaired state regulation in the cognitive and behavioural sequelae of TBI.

Activation impairments for the TBI group were dissociable for resting compared to task-related activation. In the delta band, the TBI group showed increased resting activation and reduced task-related activation compared to controls. Conversely, in the theta band the TBI group showed reduced resting activation and increased task-related activation. While there were no resting activation impairments in the alpha or beta bands, the TBI group did show trend-level attenuation of task-related alpha and significant enhancement of task-related beta activation. This dissociation reflects the different processing requirements of the conditions - with EC-to-EO activation reflecting the mobilisation of visual processing networks, and task-related activation reflecting mobilisation of networks involved in attention and RI. However, from a CEM-perspective the difference between resting and task-related activation might also reflect the difference between intrinsic (internally driven, top-down) and extrinsic (stimulus driven, bottom-up) state regulation. That is, the change in state from EC to EO reflects an internally driven activation of arousal since there are no specific external cognitive demands in the resting

conditions, whereas state change from EO to the task condition is likely driven by the specified external task demands and is thus more reflective of extrinsic state regulation. Of course it is likely and in line with the CEM (given the reciprocal top-down and bottom-up influences) that both intrinsic and extrinsic state regulation are at play during both resting and task conditions. It is suggested here that is a matter of weighting, such that regulation is more extrinsic and less intrinsic in task conditions (and vice versa for the resting conditions). Theta activation was particularly sensitive to manipulations of energetic state in this thesis (resting, task-related, and event-rate manipulations) and also responded differently to these manipulations in the TBI group, compared to controls. Theta activation therefore, might be a good index of intrinsic vs. extrinsic state regulation in TBI and is therefore discussed in more detail in the following section (6.3.1.1). Briefly though, compared to controls, the TBI group showed reduced resting theta activation but enhanced task-related theta activation (particularly in the most demanding fast event-rate task), suggestive of reduced intrinsic but enhanced extrinsic state regulation, respectively.

Relationships between the CEM-defined activation measures and cognitive performance measures were also demonstrated. These relationships did not differ between groups, thus it appears that TBI does affect the nature of these relationships. Rather, this suggests that TBI induces impairment in state regulation which, in line with the CEM, impedes cognitive processing. Note that this interpretation is offered with a degree of caution given the small sample size involved in the correlation analyses. It is possible that correlation coefficients would differ between groups in a more highly powered sample, and this needs to be clarified in future research. Some imaging research has suggested that cortical reorganisation which occurs as a result of TBI may change the nature of activation-cognition relationships (Newsome et al., 2007).

The activation-cognition relationships demonstrated in this thesis suggest broad impacts of energetic state on cognition. The presence of relationships for Go and Nogo accuracy, RT, and RT variability suggest a role for activation in efficient attention, inhibition, response speed, and response variability, respectively. The aim of this thesis was not to map activation measures on to the specific information processing stages outlined in the CEM (i.e. pre-processing, feature

extraction, response choice, motor adjustment), but rather to provide an initial investigation of the association between CEM-defined energetic state measures and cognitive task performance deficits in TBI. Research using event-related potentials to map the more precise relationships between ongoing EEG oscillations and the discrete temporal stages of information processing is progressing in healthy controls (Karamacoska et al., 2017, 2018, 2019). Though beyond the scope of this thesis, clarification of these relationships (first in controls, then in TBI samples), might narrow down the energetic state variables most relevant to target in cognitive rehabilitation for TBI.

Associations between energetic state and everyday EF behaviours were also observed for resting, but not task-related activation. Enhanced resting delta activation (larger EC-to-EO amplitude increase) and enhanced resting alpha activation (larger EC-to-EO amplitude reduction) were associated with everyday EF measures specific to RI. The direction of delta and alpha activation relationships were consistent for both lab-based measures (Nogo accuracy) and everyday measures (BIS-11 Motor subscale) of RI, suggesting a distinct role of resting delta and alpha activation in cognitive and behavioural manifestations of deficient inhibitory control. In contrast, resting theta and beta activation were associated with broad everyday EF measures, reflecting a more generalised role in in both disinhibited and inattentive behaviours.

An association between reduced arousal and everyday RI was observed. Based on AD/HD models, it has been suggested that arousal may have an indirect effect on EF, through compensatory over-activation (Zhang et al., 2018). However, this indirect relationship was not examined in this thesis, and would need to be clarified. Importantly, there were no group differences in arousal, nor was arousal associated with injury variables, suggesting that the role of arousal in everyday EF is not specific to TBI. Overall, the results of Studies 1-to-3 establish a specific deficit in *activation* in TBI and provide evidence that this deficit is associated with impaired cognition and behaviour. These findings highlight the need for interventions that involve regulation of energetic state, and the importance of measures of activation (i.e. change measures) to assess outcomes in intervention studies.

6.3.1.1 Theta activation as an index of impaired state regulation in TBI

A number of findings from the first three studies of this thesis converge to propose theta activation as a good index of impaired top-down state regulation in TBI. Firstly, reduced *resting* theta activation (intrinsic/top-down state regulation) and *enhanced* task-related theta activation (extrinsic/bottom-up regulation) differentiated the TBI group from controls. Second, theta activation was the only EEG measure to show sensitivity to external modulation by event-rate, and this modulation was enhanced in the TBI (cf. control) group. Third, resting theta activation was associated with broad impairments in everyday attention and EF behaviours. Fourth, theta activation was associated with injury severity and chronicity in the TBI group. Finally, the results observed here align with existing functional interpretations of the role of theta activity in top-down attentional control (Cavanagh & Frank, 2014; Clayton et al., 2015), via the ACC and arousal-regulation network of the brain (Aston-Jones & Cohen, 2005; Shah et al., 2017).

Across groups, theta amplitude showed an incremental increase from EC to EO to Task conditions – an effect in line with up-regulation of cortical arousal in response to increasing environmental/processing demands. The results of the group comparisons, suggest a deficit in top-down regulation of energetic state (indexed by theta activation) in TBI, which can be ameliorated to a degree by extrinsic/bottom-up stimulation. Evidence for this is that the TBI group showed reduced resting activation (smaller EC-to-EO increase) compared to controls, suggesting an attenuated increase in arousal in the EO condition which has no specific external cognitive demands (cf. EC). In contrast, in the presence of the specified, external cognitive demands of the Go/Nogo task condition the TBI group showed greater theta activation (greater EO-to-Task increase) than controls. When cognitive demands were further amplified by the faster event-rate, the TBI group showed an additional increase in frontal hemispheric theta activation, suggesting an additional up-regulation of cortical arousal. This likely reflects a compensatory effect of extrinsic modulation of energetic state by the demands of the task. This is consistent with evidence that the provision of exogenous cues can stimulate bottom-up regulation to

normalise performance and engagement of attention networks in TBI (Fish et al., 2007; Manly et al., 2004; Richard et al., 2018). In terms of rehabilitation, this is relevant as a compensatory strategy for increasing alertness or arousal to improve attention and EF. However, for restorative EF rehabilitation in TBI, the observation that resting theta activation (more reflective of intrinsic/top-down regulation), but not task-related theta activation (more reflective of extrinsic/bottom up regulation), was associated with everyday attention and EF behaviours, points also to the potential of targeting impaired *intrinsic* control of energetic state for improving everyday functioning. This deficit in intrinsic energetic state regulation (indexed by theta activation) might therefore be an appropriate target for neurofeedback training.

In terms of integrating these findings with the broader literature, the association between theta activity and the ACC (Raghavachari et al., 2001; Sauseng et al., 2007; Wang et al., 2005) is of relevance. The ACC has been implicated in top-down modulation of the arousal network (including the thalamus, locus-coeruleus, and norepinephrine system) in response to environmental demands (Aston-Jones & Cohen, 2005; Mottaghy et al., 2006; Paus, 2001). In TBI, the ACC and its thalamic connections are particularly susceptible to diffuse axonal injury and degeneration (Stamatakis et al., 2002; Zhou et al., 2013). Furthermore, TBI-related attentional control deficits have been associated with impairments in ACC activation measured by fMRI (Kim et al., 2009; Richard et al., 2018) and by FM-theta activity (Shah et al., 2017). In this thesis, reduced resting theta activation was associated with more impaired everyday attention and EF behaviours in the overall sample, but also conversely with reduced injury severity and chronicity in the TBI group. The unexpected direction of the association with injury variables could indicate more effortful top-down regulation (Mayer et al., 2011; Sheth et al., 2021) and/or allocation of more widespread neural resources (Olsen et al., 2015; Scheibel et al., 2007, 2009) in the more severe injuries. Though the direction of these effects needs replication and clarification, they present additional support for the distinct sensitivity of theta activation to TBI.

The ACC and the evaluation mechanism of the CEM have parallels. They are both proposed to have top-down influences on the regulation of arousal (Aston-Jones & Cohen, 2005;

Mottaghy et al., 2006; Paus, 2001; Sanders, 1983), and a role in performance monitoring (Botvinick et al., 2001; Sergeant, 2005; Shiels & Hawk, 2010; Von der Gablentz et al., 2015; Yeung, 2014). Accordingly, theta activity might index the regulation of energetic state (via the arousal network) by the evaluation and effort mechanisms (involving the ACC), in response to monitoring of external processing demands.

6.3.1.2 Limitations of the CEM and consideration of other EF models

The focus on the CEM in this thesis was based on its ability to provide a theoretical account for the role of energetic state in cognition, as well as established EEG measures for its energetic state constructs. A theoretical account of the relationship between tonic EEG measures and cognition is lacking in TBI, and may have potential implications for cognitive rehabilitation. Though the CEM provides an account of cognitive *processes* (e.g. encoding, search, response selection, and motor organisation), this sequential, information processing component of the model might be considered outdated compared to newer EF models that favour more complex, neural network explanations of cognition (e.g. D. S. Levine, 2017; Miyake & Friedman, 2012; Niendam et al., 2012; Petersen & Posner, 2012; Posner et al., 2019). More recent and prominent models of EF (Diamond, 2013; Miyake et al., 2000; Petersen & Posner, 2012) have established behavioural and phasic electrophysiological correlates of cognitive *processes*, but do not address the energetic *state* that underlies processing.

The present studies have shown that the activation component of the CEM can differentiate adults with TBI from controls, and that arousal and activation measures are associated with RI performance and everyday EF. Therefore, with replication, the arousal and activation concepts may offer additional explanatory value to more prominent models of EF, when applied to TBI. The Posner attentional network model (Petersen & Posner, 2012; Posner et al., 2019) is a good candidate for integration, given that the alerting system in this model already has commonality with energetic state factors in the CEM, i.e. both are related to the physiological

energy of the brain that reflects the readiness to process and respond to stimuli (Martella et al., 2020). Empirical validation for the alerting network has focused on phasic behavioural and electrophysiological (ERP and ERS/ERD) correlates of alertness and these have been associated with specific neural networks (see section 1.3.4). However, this thesis has shown the relevance of tonic EEG measures of arousal and activation in relation to EF in TBI, and these might complement the alerting component of Posner's model. Empirical validation of this compatibility would involve investigating the relationships between tonic oscillatory measures of arousal and activation with the phasic behavioural (RT) and electrophysiological (CNV) measures of the alerting system. A recent resurgence in brain dynamics research provides sophisticated methods to investigate these relationships (Barry & De Blasio, 2018; Karamacoska et al., 2018, 2019). Another avenue for this integratory approach is to investigate associations between tonic oscillatory measures of arousal and activation and neural networks associated with alerting through the combination of EEG and fMRI methods (e.g. Laufs et al., 2003; Mayeli et al., 2019; Tang et al., 2012).

6.3.2 Neurocognitive training and the idiographic approach

The hypothesis that the CEM-based neurocognitive training program would lead to improvements in state regulation, cognition, and everyday EF behaviour was not supported. Nonetheless, Study 4 provided three considerable contributions: 1) it demonstrated the usability of an independently administered neurocognitive training program in TBI patients; 2) it demonstrated the feasibility of the SCED methodology to investigate the efficacy of neurocognitive training in TBI; and 3) it identified potential predictors of *who* is likely to engage and benefit from this training approach, to guide future research and practice.

Study 4 demonstrated that a group of individuals with TBI of diverse severity were able to use the neurocognitive training hardware and software independently. There was variability in engagement between participants, as measured by training rate and progression through difficulty levels, suggesting that some individuals may require additional support and reinforcement (e.g.

from a significant other) to engage in regular sessions. The results pattern also suggested that individuals of younger age, that are more familiar with technology, and with high levels of motivation would be better able to engage in this type of training independently. This understanding is valuable, given the considerable time (for clinician and patient) and financial cost of traditional, sequential cognitive rehabilitation, and could thus serve as an economical adjunct to a holistic rehabilitation program.

Importantly, Study 4 showed that the SCED methodology was sensitive to detecting EEG changes, and specifically changes in activation, between the experimental phases. The SCED method has been underutilised in the electrophysiology and NF literature (Gustafson et al., 2011) and to the authors knowledge has been scarcely used in the TBI literature. Based on neuroplasticity theory, neural changes underlie the functional rehabilitation of cognition and behavior (Cramer et al., 2011; Mukundan, 2013), and these underlying neural mechanisms need to be better understood to enhance interventions in TBI (Ali et al., 2020; Hampstead & Bahar-Fuchs, 2020; Sigmundsdottir et al., 2016; Whyte et al., 2014). According to the CEM, neural measures of energetic state regulation (EEG activation measures) should underlie cognitive changes induced by NF training. The sensitivity of the SCED to detecting changes in EEG measures of energetic state will be useful for future research aiming to clarify the electrophysiological mechanisms that underlie rehabilitation of cognitive function.

The need for a more idiographic approach to intervention research in TBI has been highlighted in the literature. The inherent heterogeneity of the TBI population presents a challenge to recruiting large homogenous samples required for randomised controlled trials, and even where large sample sizes are achieved, strict exclusion criteria limits the representation of the true heterogeneity in the population (Ali et al., 2020; Cicerone et al., 2019; Thomas & Smith, 2015). The SCED approach can overcome these challenges and has value in its focus on individual differences in, and predictors of, treatment response (Ali et al., 2020; D. H. Barlow & Nock, 2009; Cicerone et al., 2019). Study 4 supported the value of this approach, by identifying that younger age, shorter PTA, greater pre-injury education, and maintenance of pre-injury

educational/occupational functioning were associated with more consistent training rate and higher progression through training levels. The predictive nature of these factors for engagement in neurocognitive (or similar) training could be further investigated with mediation/moderation analyses in larger group studies (e.g. Bertens et al., 2016), or with inter-case replication in SCED studies, with the inclusion of at least three cases matched on the key clinical and demographic variables. The potential predictors of training engagement identified in Study 4 are factors already known to the cognitive rehabilitation field (Barlati et al., 2019; Gehring et al., 2011; Ramsay et al., 2018), however, future SCED studies are likely also to uncover novel predictive factors for continued investigation.

6.4 Limitations and future directions

The limitations specific to each study have been addressed in the relevant chapters. General limitations that intersect the studies, and relevant future directions for the field, will be discussed below. The first three studies involved averaging across a heterogeneous sample of adults with TBI, to identify generalised patterns of energetic state abnormalities. These studies were affected by the typical challenges of TBI research (Ali et al., 2020; Boukrina et al., 2020; Kennedy & Turkstra, 2006). Firstly, due to the limitations of the local TBI recruitment pool, inclusion criteria were broad, resulting in a TBI sample with a broad range of injury severity (mild-to-severe) and a range of cognitive impairments. Though all TBI participants had subjective cognitive complaints, only 13 of 26 participants in Study 1, and 11 of 16 participants in Studies 2 and 3, had cognitive impairment confirmed via neuropsychological measures. The limitations of group averaging in such a heterogeneous population have been argued throughout this thesis.

Another limitation was the significant age difference between groups. Ageing in adults is associated both with cognitive (Hedden & Gabrieli, 2004) and EEG (Hashemi et al., 2016) changes. Age correlated with specific EEG variables (resting theta and beta amplitudes) and cognitive variables (Go/Nogo Medium Go accuracy and RT) in Study 1. To control for this confounding factor, age was entered as a covariate into group comparison and correlational

analyses. However, there are statistical limitations to ANCOVA when there are pre-existing group differences on the covariate (Adams et al., 1985; Miller & Chapman, 2001). As a result, the ability to infer TBI-related effects as distinct from age-related group differences is limited. Therefore, the results of group comparisons in this thesis require replication in age-matched groups.

Furthermore, sample sizes were relatively small, especially for the TBI group, and a number of analyses (particularly correlations and Fisher r-to-z analyses) may have been underpowered. The effects reported in this thesis warrant replication with larger and more homogenous samples. The SCED study aimed to address the limitations of small and heterogenous sample sizes, resulting most significantly in the generation of hypotheses for further investigation. Future research will benefit from a reciprocal process, whereby SCED studies identify variables of interest (e.g. moderators of treatment effect) that can be confirmed in larger studies (whether this be inter-case replication in SCED, or RCT group studies), thus leveraging the strengths of both methodologies.

Effective rehabilitation must be evaluated in terms of functional outcomes that have meaningful implications for patients' lives (Cicerone et al., 2011; Ponsford, Bayley, et al., 2014). However, in order to develop the most effective interventions, it is imperative to understand the mechanisms of change (e.g. neural, cognitive, behavioural) that drive these outcomes (Ali et al., 2020; Hampstead & Bahar-Fuchs, 2020; Sigmundsdottir et al., 2016; Whyte et al., 2014). Studies 1 to 3 showed correlations between energetic state and cognition and behaviour, but do not provide evidence of a causal effect of energetic state on cognition. NF training studies can facilitate causal inferences, by establishing the effect of direct modulation of energetic state on cognitive outcomes (Herrmann et al., 2016), and could thus provide support for the propositions of the CEM. However, the design of Study 4 did not permit evaluation of the unique contributions of cognitive vs. NF training to outcomes. The relative effectiveness of each training approach separately, compared to the combined approach, is an important question that remains unanswered. The specific components of cognitive training (WM and IC training), and the

specific EEG targets of the NF training (e.g. the frequency bands for reinforcement), would need to be investigated separately to ascertain the active components. The effective components might be generalised for TBI groups, or more likely, specific to individuals' baseline deficits. Future investigations would benefit from an active or sham control condition to differentiate training effects from expectation effects.

Though specific activation deficits for the TBI group were identified in Studies 1 to 3, the neurocognitive program employed a generalised approach to state regulation training. Participants were instructed to achieve focused, relaxed, or "zen" states, and EEG frequency bands known to reflect these states were reinforced. It was not possible to individualise the target frequencies or electrode locations for either TBI-specific impairments or for patient-specific impairments and, given consensus that tailored and individualised cognitive rehabilitation may be more effective (Koehler et al., 2011), this tailored approach might facilitate better outcomes. Interestingly though, it has been suggested that the effectiveness of NF training might rest on the enhancement of one's ability to consciously and flexibly regulate energetic state in a general sense, rather than specific effects on the targeted EEG frequencies (Kober et al., 2017), a hypothesis that is particularly relevant to the heterogeneous TBI population.

The focus on the CEM construct of activation in this thesis is a theoretical simplification of the complex dynamics of oscillatory activity and communication within and between neural networks. Though this simplification is appropriate for the aim of establishing a clinically useful theory of state regulation in TBI, it must be acknowledged that there are alternative methods for measuring EEG activation. In this thesis, activation was quantified using traditional, pre-defined frequency bands. While this approach is standard in the EEG literature (Rapp et al., 2015), it has been criticised for the arbitrary choice of band limits, which does not account for inter-individual variability (Barry et al., 2019; Haegens et al., 2014; Klimesch, 1999). Some novel approaches to address this are the frequency-PCA (Barry & De Blasio, 2018; Karamacoska et al., 2019), and individual frequency peak analysis (Klimesch, 1999, 2012) methods. Alternatively, connectivity measures (e.g. EEG coherence) may better characterise the impact of DAI compared to EEG

amplitude measures. These alternative approaches are compatible with the CEM operationalisation of activation and should be considered in future investigation. Another limitation is that this thesis did not empirically investigate an alternative EF model to the CEM and therefore the utility of the CEM in comparison to other models cannot be evaluated. Efforts to replicate the present findings should consider a comparative approach and/or the integrative approach suggested in section 6.3.1.2.

The wireless EEG headsets used in this thesis had significant practical advantages for use in a TBI group, especially those individuals with pain and scalp sensitivities as a result of their injuries. However, this choice resulted in a reduced opportunity to analyse topographical effects, which is important given activation is characterised by topographical differences (Barry et al., 2007) and the reorganisation of neural networks that follows TBI may be reflected in topographical changes.

6.5 Conclusion

This thesis aimed, firstly, to investigate the applicability of the CEM arousal and activation concepts to understanding energetic state abnormalities and their relation to EF impairment in TBI, and secondly, to evaluate the effectiveness of a CEM-based neurocognitive training program for improving EF in TBI. Overall, this thesis established specific impairments in EEG measures of resting and task-related *activation*, but not of baseline resting *arousal*, in TBI. This suggests that it is the ability to *regulate* energetic state (indexed by activation) in response to environmental and processing demands that is impaired. The present findings replicate prior research using alpha measures of arousal and activation in TBI, and extend this evidence to the delta, theta, and beta bands, and to external manipulations of energetic state via event-rate. Furthermore, present findings contribute evidence for associations between activation impairments and cognitive performance, everyday EF, and injury variables, suggesting a role for impaired state regulation in the cognitive and behavioural sequelae of TBI.

Specifically, the TBI group was characterised by reduced resting theta activation,

increased task-related theta activation, and task-related delta and beta activation that was in the opposite direction compared to controls. Frontal hemispheric theta activation was further enhanced at the fastest event-rate for the TBI group, suggesting a compensatory effect of exogenous state modulation. Activation abnormalities were associated with impairment to both Go and Nogo processes in the Go/Nogo task, suggesting a general role in cognition and attention, not distinct to response inhibition per se. Likewise, broad associations were observed between reduced resting theta and increased resting beta activation and impaired everyday attention and EF behaviours, replicating the more generalised role.

Across studies, theta activation showed a consistent sensitivity to intrinsic and extrinsic state modulation, EF impairments, and injury variables. Combined with associations between theta activity and top-down attentional control via the ACC and cortico-thalamic arousal system in prior research, the present findings suggest theta activation to be a good index of impaired intrinsic/top-down state regulation underlying executive dysfunction in TBI. It is therefore a good candidate measure for further investigation of energetic state impairments in TBI, and a potentially suitable treatment target for cognitive rehabilitation. Although the present intervention study did not establish effectiveness of the neurocognitive training program; it did nonetheless, support the SCED as an appropriate and valuable methodology in this area. Further, it identified some potential predictors of training engagement and benefit, which require replication in order to guide future research and clinical practice.

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Appendices

Appendix A: Supplemental material for Study 1

Table S1.

Correlation Coefficients (r) for Relationships between EEG Activation and Go/Nogo Task Performance Variables for Each Group.

			Slow				Medium				Fast			
Band	**Region**	**Group**	**Go Acc**	**Nogo Acc**	**RT**	**RT Var**	**Go Acc**	**Nogo Acc**	**RT**	**RT Var**	**Go Acc**	**Nogo Acc**	**RT**	**RT Var**
Delta	Frontal	Control	-0.63	-.493*	-.083	-0.32	-.095	-.427*	.166	.166	-.037	-.139	-.139	.135
		TBI	-.387	-.384	.346	.392	-.603*	-.164	.216	.439	-.398	-.408	-.121	.426
Theta	Frontal	Control	.081	.267	-0.62	.094	-.032	.008	-.248	.052	-.214	-.091	-.127	.275
		TBI	.395	.250	-.083	-.324	.319	.103	.002	-.179	.029	-.019	.115	-.188
Alpha	Frontal	Control	.221	.283	-.063	-.144	.066	.392	-.219	-.272	.162	.305	.166	-.304
		TBI	.223	.195	-.294	-2.35	.399	.068	-.057	-.262	.237	.400	.137	-.288
Beta	Frontal	Control	-.323	.192	.378	.317	.297	.232	.031	-.200	-.092	-.080	.176	.092
		TBI	.145	.240	-.065	-.164	.366	.104	-.276	-.417	.309	.310	.187	-.313

Note: Acc = accuracy, RT = reaction time, Var = variability; ** $p < .01$, * $p < .05$.

Appendix B: Supplemental material for Study 2

Table S2.

Correlation Coefficients (r) for Relationships between EEG Activation and Go/Nogo Task Performance Variables for Each Group.

			Slow				Medium				Fast			
Band	**Region**	**Group**	**Go Acc**	**Nogo Acc**	**RT**	**RT Var**	**Go Acc**	**Nogo Acc**	**RT**	**RT Var**	**Go Acc**	**Nogo Acc**	**RT**	**RT Var**
Delta	Frontal	Control	.206	.117	-.410	-.168	.399	-.013	-.098	-.228	-.068	-.283	.144	.155
		TBI	.359	.045	-.410	-.340	.472	-.376	-.236	-.007	.446	-.309	-.430	-.210
Theta	Left	Control	-.072	0.44	-.045	.012	.087	-.059	-.085	-.061	-.451	.485	-.223	-.567*
		TBI	-.119	.199	.052	.132	-.030	.248	.448	.421	-.281	-.040	-.137	.379
	Medial	Control	-.152	-.240	.175	.236	.171	.069	.014	.050	.358	.477	-.208	-.451
		TBI	-.085	.339	.208	.117	.021	.406	.143	-.112	-.081	.081	-.043	.133
	Right	Control	-.164	.082	.201	.193	.082	.299	.059	.018	-.181	-.038	-.015	.167
		TBI	-.099	.162	.220	.136	.086	.541*	.292	-.084	.102	-.164	-.235	.108
	Frontal	Control	-.244	.052	.254	.251	.186	.131	.034	-.006	.407	.492	-.289	-.450
		TBI	-.231	.163	.282	.269	.064	.526*	.230	-.039	-.069	.063	-.065	.132
Alpha	Frontal	Control	-.227	-.271	.429	.116	-.245	.029	.154	.318	-.174	.194	-.026	.134
		TBI	-.439	-.271	.573*	.449	-.548*	.085	.098	.046	-.439	.310	.494	.166
Beta	Frontal	Control	-.132	-.173	.225	.036	-.400	-.206	.089	.237	.181	.312	-.422	-.188
		TBI	-.047	-.034	.011	-.031	-.222	.260	.089	-.112	-.335	.235	.341	.065

Note: Acc = accuracy, RT = reaction time, Var = variability; ** $p < .01$, * $p < .05$.

Appendix C: Supplemental material for Study 3

Table S3.

Correlation Coefficients (r) for Relationships between Resting Arousal and BRIEF-A Subscale T-Scores for Each Group.

			BRIEF-A subscale											
Task/ band	**Region**	**Group**	**Inhibit**	**Shift**	**Emotional control**	**Self-monitor**	**BRI**	**Initiate**	**Working memory**	**Plan/ Organise**	**Task monitor**	**Organise materials**	**MI**	**GEC**
EC/	Frontal	Control	.234	.041	-.051	.368*	.077	-.022	.097	-.023	.131	.148	.118	.088
alpha		TBI	.007	-.003	.067	.135	.042	.101	.063	-.030	-.033	-.092	-.010	.010

Note: EC = eyes-closed, BRI = Behaviour Regulation Index, MI = Metacognition Index, GEC = Global Executive Composite, * $p < .05$.

Table S4.

Correlation Coefficients (r) for Relationships between Resting Arousal and BIS-11 Subscale Scores for Each Group.

			BIS-11 subscale			
Task/band	**Region**	**Group**	**Attentional**	**Motor**	**Nonplanning**	**Total**
EC/alpha	Frontal	Control	.284	.580**	.098	.359
		TBI	-.033	.382	.392	.271

Note: EC = eyes-closed, ** $p < .01$, * $p < .05$.

Table S5.

Correlation Coefficients (r) for Relationships between Resting Activation and BRIEF-A Subscale T Scores for Each Group.

			BRIEF-A subscale											
Band	**Region**	**Group**	**Inhibit**	**Shift**	**Emotional control**	**Self-monitor**	**BRI**	**Initiate**	**WM**	**Plan/ Organise**	**Task monitor**	**Organise materials**	**MI**	**GEC**
Delta	Frontal	Control	.015	-.009	-.213	.082	-.165	-.099	-.173	-.278	-.045	.084	-.071	-.148
		TBI	.089	.041	.007	.260	.102	.105	.216	.036	.060	.015	.074	.088
Theta	Frontal	Control	-.128	-.067	-.212	-.074	-.156	-.005	.144	.171	.151	.170	-.045	-.021
		TBI	-.584**	-.258	-.307	-.441*	-.476*	-.420*	-.392	-.282	-.330	-.129	-.316	-.419*
Alpha	Frontal	Control	-.072	-.015	.215	-.189	.0113	.075	.009	.190	-.069	-.214	-.030	.050
		TBI	-.100	-.012	-.081	-.174	-.089	-.061	-.092	.037	.013	.026	-.012	-.052
Beta	Frontal	Control	.223	.135	.298	.042	.327	-.053	.112	-.020	-.059	-.204	-.009	.181
		TBI	.420*	.057	.435*	.206	.332	.191	-.024	-.005	.098	.010	.059	.188

Note: BRI = Behaviour Regulation Index, MI = Metacognition Index, GEC = Global Executive Composite, ** $p < .01$, * $p < .05$.

Table S6.

Correlation Coefficients (r) for Relationships between Resting Activation and BIS-11 Subscale Scores for Each Group.

			BIS-11 subscale			
Band	**Region**	**Group**	**Attentional**	**Motor**	**Non-planning**	**Total**
Delta	Frontal	Control	.041	.219	.163	.084
		TBI	-.129	.299	.359	.265
Theta	Frontal	Control	-.185	-.116	-.301	-.207
		TBI	-.619**	-.451	-.427	-.572*
Alpha	Frontal	Control	-.040	-.359	-.112	-.111
		TBI	.106	-.249	-.230	-.196
Beta	Frontal	Control	.187	.223	-.123	.172
		TBI	.454	.380	.037	.298

Note: ** $p < .01$, * $p < .05$.