Effects of Sleep Deprivation on Functional Connectivity and Integration During Cognitive Tasks

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Alex Nguyen

B.A., B.Sc. (Hons), M.D.C.M. (c)

A Thesis in the Department

of

Health, Kinesiology, and Applied Physiology

Presented in Partial Fulfillment of the

Requirements for the Degree of

Master of Science (Health and Exercise Science)

at Concordia University

Montreal, Quebec, Canada

September 2022

CONCORDIA UNIVERSITY
School of Graduate Studies

This is to certify that the thesis prepared

By: **Alex Nguyen**

Entitled: **Effects of Sleep Deprivation on Functional Connectivity and Integration During Cognitive Tasks**

and submitted in partial fulfilment of the requirements for the degree of

Master of Science

complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the final Examining Committee:

_____ Chair
Dr. Robert Kilgour

_____ Examiner
Dr. Richard Courtemanche

_____ Examiner
Dr. Claudine Gauthier

_____ Co-supervisor
Dr. Christophe Grova

_____ Co-supervisor
Dr. Thanh Dang-Vu

Approved by _____
Graduate Program Director – Dr. Geoffrey Dover

Date:

ABSTRACT

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By: Alex Nguyen

Introduction: We previously demonstrated that sleep deprivation (SD) alters the balance of integration and segregation of brain activity in cortical networks, which was correlated to cognitive impairment following SD. The objectives of this study is to examine the effects of total sleep deprivation and recovery nap on (i) cognitive performances, (ii) functional connectivity, (iii) integration and (iv) compare changes in integration with cognitive changes during different cognitive tasks individually. We hypothesized that sleep deprivation will lead to increase integration within-networks relative to between-networks and associated with cognitive impairment for all three tasks.

Methods: 20 healthy adults (M_{AGE}=21.32, 12 females) were scanned using simultaneous EEG-fMRI during three cognitive tasks (attention, working memory, vigilance) in three conditions: following a normal night of sleep, 24-hour of total SD, and 1-hour recovery nap. A general linear model was performed to compare functional connectivity between the three conditions. Functional clustering ratio (FCR) was used to calculate integration and Pearson's correlations was used to compare the changes in integration and cognitive changes between each conditions.

Results: SD was associated with increased FCR, driven by a rise of integration within cortical networks which was associated with deficits in performance of working memory and attention tasks, but not vigilance task. Restoration of balance between integration and segregation of cortical activity was related with performance following recovery nap demonstrating bidirectional effect.

Conclusions: These results demonstrate intra- and interindividual differences in cortical network integration and segregation during task performance may play a critical role in vulnerability to cognitive impairment in the SD state.

Word count (Abstract): 249/250

ACKNOWLEDGEMENTS

This master's thesis would not have been possible without the help and support of the following people:

To my co-supervisors, Dr. Thanh Dang-Vu & Dr. Christophe Grova, you have both been extremely supportive through this process. Your patience and guidance to help me complete this thesis despite the challenges of the COVID-19 pandemic and medical school has meant the world to me. It is truly an honour and privilege to have worked under the supervision of inspiring scientists. Thank you for believing in me!

To my committee members, Dr. Richard Courtemanche & Dr. Claudine Gauthier, I am grateful to have such talented and passionate researchers who have always taken the time to assure the highest quality in my thesis work. Your insight and feedbacks were critical in the completion of this project.

To my mentors, Dr. Nathan Cross, Dr. Aurore Perrault, Dr. Florence Pomares, you are the best big brother and sisters that anyone could ask for. From our lab outings around Montreal, lunch breaks together, to me rolling my chair into your offices to ask questions, you have made this experience a truly memorable one to never forget. Thank you for creating such a positive environment and making the lab feel like a second home to me.

To the staff and faculty members, Dr. Geoff Dover, Dr. Angela Alberga, Dr. Robert Kilgour, Dr. Veronique Pepin, Dr. Simon Bacon, Dr. Patrice Desaulniers, Dr. Melodee Mograss, Dr. Mary Roberts, Christina Grace, Robert Panenic, Karl Stamp, you have all made a huge impact in my life and provided me with opportunities to grow, and I will forever be grateful for that.

To the sleep deprivation lab volunteer team, Benoit Harvey, Christy Lo, Joelle Ducharme, Agata Kasprzyk, Jean-Louis Zhao, thank you for your hard work and commitment. You all made overnights at the sleep lab more entertaining, and this project could not have been completed without your help.

Finally, I would like to thank my friends and family. You always believed in me, and your encouragements has got me through the finish line. You are the reason to my success!

AUTHOR CONTRIBUTIONS

Role of other co-authors:

Conception and design: Aude Jegou, Umit Aydin, Florence B. Pomares, Thien Thanh Dang-Vu, Christophe Grova

Data Collection: Alex Nguyen, Aude Jegou, Nathan Cross, Umit Aydin

Data Analysis: Alex Nguyen, Nathan Cross, Florence B. Pomares, Aurore Perrault

Data Interpretation: Alex Nguyen, Nathan Cross, Florence B. Pomares

Edit/draft manuscript: Alex Nguyen, Nathan Cross, Thien Thanh Dang-Vu, Christophe Grova

PUBLICATIONS FROM THIS STUDY

Peer-Reviewed Journal Article Publications

1. Uji, M., Cross, N., Pomares, F. B., Perrault, A.A., Jegou, A., **Nguyen, A.,** Aydin, U., Lina, J. M., Grova, C., Dang-Vu, T.T. *Beamforming BCG Artefact Correction in EEG-fMRI*. Published in Human Brain Mapping (2021). doi.org/10.1002/hbm.25535
2. Cross, N., Pomares, F. B., **Nguyen, A.,** Perrault, A.A., Jegou, A., Uji, M., Lee, K., Razavipour, F., Ali, O. B. K., Aydin, U., Benali, H., Grova, C., Dang-Vu, T.T. *Altered Functional Intergration of Brain Activity is a Marker of Impaired Cognitive Performance Following Sleep Deprivation*. Published in PLoS Biology (2021). doi.org/10.1371/journal.pbio.3001232
3. Cross, N., Paquola, C., Pomares, F. B., Perrault, A.A., Jegou, A., **Nguyen, A.,** Aydin, U., Bernhardt, B., Grova, C., Dang-Vu, T.T. *Trait-like Gradients of Functional Connectivity are Robust to State-Dependent Changes Following Sleep Deprivation*. Published in NeuroImage (2020). doi.org/10.1016/j.neuroimage.2020.117547
4. Uji, M., Jegou, A., Cross, N., Pomares, F. B., Perrault, A.A., **Nguyen, A.,** Aydin, U., Lee, K., Abdallah, C., Frauscher, B., Lina, J. M., Dang-Vu, T.T., Grova, C. *Short Title: Beamforming Sleep Spindle in EEG-fMRI.* Under Review.

Abstract/Poster/Oral - Conferences

1. Cross, N., Pomares, F. B., Jegou, A., **Nguyen, A.,** Perrault, A.A., Lee, K., Uji, M., Aydin, U., Grova, C., Dang-Vu, T.T. *The Impact of Sleep Deprivation on Integrated Network States during Cognitive Task Performance.* Organization for Human Brain Mapping Conference 2022
2. Uji, M., Jegou, A., Cross, N., Pomares, F. B., Perrault, A.A., **Nguyen, A.,** Aydin, U., Lee, K., Abdallah, C., Frauscher, B., Lina, J. M., Dang-Vu, T.T., Grova, C. *EEG source imaging technique for EEG-fMRI acquired during sleep to investigate sleep oscillations*. Organization for Human Brain Mapping Conference 2022
3. Wang, Y., Lee, K., Cross, N., Jegou, A., Razavipour, F., Pomares, F. B., Perrault, A.A., **Nguyen, A.,** Aydin, U., Grova, C., Dang-Vu, T.T. *The Impact of Sleep Deprivation on Integrated Network States during Cognitive Task Performance.* Organization for Human Brain Mapping Conference 2022
4. Uji, M., Cross, N., Pomares, F. B., Perrault, A.A., Jegou, A., **Nguyen, A.,** Aydin, U., Lina, J. M., Grova, C., Dang-Vu, T.T. *Beamforming BCG Artefact Correction in EEG-fMRI*. Organization for Human Brain Mapping Conference 2021
5. Cross, N., Pomares, F. B., Jegou, A., **Nguyen, A.,** Perrault, A.A., Smith, D., Aydin, U., Grova, C., Dang-Vu, T.T. *The Impact of Sleep Deprivation on Cortical Functional Integration and Cognitive Performance.* European Sleep Research Society Conference 2020
6. Cross, N., Pomares, F. B., Jegou, A., **Nguyen, A.,** Perrault, A.A., Smith, D., Aydin, U., Grova, C., Dang-Vu, T.T. *The Impact of Sleep Deprivation on Cortical Functional Integration and Cognitive Performance.* Organization for Human Brain Mapping Conference 2020
7. **Nguyen, A.,** Cross, N., Pomares, F. B., Jegou, A., Lee, K., Aydin, U., Perrault, A.A., Smith, D., Grova, C., Dang-Vu, T.T. *Effects of Sleep Deprivation and Performance During a Psychomotor Vigilance Task.* World Sleep Conference 2019
8. Pomares, F. B.*, Cross, N., Jegou, A., **Nguyen, A.,** Perrault, A.A., Lee, K., Smith, D., Aydin, U., Grova, C., Dang-Vu, T.T. *Cognitive Performance and Brain Activation Recovery After a Nap Following Total Sleep Deprivation.* World Sleep Conference 2019
9. **Nguyen, A.,** Cross, N., Pomares, F. B., Jegou, A., Lee, K., Aydin, U., Smith, D., Grova, C., Dang-Vu, T.T. *Effects of Sleep Deprivation on Cortical Connectivity and Performance during Cognitive Tasks.* PERFORM Conference 2019
10. Lee, K., Cross, N., Jegou, A., Pomares, F. B., Perrault, A.A., **Nguyen, A.**, Aydin, U., Gotman, J., Dang-Vu, T.T., Grova, C. *Reorganization of Functional Hubs during Non-Rapid Eye Movement Sleep after Sleep Deprivation*. Organization for Human Brain Mapping Conference 2019

ABBREVIATIONS

ANCOVA – Analysis of Covariance
ANOVA – Analysis of Variance
ANT – Attention Network Task
BOLD – Blood Oxygenation Level-Dependent
CCER – Comité Central D'Éthique de la Recherche
CIHR – Canadian Institutes of Health Research
DMN – Default Mode Network
EEG – Electroencephalography
EGI – Electrical Geodesics Inc.
EPI – Echo-Planar Imaging
ESS – Epworth Sleepiness Scale
FOV – Field-Of-View
FRQ – Fonds de Recherche du Québec
fMRI – Functional Magnetic Resonance Imaging
FCR – Functional Clustering Ratio
FDR – False Discovery Rate
GE – General Electric
I_{ws} – Integration within systems
I_{bs} – Integration between systems
KSS – Karolinska Sleep Scale
MNI – Montreal Neurological Institute
MSLT – Multiple Sleep Latency Test
MWT – Maintenance Wakefulness Test
NREM – Non-Rapid-Eye-Movement
NSERC – Natural Sciences and Engineering Council of Canada
PRN – Post-Recovery Nap
PSG – Polysomnography
PVT – Psychomotor Vigilance Test
REM – Rapid-Eye-Movement
SD – Sleep Deprivation
SSS – Stanford Sleepiness Scale
TE – Time-to-Echo
TR – Repetition Time
TST – Total Sleep Time
VLPO – Ventrolateral Preoptic
WR – Well-Rested

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1. INTRODUCTION

1.1. Sleep

1.1.1. Why Do We Sleep?

As humans, we spend approximately a third of our lives sleeping (Aminoff et al., 2011). The daily average sleep duration varies between individuals from 6 to 8.5 hours (Kronholm et al., 2006; Keenan et al., 2010). Sleep is defined as spontaneous and reversible behavior during which one's responsiveness to external stimuli is decreased while adopting a posture of relaxation (Peigneux et al., 2001). Although the body is inactive, it is important to note that the brain is far from that state. To answer the question as to why we sleep, research has focused on the role of sleep in biological and cognitive processes.

1.1.2. Biological & Cognitive Function of Sleep

Sleep is believed to maintain both the physical and mental health of individuals. It plays an essential role in energy conservation (Berger et al., 1995), thermoregulation (Krauchi et al., 2010), and brain detoxification (Inoué et al., 1995). While the waking state consumes a high amount of energy through creating and maintaining synaptic connections, it creates waste products that are considered toxins to neurons (Cirrito et al., 2005). Hence, sleep has been hypothesized to hold a glymphatic function where removal of toxins is performed through the exchange between cerebrospinal fluid and interstitial fluid (Ooms et al., 2014; Iliff et al., 2013; Xie et al., 2013).

Sleep processes can also be quite effective in facilitating different cognitive functions such as language processing (Dumay et al., 2007), creativity (Ritter et al., 2012), and decision making (Pace-Schott et al., 2012). Sleep also seems to play a role in the consolidation of memory traces (Maquet, 2001; Stickgold, 2005) A large amount of focus in sleep and cognition has been directed towards the domain of memory as it is essential for individuals and society (e.g. academics, workplace, personal relationship)

(Rasch et al., 2013). Sleep promotes the reprocessing of new memories and their transition into long-term memories (Diekelmann et al., 2010; Stickgold et al., 2013). There exist two main theories that explain the possible effects of sleep on memory. First, there is the active system consolidation theory which assumes new memories become reactivated and reorganized with particular neural connections being strengthened during sleep (Lewis et al., 2011; Rasch et al., 2013). Alternatively, the synaptic homeostasis hypothesis suggests that synaptic connections become depotentiated during sleep whereas selected memories are less depotentiated and thus become relatively stronger (Tononi et al., 2014). Meanwhile, the effects of sleep on sustaining vigilant attention have been investigated more in studies on sleep loss due to its strong sensitivity (Doran et al., 2001; Bermudez et al., 2016; Lim et al., 2008; Van Dongen et al., 2005). The effects of sleep loss on cognition will be discussed in Section 1.3.

1.2. Sleep-Wake Cycle

1.2.1. Sleep Stages

To understand the mechanisms of the sleep-wake cycle, it is important to first briefly understand that sleep is divided into two main types. Rapid-eye-movement (REM) sleep, also known as paradoxical sleep, is characterized by its high-frequency low-amplitude electroencephalography (EEG) activity, along with rapid eye movements, and a strongly reduced muscle tone. Approximately 18-22% of the total sleep duration is made of REM sleep although this decreases with age in adults (Ohayon et al., 2004). Non-rapid-eye-movement (NREM) sleep, consists of three stages (i.e. N1 “light sleep”, N2, N3 “deep sleep”) each constituting different amplitude and frequency characteristics of EEG activity (Iber, 2007). Furthermore, NREM sleep consists of EEG events such as slow-wave activity, sleep spindles, and K complexes (Loomis et al., 1938). Although the function of each stage is not really known, a popular hypothesis exists where NREM sleep (more specifically, N3 also called slow-wave sleep) is involved in restorative functions (Edinger et al., 2000) and memory consolidation (Born, 2010; Walker, 2009; Diekelmann et al., 2010).

Meanwhile, REM sleep is believed to be involved in learning (Mandai et al., 1989), emotional memory formation (Wagner et al., 2001; Maquet et al., 1996), and problem-solving (Walker et al., 2002).

The sleep cycle consists of the alternation between NREM and REM stages, often beginning with NREM sleep that progressively advances to deeper stages. Approximately 80 to 100 minutes later, REM sleep usually makes its first appearance. In humans, NREM and REM exist in sleep cycles lasting approximately 90 minutes each across the night. Although the duration of these cycles remains fairly consistent throughout the night, the ratio of NREM-REM sleep differs as the night progresses. During the beginning of the night, stage N3 in NREM sleep dominates while REM sleep slowly lengthens and eventually prevails later in the night (Keenan et al., 2010). The functional role of each stage and its organization is still not yet fully understood.

1.2.2. Wake & NREM Promoting Systems

The fundamental of sleep revolves around the mechanism that induces wake and sleep. Although there is a solid understanding of the neurophysiology behind sleep and wake states, the mechanism of alternation between both states is still less known. For the purpose of this literature review, the focus of sleep-wake cycles will remain from wakefulness to NREM sleep.

In the past, the reticular formation of the brainstem has been recognized as the activation center of wakefulness (Moruzzi et al., 1949). It follows a pathway called the ascending arousal pathway which branches out into two branching projections to promote wakefulness (Saper et al., 2001). One branch projects to the thalamus while the other projects to the hypothalamus and basal forebrain (Moruzzi et al., 1949; Saper et al., 2001). The thalamic projection starts at the pedunculopontine and laterodorsal tegmental nucleus of the upper brainstem which then projects to the thalamus and then to the reticular nucleus (Saper et al., 2001). The other projection that goes to the lateral hypothalamus originates from the locus coeruleus,

raphe nucleus, parabrachial nucleus, and tuberomammillary nucleus (Saper et al., 2005). The hypothalamic projection then continues to the basal forebrain which evokes arousal to the entire cortex (Saper et al., 2001).

The activated brain state during wake is the result of multiple arousal systems including the serotonergic, noradrenergic, cholinergic, and hypocretin systems located at different subcortical regions (Luppi et al., 2011). Contrarily, the major region for the activation of NREM sleep is the ventrolateral preoptic area (VLPO) (de Andrés et al., 2011). The VLPO consists of gamma-aminobutyric acid and galanin neurons which inhibit the arousal regions during sleep (Szymusiak et al., 2007; Sherin et al., 1998).

The inhibitory relationship between the sleep and wake systems is reciprocal. The wake-NREM sleep cycle functions through dynamic inhibitory connections between arousal systems. Moreover, the preoptic area is inhibited during wakefulness but then inhibits arousal regions during sleep (Sherin et al., 1998). The two-way inhibition relationship allows for an effective circuit where the activity of one system inhibits the other while disinhibiting itself and increasing its own activity. The model is known as a "flip-flop" switch which allows for quick transitions between sleep and wake (Saper et al., 2001). One of the ways the stability of this sleep-state circuitry is kept from switching back and forth constantly is due to a group of neurons called orexins located in the hypothalamus. These neurons are primarily active during wake and project to the cortex as well as the VLPO and arousal pathway (Estabrooke et al., 2001). However, the VLPO has no orexin receptors which prevents it from being influenced by the projections of orexin neurons.

1.3. Sleep Deprivation

1.3.1. Prevalence of Sleep Deprivation

Sleep deprivation is a rising issue affecting many adults in society with an estimate of 35% of individuals aged 15 or older, and approximately 30% of Canadian students in high school and university reporting insufficient sleep (Chaput et al., 2017). Insufficient sleep is defined as having a sleeping less than the recommended sleep time which is 7-9 hours for adults as per the National Sleep Foundation (Hirshkowitz et al., 2015). Sleep loss may be attributed to several factors in the modern world such as the increase in nocturnal artificial light, caffeine consumption, in addition to shift work and academic demands (Chaput et al., 2017).

1.3.2. Types of Sleep Deprivation

It is important to define the two types of sleep deprivation: (i) total sleep deprivation (>24 hours of continuous wake), (ii) partial sleep deprivation (<24 hours of continuous wake), and (iii) chronic partial sleep deprivation (e.g., only 4-6 hours of sleep in the span of several consecutive days). Researchers have chosen to investigate the different types of sleep deprivation based on their questions of interest. Partial sleep deprivation offers distinguishing effects of NREM and REM sleep and chronic partial sleep deprivation allows for a more pragmatic outcome of sleep loss in today's society. Meanwhile, total sleep deprivation provides the direct consequences of a sleepless night.

1.4. Consequences of Sleep Deprivation

The lack of sleep and productivity among the Canadian working population is costing the economy up to $27.7 billion a year (Hafner et al., 2017). The daytime impairment is related to the excessive wake duration (Van Dongen et al., 2003) and can only be restored through sleep (Banks et al., 2010; Vyazovskiy, 2015). Sleep deprivation has been shown to impair visuomotor performance (Van Dongen et al., 2004; Blatter et al., 2005), decision making (Linde et al., 1999; Killgore et al., 2006), attention (Karakorpi et al.,

2006; Choo et al., 2005), logical reasoning (Drummond et al., 2004), fine motor skills (Ayalon et al., 2008) and long-term memory (Drummond et al., 2000; Forest et al., 2000). However, the two most widely studied cognitive domains in sleep deprivation research are vigilance and working memory, both of which act as an important fundamental basis for other cognitive functions (Alhola et al., 2007). Vigilance is defined as the ability to sustain attention for a task for a period amount of time while working memory is defined as the ability to encode, manipulate, and retrieve information in a goal-oriented manner. There are significant effects on cognitive performances such as deficits in memory and vigilance, consequences that could considerably result in decreased productivity and increased risk of motor vehicle accidents (Hafner et al., 2017). Cognitive and behavioural impairments usually occur after just one night of sleep loss and amplifies until sleep recovery (Van Dongen et al., 2003; Gillberg et al., 1998). Sleep deprivation has its known effects on subjective and objective measures of sleepiness. Objective measures used in clinical and research settings include different tests such as the multiple sleep latency test (MSLT) (Carskadon, 1986), maintenance wakefulness test (MWT) (Mitler et al., 1982), and psychomotor vigilance task (PVT) (Doran et al., 2001). Subjective measures include self-rating scales such as the Stanford Sleepiness Scale (SSS; (Hoddes et al., 1973)), Epworth Sleepiness Scale (ESS) (Johns, 1991), and Karolinska Sleep Scale (KSS) (Åkerstedt et al., 1990). Disparity between subjective and objective measures of sleepiness have been observed where subjective sleepiness returned to baseline earlier than objective performance measures (Balkin et al., 2008; Belenky et al., 2003). This could potentially explain why some people may deny excessive sleepiness despite poorer cognitive functioning.

1.4.1. Sleep deprivation and Attention

In the past, attention was viewed as a unified construct where a decrease in performance after sleep loss was associated with attentional deficits (Dinges, 1992; Kjellberg, 1977). However, the field of cognitive science has agreed on interpreting attention as a multidimensional system (Posner et al., 1990; Raz, 2004). The attention system involves three neural networks serving three subfunctions of attention: 1)

Alerting – defined as maintaining a state of activation of the cognitive system or vigilance. This will be covered more in the following section. 2) Orienting – defined as selectively placing attentional focus on relevant objects or space of the visual field. 3) Executive – defined as the ability to control one's behavior to achieve a goal (Raz, 2004). To manipulate all three attentional networks at the same time, the Attention Network Test (ANT) (Fan et al., 2002) is commonly used. Although past studies may use cognitive tests other than the ANT, the impact of sleep deprivation on attention is remarkable. Sleep deprivation lasting 24 hours shows a decrease in alertness while not affecting the orienting mechanisms suggesting these two systems are independent of each other (Casagrande et al., 2006). As for executive control, a one night of sleep deprivation impaired error detection and highlighted the inability to avoid repeating the errors (Tsai et al., 2005; Hsieh et al., 2007) despite no significant difference in subjective effort to remain aware and motivated (Timothy I. Murphy et al., 2006).

1.4.2. Sleep deprivation and Vigilance

The largest effect sleep deprivation has on cognitive function is on vigilance levels. As a subserving attentional function, vigilance (also known as tonic alertness) is defined by cognitive neuroscientists as sustained attention on tasks for over an extended period. The effects of sleep deprivation on vigilance and fatigue has been extensively studied showing its role in the impairment of cognitive performance (Lo et al., 2012; Drake et al., 2001; Härmä et al., 1998; Van Dongen et al., 2003; Lim et al., 2008; Bermudez et al., 2016). The most common test used to assess vigilance in sleep deprivation is the Psychomotor Vigilance Task (PVT) (Doran et al., 2001). It is a simple task that records the reaction time for a subject to respond to a particular stimulus. The PVT requires sustained attention and has been validated to be highly sensitive to sleep deprivation (Basner et al., 2011). As alertness decreases and cognitive fatigue heightens during a sleep-deprived state, the reaction time becomes slower, and there is an increase in lapses (failure to respond within 500ms after stimuli) and error of commission (false positive) (Lim et al., 2008b).

1.4.3. Sleep deprivation and Working Memory

Past studies found working memory to also be a cognitive domain that is negatively impacted following 20 or more hours of total sleep deprivation (Alhola et al., 2007; Turner et al., 2007; Mu et al., 2005; Smith et al., 2002; Raidy et al., 2005; Choo et al., 2005). Response time and accuracy for working memory tasks, as well as working memory span, saw a decline following total sleep deprivation (Raidy et al., 2005; Choo et al., 2005; Turner et al., 2007). Furthermore, studies looking at the effects of sleep deprivation on working memory task also demonstrated the importance of sleep to acquire new information along with the stabilization and assimilation of new knowledge (Diekelmann et al., 2010; Walker, 2009). Most studies used a memory task called N-back to assess working memory functioning. The N-back task is a computerized version of a popular paradigm consisting of a series of letters presented in sequence (M. W. L. Chee et al., 2004).

1.4.4. Effects on Cognition at Various Doses of Restricted Sleep

Although chronic partial sleep loss has a less immediate and less pronounced cognitive deficit than total sleep deprivation, the issue tends to worsen over the buildup of lack of sleep (Banks et al., 2010). To further understand the implication of sleep deprivation, it would be informative to look at the effects of the sleep deprivation at different levels (e.g., partial, total). A study done by (Van Dongen et al., 2003), see *Figure 1*) investigated the neurobehavioral responses to varying doses of daily sleep showed that chronic partial sleep deprivation consisting of two weeks of 4 hours of sleep per night can eventually lead to same degree of deficit in sustained attention (measured by the psychomotor vigilance task) and working memory (measured by digit symbol substitution task) as 48 hours of total sleep deprivation (Van Dongen et al., 2003). In particular, by the end of 14 days of sleep restriction, subjects in the 4 hours and 6 hours sleep period condition only reported slight sleepiness when cognitive performance was at its worst. The authors hypothesized that sleepiness perhaps was able to adapt to chronic partial sleep deprivation (Van Dongen et al., 2003). The findings suggest that when chronically sleep deprived, subjects should either not rely on

their subjective sleepiness levels to assess their actual cognitive impairment, or around 4 hours of sleep is sufficient to avoid the sense of sleepiness found in total sleep deprivation (Van Dongen et al., 2003). The outcomes from this study are striking as they may illustrate the reason sleep restriction is becoming more common due to people's false belief of having adapted to sleep deprivation since they do not feel as sleepy.

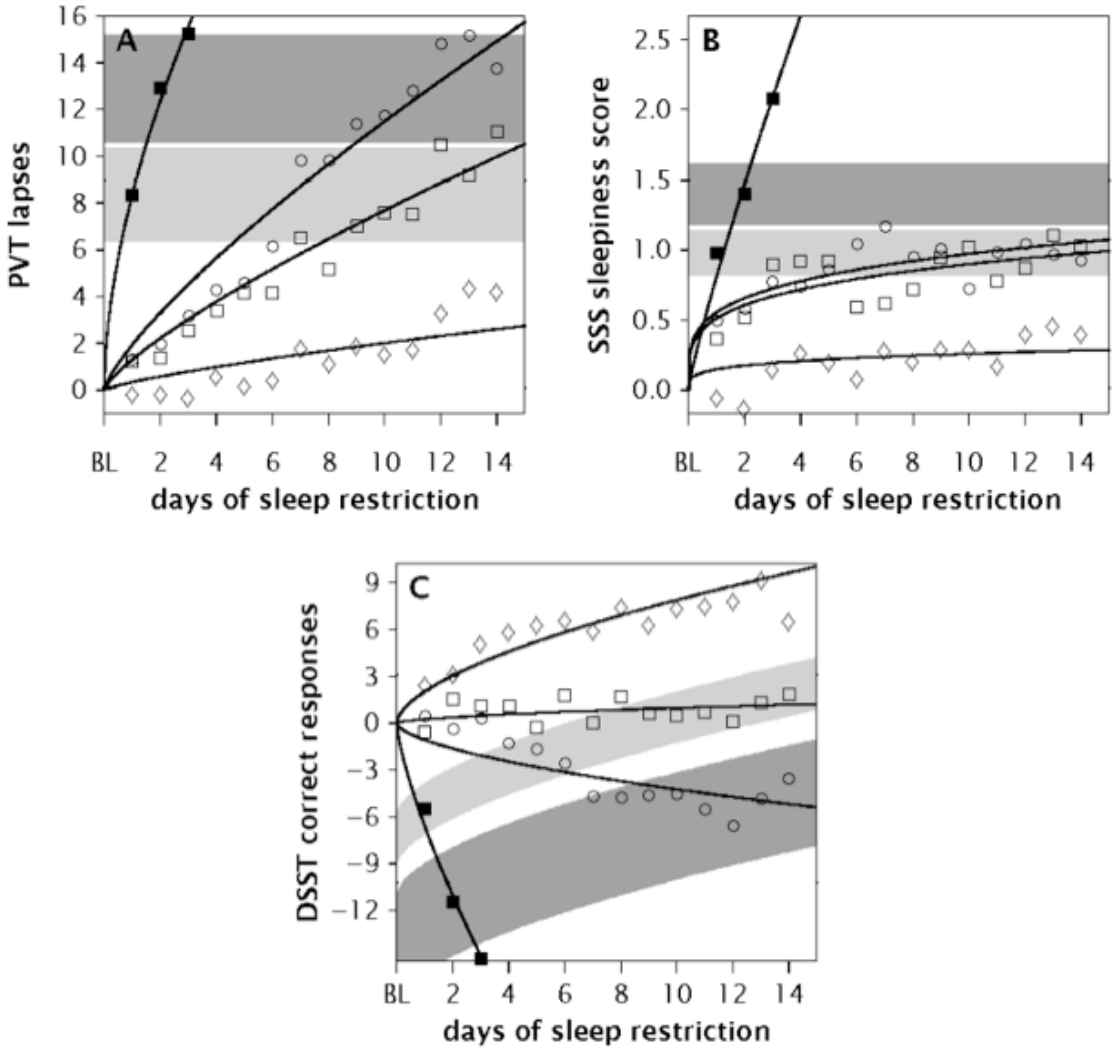

Figure 1. Obtained from (Van Dongen et al., 2003) – Three different neurobehavioral assays measured cognitive performance and subjective sleepiness. Each panel displays 8 hours (◊), 6 hours (□), and 4 hours (○) for chronic sleep period conditions across 14 days and 0 hour (■) sleep condition across 3 days (Van Dongen et al., 2003). *Panel A shows psychomotor vigilance task (PVT) performance lapses; Panel B shows Stanford Sleepiness Scale (SSS); and Panel C shows Digit Symbol Substitution Task (DSST) correct responses. Upward trends represent worse performance on PVT and greater sleepiness on SSS and downward trends correspond to worse performance on DSST. These cognitive impairments for all four sleep restricted conditions followed a near-linear trend with slim differences between chronic partial sleep deprivation and total sleep deprivation. In contrast, the sleepiness ratings for both partial and total sleep deprivation differed more drastically where total sleep deprivation followed a near-linear trend and chronic partial sleep loss had a near-saturating trend. For DSST, gray bands are curved parallel to the practice effect displayed by subjects in 8 hours sleep condition.*

In summary, the disruption of sleep in normal healthy subjects has significant negative effects on cognitive performances. More specifically, the impairment in sustained attention and working memory really become evident when subjects have been partially sleep deprived or totally sleep deprived (Van Dongen et al., 2003; Basner et al., 2011; Alhola et al., 2007; Raidy et al., 2005; Choo et al., 2005; Turner et al., 2007). These findings are profoundly relevant in modern society where sleep restriction is widely encountered. From a social point of view, investigation of the consequences of sleep deprivation can help educate the population on sleep recommendations for health policies in a modern society where there is an epidemic of sleep loss (Hafner et al., 2017; Ocampo et al., 2017). To date, total sleep deprivation remains one of the most common manipulations performed in the laboratory and still can be translatable to chronic partial sleep loss (Reynolds et al., 2010). By pinpointing the effects of sleep deprivation on cognitive functions, we can bring more emphasis on the danger of sleep deprivation in these safety-sensitive jobs.

1.4.5. Sleep Deprivation and Recovery Sleep

A study found that thalamocortical activity decreases following a night of total sleep deprivation, and the impairments were only partially reversed following a night of recovery sleep (Wu et al., 2006). Another study by (Lim et al., 2017) showed a daily one-hour nap led to greater processing speed in the blocked symbol decoding task compared to a group that did not take a nap following five nights of restricted sleep (5 hours). Finally, a recent study found evidence that sleep restriction of 5 hours in bed over five nights resulted in deficits in adolescents' cognitive functions and alertness (Lo et al., 2017). Moreover, two nights of 9 hours of sleep did not lead to full recovery from these deteriorations. However, a daily 1 hour afternoon nap after each restricted night of sleep alleviated performance impairments; although not fully restored (Lo et al., 2017). However, there have been studies that have shown recovery sleep to have a higher restorative effect. One study by (Philip et al., 2012) found evidence that following 5 nights of sleep restriction to 4 hours of sleep, middle-aged adults were able to obtain a full recovery to baseline levels in alertness and performance in reaction time task following a single night sleep lasting 8 hours. However,

another study showed young adults going through the same levels of sleep restriction did not recover completely in a vigilance task after being in bed for 10 hours (Banks et al., 2010). This might suggest that young adults might require a longer sleep period or require multiple nights of sleep to recover.

While sleep deprivation is known to significantly hinder cognitive functions, recovery sleep is still not fully understood. Although some studies might suggest partial recovery of cognitive performance can come from a nap or 1-2 nights of 8 hours sleep, others found full recovery effects after just one night of sleep recovery. Further investigation on the effects of sleep recovery following sleep deprivation is warranted.

1.5 Sleep Deprivation and Brain Activation

Functional magnetic resonance imaging (fMRI) is a technique to detect spontaneous or experimentally-induced changes in activation levels of brain regions (Rogers et al., 2007). fMRI measures changes in blood oxygenation level-dependent (BOLD) signal due to metabolic demands (oxygen consumption), which is used as a proxy measure of neural activity (Ogawa et al., 1990). These allow the creation of activation maps representing the engagement of different brain regions during a specific task or at rest. There are a few reasons to investigate how sleep affects brain activation. The first reason is to characterize the different regions or networks in the human brain that are vulnerable or resilient to the effects of sleep deprivation. Likewise, understanding the changes in brain activity and function from sleep loss can explain the disruptive changes in behavior. For example, total sleep deprivation elicited a decrease in activation in the intraparietal sulcus, a region corresponding to visual short-term memory capacity (Michael W.L. Chee et al., 2007). However, the way sleep deprivation affects working memory activation (prefrontal regions) has differed across studies due to possible task difficulty differences. In one study, there was a compensatory prefrontal activation when task difficulty of working memory task was increased (M. W. L. Chee et al., 2004) while other studies did not replicate the same outcome (Bell-McGinty et al., 2004; Michael W.L. Chee et al., 2006; Habeck et al., 2004). The study by (M. W. L. Chee et al., 2004) also found

that after a night of total sleep deprivation, there was reduced activation in the bilateral parietal regions, commonly known to be activated during working memory tasks (Cabeza et al., 2002). More interestingly, a study by (Drummond et al., 2000) showed greater responses during a verbal reasoning task to regions associated with working memory after a night of total sleep deprivation. This was intriguing as verbal reasoning typically does not rely on working memory systems but due to sleep deprivation, the authors suggested that the systems became active in order to help compensate for the lack of learning resources (Drummond et al., 2000). The study also found these same regions associated with working memory to be active during the arithmetic task at normal waking state but not after total sleep deprivation. Since the arithmetic task indeed may rely on the working memory systems, the resources necessary for compensation may not be available following total sleep deprivation. This emphasizes how different cognitive demands in tasks may play an important role in the adaptive response of compensatory activation. Furthermore, the increase and decrease in activation in different brain regions during a particular task following sleep deprivation further underlines the need for research to examine the way these different regions function with one another when individuals are sleep deprived.

1.6. Sleep Deprivation & Functional Connectivity

1.6.1. Functional Connectivity

Complementary analyses that inform how the different neural systems interact together may provide a better insight into how the brain executes a particular function. The term functional connectivity is defined as the temporal inter-relationship (measured as Pearson's correlation) of the different brain regions (Michael D. Fox et al., 2007; Greene et al., 2015). More specifically, the correlations of activities are derived from changes in BOLD signal across time found within and between regions, voxels (3D brain images), or networks during resting-state or during the task (Michael D. Fox et al., 2007). It is important to consider that functional connectivity does not provide information on the direction of these connections (i.e., feedforward, feedback), but provides information on how strong the time course of activity of two

areas may be related to one another. The advantage of examining functional connectivity over task activation is the fact that it offers an overall perspective of the brain network activities and the way the different networks function together rather than just viewing a small set of regions involved in a task. It is important to note though that functional connectivity can change in response to hypercapnia, where a decrease in oxygen inspired can decrease spontaneous low-frequency fluctuations (Biswal et al., 1997). However, one of the more prominent confounds measuring functional connectivity is the physiological noise from the BOLD signal (Krüger et al., 2001). The noise can come from fluctuations in cerebral blood flow and metabolism as well as cardiac and respiratory pulsatility (Birn et al., 2006). Another common noise is physical motion made by human subjects including nodding or swallowing (Mayer et al., 2019).

1.6.2. Functional Cortical Networks

Functional networks are a group of voxels or regions that elicit the same temporal activation pattern during resting-state or task. By examining the brain in this way, it may grant insight into the larger scale of neuronal communication in the brain. This perspective creates a platform to allow for a better understanding of how the functional networks relate to human behavior (Bullmore et al., 2009; Michael D. Fox et al., 2007). There is a staggering amount of studies done on functional networks during resting-state, notably by (Power et al., 2011) and (Thomas Yeo et al., 2011) who created two of the most widely-utilized functional network partitions (Ji et al., 2019). Functional cortical networks, as opposed to structural cortical networks, categorize parcels of the brain by their similarity in functional properties involved in processes through a time-series rather than any similarities in microstructure. For this study, we have chosen the popular partition by (Thomas Yeo et al., 2011) that was designed to cluster voxels into regions and networks of 1000 individuals' resting-state scans. This led to a set of 100 parcels grouped into seven cortical networks described as visual, somatomotor, dorsal attention, ventral attention, limbic, default, and frontoparietal networks.

The visual and somatomotor networks are well known to support externally driven functions of vision, tactile sensation, and motor coordination (Doucet et al., 2011). The limbic network consists of mainly the orbitofrontal cortex and is involved in decision making (Mega et al., 1997). The remaining networks are sometimes classified into two categories: *task-positive* (i.e., frontoparietal, dorsal attention, and ventral attention networks) or *task-negative* (i.e., default mode network) based on their activation increasing or decreasing during cognitive tasks. The frontoparietal network is usually involved during higher-level functioning such as fine-tuning behaviors as demands for task increase (Dosenbach et al., 2008). The dorsal attention network is involved in top-down attention referring to internal guidance based on previous experiences and goals (Vossel et al., 2014). Alternatively, the ventral attention network involves bottom-up attention requiring selective attention from external guidance driven by stimuli from the environment (Vossel et al., 2014). Lastly, the task-negative default mode network (DMN) is involved in self-related activities such as imagination and recollection (Andrews-Hanna, 2012). A possible explanation for the decrease in activation of the default mode network during tasks could be due to the reduction of focus to the self-related processes to increase the attention for the task at hand (Michael D. Fox et al., 2005).

During tasks and resting-state, relevant functional networks (especially task-positive networks) have been said to become more functionally connected with each other, in other words, more connected with each other to process the information necessary (Cocchi et al., 2013). Meanwhile, the non-relevant functional regions that do not contribute to the task performance are highly segregated from these task-positive networks (Anticevic et al., 2012).

1.6.3. Sleep Deprivation and Functional Connectivity

Research on sleep deprivation and functional connectivity has been recently gaining interest due to its potential role in cognition and behavior. Several studies have reported changes in functional connectivity

during resting-state after a partial (Sämann et al., 2010) and total sleep deprivation (De Havas et al., 2012; Yeo et al., 2015). More specifically, it takes only one night of partial sleep deprivation (3.5 hours of sleep) for an observable decrease in connectivity during resting wakefulness within the DMN and the task-positive networks (Sämann et al., 2010) and a total night of sleep deprivation showed a decreased anti-correlation between these two networks (De Havas et al., 2012). In addition, highly functionally connected cortical networks (e.g. within DMN) became less functionally connected whereas those that are generally highly anti-correlated (e.g. between DMN and attention networks) became less anti-correlated following a night of total sleep deprivation (Yeo et al., 2015). It has been suggested that the nature of a network to segregate itself is important in order for directed awareness and computation in any goal-oriented task (Shao et al., 2013; Yeo et al., 2015). Other studies have also shown that sleep deprivation also affects the connectivity of the subcortical regions where the connectivity between the thalamus and frontal and temporal gyri decreased following sleep deprivation which may lead to a decline in arousal levels and information processing and consequently, affects human cognitive functions (Shao et al., 2013). The outcomes of sleep deprivation on functional connectivity imply that there are overall changes in the brain networks, but this needs to be more refined to further our understanding of the potential networks that may be more vulnerable to sleep deprivation.

1.7. Cognition & Integration

1.7.1. Cognition and Functional Integration of Brain Areas

The different cortical networks have their independent activity patterns from one another during cognitive tasks (Peter T. Fox et al., 2012; Di et al., 2013; Friston, 2011; Rao et al., 2008). Although acting independently, cognitive processing requires interactions (integration) across brain regions (Klimova, 2014; Varela et al., 2001). More specifically, integration provides the shared dynamic fluctuation of neural information occurring spontaneously in response to different cognitive demands (Tononi, 2008). The optimal cognitive functioning requires the balance of both the integration and segregation (i.e. functional

regions becoming less connected with each other) of neural signals across the different networks (Sporns, 2013; Deco et al., 2015). Integration is different from functional connectivity which measures the temporal inter-relationship of the different brain regions as mentioned in section 1.6.1. While functional connectivity measures time-series signal using Pearson's correlation between parcels with ranging values from -1 to 1, integration is preferred for quantifying grouped signals using a covariance matrix at the cortical and network level.

One way to quantify the changes in information integration in brain networks from different states of sleep and wakefulness can be calculated by computing both the total integration and hierarchical functional clustering (Boly et al., 2012). To clarify, functional clustering uses seed regions from the BOLD signal and transforms them into clusters/subsystems based on how functionally close these regions are related to each other. Furthermore, it looks at the interactions within each subsystem relative to between subsystems using the functional clustering ratio (FCR) and quantifies the degree of segregation (refer to section 2.11) of a given system (Boly et al., 2012). Alternatively, total integration is the result of the combination of both the within and between subsystems (Boly et al., 2012).

1.7.2. Sleep and Integration

The study by Boly et al., found that during sleep, there was a significant increase in total integration during NREM sleep (Boly et al., 2012). Beyond the changes in total integration, interactions within subsystems became proportionately larger than between subsystems in NREM sleep compared to wakefulness resulting in an increased FCR. This phenomenon reflects a hierarchical segregation in information flow during NREM sleep. As such, the level of consciousness appears to be a function of not only the total amount of connectivity in the brain, but the dynamic complexity of interactions between its subsystems (Tononi, 2005). It has also been proposed that a dynamic balance of segregation and integration of information across brain networks for proper cognitive functioning (Sporns, 2013; Tononi, 2005). Following this model, an increased in functional clustering of cortical activity during sleep results in a

decrease of information integration despite the preserved total information processing. This finding aligns well with theories suggesting that reduced consciousness during NREM sleep is a result of an increase in brain segregation (Sporns, 2013; Tononi, 2005). The results have been replicated wherebyby higher interactions within the networks (segregation) immediately decreased once participants were woken up (Tagliazucchi et al., 2013; Boly et al., 2012).

1.7.3. Sleep Deprivation on Integration

A previous study showed a reduction in network modularity during resting-state following total sleep deprivation (Ben Simon et al., 2017). Network modularity quantifies the integration and segregation balance of brain activity (Godwin et al., 2015). To clarify, network modularity looks at the number of within-network connections compared to all connections (instead of between-network connections in FCR). More specifically, reduced modularity supports an increase in functional integration as opposed to an increase in functional segregation from increased modularity. Reduction in network modularity from sleep deprivation was found in the DMN, limbic, somatomotor, and attention networks during resting-state (Ben Simon et al., 2017). Furthermore, the findings reported that worsening vigilance task performance was significantly correlated with reduced somatomotor network modularity (Ben Simon et al., 2017).

1.8. Knowledge Gap, Objectives, Hypotheses

1.8.1. Knowledge Gap & Current Study

Few studies have attempted to bring light onto the association of functional connectivity disruptions and cognitive behavior following sleep deprivation. One study (De Havas et al., 2012) did not report any significant correlations between measures of functional connectivity and declines in vigilance performance. A later study found that subjects who were more resilient to vigilance decline from sleep deprivation showed higher levels of segregation of cortical networks during resting-state (Yeo et al., 2015). Since there

are changes in the functional network connectivity following sleep deprivation (e.g., DMN, attention network), this leaves the question of whether the different networks recover differently following recovery sleep. There remains a lack of comprehensive understanding of how the human brain networks and its connectivity recovery from sleep deprivation (Krause et al., 2017).

Although previous studies tend to focus on a particular region of interest within functional networks, this study will adopt a whole-cortex network approach to not limit the analysis to subjectively selected regions. We also decided to assess the hierarchical functional clustering (integration) effects of within and between cortical networks across various arousal states (well-rested state, sleep deprived state, and post-recovery nap state) during the cognitive tasks. This will allow us to have a more quantifiable understanding of the functional interactions at the cortical and network levels using measures of integration of fMRI activity within and between networks. Unlike previous literature that evaluated integration during resting-state (Ben Simon et al., 2017), this study will be the first to investigate the effects during cognitive tasks. Similar to functional connectivity, no literature to date has investigated the effects of a recovery nap on functional clustering following a night of total sleep deprivation.

To date, there have been no studies to our knowledge that have investigated the effects of a recovery nap on functional connectivity and integration following a night of total sleep deprivation during the cognitive tasks. It is important to assess functional connectivity and integration during the different cognitive tasks rather than resting-state since each cortical networks have their independent respective activity patterns that differ from one another (Peter T. Fox et al., 2012; Di et al., 2013; Friston, 2011; Rao et al., 2008). By looking at functional connectivity and integration during task, it will allow us to see ongoing dynamic changes (integration & segregation) and determine how this is also related to the cognitive changes. This will likely give a neurophysiological explanation for the decline in cognitive performance amongst those who are sleep deprived.

1.8.2. Objectives

1. Our study will examine the effects of total sleep deprivation and a partial recovery nap on three separate cognitive tasks assessing attention, vigilance, and working memory.

2. The present study will be the first to investigate the effects of total sleep deprivation and a recovery nap on cortical functional connectivity during three separate cognitive tasks.

3. This study will explore the effects of total sleep deprivation and a recovery nap on integration during the three separate cognitive tasks.

4. The study will also compare these changes in integration with the cognitive changes for each of the separate cognitive tasks.

1.8.3. Hypotheses

1. For this study, the cognitive performances during tasks are hypothesized to decrease when subjects are sleep deprived and partially restore after a recovery nap.

2. For functional connectivity of the three separate cognitive tasks, when well-rested, we hypothesize that the task-relevant networks will be highly functionally connected with each other compared to within networks. Non-relevant networks will be highly anti-correlated from the task-relevant networks. However, following a night of total sleep deprivation, we expect the highly functionally connected networks to become less functionally connected. Following a recovery nap, we hypothesized for these effects to partially recover where functionally connected networks will have partial recovery back to its baseline functional connectivity.

3. For integration of the three separate cognitive tasks, following a night of total sleep deprivation, we expect the interactions within-networks to be more integrated relative to between-networks. Following a recovery nap, we hypothesized the highly integrated networks have partial return to baseline integration and segregated networks will restore partially to its baseline segregation.

4. We hypothesize that the increase in integration after total sleep deprivation will be associated with worsening of cognitive performance while decreased integration after a recovery nap will be associated with cognitive improvement in all three separate tasks.

2. METHODS

2.1. Subject Recruitment

Participants aged between 18 to 30 years and considered normal good sleepers (>6 hours of sleep per night) were recruited using advertisements posted online and within Concordia University and the PERFORM Centre. A semi-structured interview was conducted to assess their eligibility. Due to the involvement of functional magnetic resonance imaging (fMRI) and sleep study criteria, participants were screened for the following exclusion criteria: claustrophobia; pregnancy; neurological disorders (e.g., epilepsy, migraine, and stroke); medical conditions (e.g., chronic pain, chronic respiratory diseases); and metallic objects in body (e.g., pacemaker, prosthetic valve, clip). Participants were also excluded for psychological conditions (e.g., major depression, anxiety disorder, psychotic disorder), current use of psychotropic medications, drugs, and alcohol. Manual scoring of the polysomnography (PSG) from two sleep experts from the lab ruled out sleep disorders such as sleep apnea (apnea-hypopnea index >5/h), restless leg syndrome, and periodic limb movement disorder (periodic limb movements during sleep index >15/h).

In total, 53 participants responded to advertisement, of which 34 passed initially screening. A total of fourteen were excluded (N=3 for sleep disorders, N=5 for technical reasons, N=6 withdrew due to personal reasons). Consequently, 20 participants (12 females) completed the study (see *Figure 2*). All participants signed an informed consent form approved by the *Comité Central D'Éthique de la Recherche (CCER)*.

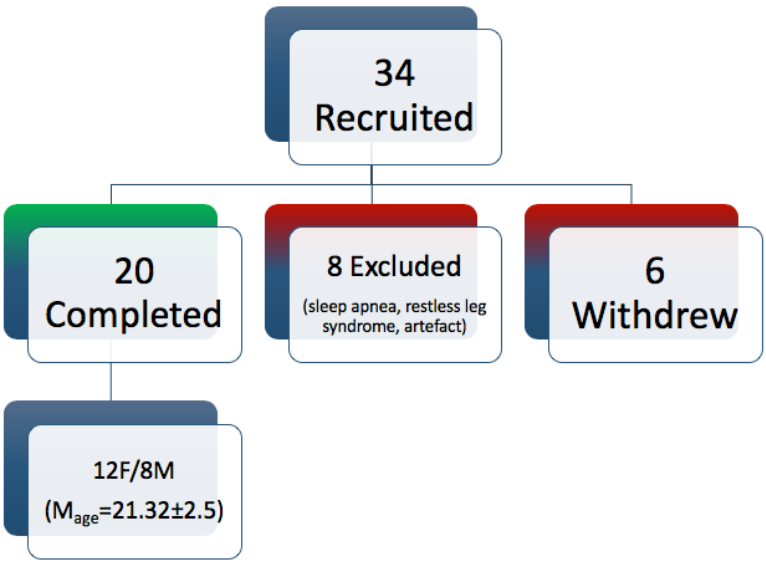

Figure 2. Subject Recruitment

2.2. Study Design

Participants deemed eligible following the PSG screening night were scheduled for two subsequent sessions, separated by one week in a randomized counter-balanced design. One session took place after a normal night of regular sleep while the other session took place after a night of total sleep deprivation, both which were controlled in the sleep laboratory. Participants were allowed to sleep as per their regular (>6 h) sleep schedule during the normal night in the sleep lab at the PERFORM Centre. During the sleep deprivation night, a member of the study stayed overnight with the participant and ensured that he/she did not fall asleep by offering to talk, watch movies or play games. Following both nights, participants were taken to the imaging suite at 7:15 AM for their MRI sessions, where they were asked to perform a resting-state scan and cognitive tasks which will be discussed in more detail in the next section.

Figure 3. Randomized counterbalanced design of the three nights for the study

2.3. MRI Sessions

Prior to being scanned, subjects performed one practice run for each cognitive task (covered in the next section) to familiarize themselves with the instructions. Participants had an MRI-compatible EEG cap set up onto their heads prior to entering the MRI scanner (covered in section 2.5). Once the session began, they were introduced to the three cognitive tasks and resting tasks in the order shown in *Figure 4*. After each task, they were asked to rate their subjective sleepiness on the 9-point Karolinska Sleepiness Scale (KSS). Anatomical scans were also collected using T1w imaging and diffusion weighted MRI following the normal night. As for the sleep deprivation night, participants were allowed to take a one-hour opportunity nap inside the MRI scanner following the cognitive and resting tasks to monitor the brain recovery during sleep. They were asked to rate their subjective sleepiness (KSS) prior to and post-nap (Åkerstedt et al., 1990). After the nap, they were woken up to perform the same tasks again (in the same order) to examine potential improvements after sleep recovery. Participants were free to stop the study anytime if needed.

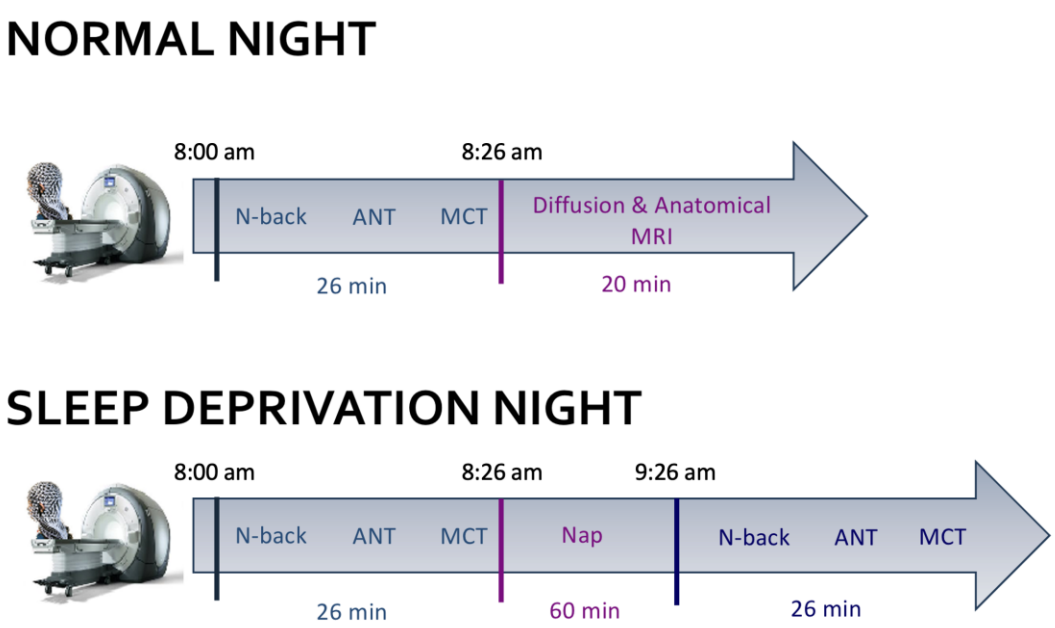

Figure 3. MRI session flowchart

2.4. Experimental Tasks

2.4.1. Cognitive Tasks

In all MRI sessions (WR, SD and post-nap), participants were asked to perform the same three different tasks. Repeated measures analysis of variance (ANOVA) and post-hoc t-tests were used to compare the accuracy (% of correct responses) and reaction time (reaction time, in ms) of the MCT, N-back, and ANT tasks between the three different states.:

1) **N-back task:** a working memory task with 3 difficulty levels (0, 1, and 2) where a series of letters is presented at a rate of one letter every 2.5 seconds to the participant. The participant is required to press the button if the letter presented is the same letter presented "N" times prior (ex. In a 3-back, the participant pressed a button to the sequence, "C A E C", upon the appearance of the second "C") (Kulikowski et al., 2016; Jaeggi et al., 2010). The task is presented in blocks of X seconds with rest periods in between (X-Ys) for 8 minutes. Accuracy (percentage of correct

responses) and reaction times (delay between stimuli presentation and trigger response in milliseconds) were extracted across all difficulty levels. (*Figure 5*)

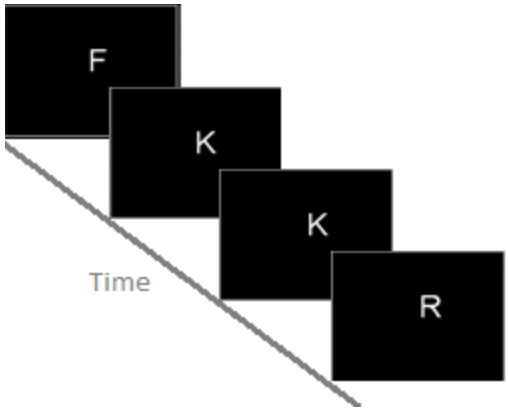

Figure 4. N-back task

2) **Attention Network Task (ANT):** an attention task where the participant is required to identify the direction of the arrow in the middle of an array of five arrows. Different cues such as valid, invalid, or double (i.e., both boxes are flashing) are sent before the appearance of the arrow to distract the participant. There are three different types of stimulus presentations (uncued, congruent cued, and incongruent cued) which yield three components of this task: alerting, orienting, and executive control. Congruent cues consist of five arrows presented in the same direction whereas incongruent cues have arrows pointing in different directions. This ensures that the level of attention of the participant is maintained (Fan et al., 2002; Weaver et al., 2013). Accuracy (percentage of correct responses) and reaction times (delay between stimuli presentation and trigger response in milliseconds) were extracted across all different cues. This task lasted for 13 minutes. (*Figure 6)*

Figure 5. Attention network task

3) **Mackworth Clock Task (MCT):** a vigilance task that involves a series of stimuli presented sequentially on-screen spatially similar to a ticking clock. The participants were asked to press the trigger when the stimuli skipped an element in the sequence (Lichstein et al., 2000; Loh et al., 2004). This task lasted for 5 minutes. Accuracy (percentage of correct responses) and reaction times (delay between stimuli presentation and trigger response in milliseconds). (*Figure 7*)

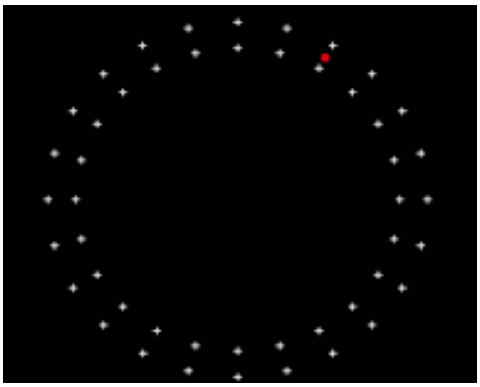

Figure 6. Mackworth Clock Task

For the purpose of the master's thesis, we will mainly be focusing on the MCT, N-back, and ANT tasks in order to cover the aspects of vigilance, working memory, and attention, respectively. ANT task was developed to test for three different attention networks: alerting, orienting, and executive control. Since these falls beyond the scope of my thesis and was not included in the proposal, the analysis will not go into the depth of the 3 components of the ANT task as it is not feasible when examining functional connectivity.

2.5. EEG Acquisition

An MRI-compatible, 256 electrode, high-density EEG cap used (Electrical Geodesics Inc. (EGI),) was used during both MRI sessions. The cap was first soaked in a saline solution mixed with neutral 0% baby shampoo and potassium chloride to ensure proper conductivity between electrodes and the participants' scalp. The impedance of the electrodes was kept below 100 kΩ. Lastly, polyethylene was wrapped around the electrodes to maintain the moisture and thus impedance of the electrodes in order to

maintain the quality of the EEG recording throughout the session. EEG data were sampled at 1000 Hz through a specialized amplifier and recorded with *Net Station* software (EGI Ltd).

2.6. Imaging (fMRI) Acquisition

Images were acquired on a 3T General Electric (GE) scanner (GE Medical Systems, Milwaukee, Wisconsin, US) using a gradient-echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2500 ms, time-to-echo (TE) = 26 ms, field-of-view (FOV) = 256 mm, and matrix size 64 x 64. Forty-one axial slices of thickness 4 mm were collected in a sequential descending manner. A mirror was placed above participants on the head coil for them to view stimuli being projected onto a screen from a projector. Participants were instructed to press a button with their index finger and thumb on the response box. Foam-padded cushions were used to stabilize the head and minimize movements during the scan.

2.7. Imaging (structural) Acquisition

To ensure proper registration of the functional and anatomical images, high-resolution coplanar T1-weighted anatomical images were obtained after the functional runs. High-resolution T1-weighted images were acquired during the normal night session (BRAVO, TR 7908, TE 3.06 ms, flip angle 12°, FoV 256mm matrix 256 x 256, 1 x 1 x 1mm, 196 axial slices, resolution 1 mm isotropic) and were also used for image normalization in the Montreal Neurological Institute (MNI) space (Evans et al., 1994).

2.8. Preprocessing of fMRI Data

Functional MRI data preprocessing was performed through the open access and standardised *fMRIPrep 1.3.1* pipeline (Esteban et al., 2019) which is based on *Nipype 1.1.9* (Esteban et al., 2020;

Gorgolewski et al., 2011). All MRI preprocessing were performed on the Compute Canada servers Cedar and Graham ((https://www.computecanada.ca/research-portal/accessing-resources/available-resources/). The pipeline included the following steps:

1. Creation of a reference image and brain mask. Time-points in the fMRI signal demonstrating non-steady state artifacts (in excess of the T1w contrast) were aligned and averaged to generate a reference image in each participant's native space.
2. The BOLD reference were co-registered to the T1w reference using bbregister (*FreeSurfer v6.0*) which implements boundary-based registration (Greve et al., 2009). The co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference.
3. Parameters corresponding to bulk head motion (due to involuntary drift, swallowing, etc.) of each time point with respect to the reference image were estimated using *mcflirt* (*FSL v5.0.9*; (Jenkinson et al., 2002)). These parameters are 6 motion parameters (x, y, z translations and α, β, γ rotations) from which the average frame displacement is computed.
4. Slice timing correction (*AFNI*; (Cox, 1996)). Based on the acquisition time of each 2D axial slice, the temporal dynamics were estimated, and all slices were resampled onto their original native space by applying a single composite transform to correct for head motion and susceptibility distortions. The transforms are concatenated and applied all at once with interpolation (Lanczos) step to minimize the loss of information.
5. Frame Displacement and spatial standard deviation of successive difference images (DVARS) were calculated for each functional run using implementations in *Nipype*.
6. Brain tissue segmentation of white and gray matter, and cerebrospinal fluid were performed on the brain-extracted T1w using FAST (*FSL v5.0.9;* (Zhang et al., 2001)). The average time-series of the white matter, cerebrospinal fluid, and whole-brain were also extracted.
7. Following the sampling of the BOLD data onto their original native space, these were resampled via nonlinear transformation to the MNI152NLin2009cAsym standard volumetric space for all

subjects for subsequent processing and analysis while maintaining the original resolution of the BOLD data.

8. The BOLD data time-series in standard space were further denoised using a 36-parameter stream of *xcpEngine* (Ciric et al., 2017).
    a. Temporal filter (0.01-0.08 Hz) was applied to the data.
    b. Six realignment parameters, the mean white matter and cerebrospinal fluid time series (extracted from *fMRIPrep* in step 6), as well as derivative and quadratic expansions were all regressed out from the BOLD time-series.
9. The final preprocessed BOLD time-series for each subject were projected onto the cortical surface (white matter boundary, default) using *fsaverage5* template from the *Freesurfer* package (*mri_vol2surf; FreeSurfer v6.0)*. It was then smoothed along the surface space using a 6mm smoothing kernel.

2.9. Functional Connectivity Analysis

To calculate functional connectivity, the BOLD data sampled in the surface space (20,484 vertices) were first divided into 100 cortical parcels based on resting-state functional imaging data from a sample of 1000 subjects (Schaefer et al., 2018). Firstly, for each individual tasks, the functional time-series of each of the 20,484 vertices were assigned a parcel number from 1 to 100 based on the template. These time-series were then averaged within each parcel to provide 100 time-series with 50 on each hemisphere (one averaged time series per parcel). Pearson's pointwise correlations between the timeseries of each parcel are then calculated. This results in a 100 by 100 correlation matrix providing the calculated functional connectivity between all parcels.

These parcels were further clustered into 17 functional networks using a template previously described in the literature, in order to compare the functional connectivity within and between these

networks (Thomas Yeo et al., 2011). The parcellation scheme used directly allows for an allocation of each parcel to one of 17 functional networks.

2.9.1. Whole-Brain Signal Regression

The debate on whether to regress whole-brain signal in fMRI preprocessing still exists. On one hand, a study done by (Yeo et al., 2015) investigated the matter further and found it beneficial to regress whole-brain signal as it allowed for clearer group contrasts that are usually masked from the elevated whole-brain signal amplitude resulting from sleep deprivation. Since whole-brain signal regression examines the relationship of fMRI signals relative to the whole brain signal in sleep deprivation, this could potentially introduce negative correlations between cortical regions (Michael D. Fox et al., 2009; Kevin Murphy et al., 2009). In contrast, the whole-brain signal has been positively correlated with vigilance decline (Wong et al., 2013). Thus, regressing whole-brain signals might remove important information on sleep deprivation. Whole brain regression was not performed for our study due to the small sample size and to avoid removing limited information.

2.10. Statistical fMRI Analysis

A traditional analysis of covariance (ANCOVA) and post-hoc test was not performed due to the effects of nap duration. The effects of nap duration only affected two of the three comparisons (sleep-deprived vs. post-recovery nap and well-rested vs. post-recovery nap) and not well-rested vs. sleep-deprived state (given there is no sleep in this comparison). Therefore, we compared for nap duration only for the two conditions that included sleep. A standard t-test was performed when comparing well-rested to sleep-deprived state. Due to the great variability in nap duration across subjects, a general linear model was performed to control for sleep stage time covariates between the sleep-deprived and post-recovery nap state, well-rested and post-recovery nap state. We controlled for the following separate sleep stage time covariates: total sleep time (TST), stage N2 time only (N2), stage N3 time only (N3). A t-test matrix of

change in functional correlation between time series of 100 cortical parcels during task performance was produced. A generalized linear model was applied to the connectivity matrices to obtain the mean value and percentage of edges with significant changes. Furthermore, due to a high number of multiple comparisons conducted simultaneously, a false discovery rate correction was applied ($p<0.05$) (Whitfield-Gabrieli et al., 2012).

2.11. Functional Integration Analysis

Functional data was considered as N regions of interest (parcels) characterized by their mean time courses $y = (y_1, \ldots, y_N)$ gathered into K systems (networks) defined as $S = \{S_1, \ldots, S_K\}$. For any partition of y, integration can then be defined as the Kullback-Leibler information divergence between the joint distribution $p(y_1, \ldots, y_K)$ and the product of the marginal distributions of the N-dimensional fMRI BOLD time series y divided into K subsets, such that:

$$I[y_1, \ldots, y_K] = D_{KL}\left[p(y_1, \ldots, y_K); \prod_{k=1}^{K} p(y_k)\right]$$

which can be rewritten as:

$$I[y_1, \ldots, y_K] = \sum_{k=1}^{K} H\left(p(y_k)\right) - H(p(y_1, \ldots, y_K))$$

where H is the entropy measure (Marrelec et al., 2008). For multivariate normal data with mean mu and covariance matrix Sigma, entropy can be computed as:

$$H\big(p(y)\big) = \frac{1}{2}\ln\left(|Sigma|\right)$$

The total integration can be decomposed, according to the organization of ROIs into systems, as the sum of within-system integration (I_{ws}) and a between-system integration (I_{bs}) term:

$$I[y_1, \ldots, y_N] = I_{ws} + I_{bs}$$

or alternatively:

$$I[y_1, \ldots, y_N] = \sum_{k=1}^{K} I\left((y_n)_{n \in S_k}\right) + I\left[y_{S_1}, \ldots, y_{S_K}\right]$$

Integration was calculated at two levels in the hierarchical model. Firstly, integration was calculated across the whole cortex where 100 parcels were divided into 17 networks. (Thomas Yeo et al., 2011). To calculate integration, we used a measure called the functional clustering ratio (FCR) which refers to the interactions within each subsystems (I_{ws}) relative to the integration between subsystems (I_{bs}) (Boly et al., 2012). It represents a quantifiable measure of clustering inside a given system. A higher FCR means that there are more interactions within subsystems compared to between subsystems. To clarify, the increase in FCR indicates that the sub-systems are more functionally independent (segregated) from one another.

$$Functional\ clustering\ ratio\ (FCR) = \frac{Integration\ within\ subsystems\ (I_{ws})}{Integration\ between\ subsystems\ (I_{bs})}$$

Similar to the functional connectivity analysis, a false discovery rate correction was applied due to multiple comparisons (Whitfield-Gabrieli et al., 2012) and standard t-tests compared the integration between different states.

2.12. Integration & Behavioral Tasks

Upon obtaining the differences between different states, Pearson's correlations were used to compare the changes in integration across the whole cortex between each different states (well-rested, sleep deprived, and post-recovery nap) and the behavioral changes in performances each of the three different tasks individually (MCT, N-back, and ANT). The integration changes in each individual network were then correlated with the changes in performance on the separate cognitive tasks using another Pearson's correlation ($p<0.05$).

3. RESULTS

3.1. Cognitive Tasks

The mean performance scores, reaction time (ms), and accuracy (% of correct responses), for each cognitive task across 3 states: well-rested (WR), sleep-deprived (SD), and post-recovery nap (PRN), are reported in Table 1A. None of the participants in the final sample fell asleep during the cognitive tasks. Furthermore, head movement inside the scanner during the cognitive tasks was not significantly different between sessions (average frame-wise displacement: 0.17 ± 0.11mm (WR) vs. 0.20 ± 0.12mm (SD); F = 2.36, p=0.109). The results also looked at the following sleep stage time covariates: total sleep time (TST), stage N2 time only (N2), stage N3 time only (N3). As predicted, each task outcomes were significantly impaired following sleep deprivation and improved following a recovery nap (Table 1A & 1B).

Cognitive Tasks		**Well rested (WR)**	**Sleep-deprived (SD)**	**Post-recovery nap (PRN)**
MCT	Reaction time (ms)	473.35 ± 59	500.20 ± 46	468.9 ± 56
	Accuracy (%)	72.1 ± 19	60.2 ± 16	71.1 ± 17
N-back	Reaction time (ms)	699.25 ± 235	1003.51 ± 416	783.49 ± 249
	Accuracy (%)	95.8 ± 3	84.7 ± 13	92.7 ± 7
ANT	Reaction time (ms)	736.56 ± 113	809.30 ± 131	751.31 ± 98
	Accuracy (%)	89.1 ± 13	64.8 ± 22	82.0 ± 18

Table 1A. Mean reaction time and accuracy of cognitive tasks across 3 different states

Cognitive Performance Comparisons		**WR → SD** ***p* values (95% CI)**	**SD → PRN** ***p* values (95% CI)**	**WR → PRN** ***p* values (95% CI)**
MCT	Reaction time (ms)	p=0.007 (10.3 to 57.4)*	p<0.001 (-65.1 to -24.5)*	p=0.414 (-38.1 to 16.4)
	Accuracy (%)	p=0.004 (-19.2 to -4.3)*	p=0.004 (-17.8 to -3.9)*	p=0.742 (-6.4 to 4.6)
N-back	Reaction time (ms)	p=0.007 (17.9 to 96.9)*	p=0.039 (-79.9 to -2.2)*	p=0.341 (-18.7 to 51.5)
	Accuracy (%)	p=0.002 (-18.3 to -5.1)*	p=0.002 (3.6 to 13.2)*	p=0.092 (-7.1 to 0.6)
ANT	Reaction time (ms)	p<0.001 (29.5 to 94.4)*	p<0.001 (-72.3 to -24.1)*	p=0.283 (-12.3 to 39.8)
	Accuracy (%)	p<0.001 (-34.0 to -11.8)*	p=0.001 (7.9 to 25.2)*	p=0.124 (-14.7 to 1.9)

*Table 1B. Comparison p-values of mean reaction time and accuracy of cognitive tasks across 3 different states. * = p < 0.05*

3.1.1 Task – MCT

For the MCT, the mean reaction time (*Fig. 9B*) increased from WR state to the SD state (d = 33.882, 95% CI = 10.3 to 57.4, p=0.007), and decreased from SD to PRN state (d = -44.77, 95% CI = -65.1 to -24.5, p<0.001), but there were no differences between WR and PRN state (d = -10.88, 95% CI = -38.1 to 16.4, p=0.414; $F_{1,19}$ = 8.39, p=0.002). The accuracy on the MCT (*Fig. 9A*) also decreased from WR state to SD state (d = -11.75, 95% CI = -19.2 to -4.3, p=0.004) and increased from SD to PRN state (d = 10.87, 95% CI = -17.8 to -3.9, p=0.004), but there was no difference between the WR and PRN states (d = -0.87, 95% CI = -6.4 to 4.6, p=0.742; $F_{1,19}$ = 8.44, p=0.001).

When controlling for sleep stage time covariates, the change in accuracy was similar for SD to PRN state (F_{TST} = 4.85, p_{TST}=0.041; F_{N2} = 4.45, p_{N2}=0.049; F_{N3} = 9.01, p_{N3}=0.008), WR to PRN (F_{TST} = 0.05, p_{TST}=0.825; F_{N2} = 0.96, p_{N2}=0.341; F_{N3} = 1.58, p_{N3}=0.225). Likewise, the change in reaction time remained the same after controlling for sleep stage time for SD to PRN state (F_{TST} = 9.293, p_{TST}=0.007; F_{N2} = 5.886, p_{N2}=0.026; F_{N3} = 18.615, p_{N3}<0.001), WR to PRN (F_{TST} = 3.187, p_{TST}=0.091; F_{N2} = 3.048, p_{N2}=0.098; F_{N3} = 0.221, p_{N3}=0.644).

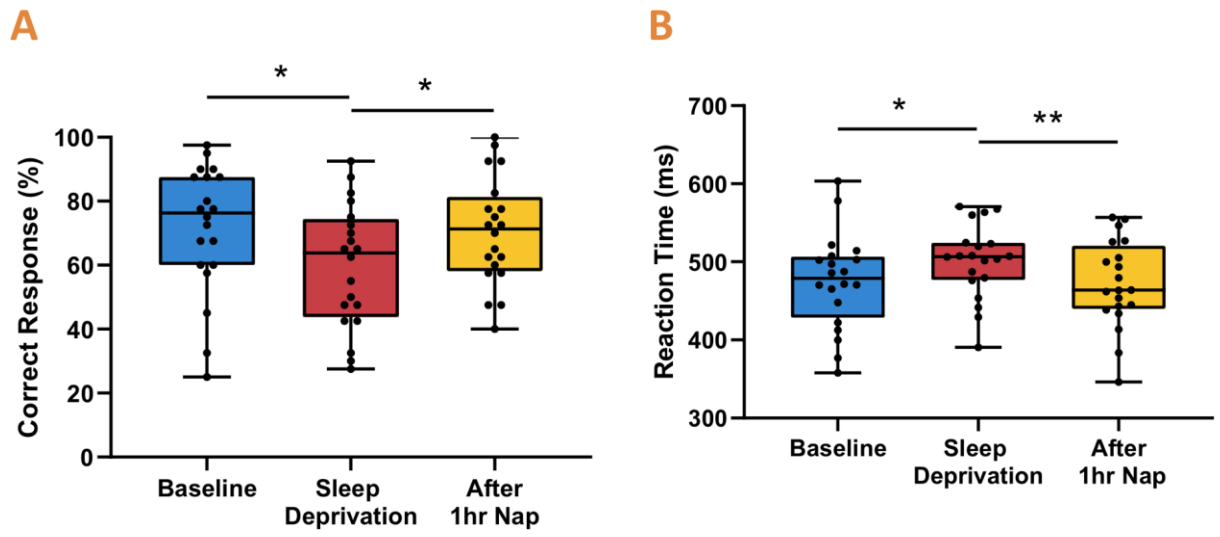

*Figure 7. Accuracy and reaction time of the MCT task across 3 different states. * = p<0.05; ** = p<0.001*

3.1.2 Task – N-back

In the N-back, the mean reaction time (*Fig. 10B)* also increased from WR to SD state (d = 57.43, 95% CI = 17.9 to 96.9, p=0.007), and decreased from SD to PRN state (d = -41.05, 95% CI = -79.9 to -2.2, p=0.039), but there were no differences between WR and PRN state (d = 16.38, 95% CI = -18.7 to 51.5, p=0.341; $F_{1,19}$ = 5.35, p=0.009). The accuracy on the N-back (*Fig. 10A)* decreased from WR state to SD state (d = -11.68, 95% CI = -18.3 to -5.1, p=0.002) and increased from SD to PRN state (d = 8.40, 95% CI = 3.6 to 13.2, p=0.002), but there was no difference between the WR and PRN states (d = -3.28, 95% CI = -7.1 to 0.6, p=0.092; $F_{1,19}$ = 11.66, p=0.001).

When controlling for sleep stage time covariates, there was no difference in accuracy from SD to PRN state when controlling for the sleep stage covariates (F_{TST} = 0.004, p_{TST}=0.952; F_{N2} = 1.09, p_{N2}=0.310; F_{N3} = 1.47, p_{N3}=0.241) and no difference from WR to PRN state (F_{TST} = 0.05, p_{TST}=0.830; F_{N2} = 0.43, p_{N2}=0.519; F_{N3} = 0.63, p_{N3}=0.438). Similarly, after controlling for sleep stage covariates, there were no changes in reaction time from SD to PRN state (F_{TST} = 0.001, p_{TST}=0.980; F_{N2} = 1.31, p_{N2}=0.268; F_{N3} = 0.98, p_{N3}=0.334) and from WR to PRN state (F_{TST} = 0.10, p_{TST}=0.760; F_{N2} = 0.28, p_{N2}=0.603; F_{N3} = 1.05, p_{N3}=0.319).

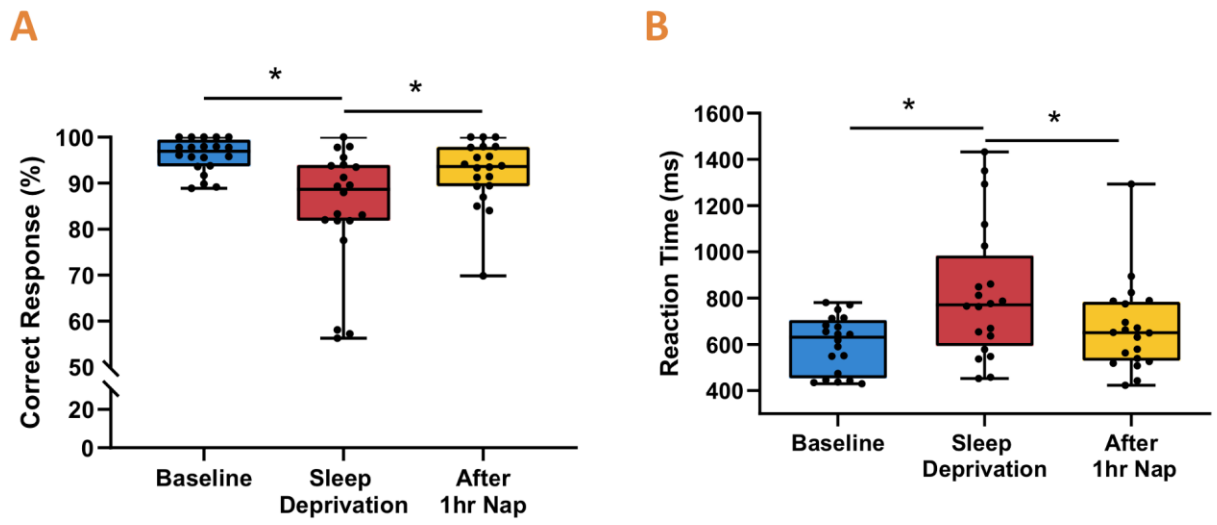

*Figure 8. Accuracy (A) and reaction time (B) of the N-back task across 3 different states. * = p<0.05; ** = p<0.001*

3.1.3 Task – ANT

In the ANT, the mean reaction time increased from WR to SD state (d = 61.95, 95% CI = 29.5 to 94.4, p<0.001), and decreased from SD to PRN state (d = -48.19, 95% CI = -72.3 to -24.1, p<0.001), but there were no differences between WR and PRN state (d = 13.76, 95% CI = -12.3 to 39.8, p=0.283; $F_{1,19}$ = 12.03, p<0.001). Accuracy on the ANT decreased from WR state to SD state (d = -22.92, 95% CI = -34.0 to -11.8, p<0.001) and increased from SD to PRN state (d = 16.53, 95% CI = 7.9 to 25.2, p=0.001), but there was no difference between the WR and PRN states (d = -6.39, 95% CI = -14.7 to 1.9, p=0.124; $F_{1,19}$ = 13.73, p<0.001).

When controlling for sleep stage time covariates, there was no difference from SD to PRN state when controlling for the sleep stage covariates (F_{TST} = 0.89, p_{TST}=0.357; F_{N2} = 3.60, p_{N2}=0.074; F_{N3} = 2.87, p_{N3}=0.107) and no difference from WR to PRN state too (F_{TST} = 0.07, p_{TST}=0.799; F_{N2} = 0.44, p_{N2}=0.514; F_{N3} = 0.56, p_{N3}=0.464). Similarly, there were no changes in reaction time after controlling for sleep stage covariates from SD to PRN state (F_{TST} = 0.72, p_{TST}=0.406; F_{N2} = 3.24, p_{N2}=0.088; F_{N3} = 2.50, p_{N3}=0.131) and from WR to PRN state (F_{TST} = 0.12, p_{TST}=0.734; F_{N2} = 0.24, p_{N2}=0.632; F_{N3} = 1.54, p_{N3}=0.231).

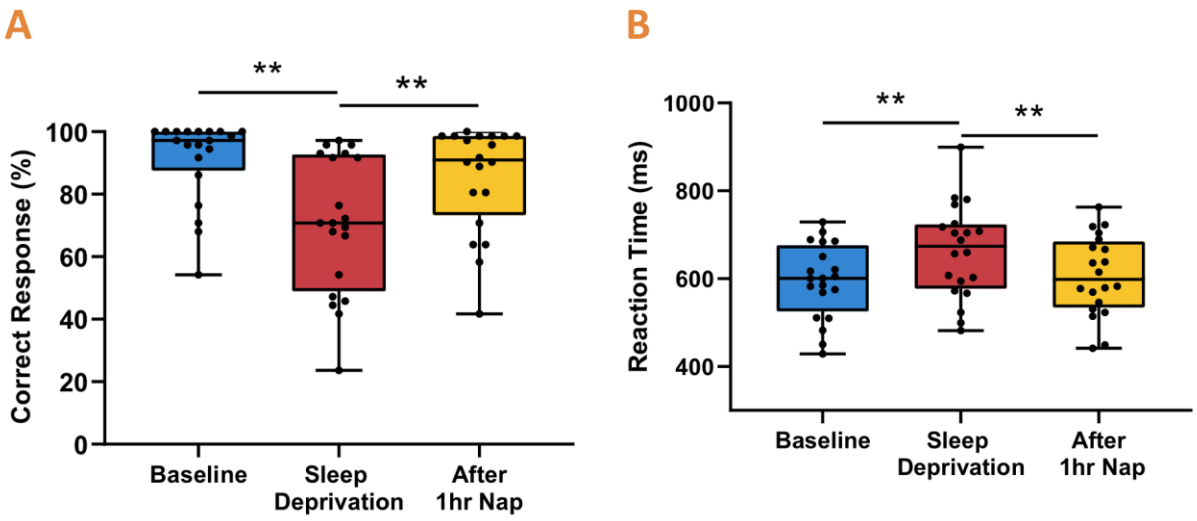

*Figure 9. Accuracy (A) and reaction time (B) of the ANT task across 3 different states. * = p<0.05; ** = p<0.001*

3.2. Functional Connectivity

3.2.1. Functional Connectivity – MCT

Connectivity matrixes during MCT tasks for each state can be found in *Figures S1-S3*. From the WR to SD state, there was an increase in functional connectivity in cortical parcels (47.59% significant of total parcels; *Fig. S4*). After performing a false discovery rate (FDR) correction, there were no changes except for a minimal increase in functional connectivity in voxels between Default C and Dorsal Attention B, Visual A and Control C, and Visual A and Salience/Ventral Attention B networks (0.06% of total parcels; *Fig. 12A)*.

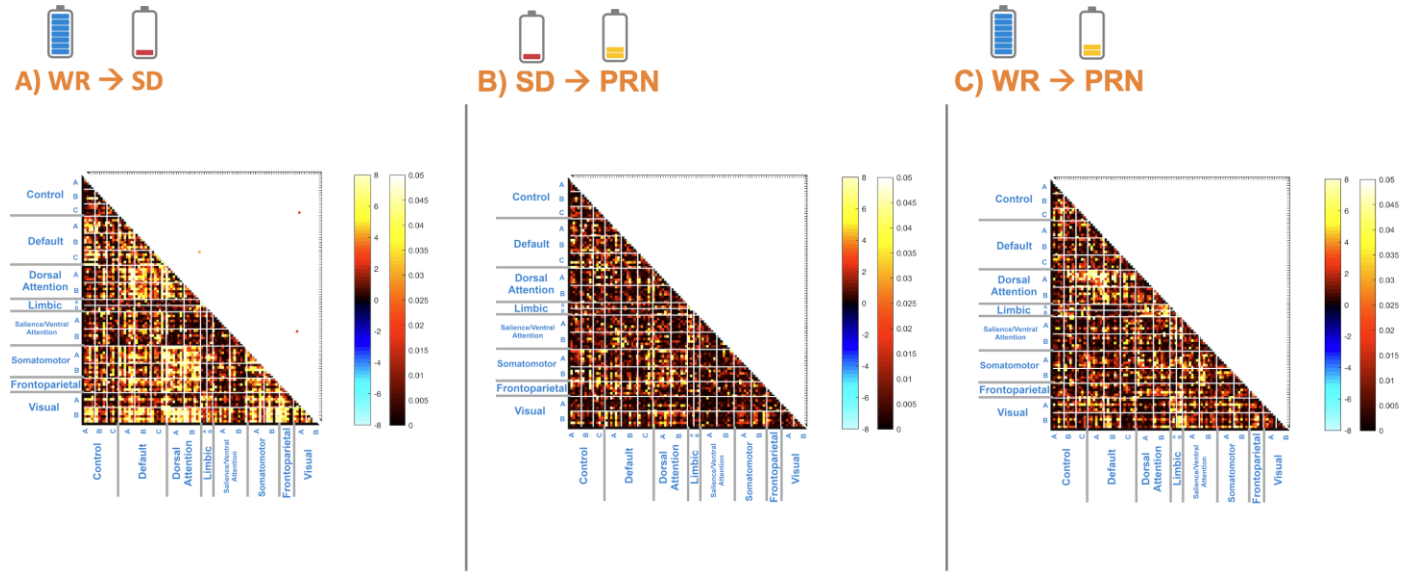

Figure 10.Functional Connectivity during MCT Task. (A) Changes from WR to SD state with FDR correction; 0.06% of total parcels significant. (B) Changes from SD to PRN state with FDR correction. (C) Changes from WR to PRN state with FDR correction.

From SD to PRN state, there was a decrease in functional connectivity in cortical parcels (15.06% significant of total parcels; *Fig. S5*). However, there were no significant changes in functional connectivity after FDR correction (*Fig. 12B*). The results had no significant changes when controlling for covariates TST, N2 only, and N3 only (*Fig. S6-S8)*.

When looking at changes from WR to PRN state, there was an increase in functional connectivity in cortical parcels (24.49% significant of total parcels; *Fig. S9*). After FDR correction, there were no significant changes in functional connectivity (*Fig. 12C*). The results remained the same when controlling for covariates TST, N2 only, and N3 only (*Fig. S10-S12)*.

3.2.2. Functional Connectivity – N-back

Connectivity matrixes during N-back tasks for each state can be found in *Figures S13-S15*. From WR to SD state, there was an increase in functional connectivity in cortical parcels (57.43% significant of total parcels; *Fig. S16*). After FDR correction, there was an increase in functional connectivity, notably in cortical parcels between the Salience/Ventral Attention (A & B) with the Dorsal Attention B, and Control (A, B, C) networks (5.80% of total parcels; *Fig. 13A*).

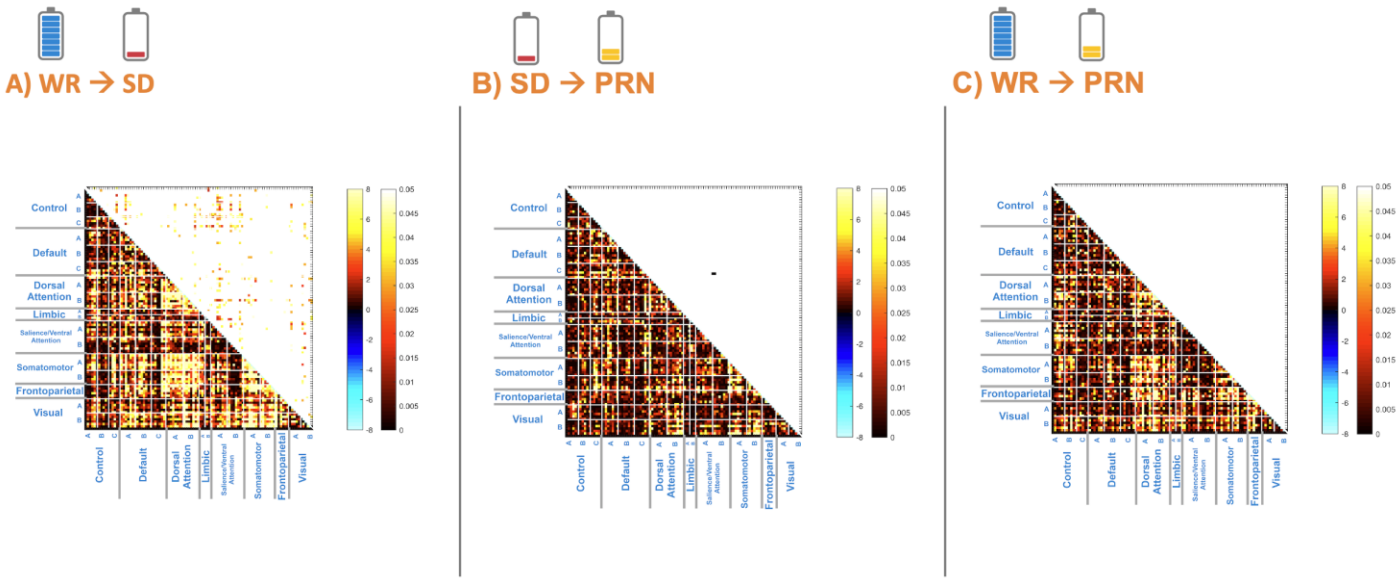

Figure 13. Functional Connectivity during N-back Task. (A) Changes from WR to SD state with FDR correction; 5.80% of total parcels significant. (B) Changes from SD to PRN state with FDR correction; 0.04% of total parcels significant. (C) Changes from WR to PRN state with FDR correction.

From SD to PRN state, there was a decrease in functional connectivity in cortical parcels (25.88% significant of total parcels; *Fig. S17*). After FDR correction, there were no significant changes except for a small voxel between Salience/Ventral Attention B and Default C networks (0.04% of total parcels; *Fig 13B*.) There were no significant changes when controlling for covariates TST, N2 only, and N3 only (*Fig. S18-S20)*.

From WR to PRN state, there was an increase in functional connectivity in cortical parcels (32.78% significant of total parcels; *Fig. S21*). After FDR correction, there were no significant changes in functional connectivity (*Fig. 13C)*. The results remained the same when controlling for covariates TST, N2 only, and N3 only (*Fig. S22-S24)*.

3.2.3. Functional Connectivity – ANT

Connectivity matrixes during ANT tasks for each state can be found in *Figures S25-27.* From WR to SD state, there was a large increase in functional connectivity in cortical parcels (63.80% significant of total parcels; *Fig. S28*). After FDR correction, there was a significant increase in functional connectivity within and between various networks including Salience/Ventral Attention (A & B), Dorsal Attention (A & B), Control (A, B, C), Default A, and Visual B networks (57.80% of total parcels; *Fig. 14A*).

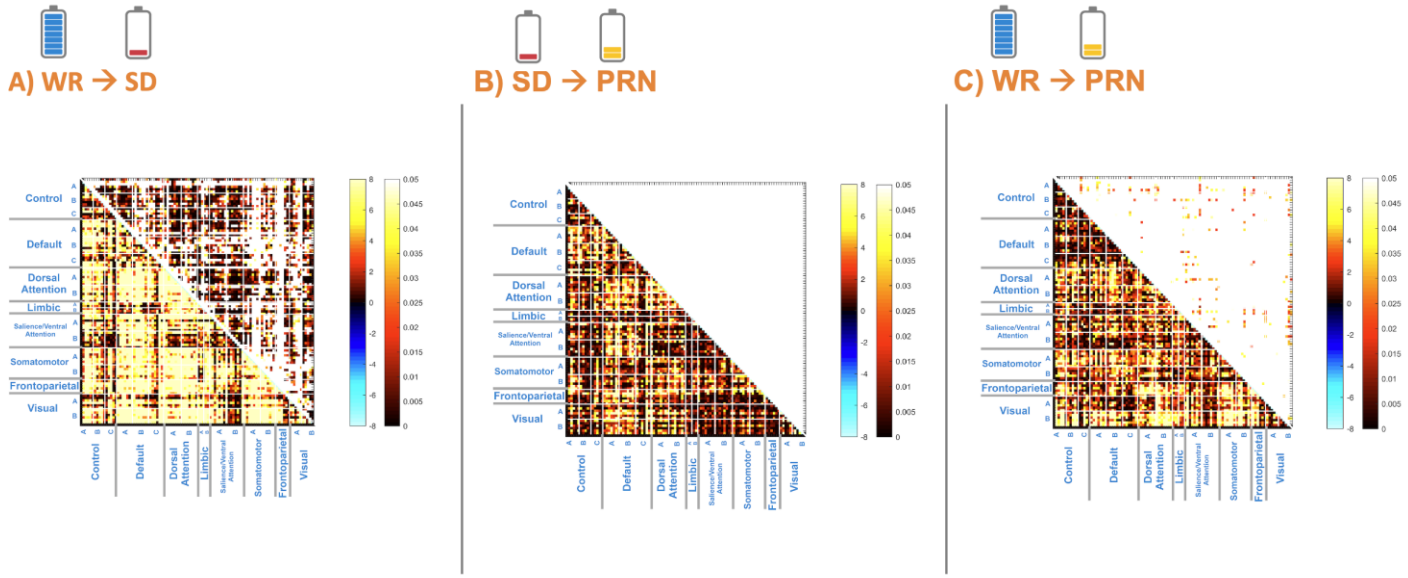

Figure 14. Functional Connectivity during ANT Task. (A) Changes from WR to SD state with FDR correction; 57.80% of total parcels significant. (B) Changes from SD to PRN state with FDR correction. (C) Changes from WR to PRN state with FDR correction; 4.67% of total parcels significant.

From SD to PRN state, there was a decrease in functional connectivity in cortical parcels (46.78% significant of total parcels; *Fig. S29*). After FDR correction, there were no significant changes in functional connectivity (*Fig. 14B*). There were no significant changes when controlling for covariates TST, N2 only, N3 only (*Fig S30-S32*).

From WR to PRN state, there was an increase in functional connectivity in cortical parcels (60.53% significant of total parcels; *Fig. S33*). After FDR correction, there was some increase in functional connectivity between Salience/Ventral Attention (A & B) with Dorsal Attention A, Default C networks. There was also an increase in connectivity between Control (A & B) across networks: Control C, Dorsal Attention (A & B), Salience/Ventral Attention B, and Visual B (4.67% significant of total parcels; *Fig. 14C*). There were no significant changes when controlling for covariates TST, N2 only, and N3 only (*Fig S34-S36*).

3.3. Integration

3.3.1. Integration – MCT

At the whole cortex level, there was a significant increase during MCT task from WR to SD state in total integration (t = 7.485, p=0.024; *Fig. S37*). There was also a significant increase in functional clustering ratio (FCR) (t = 0.012, p=0.0036; *Fig. 15*) which is the ratio of within-system (WS) integration (t = 3.248, p=0.031; *Fig. S38*) and between-system (BS) integration (t = 4.301, p=0.052; *Fig. S39*). After a recovery nap, there were no significant changes in total integration (t = 3.141, p=0.299; *Fig. S37*) or FCR (t = 0.000, p=0.0982; *Fig. 15*). From WR to PRN state, there was also no significant changes in total integration (t = 4.344, p=0.865; *Fig. S37*) or FCR (t = 0.012, p=0.650; *Fig. 15*).

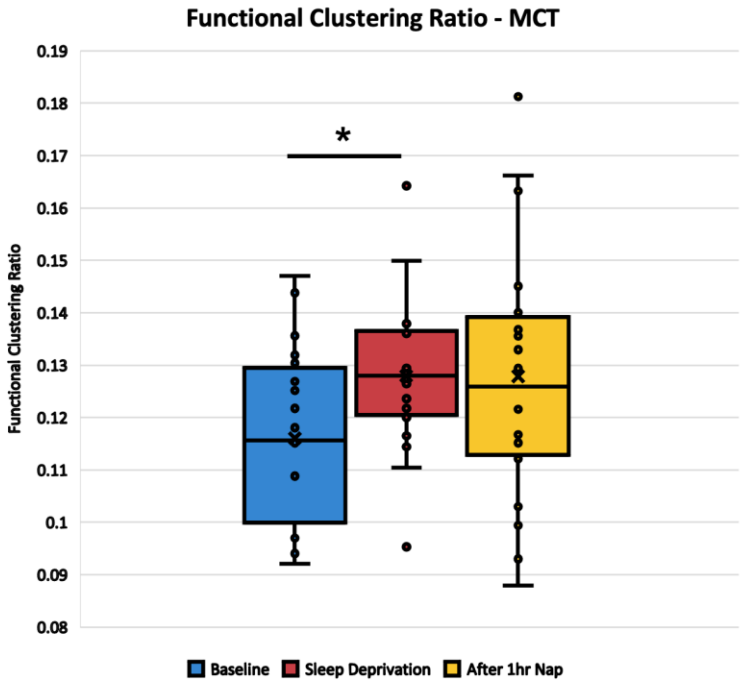

Figure 15. Functional Clustering Ratio during MCT task across 3 states (1=WR, 2=SD, 3=PRN).

At the network level, there was a significant decrease during the MCT task from WR to SD state in within-network integration of the Somatomotor B (t = 0.689, p=0.011), Default B (t = 0.662, p=0.022),

and Frontoparietal networks (t = 0.213, p=0.045). There were no significant differences in the integration of the individual networks from SD to PRN and from WR to PRN state.

3.3.2. Integration – N-back

During the N-back task, there was a significant increase in FCR from WR to SD state at the whole cortex level (t = 0.023, p=0.048; *Fig. 16*) but there were no significant changes in total integration (t = 4.844, p=0.109; *Fig. S40*). From the SD to PRN state, there were no significant changes in total integration (t = 0.766, p=0.398; *Fig. S40*) and FCR (t = 0.018, p=0.507; *Fig. 16*). There were also no changes from WR to PRN state in total integration (t = 4.078, p=0.271; *Fig. S40*) and FCR (t = 0.005, p=0.516; *Fig. 16*).

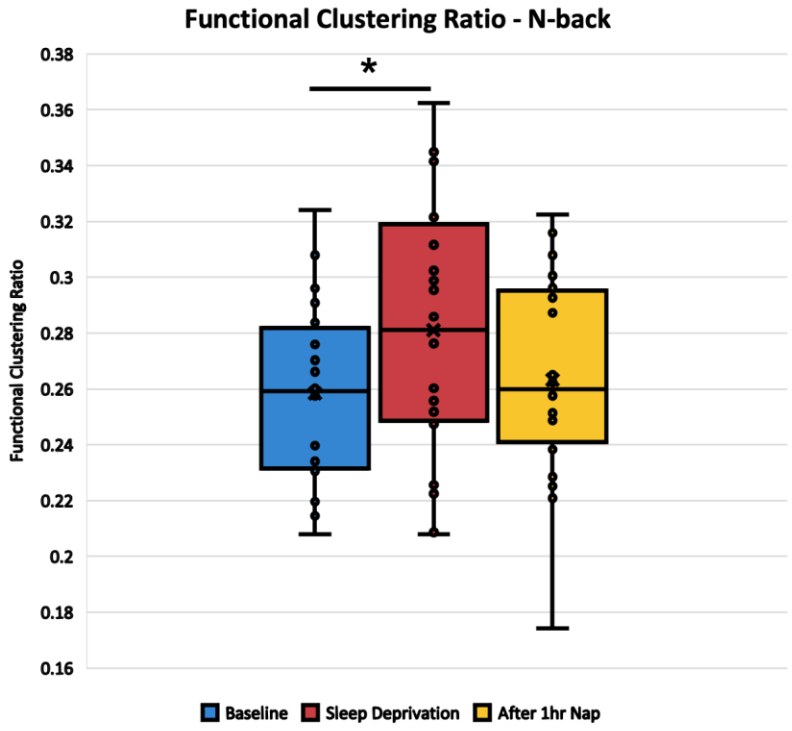

Figure 16. Functional Clustering Ratio during N-back task across 3 states (1=WR, 2=SD, 3=PRN).

At the network level, there was a significant decrease in integration during the N-back task from WR to SD state in the Somatomotor A (t = 0.829, p=0.002), Somatomotor B (t = 0.757, p=0.013), Dorsal

Attention A (t = 0.392, p=0.031) and B (t = 0.637, p=0.014) and Frontoparietal networks (t = 0.233, p=0.009). There were no significant differences in integration in the individual networks from SD to PRN and from WR to PRN state.

3.3.3. Integration – ANT

At the whole cortex level, there was a significant increase during the ANT task from WR to SD state in total integration (t = 9.464, p=0.001; *Fig. S43*) and increase in FCR (t = 0.079, p<0.001; *Fig. 17*) which was consistent with the ratio of WS integration (t = 2.606, p<0.001; *Fig. S44*) and BS integration (t = 6.859, p=0.057; *Fig. S45*). From SD to PRN state, there were no significant changes in total integration (t = 3.297, p=0.200; *Fig. S43*) but there was a significant decrease during the ANT task in FCR (t = 0.051, p =0.038; *Fig. 17*). There were also no significant differences from WR to PRN state in total integration (t = 6.167, p=0.746; *Fig. S43*) and FCR (t = 0.028, p=0.167; *Fig. 17*).

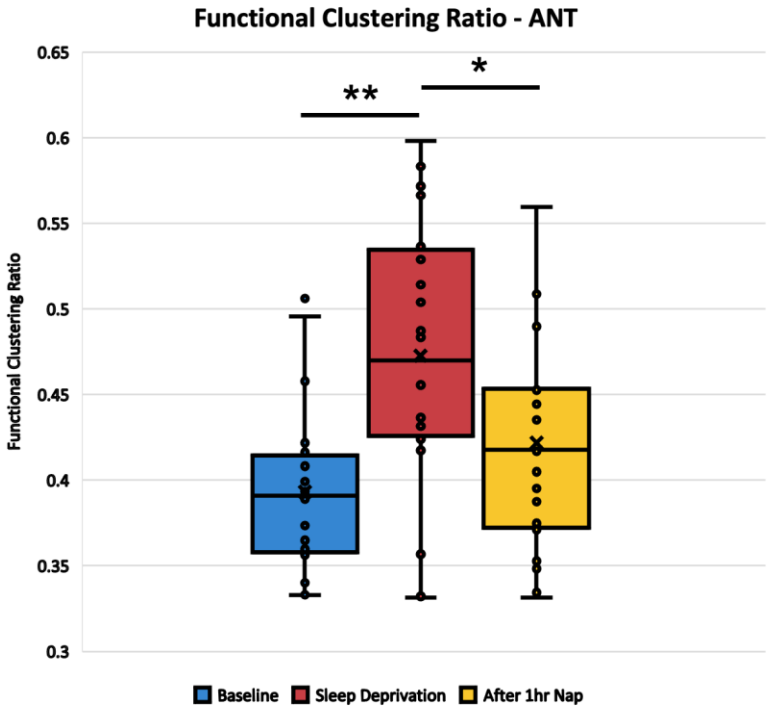

Figure 17. Functional Clustering Ratio during ANT task across 3 states (1=WR, 2=SD, 3=PRN).

At the network level, there was a significant decrease in integration during the ANT task from WR to SD state in the Visual B ($t = 0.760$, $p=0.001$), Somatomotor A ($t = 0.670$, $p=0.002$) and B ($t = 1.017$, $p<0.001$), Dorsal Attention A ($t = 0.708$, $p<0.001$) and B ($t = 0.735$, $p<0.001$), Salience/Ventral Attention ($t = 0.477$, $p=0.016$), Control A ($t = 0.311$, $p=0.014$), Default B ($t = 0.664$, $p<0.001$) and Frontoparietal networks ($t = 0.516$, $p<0.001$). From SD to PRN state, there was a significant increase in integration in the Somatomotor A ($t = 0.351$, $p=0.010$), Dorsal Attention A ($t = 0.497$, $p=0.037$), and Frontoparietal networks ($t = 0.238$, $p=0.028$).

3.4. Integration & Behavioral Tasks Performance

3.4.1. Integration & MCT Performance

There were no significant correlations between the changes in total integration or changes in FCR and changes in accuracy (*Fig. 18A, 18C)* and reaction time *(Fig. 18B, 18D)* at the whole cortex and network levels from the WR to SD and SD to PRN.

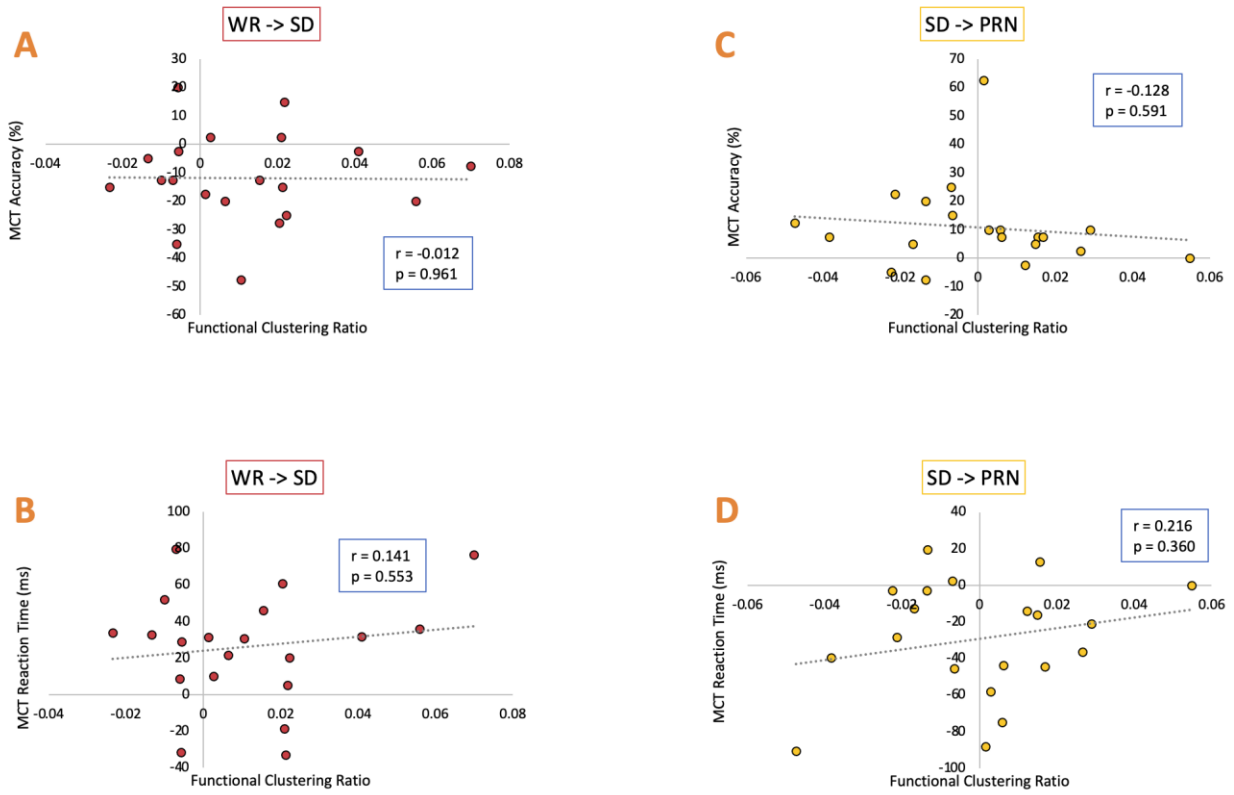

Figure 18. Scatterplot of FCR vs. accuracy (A) and reaction time (B) of the MCT task from WR to SD state. Scatterplot of FCR vs. accuracy (C) and reaction time (D) of the MCT task from SD to PRN state.

3.4.2. Integration & N-back Performance

At the whole cortex level, the increase in total integration during the N-back task was significantly correlated with a decrease in task accuracy ($r = -0.696$, $p<0.001$) and an increase in reaction time ($r = 0.728$, $p<0.001$) from WR to SD. Likewise, an increase in FCR was correlated with a decrease in accuracy ($r = -0.606$, $p=0.005$; *Fig. 19A*) and a slower reaction time ($r = 0.579$, $p=0.007$; *Fig. 19B*). The improvement in accuracy from SD to PRN state was correlated with a decrease in total integration ($r = -0.792$, $p<0.001$) and a decrease in FCR ($r = -0.803$, $p<0.001$; *Fig. 19C*). Improvement in speed was also correlated with changes in total integration ($r = 0.739$, $p<0.001$) and FCR ($r = 0.776$, $p<0.001$; *Fig. 19D*).

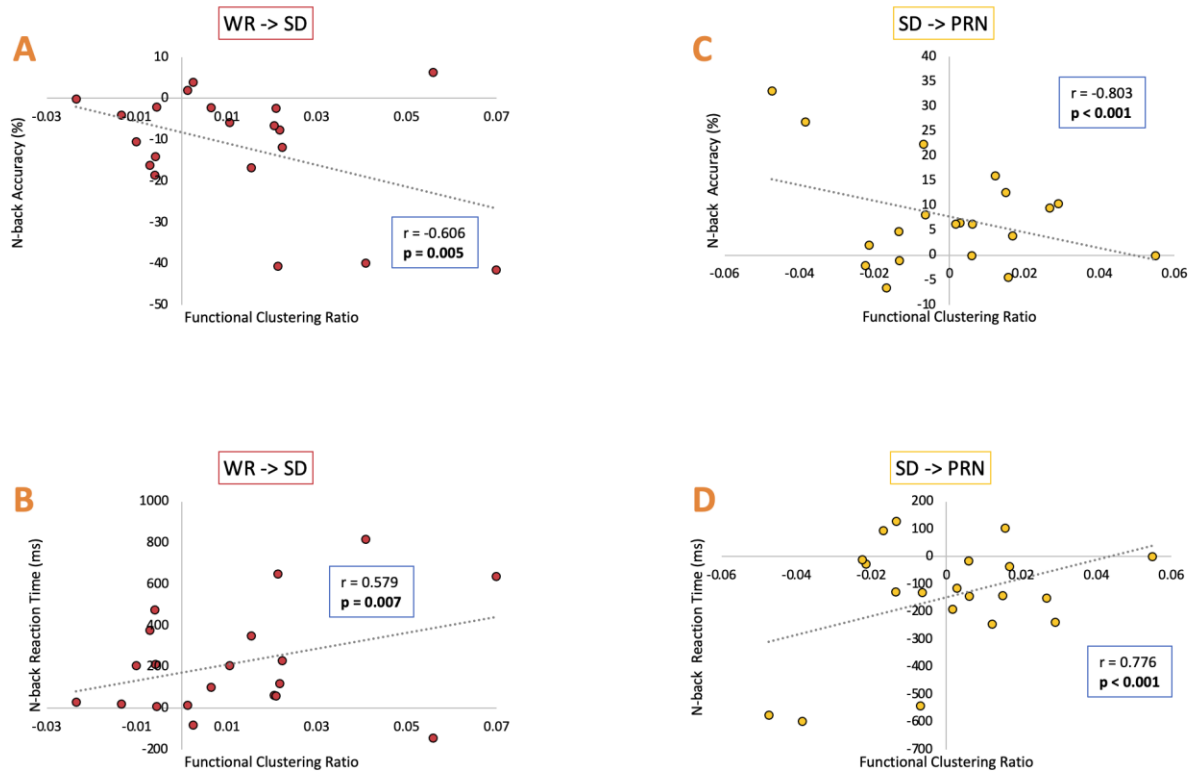

Figure 19. Scatterplot of FCR vs. accuracy (A) and reaction time (B) of the N-back task from WR to SD state. Scatterplot of FCR vs. accuracy (C) and reaction time (D) of the N-back task from SD to PRN state.

At the network level, a worse performance in the N-back task from WR to SD state was correlated with a higher integration in the Dorsal Attention A ($r_{accuracy}$ = -0.568, $p_{accuracy}$=0.022; $r_{Reaction\ Time}$ = 0.654, $p_{Reaction\ Time}$ =0.004) and B (r_{acc} = -0.760, p_{acc}<0.001; r_{RT} = 0.731, p_{RT}<0.001), and Frontoparietal networks (r_{acc} = -0.540, p_{acc} =0.023; r_{RT} = 0.573, p_{RT}<0.014).

3.4.3. Integration & ANT Performance

Total integration was negatively correlated with the change in accuracy during the ANT task from WR to SD state (r = -0.829, p<0.001) and positively correlated with a change in reaction time (r = 0.522, p<0.018). Moreover, an increase in FCR was correlated with worse accuracy (r = -0.663, p<0.001; *Fig.*

20A) and a worse speed on ANT task (r = 0.533, p=0.016; *Fig. 20B*) when sleep deprived. From SD to PRN state, an improved accuracy was correlated with a decrease in total integration (r = -0.615, p=0.004) and a decrease in FCR (r = -0.489, p=0.006; *Fig. 20C*). There was also a decrease reaction time during ANT task from SD to PRN state with a decrease in total integration (r = 0.650, p=0.002) and a decrease in FCR (r = 0.604, p=0.005; *Fig. 20D*).

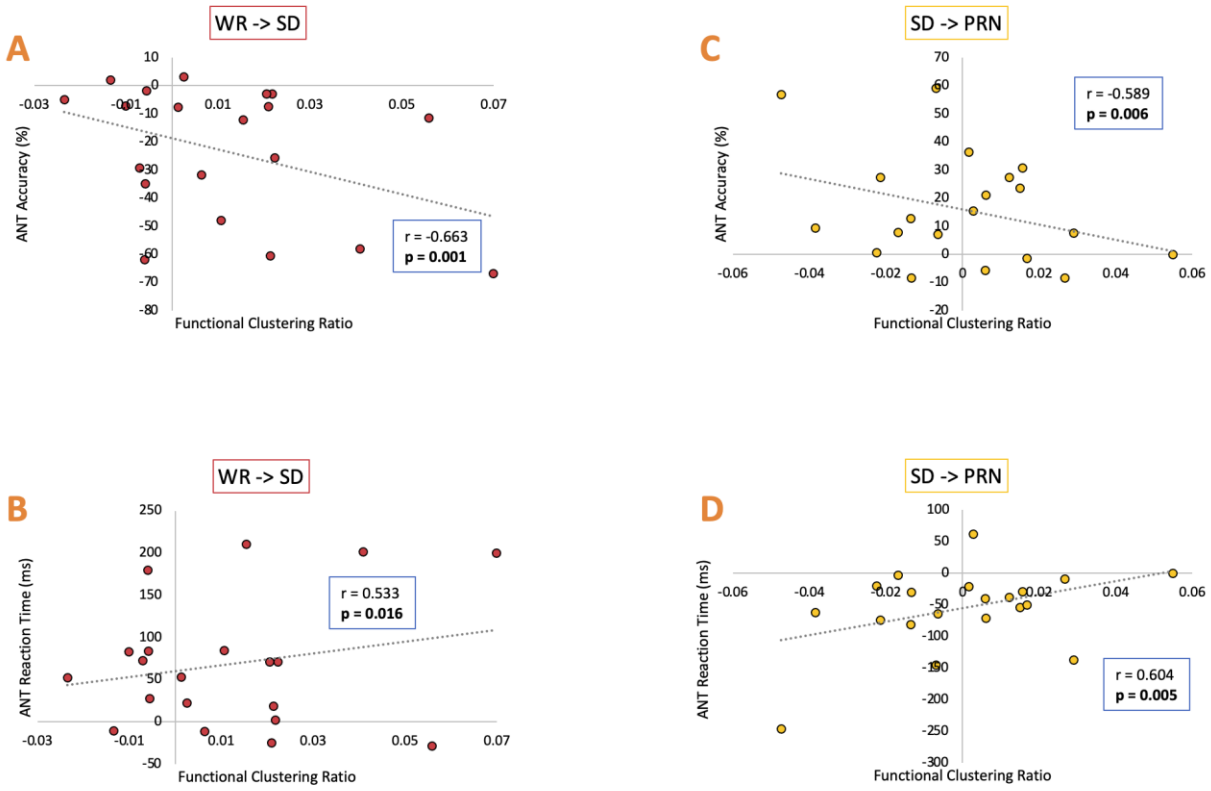

Figure 20. Scatterplot of FCR vs. accuracy (A) and reaction time (B) of the ANT task from WR to SD state. Scatterplot of FCR vs. accuracy (C) and reaction time (D) of the ANT task from SD to PRN state.

At the network level, a worse accuracy in ANT from WR to SD state was correlated with a higher integration in the Visual B (r = -0.611, p=0.006), Somatomotor B (r = -0.503, p=0.030), Dorsal Attention A (r = -0.793, p<0.001) and B (r = -0.614, p=0.006), Salience/Ventral Attention A (r = -0.631, p=0.006), Control A (r = -0.739, p<0.001), and Frontoparietal networks (r = -0.615, p<0.006). A worse reaction time

from WR to SD state was only found in the Somatomotor B ($r = 0.555$, $p=0.050$), Dorsal Attention A ($r = 0.558$, $p=0.050$) and Frontoparietal networks ($r = 0.483$, $p=0.047$). From SD to PRN state, ANT accuracy was only negatively correlated with the Dorsal Attention A network ($r = -0.624$, $p<0.010$) but was positively correlated with the Dorsal Attention A ($r = 0.516$, $p=0.047$) and the Frontoparietal network ($r = 0.483$, $p=0.047$).

4. DISCUSSION

The main objectives of this thesis were to look at the functional relationships between regions of the cortex during different cognitive tasks assessing vigilance, working memory, and attention. Furthermore, this study is the first to examine both the effects of total sleep deprivation and the effects of a recovery nap on functional connectivity and integration during cognitive tasks.

Our results revealed that integration within cortical networks increases relative to integration between networks during the SD state. This dynamic balance was observed during cognitive task performances and significantly associated with worsening of overall performance. The relationship between the interaction within and between subsystems noted as the FCR, quantifies the degree of segregation of a given system (Boly et al., 2012). That is, the FCR represents the amount of information generated by the independent cortical networks in comparison to the cortex as a whole. At the cortical level, there was an overall increase in FCR following total sleep deprivation during all 3 cognitive tasks suggesting an increase in functional segregation (driven by higher integration within the network). More specifically, since the integration between networks remained the same as in the WR state, the increase in FCR is mainly due to the increase of within networks integration. This aligns well with the results from (Boly et al., 2012) who found increased FCR during NREM sleep. Evidently, this might suggest that during task performance following sleep deprivation, the cortical network begins to increase functional segregation in an attempt to reset the brain's integration/segregation balance back into an optimal state (Boly et al., 2012; Tagliazucchi

et al., 2013). In summary, there is potentially a continuum of functional segregation from the WR state towards the NREM sleep. Another implication could be that the sleep-deprived brain is susceptible to short sleep onsets while still behaviourally awake (Cirelli et al., 2008; Vyazovskiy et al., 2011).

These findings of integration complement well with the overall increase in functional connectivity from WR to SD state. It was crucial for this thesis to use both functional connectivity and integration in other to obtain a complete overview of our results. Functional connectivity is a simple correlational measure between two sets of time series signal at the parcel level. Although this allows for us to determine the relationship between specific networks, both the length of the time series along with short and large spikes of activity can significantly impact functional connectivity measures. Meanwhile, integration uses advanced mathematical formulations to calculate the mutual information shared between two sets of data at a hierarchical model which is larger than at the level of parcels. Hence, integration is potentially more sensitive to changes in functional relationships between regions and networks as seen in our results. The integration measure also performs fewer comparisons compared to functional connectivity. This is important since the integration measures avoids running into the problem of multiple comparisons like type I error or false positives.

We demonstrated in this study that the disruption of the balance between integration and segregation of cortical networks can significantly impact the performance of cognitive tasks. Furthermore, this effect was bidirectional: increased FCR in the SD state was associated with worsening of cognitive performance while decreased FCR in PRN was associated with cognitive improvement. This was evident in the working memory and attention tasks but not the vigilance tasks suggesting the relationship to be found especially in more complex and longer duration tasks. This is especially important given that our study examines cortical changes during cognitive tasks. Not only was the vigilance task the first task presented and the shortest in duration, but it was also the simplest task requiring participants to only press a trigger when the stimulus skipped an element in the sequence. Meanwhile, the working memory N-back was a much more challenging task requiring participants to recall a series of letters presented at a 2.5 second

rate with the difficulty level becoming harder as the task continued. The attention task was the longest in duration and challenging requiring identifying directions of the middle of an array of five arrows including distracting cues to ensure sustained attention from participants. Compensatory mechanisms were likely able to make up for the cognitive and cortical changes for the simpler and shorter tasks. However, previous studies have shown potential compensatory mechanisms were likely to fail as the duration of task increased (Doran et al., 2001). Furthermore, it has been shown that connectivity patterns shift more towards integration with greater task demands (Shine et al., 2016).

At the network level, we saw an increase in segregation (or increase FCR) of specific cortical networks during different cognitive tasks at the sleep deprived state. This could be interpreted as the brain's attempt to increase focus within task-relevant networks in response to cognitive demands when sleep deprived. An example of this was seen during our N-back task in SD state, whereby the increase segregation of the Dorsal Attention and Frontoparietal networks could be an effort to improve one's efficiency in cognitive control. Both networks are considered task-relevant networks known to increase in segregation during the N-back task (Finc et al., 2020; Bressler et al., 2010).

It is thus crucial for a balance between integration and segregation of information to be maintained for the brain networks to execute cognitive functions effectively (Peter T. Fox et al., 2012; Tononi, 2005). The ability to fluctuate between the brain states of integration and segregation may be an essential mechanism that maintains ongoing cognitive processes (Sporns, 2013; Shine et al., 2016). Moreover, the fluctuation between integration and segregation allows for communication between distant brain regions reflecting periods of specialized local information processing and inter-modular information transfer in response to demands from the environment (Shine et al., 2016; Fukushima et al., 2020).

Previous studies have shown local and global fMRI activity to fluctuate significantly greater following SD (Yeo et al., 2015; Wang et al., 2016). The mechanism behind the increase in fluctuation is not yet fully understood. One possible explanation is the flushing of metabolic waste through the glymphatic system consisting of a mix of cerebrospinal fluid and interstitial fluid (Iliff et al., 2012; Xie et

al., 2013). More specifically, large amplitude slow waves have been coupled with the large oscillations of fluid inflow through the perivascular space during sleep (Fultz et al., 2019; Hablitz et al., 2019). Another explanation could be the change in cardiac or respiratory activity through the parasympathetic system found with increase in resting cerebral blood flow in SD individuals (Elvsåshagen et al., 2019). The increase in fluctuation of endogenous activity across the cortex following SD may affect the ability to integrate information between and within cortical networks leading to cognitive deficits. A possible thought to also consider is the synaptic homeostasis hypothesis (SHY) which claims that the essential function of sleep is the restore synaptic homeostasis challenged by synaptic strengthening triggered from learning during waking state (Tononi et al., 2014). The process of learning results in an increased demand for energy and requires a decrease in signal-to-noise ratios. Consequently, sleep is the price the brain pays to renormalize the synaptic strength and restore homeostasis. More specifically, the restoration of the synapses follows an activity-dependent down-selection process whereby it ensures the strongly activated synapses during sleep become more resistant to interference and survive while the less activated synapses become depressed and eventually eliminated (Tononi et al., 2014). This potentially explains the increased integration that occurs during cognitive tasks following SD state through which the brain is attempting to consolidate the strengthened synapses while depressing the less activated synapses, ultimately resulting in an increased FCR. Furthermore, following a PRN, the FCR remains slightly elevated in comparisons to the WR state suggesting that some of the consolidated strengthened synapses have been protected from depression during the nap.

This study is the first to investigate the effects of total sleep deprivation and a recovery nap on functional connectivity and integration during cognitive tasks. This bidirectional effect of FCR in SD and PRN state with cognitive performance was evident in longer and more complex tasks such as the working memory and attention tasks compared to the vigilance task. However, the study does not come without its limitations. First, our sample size was limited to 20 participants given that this was a very time consuming and complex study to conduct. For example, collecting and processing EEG-fMRI data requires extensive

expertise, sleep deprivation protocols are intensive on participants and requires the resource of multiple researchers. Furthermore, our young sample had a very small age range between 18-30 years (M_{Age} = 21.32 ± 2.5). These limitations were most likely due to our requirement of healthy good sleepers having to undergo demanding procedures of total sleep deprivation and performing tasks inside an fMRI. There were a couple of data that were collected for this study that were beyond the scope of the thesis. We collected fMRI-EEG data during the one-hour resting nap which was not analyzed for this thesis. Another limitation as previously discussed is the short 5-minute version of the vigilance tasks. This decision was based on a previous validation study where there was no difference in task performance following sleep deprivation between the 5-minute versus the 10-minute vigilance task (Loh et al., 2004). However, our results suggest that a future validation study should be done to see the differences in functional connectivity and integration between differing lengths of vigilance tasks. Our recovery nap lasted only an hour and tasks were done immediately upon awakening. It would be interesting to see how the results would vary if the recovery nap lasted longer or if the tasks were performed a couple of hours after the recovery nap.

5. CONCLUSION

This thesis describes the results obtained from the first known study to examine the effects of total SD and a recovery nap on functional connectivity and integration during cognitive tasks. SD appears to affect the dynamic balance of integration and segregation of cortical activity. It remains to be clarified whether these changes are a result of physiological process such as maintaining synaptic homeostasis. Moreover, this disruption in integration of information flow is significantly associated with cognitive impairments following sleep deprivation and recovery nap. These findings complemented well with the functional connectivity findings. While functional connectivity offered an insight on the relationship between the different cortical networks, FCR allowed for a more complete overview of the integration and segregation of these networks at a whole cortex level. These results emphasize the importance of choosing

the optimal measure that is sensitive enough to detect cortical changes in sleep deprivation during cognitive tasks. Future studies should investigate why integration and segregation of cortical activity is impaired following SD by obtaining data on cerebral blood flow while performing cognitive tasks. The observation of cerebral blood flow in the SD state during cognitive tasks would help further understand the mechanism behind the fluctuation of endogenous activity in states of greater cognitive demand. A potential method to this would be to obtain data on cerebral blood flow of sleep deprived participants during cognitive tasks. The future of sleep deprivation studies should include researchers looking at physical and mental health changes. Additional investigation to our study should include differences across individuals such as resilience to sleep deprivation, recovery nap variances (i.e. total sleep time, time spent in different NREM sleep stages, brain activity fluctuations) to determine the neuroimaging biomarkers of sleep deprivation vulnerability on cognitive performances.

6. FUNDING SOURCES

Alex Nguyen gratefully acknowledges the Concordia Undergraduate Student Research Award, Concordia's Graduate Fellowship Scholarship, Natural Sciences and Engineering Council of Canada (NSERC) Graduate Scholarship's Master Award. This research was supported by NSERC and the Canada Foundation for Innovation. The MRI-compatible high-density EEG device (Philips Neuro) and data acquisition were made possible through an internal grant from PERFORM center and the Faculty of Arts and Science of Concordia University. Dr. Thanh Dang-Vu is supported by NSERC, the Canadian Institutes of Health Research (CIHR), the Fonds de Recherche du Québec (FRQ) – Santé and Concordia University. Dr. Christophe Grova is supported by the NSERC Discovery grants as well as the CIHR and the FRQ – Nature et Technology (research team grant).

7. ETHICAL STATEMENT

This study was conducted ethically in accordance with the *Comité Central D'Éthique de la Recherche (CCER)* and all participants provided written informed consent. This study was approved by the research ethics committee of the ministry of health and social services (reference number CCER 16-17-08).

8. DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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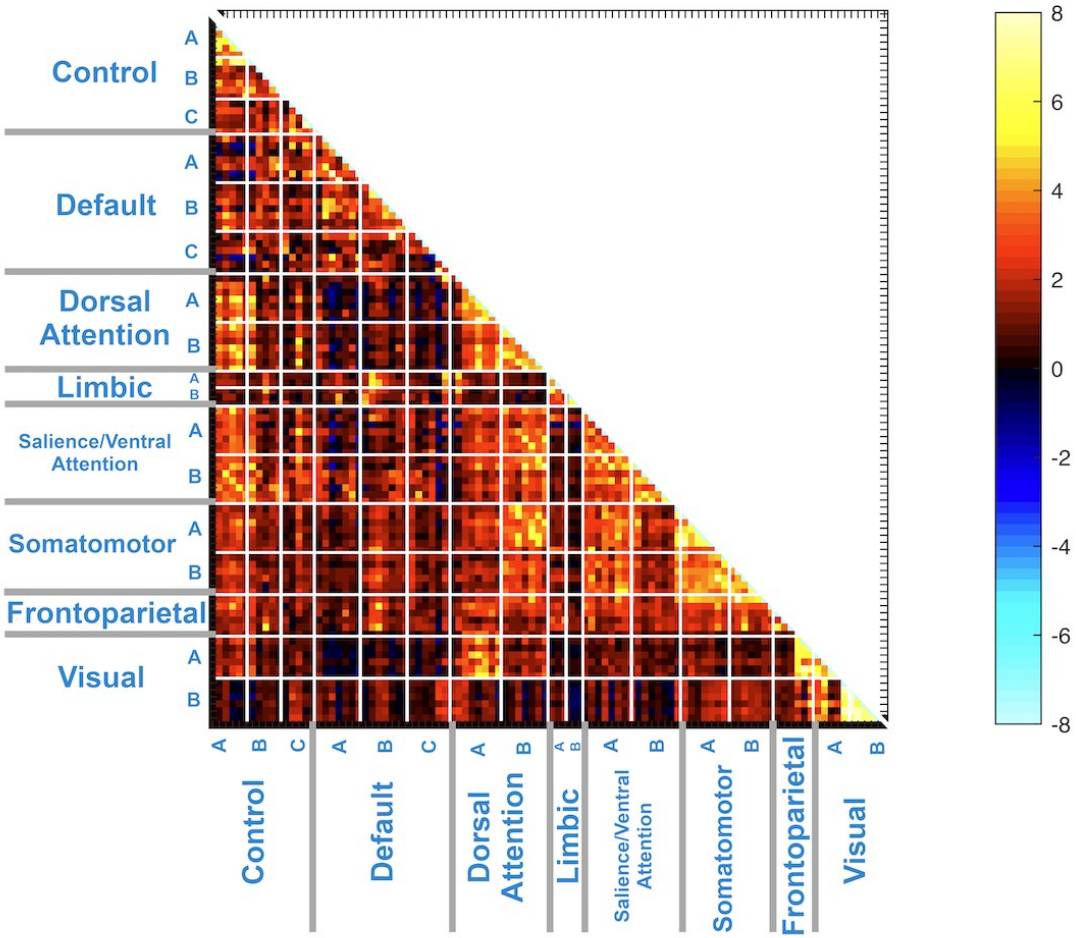
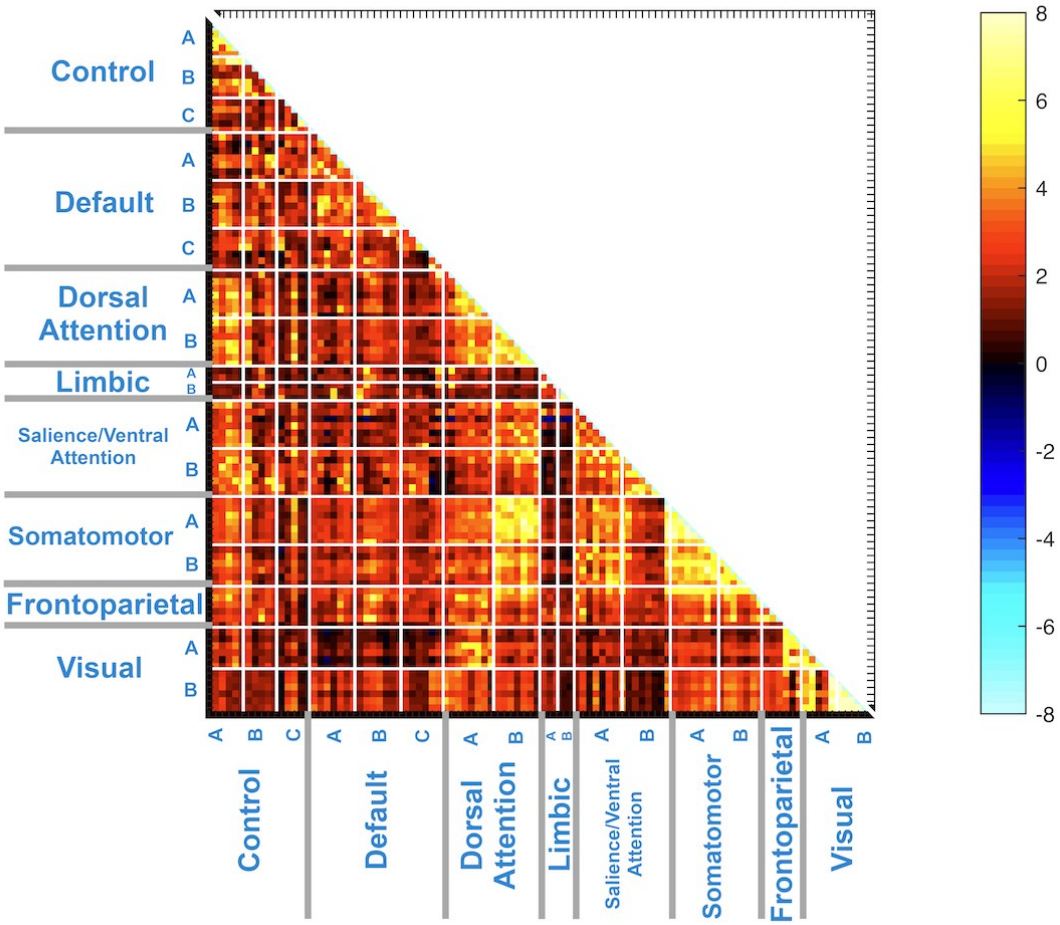
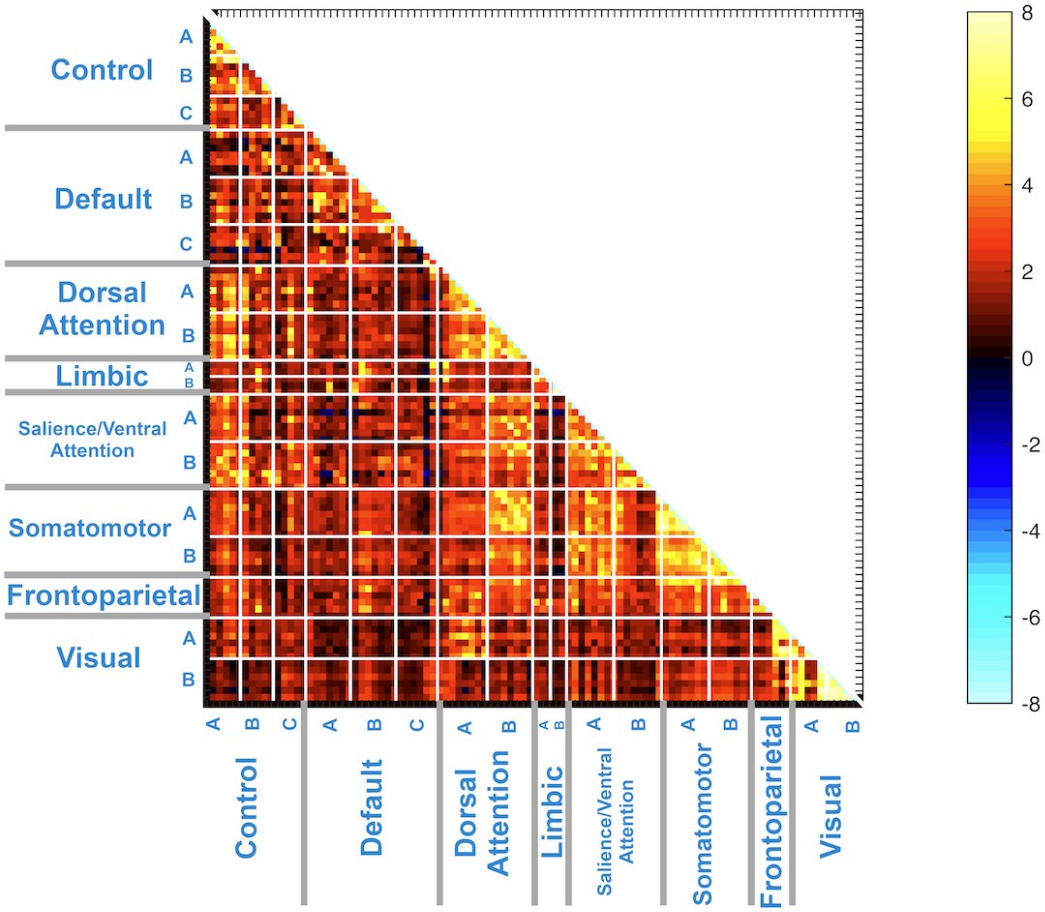
10. SUPPLEMENTAL FIGURES



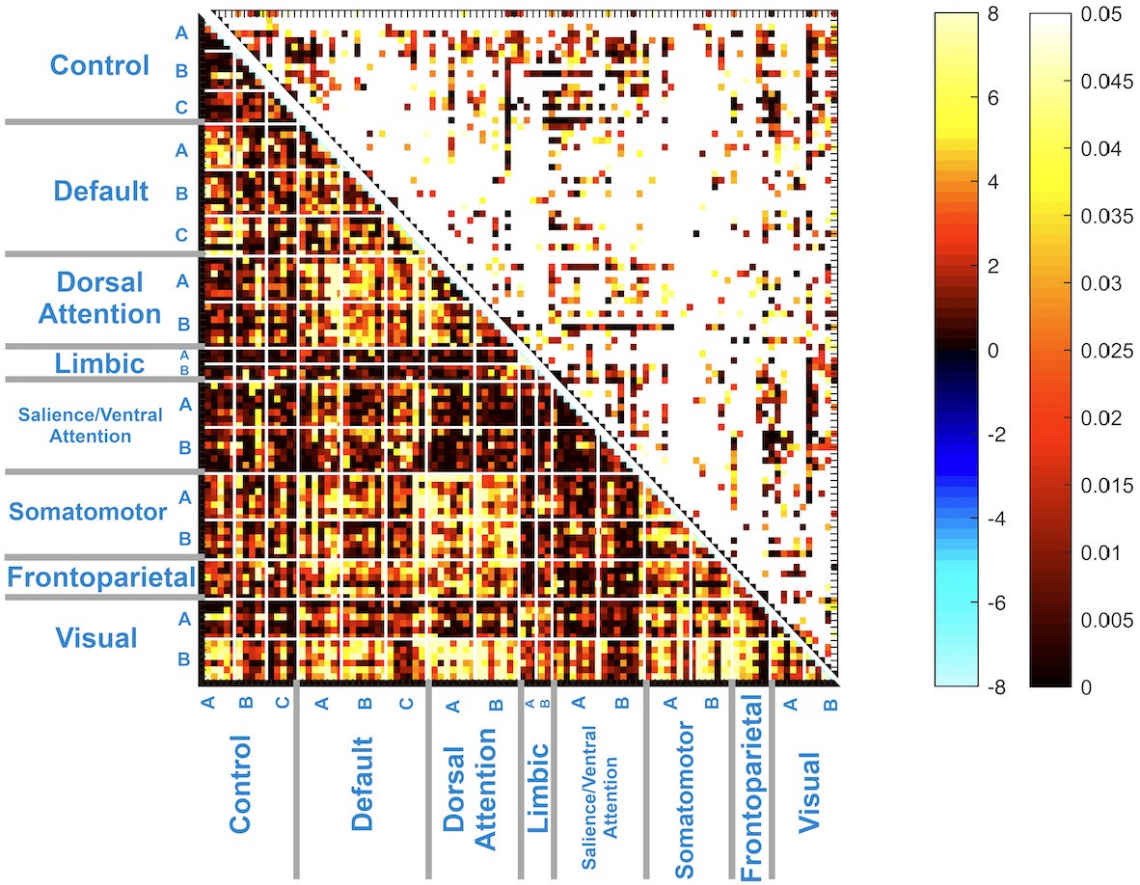
Supplementary Figure 11. Connectivity Matrix during MCT task – WR state



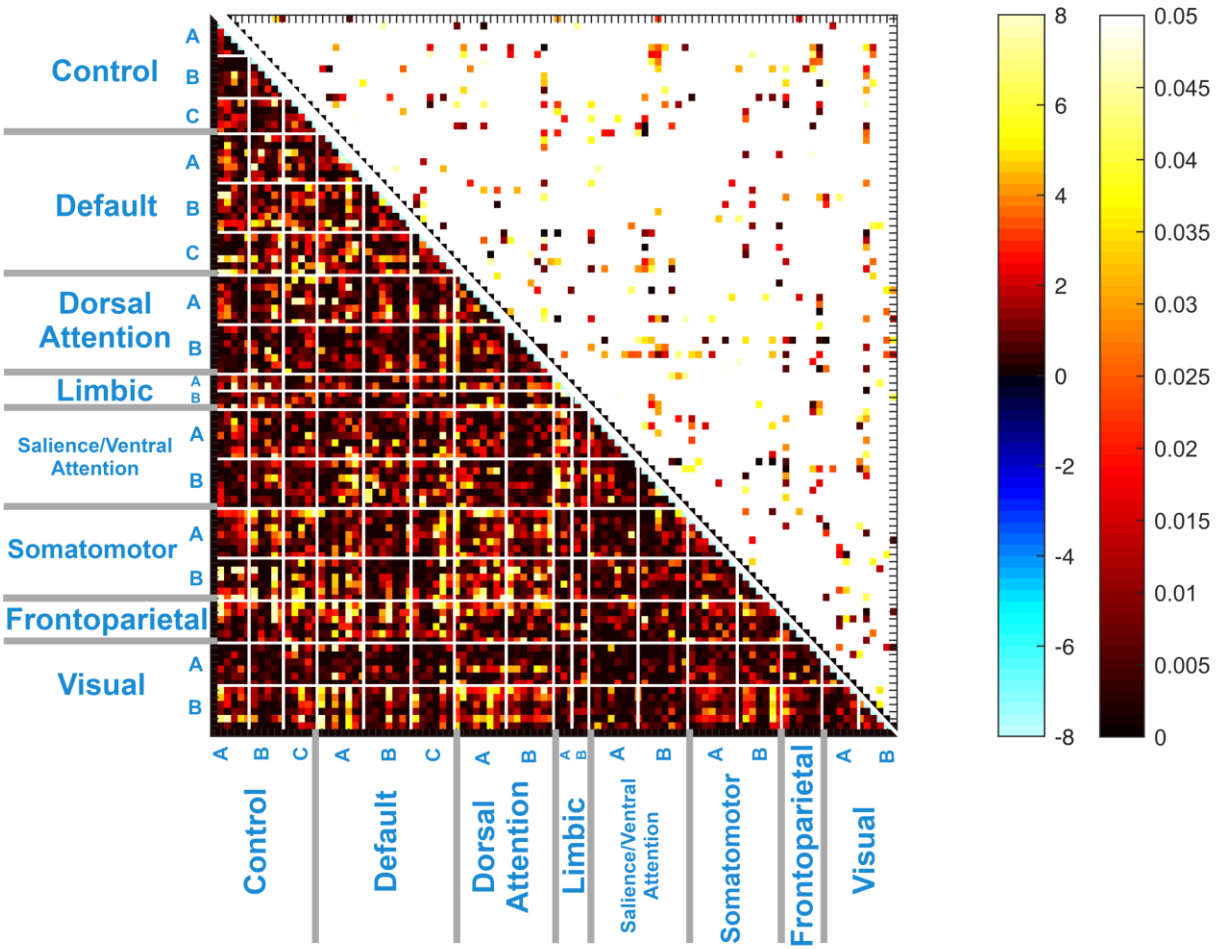
Supplementary Figure 12. Connectivity Matrix during MCT task – SD state



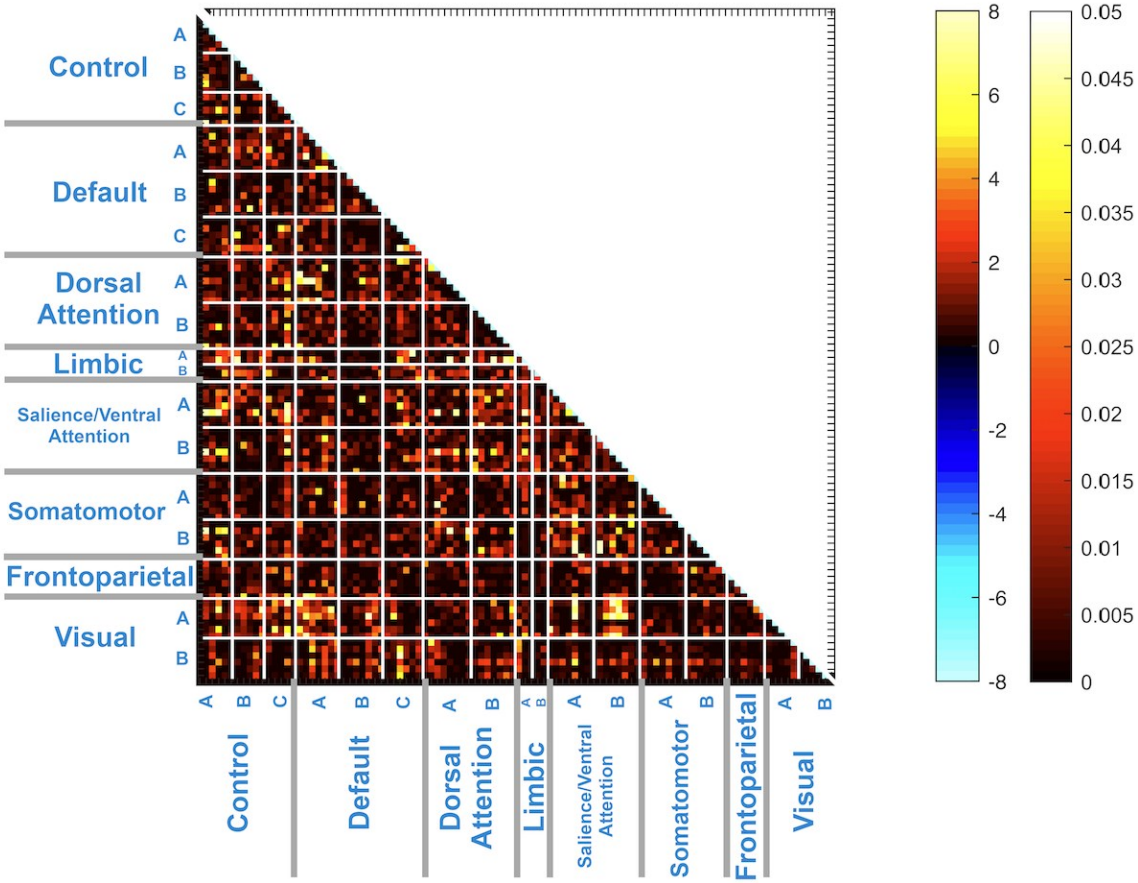
Supplementary Figure 13. Connectivity Matrix during MCT task – PRN state



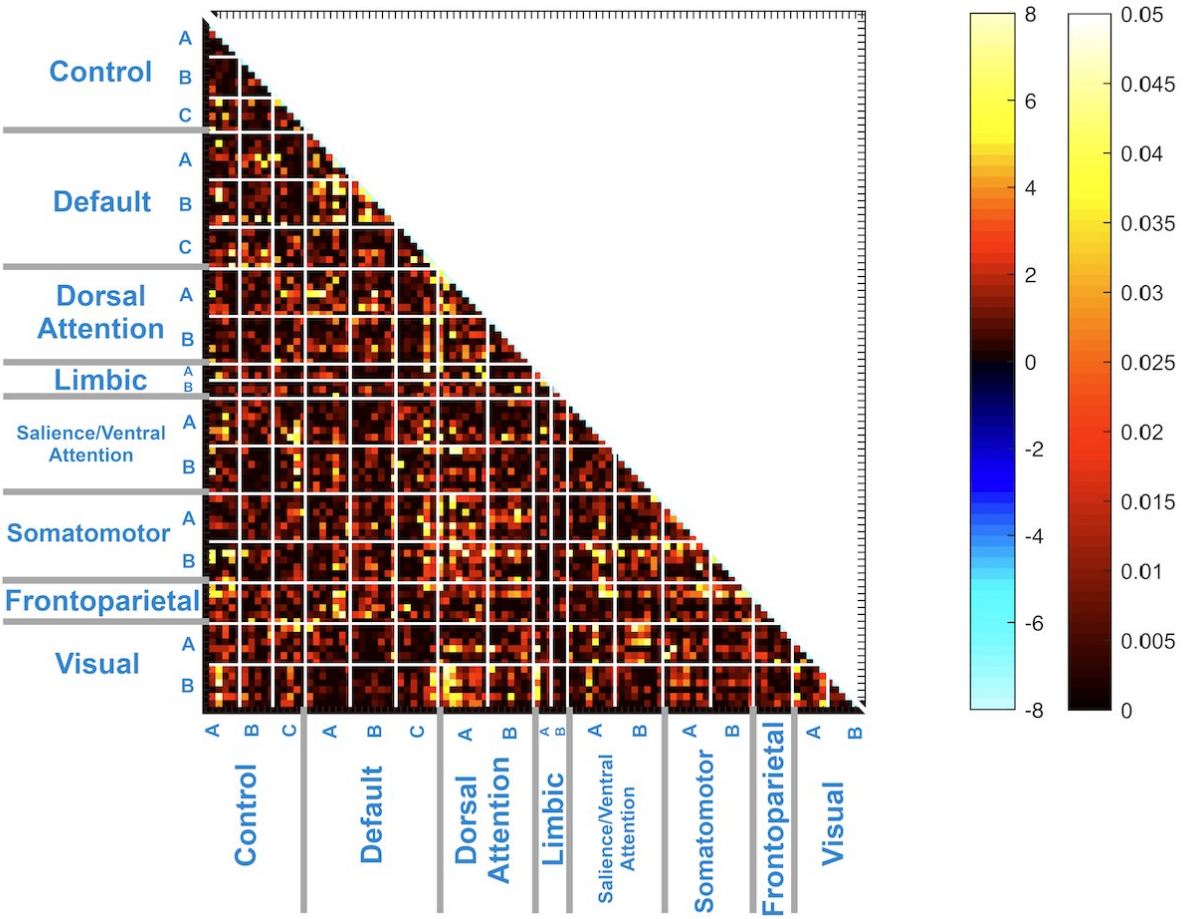
Supplementary Figure 14. Functional Connectivity during MCT Task – Changes from WR to SD state with no FDR correction; 47.59% of total parcels significant.



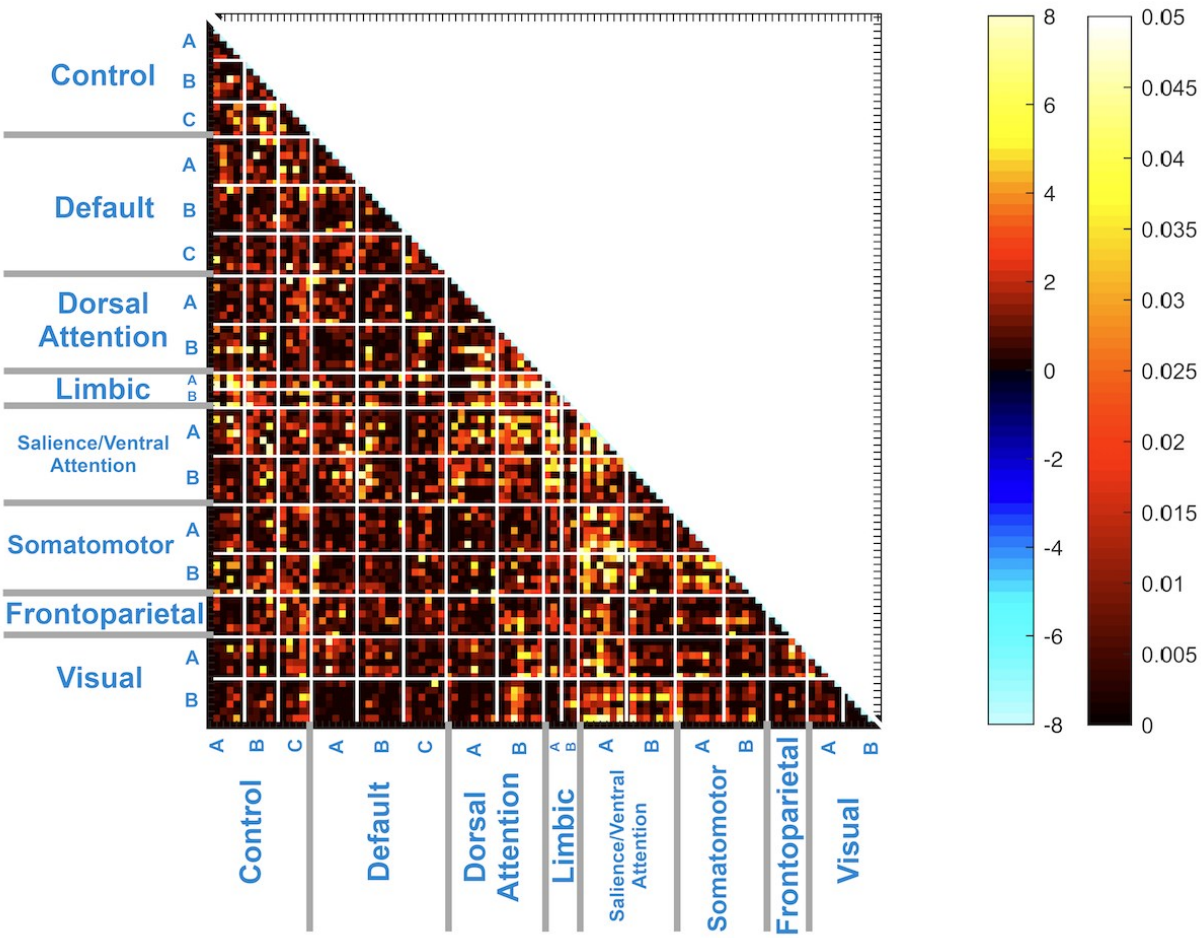
Supplementary Figure 15. Functional Connectivity during MCT Task – Changes from SD to PRN state with no FDR correction; 15.06% of total parcels significant.



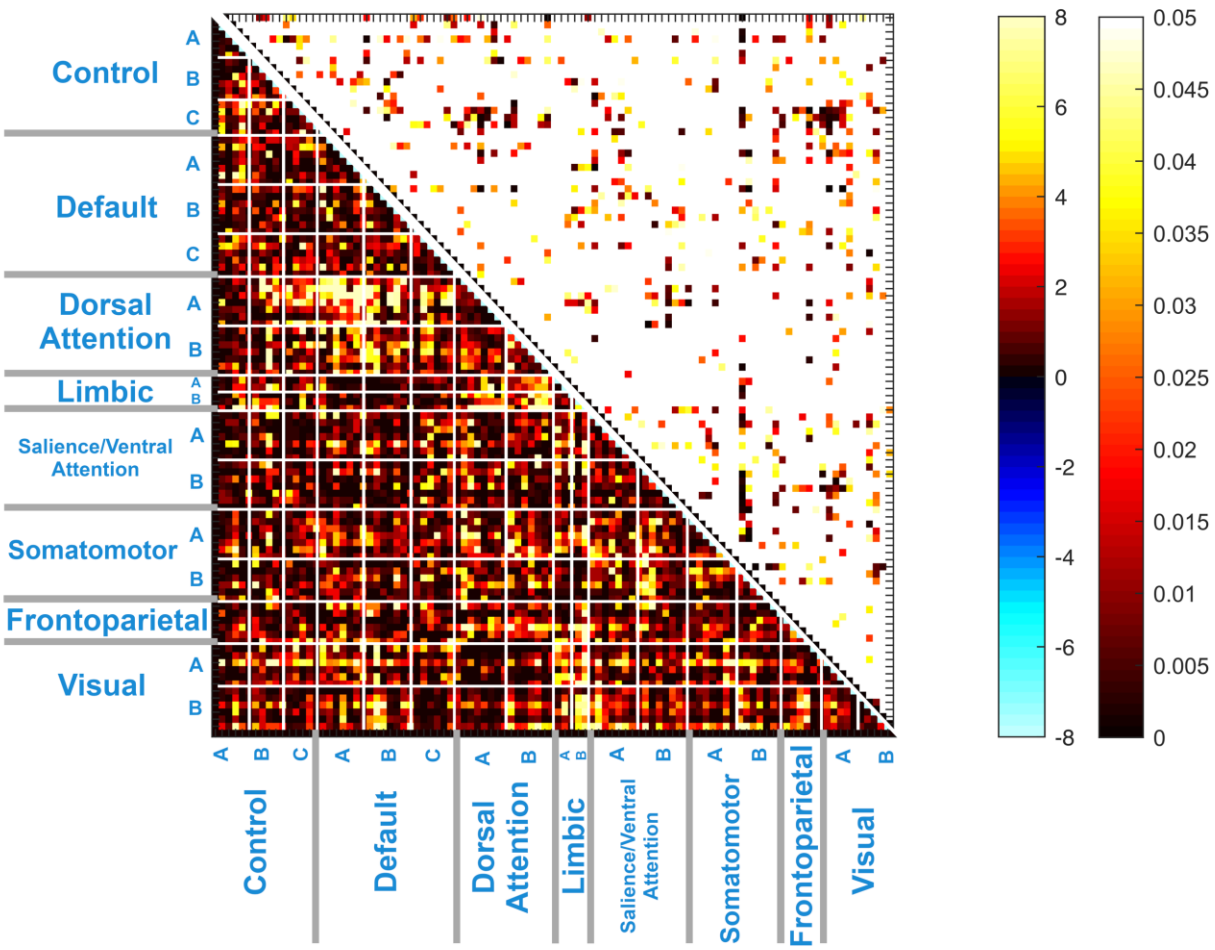
Supplementary Figure 16. Functional Connectivity during MCT Task – Changes from SD to PRN state with FDR correction, controlled for covariate total sleep time (TST).



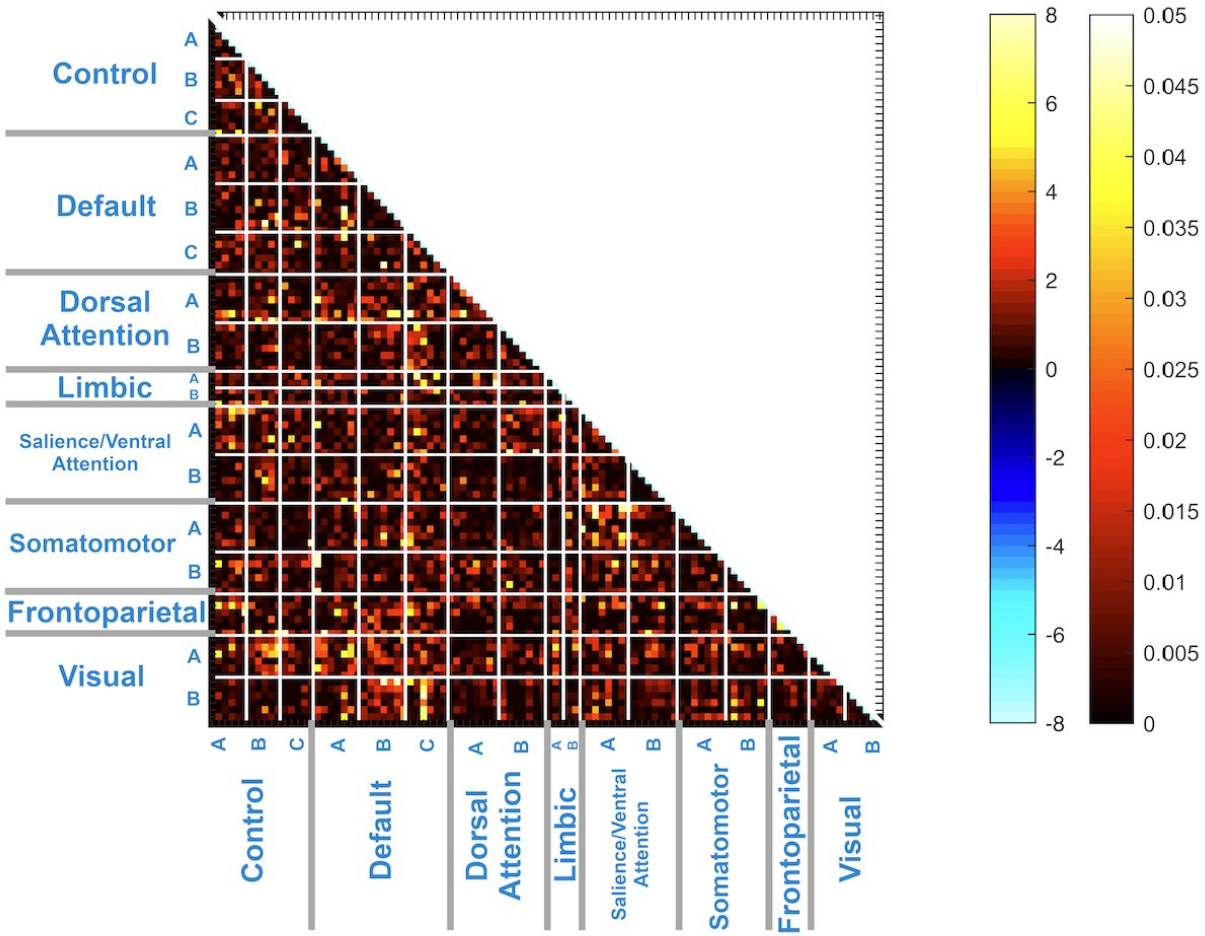
Supplementary Figure 17. Functional Connectivity during MCT Task – Changes from SD to PRN state with FDR correction, controlled for covariate N2 sleep stage time.



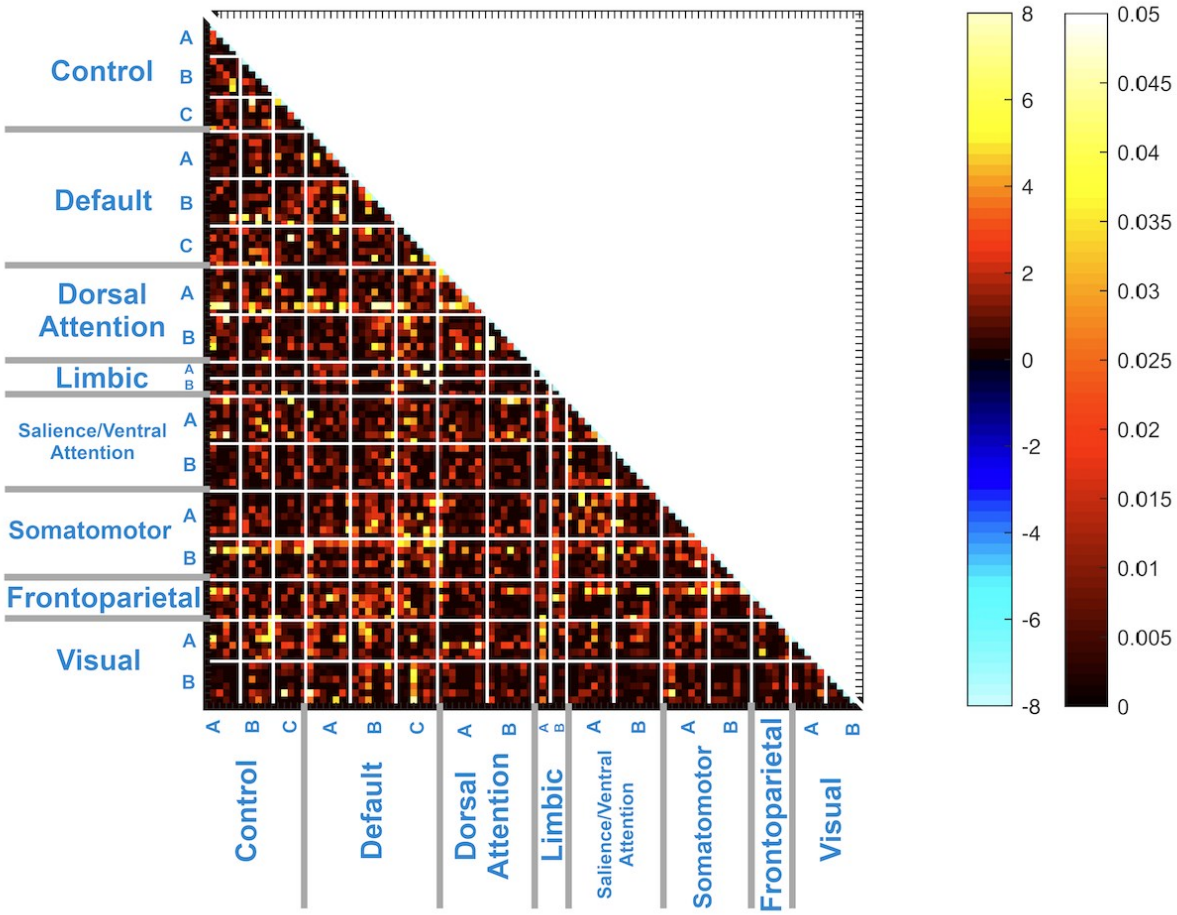
Supplementary Figure 18. Functional Connectivity during MCT Task – Changes from SD to PRN state with FDR correction, controlled for covariate N3 sleep stage time.



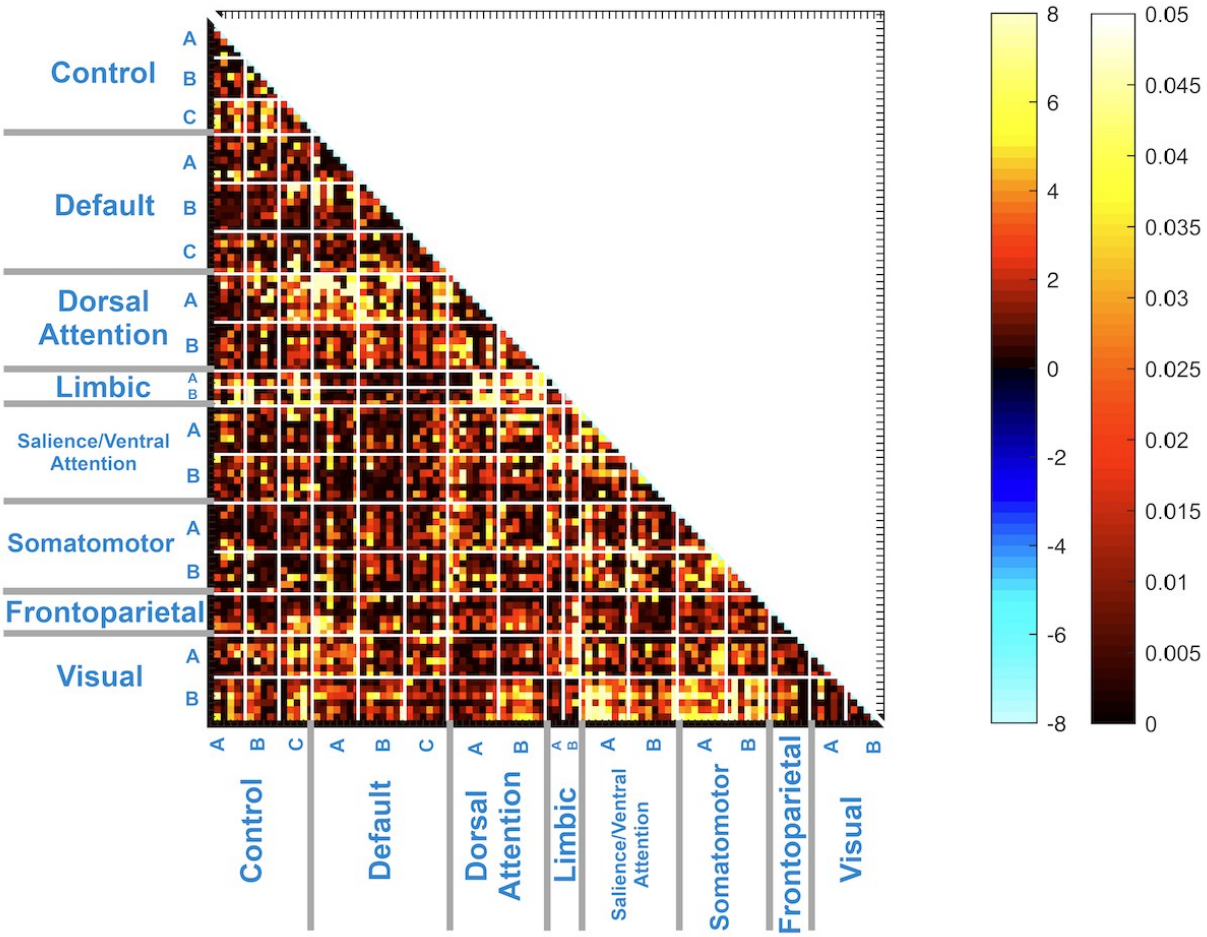
Supplementary Figure 19. Functional Connectivity during MCT Task – Changes from WR to PRN state with no FDR correction; 24.49% of total parcels significant.



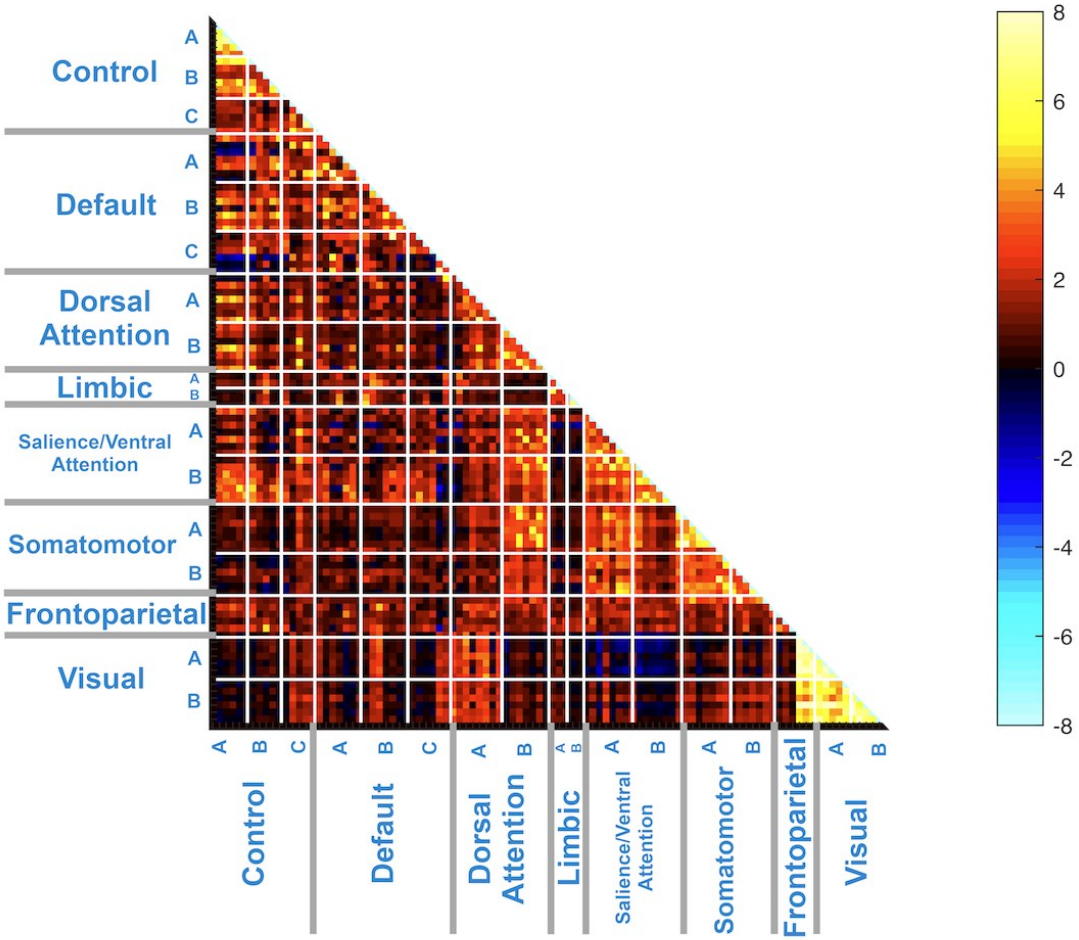
Supplementary Figure 20. Functional Connectivity during MCT Task – Changes from WR to PRN state with FDR correction, controlled for covariate total sleep time (TST).



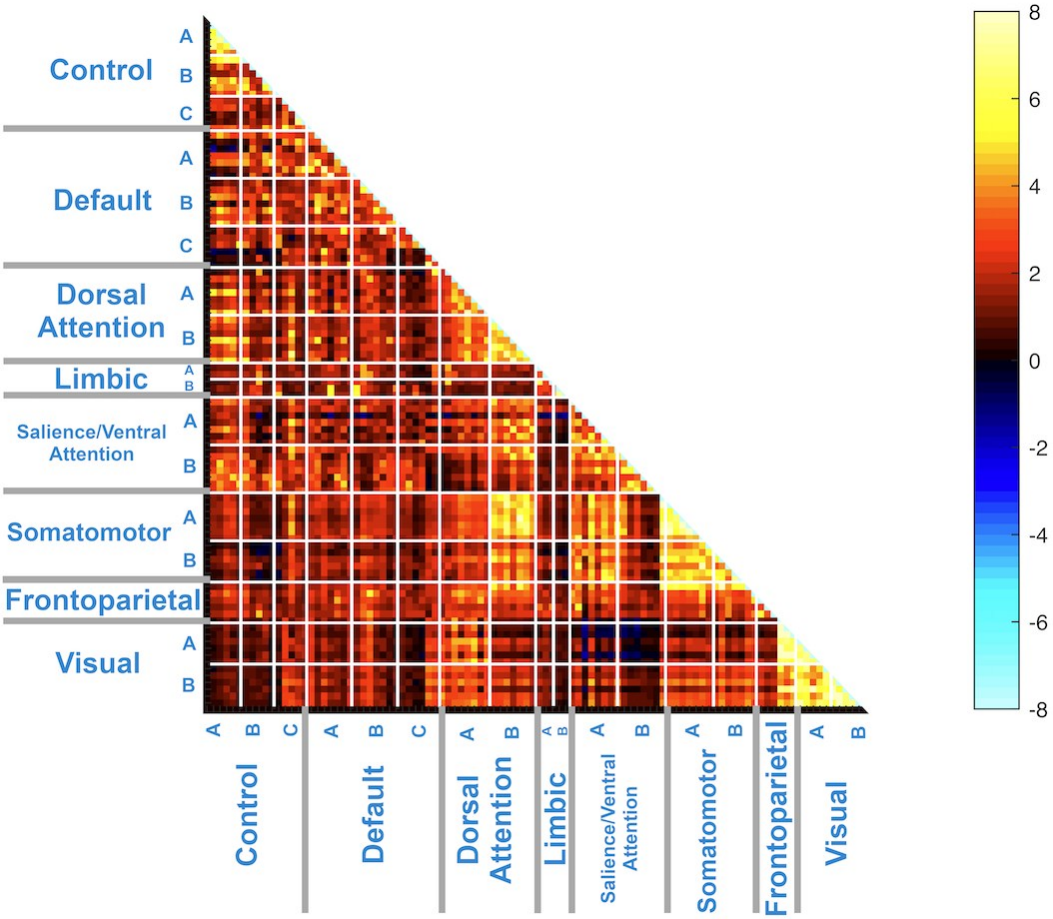
Supplementary Figure 21. Functional Connectivity during MCT Task – Changes from WR to PRN state with FDR correction, controlled for covariate N2 sleep stage time.



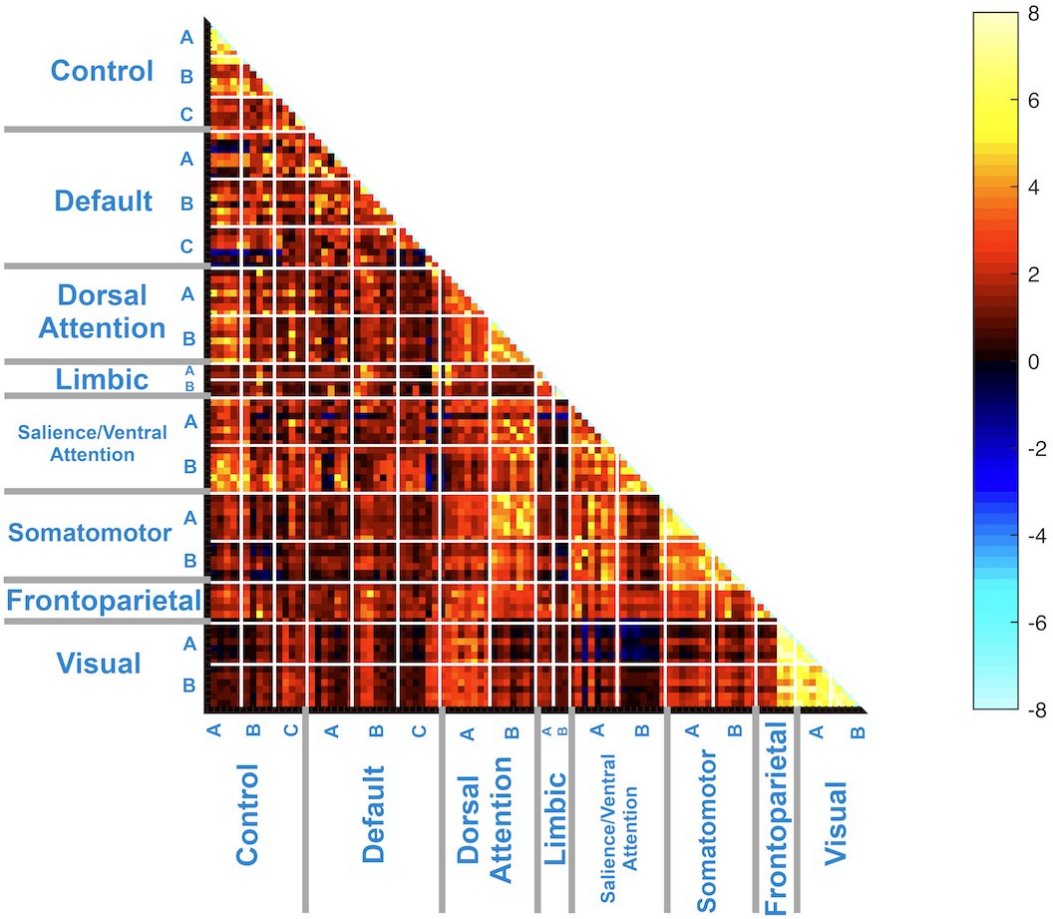
Supplementary Figure 22. Functional Connectivity during MCT Task – Changes from WR to PRN state with FDR correction, controlled for covariate N3 sleep stage time.



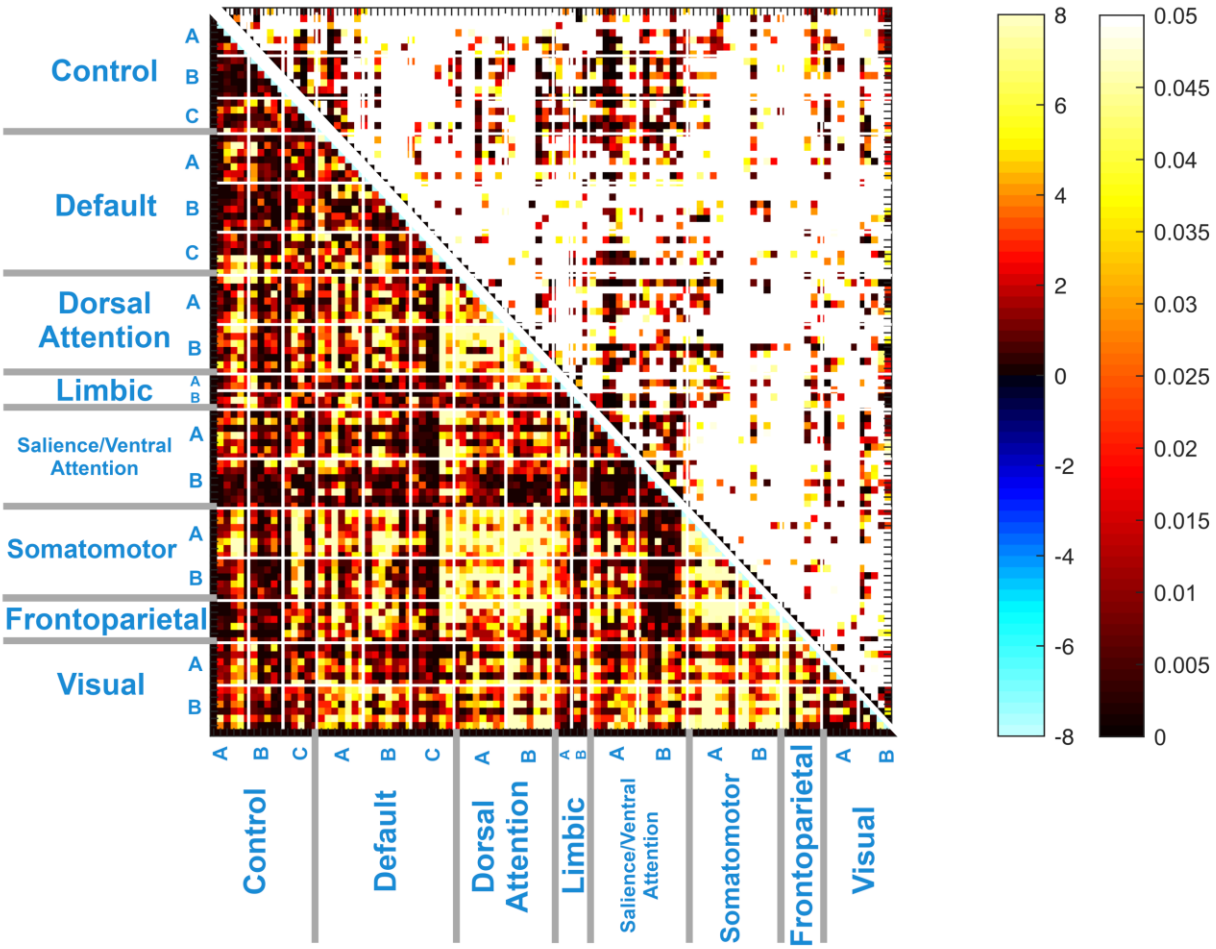
Supplementary Figure 23. Connectivity Matrix during N-back task – WR state



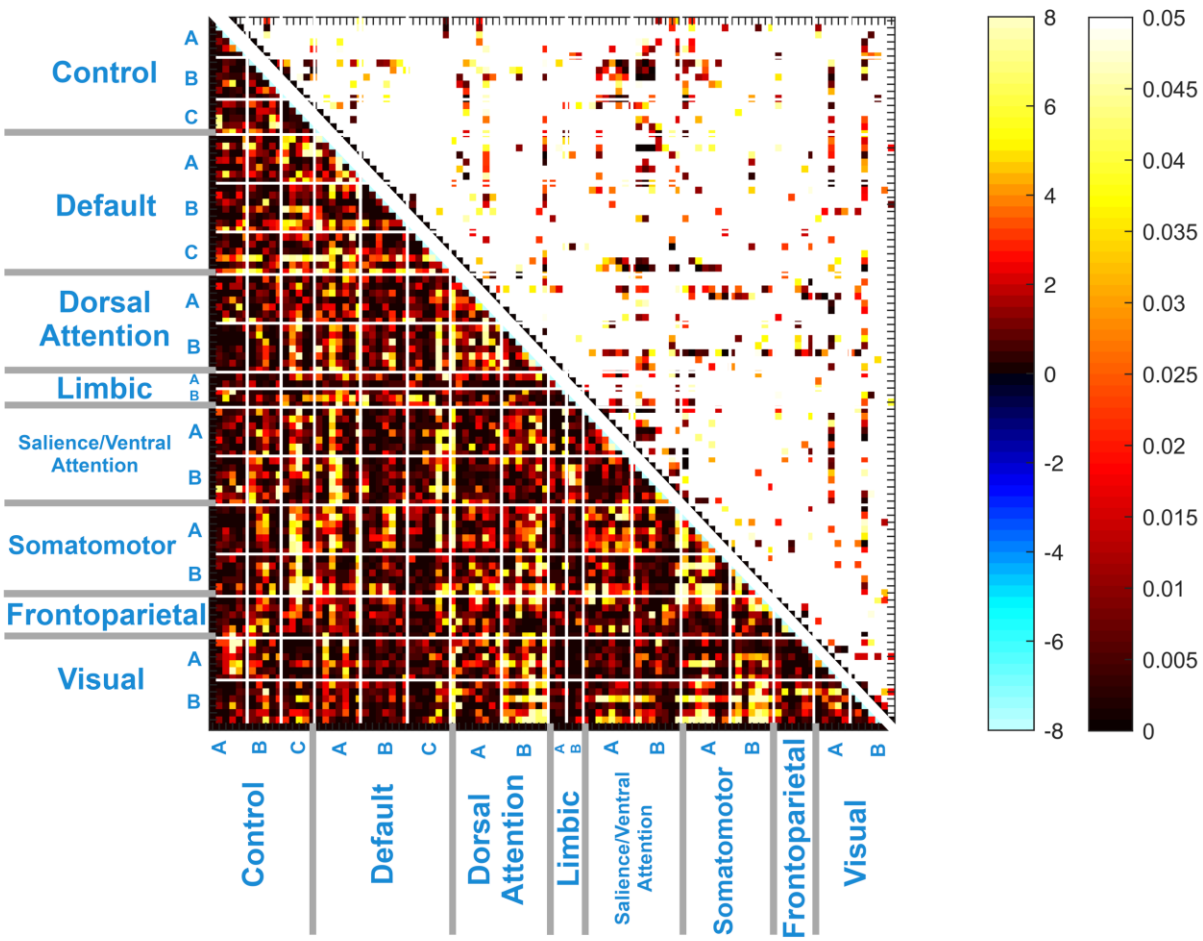
Supplementary Figure 24. Connectivity Matrix during N-back task – SD state



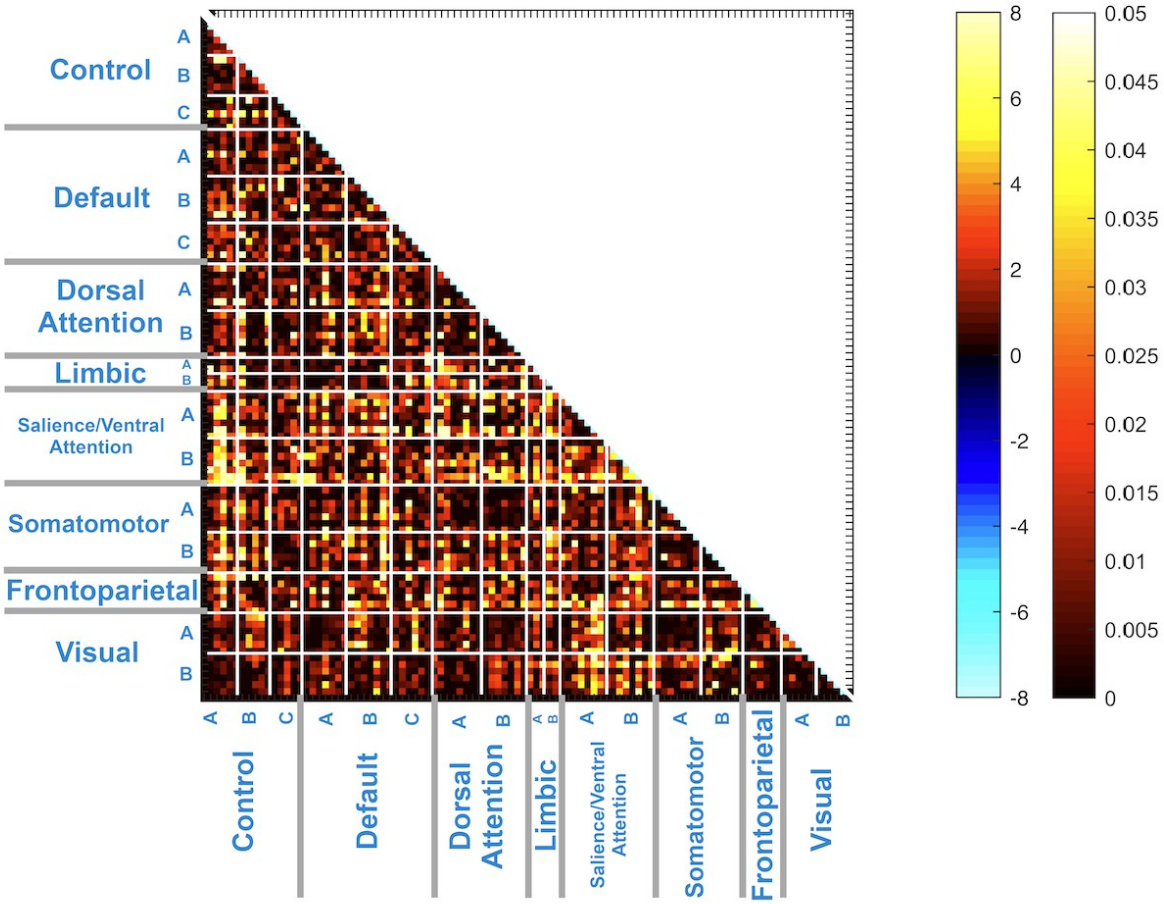
Supplementary Figure 25. Connectivity Matrix during N-back task – PRN state



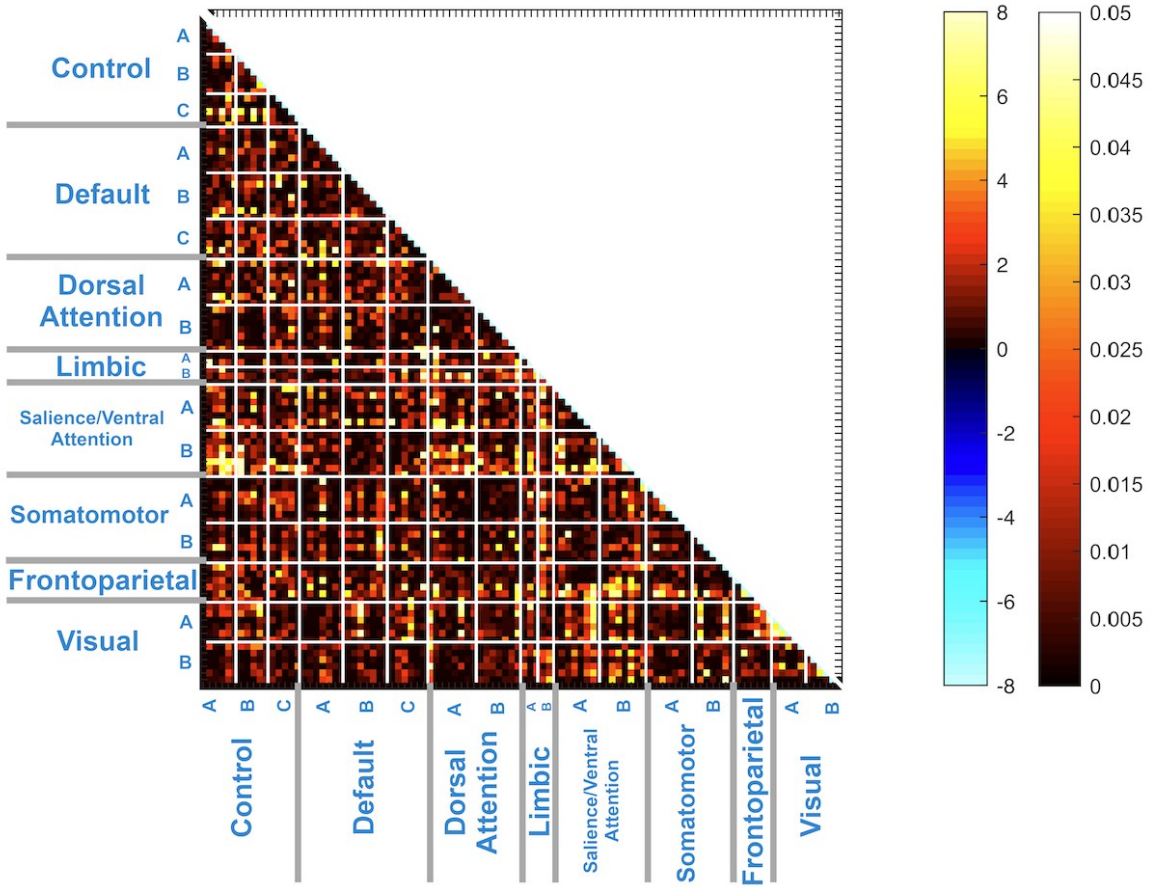
Supplementary Figure 26. Functional Connectivity during N-back Task – Changes from WR to SD state with no FDR correction; 57.43% of total parcels significant.



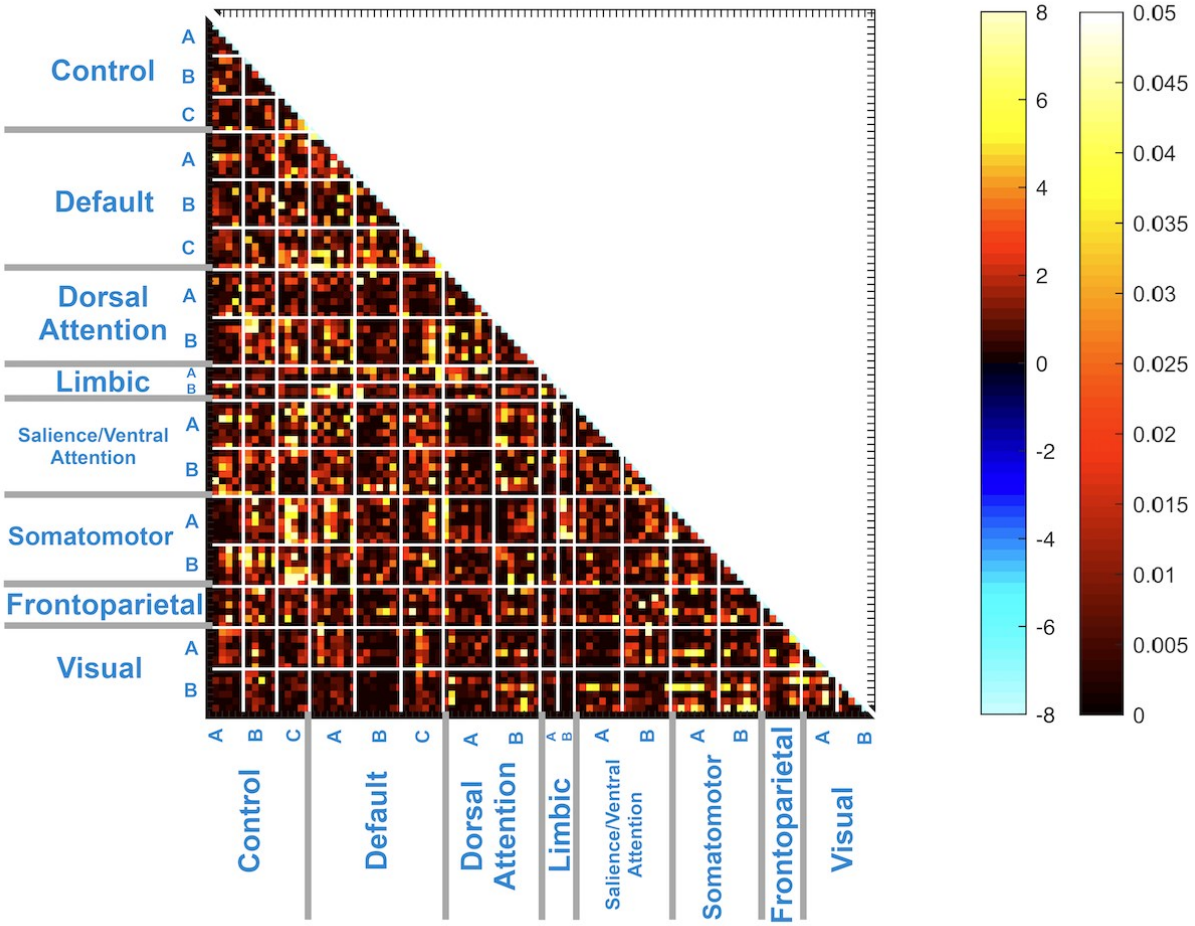
Supplementary Figure 27. Functional Connectivity during N-back Task – Changes from SD to PRN state with no FDR correction.



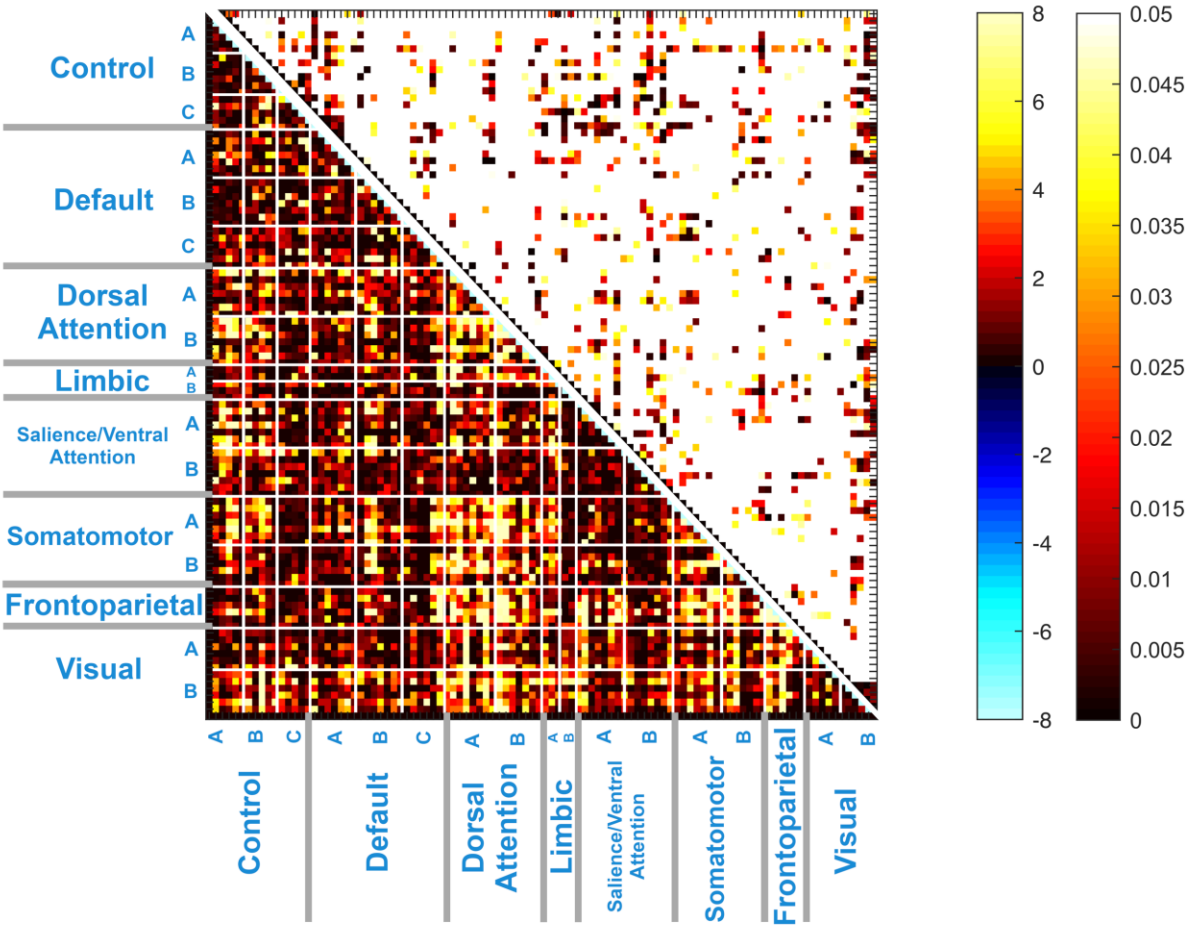
Supplementary Figure 28. Functional Connectivity during N-back Task – Changes from SD to PRN state with FDR correction, controlled for covariate total sleep time (TST).



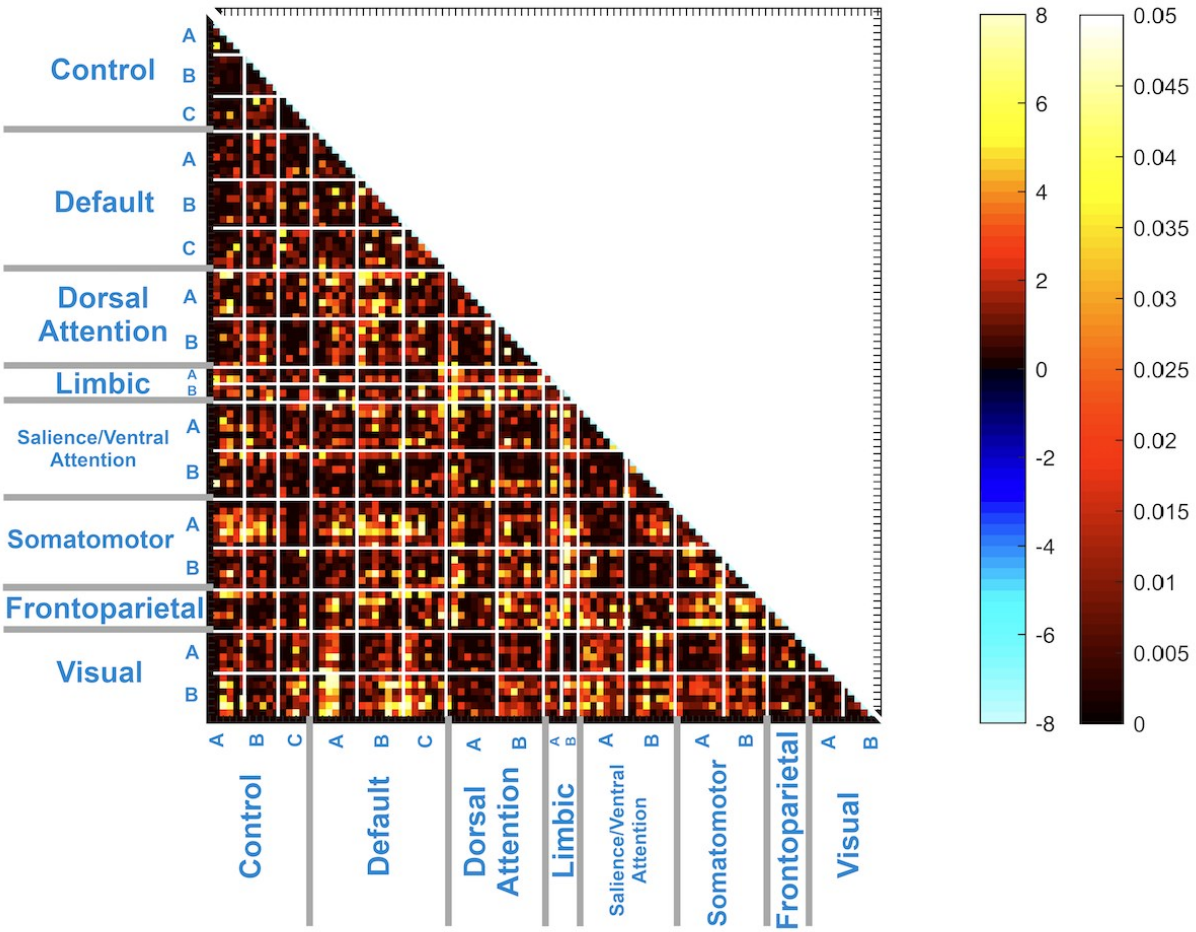
Supplementary Figure 29. Functional Connectivity during N-back Task – Changes from SD to PRN state with FDR correction, controlled for covariate N2 sleep stage time.



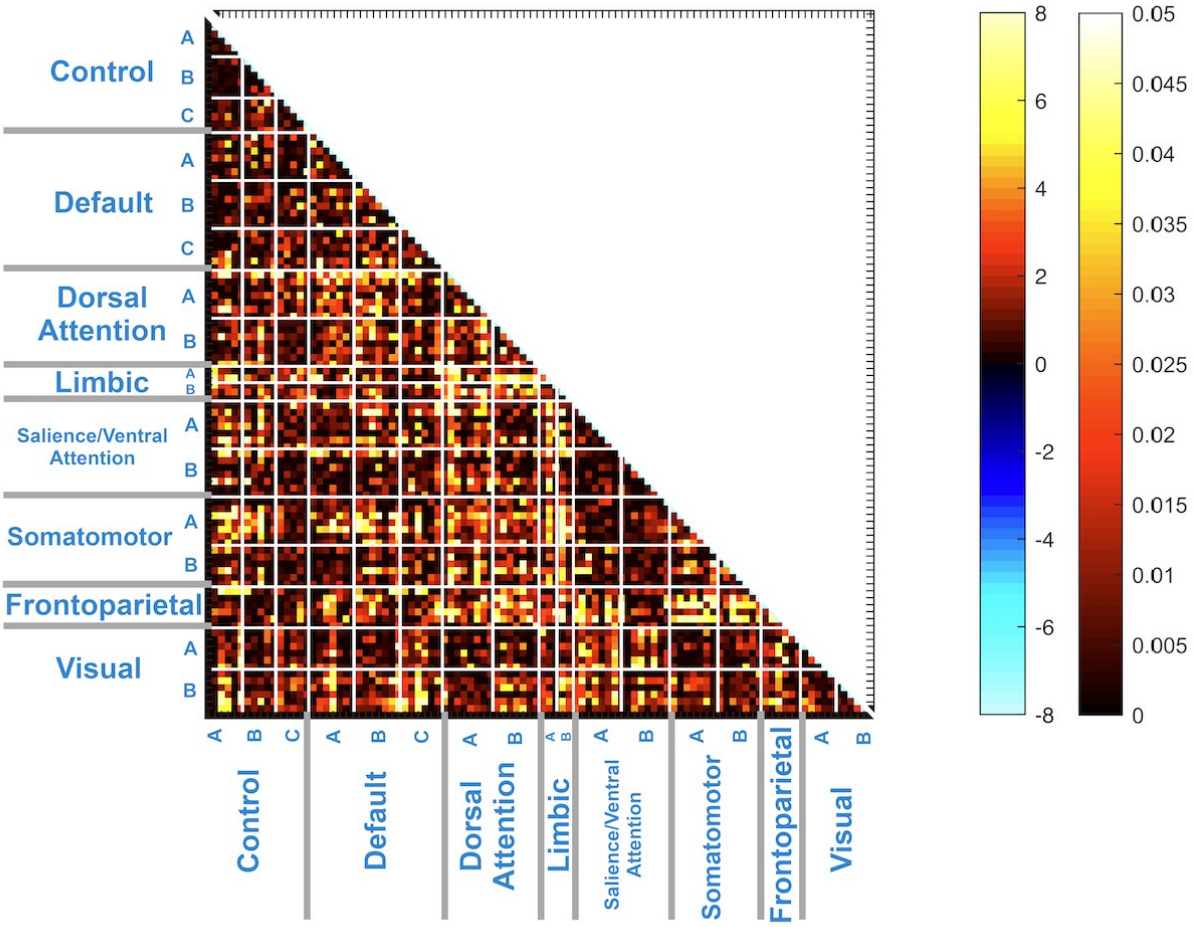
Supplementary Figure 30. Functional Connectivity during N-back Task – Changes from SD to PRN state with FDR correction, controlled for covariate N3 sleep stage time.



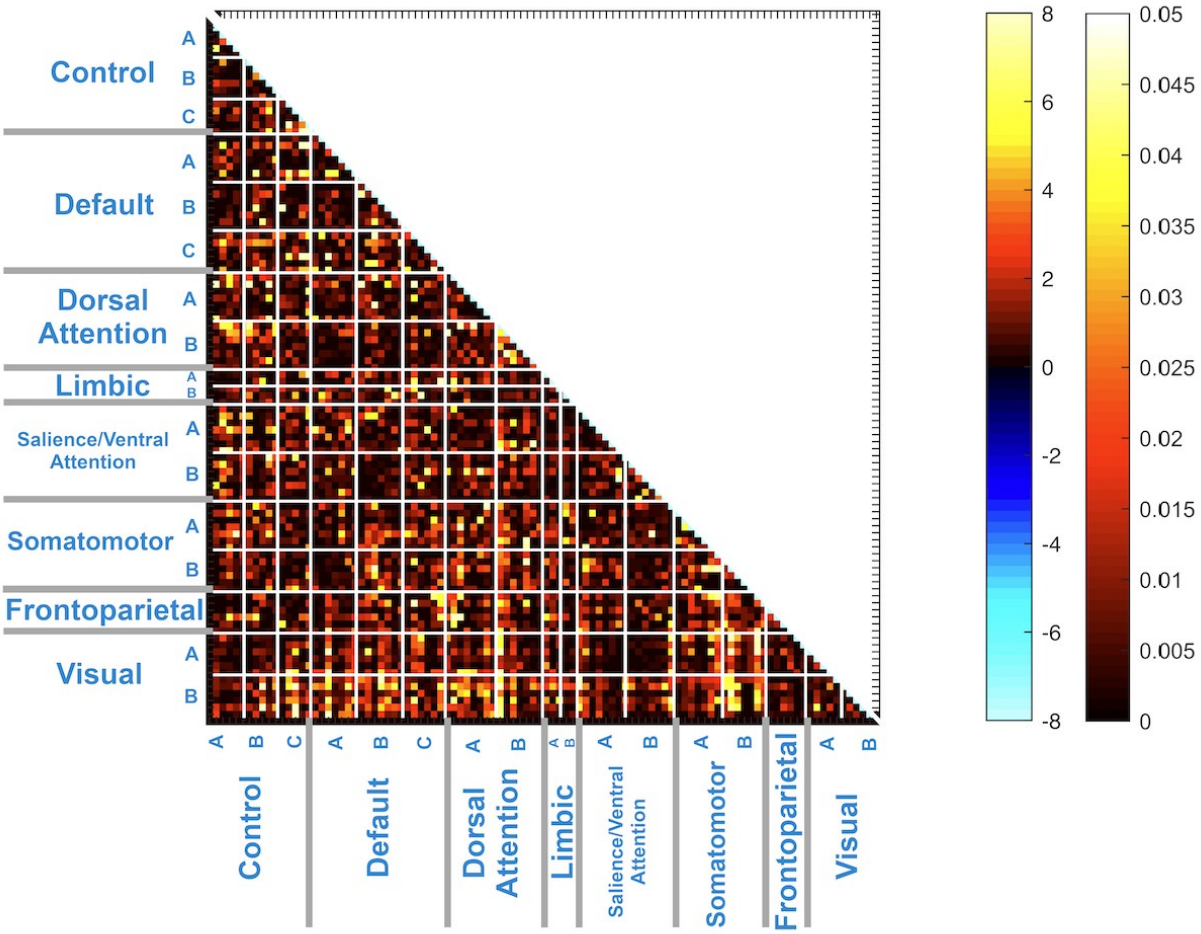
Supplementary Figure 31. Functional Connectivity during N-back Task – Changes from WR to PRN state with no FDR correction.



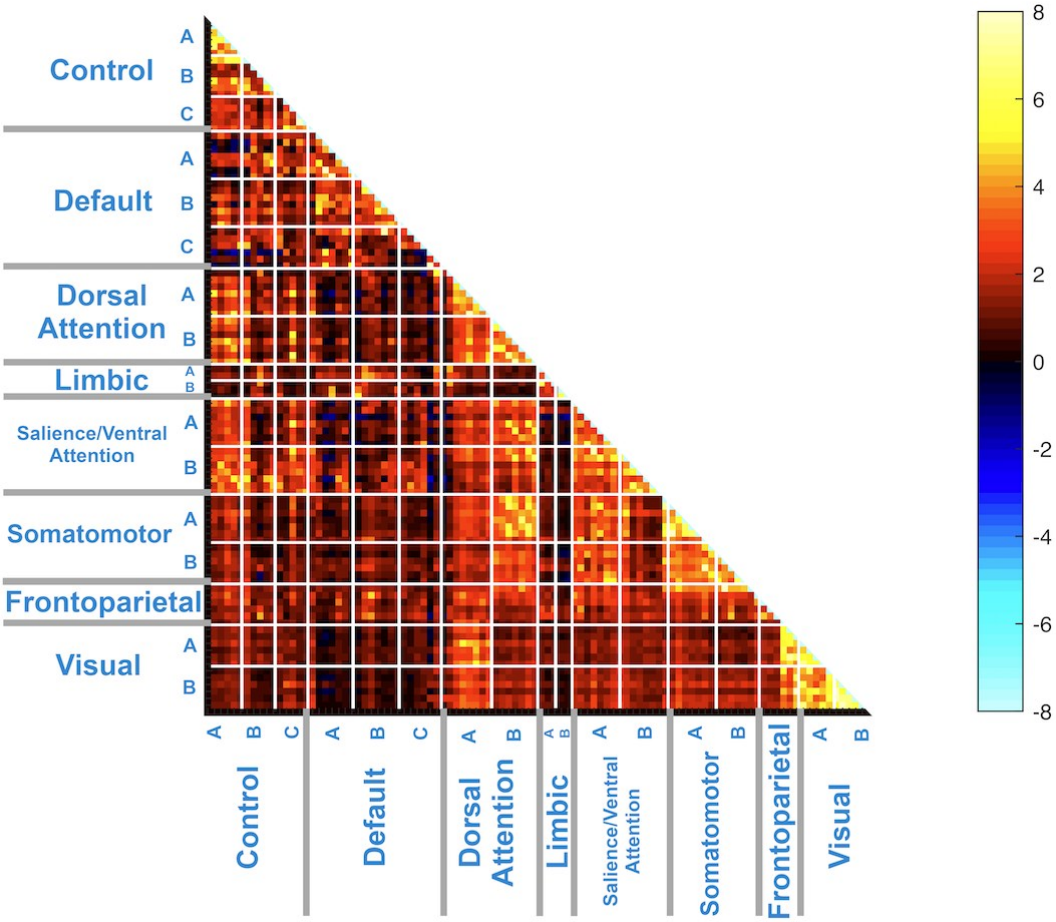
Supplementary Figure 32. Functional Connectivity during N-back Task – Changes from WR to PRN state with FDR correction, controlled for covariate total sleep time (TST).



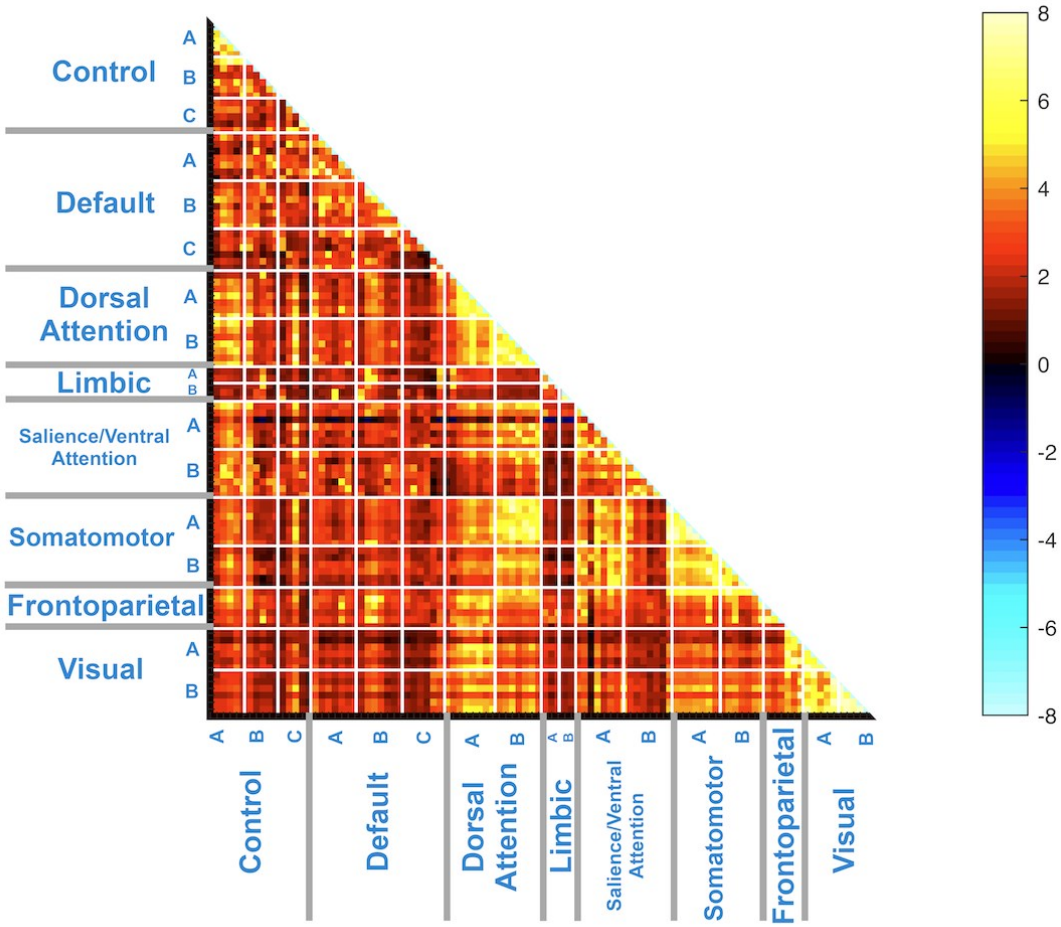
Supplementary Figure 33. Functional Connectivity during N-back Task – Changes from WR to PRN state with FDR correction, controlled for covariate N2 stage sleep time.



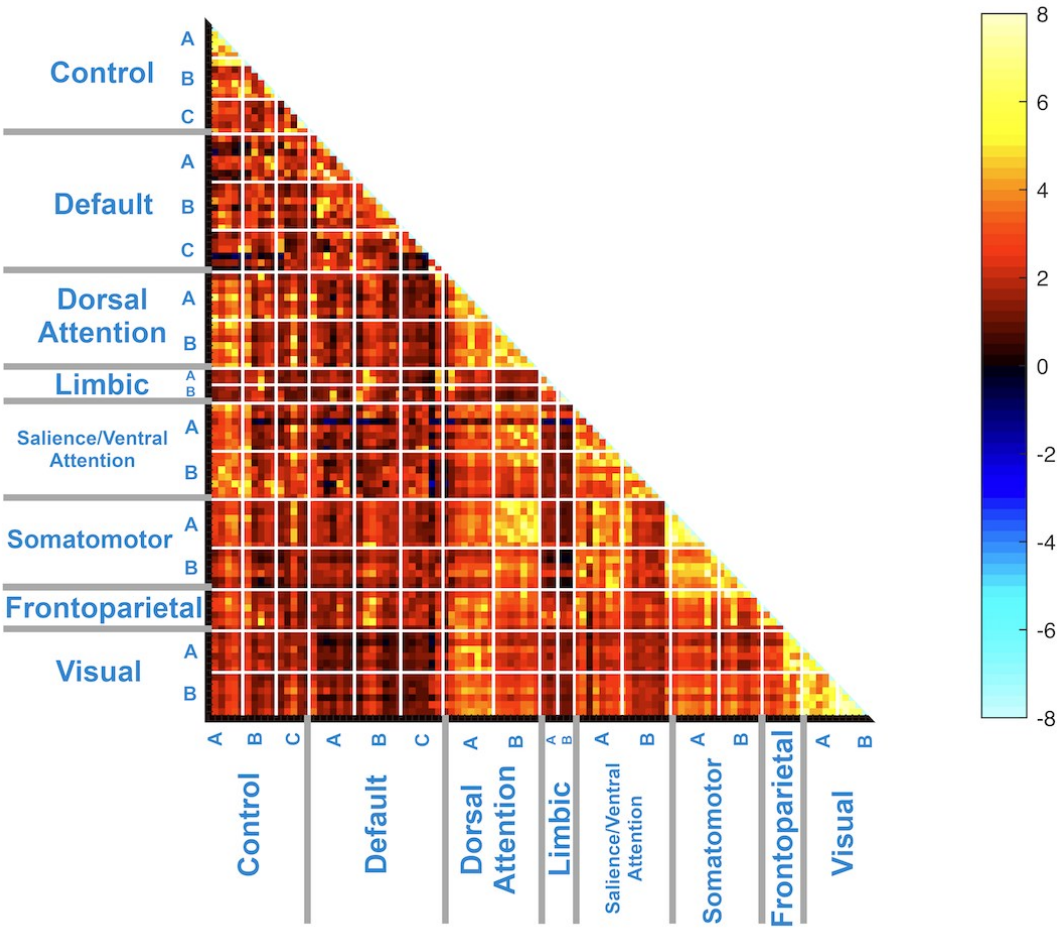
Supplementary Figure 34. Functional Connectivity during N-back Task – Changes from WR to PRN state with FDR correction, controlled for covariate N3 stage sleep time.



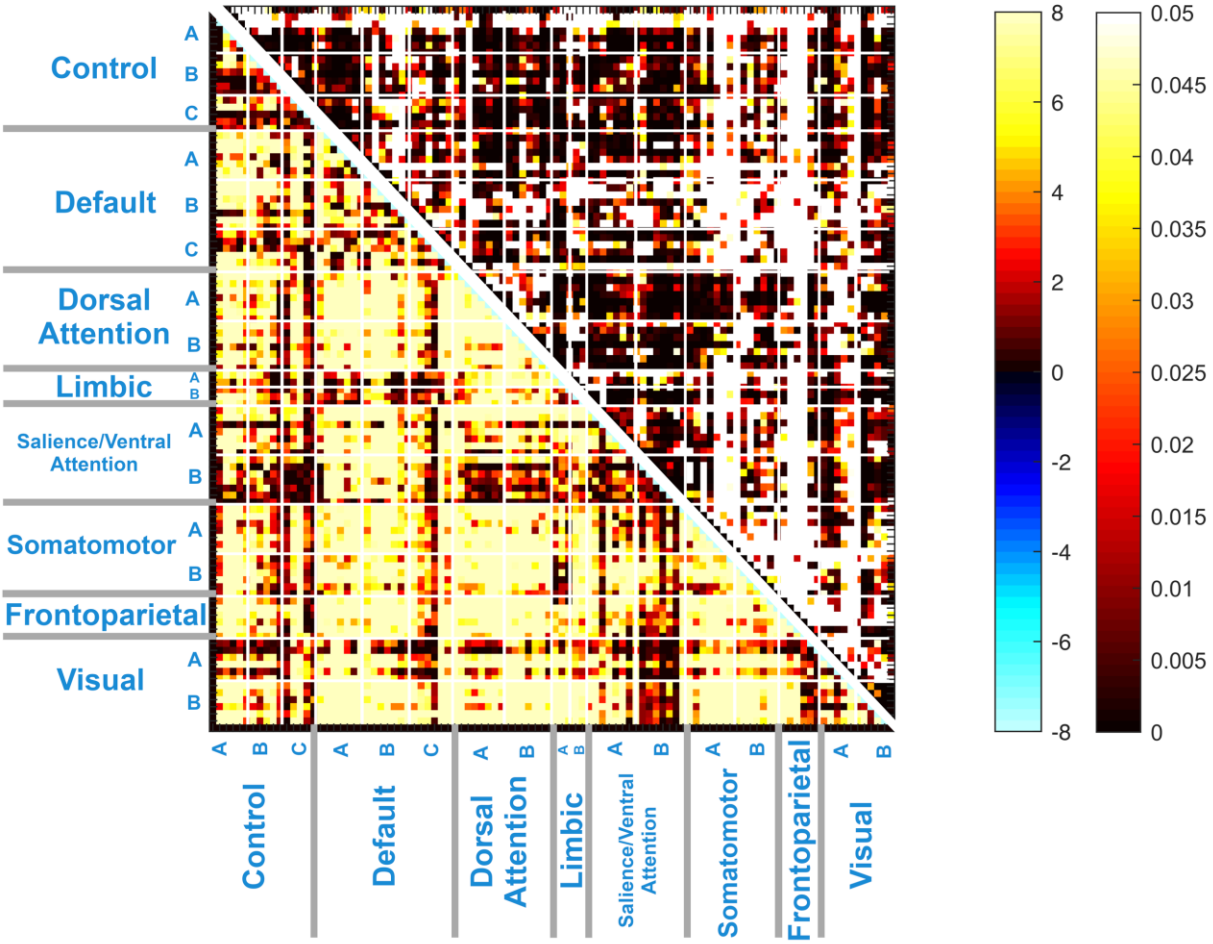
Supplementary Figure 35. Connectivity Matrix during ANT task – WR state



Supplementary Figure 36. Connectivity Matrix during ANT task – SD state



Supplementary Figure 37. Connectivity Matrix during ANT task – PRN state



Supplementary Figure 38. Functional Connectivity during ANT Task – Changes from WR to SD state with no FDR correction.

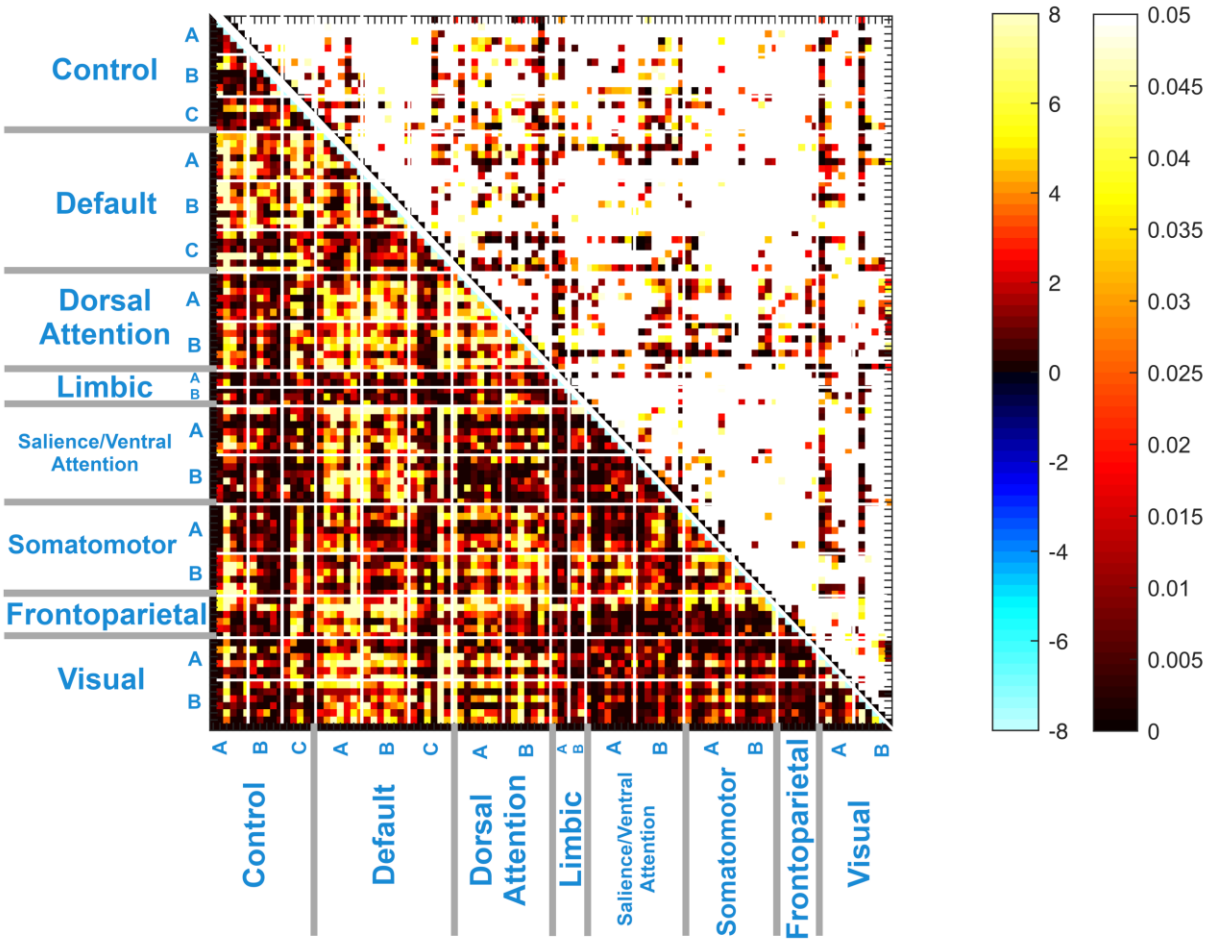
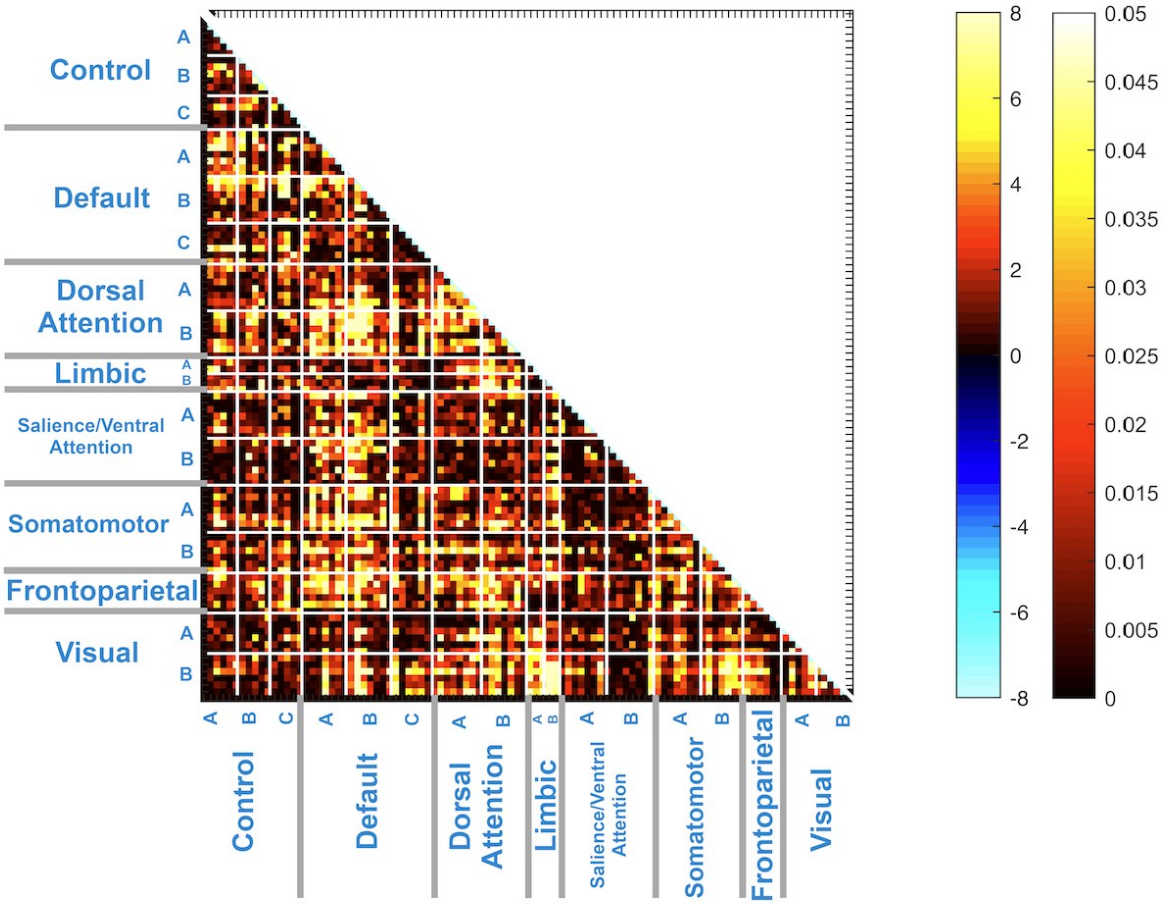
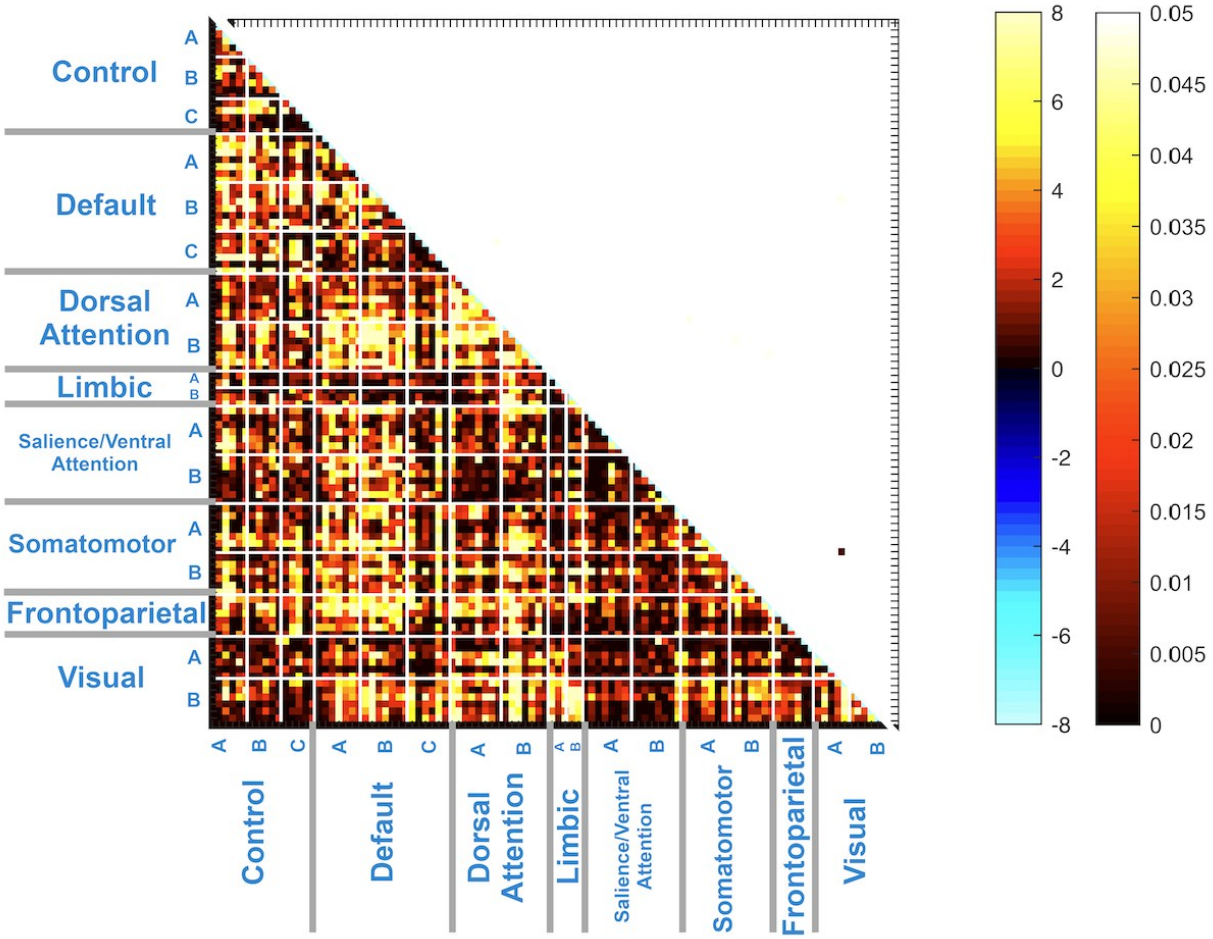


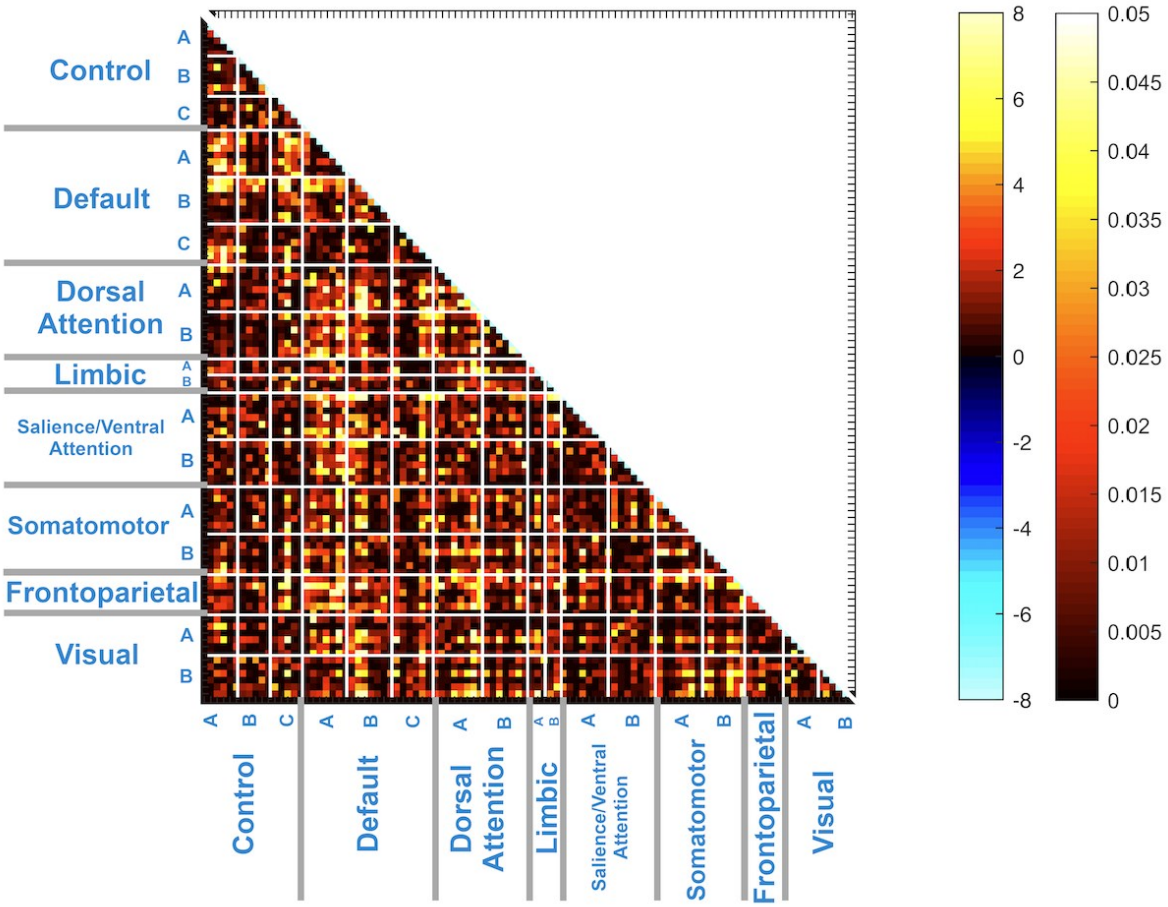
Figure 39. Functional Connectivity during ANT Task – Changes from SD to PRN state with no FDR correction.



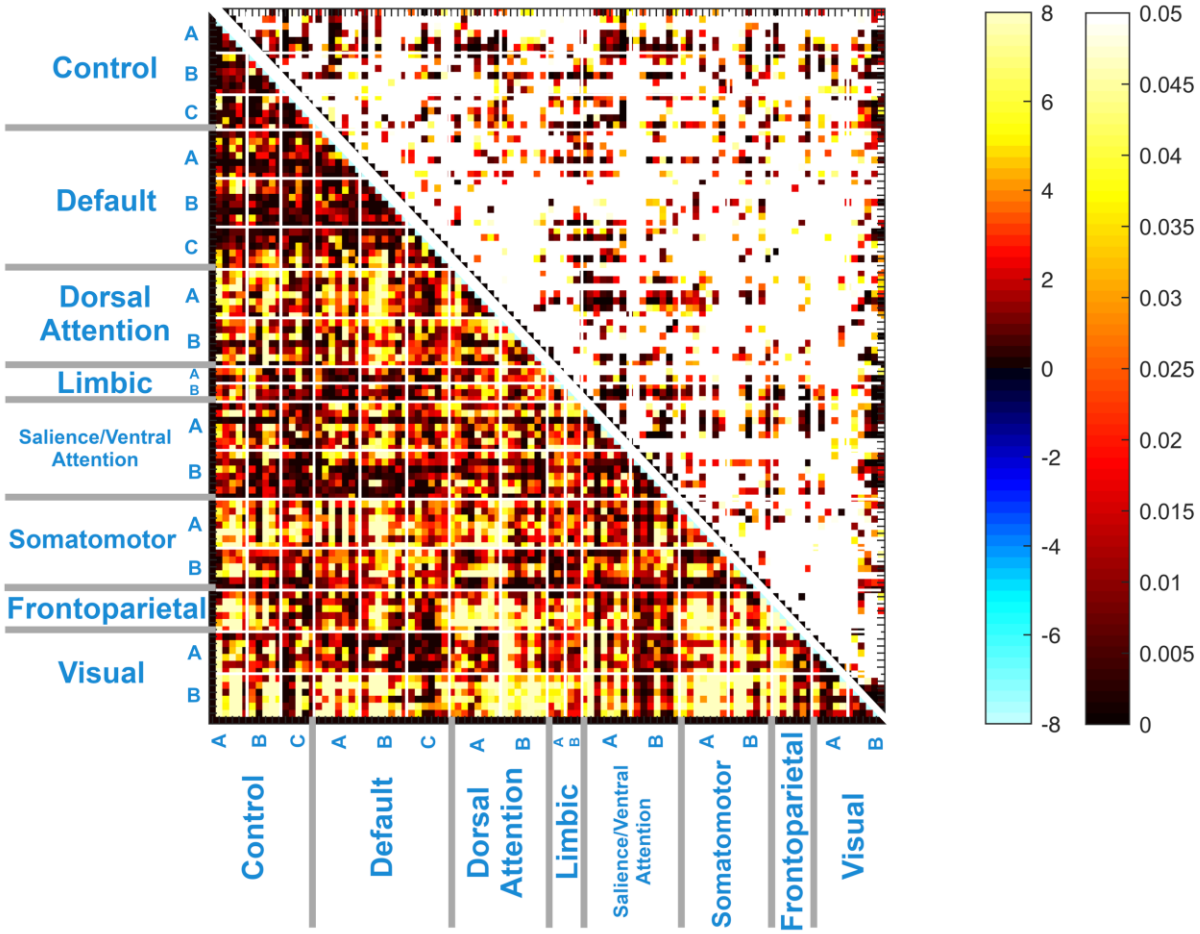
Supplementary Figure 40. Functional Connectivity during ANT Task – Changes from SD to PRN state with FDR correction, controlled for covariate total sleep time (TST).



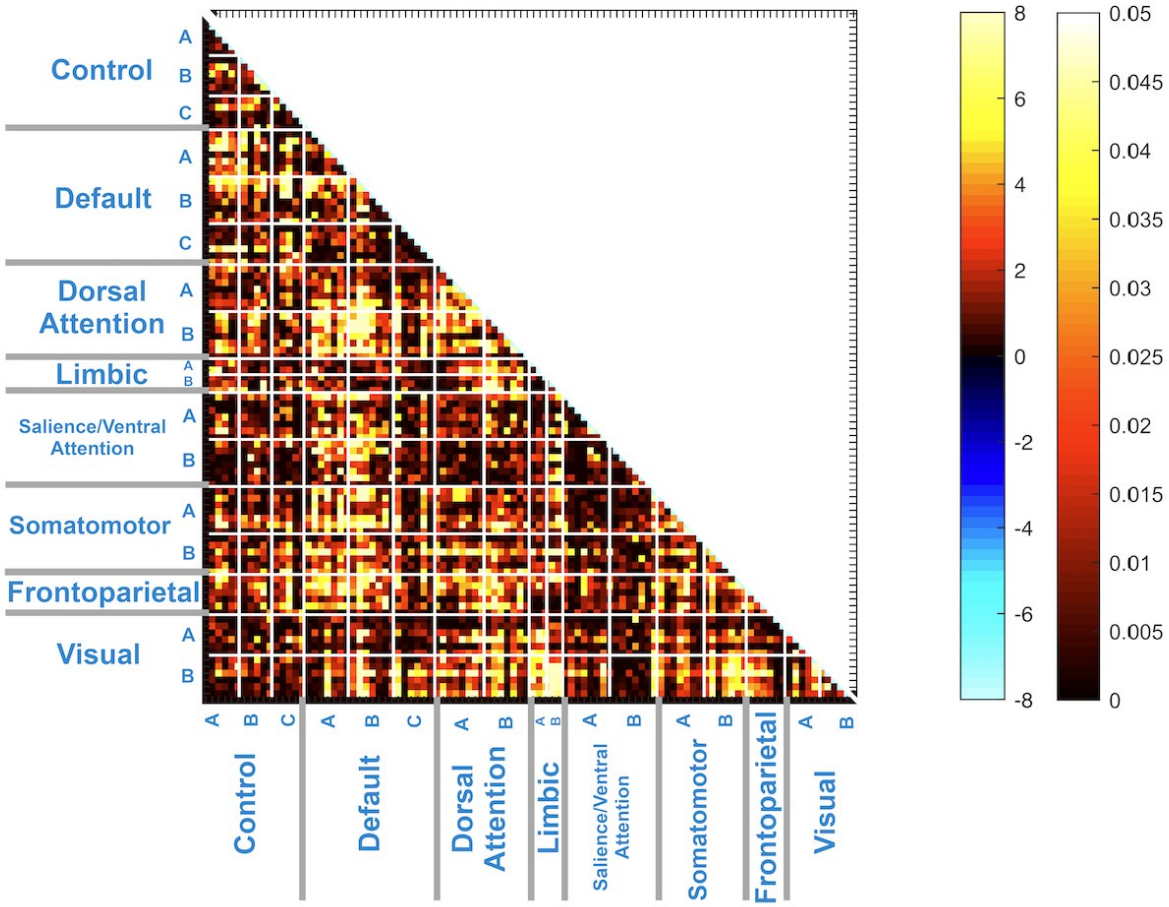
Supplementary Figure 41. Functional Connectivity during ANT Task – Changes from SD to PRN state with FDR correction, controlled for covariate N2 stage sleep time.



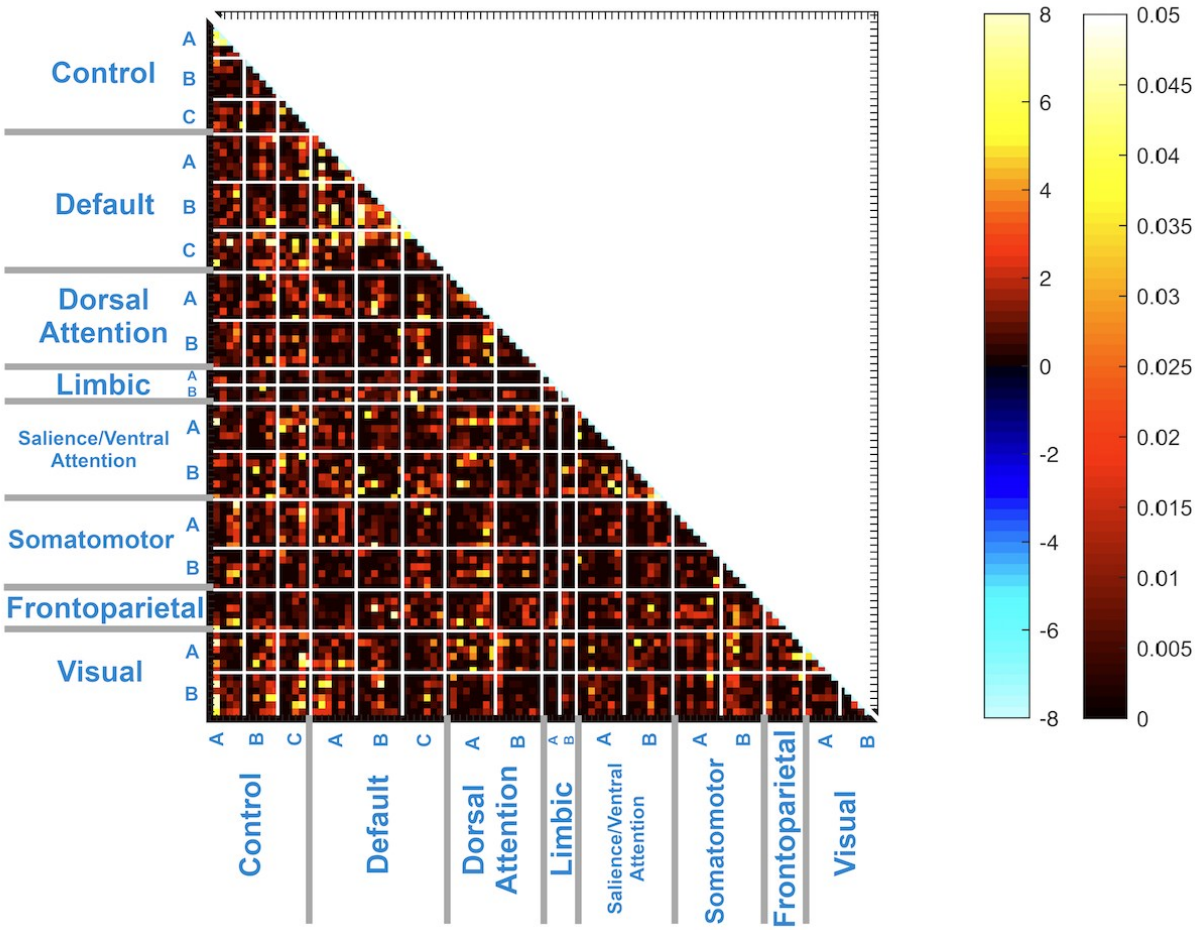
Supplementary Figure 42. Functional Connectivity during ANT Task – Changes from SD to PRN state with FDR correction, controlled for covariate N3 stage sleep time.



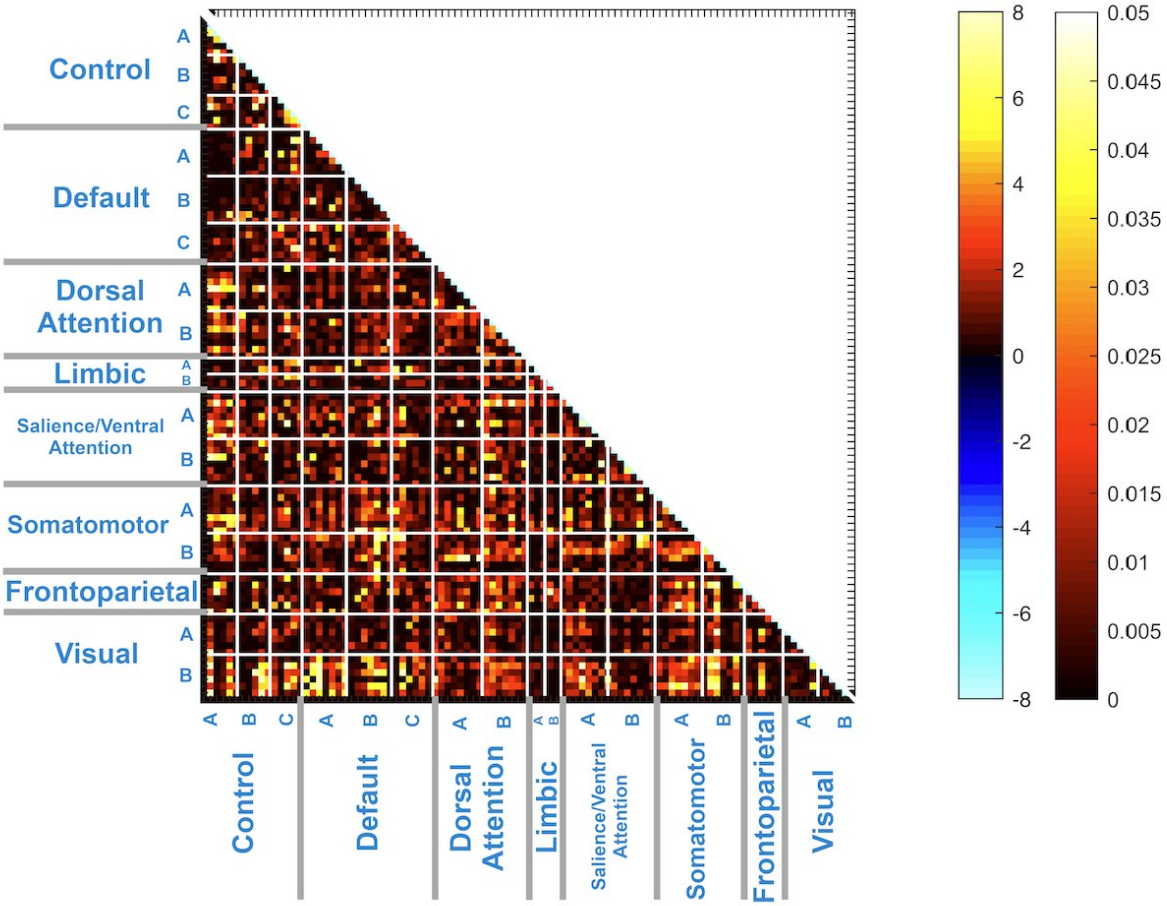
Supplementary Figure 43. Functional Connectivity during ANT Task – Changes from WR to PRN state with no FDR correction.



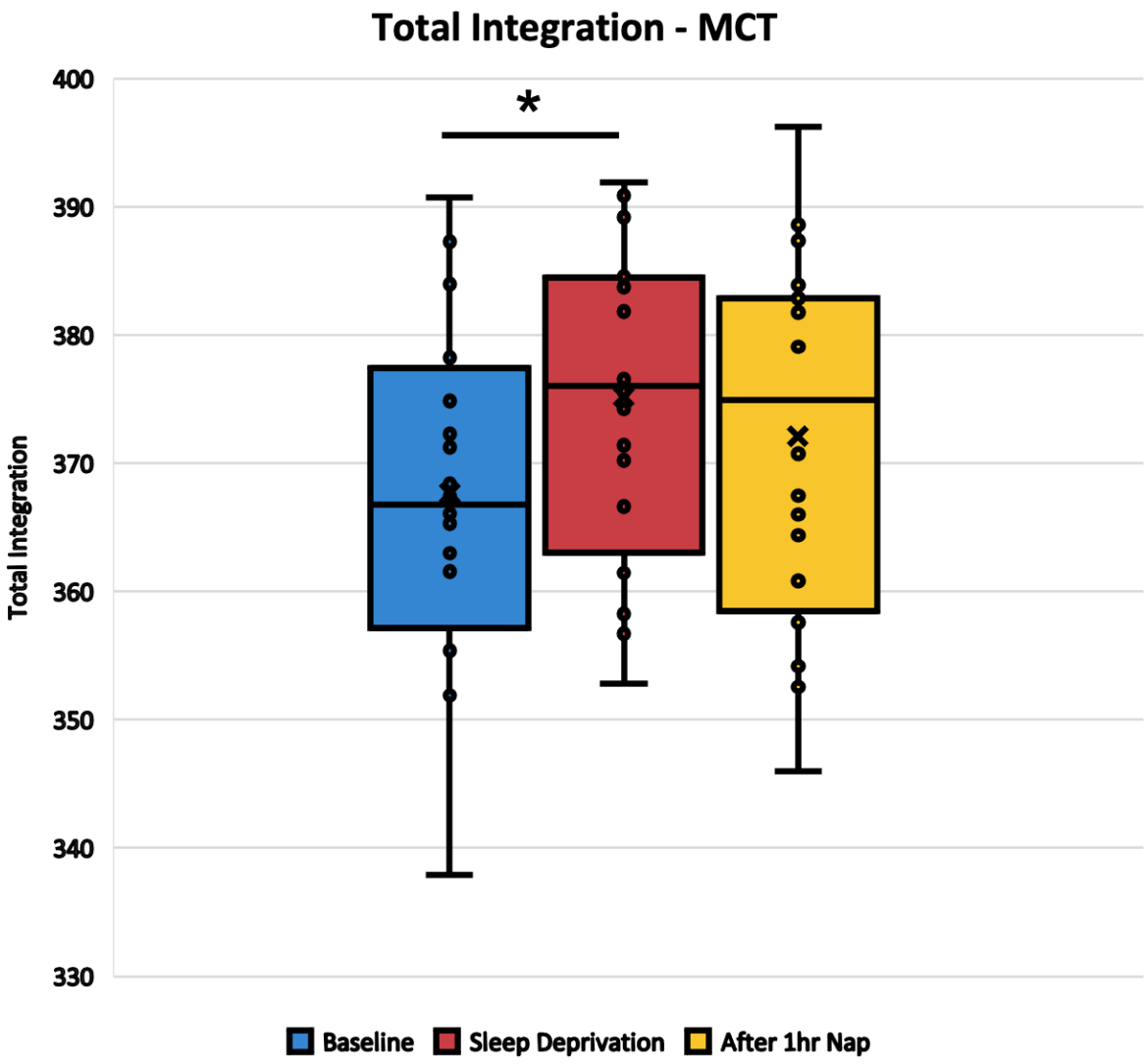
Supplementary Figure 44. Functional Connectivity during ANT Task – Changes from WR to PRN state with FDR correction, controlled for covariate total sleep time (TST).



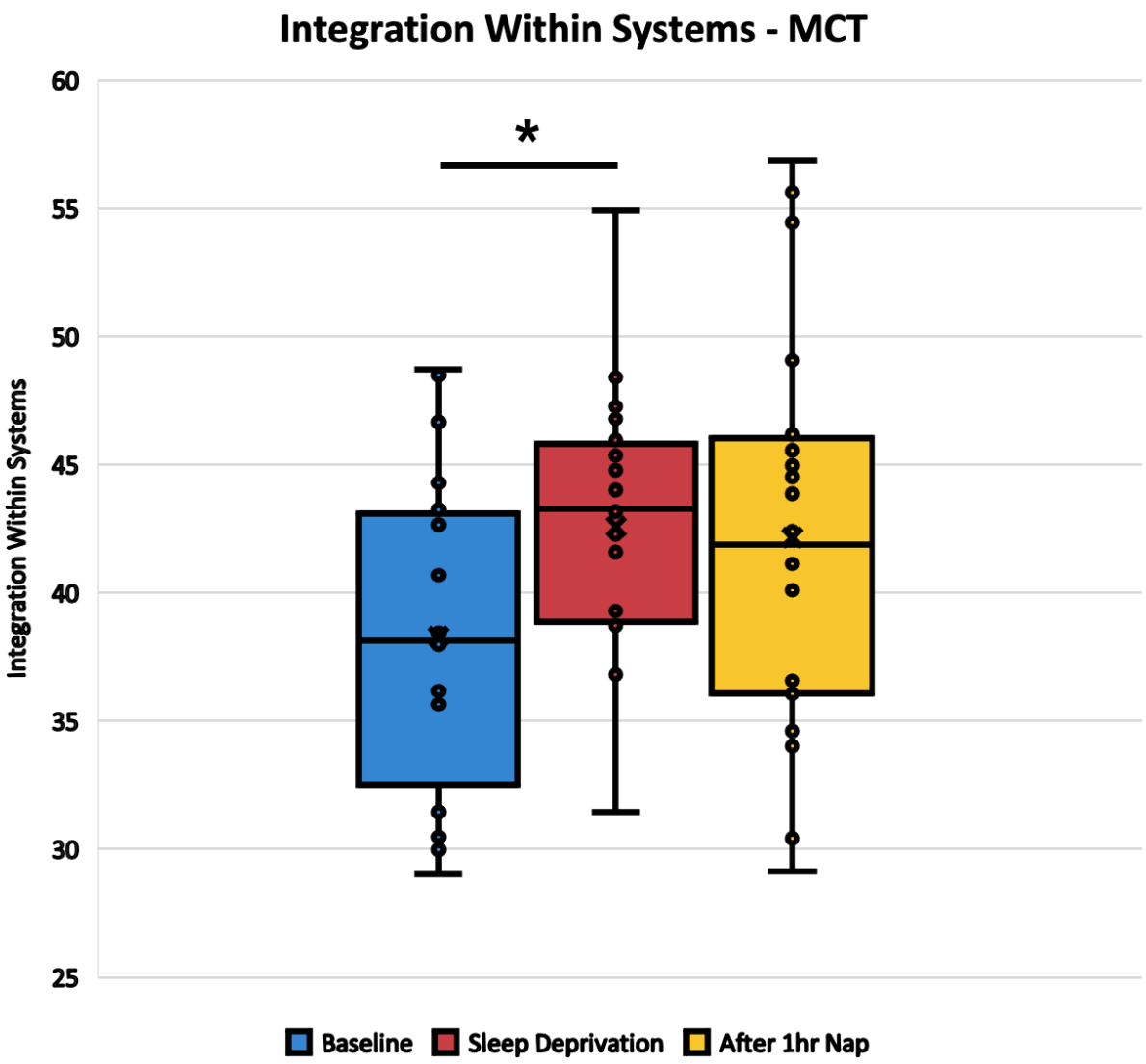
Supplementary Figure 45. Functional Connectivity during ANT Task – Changes from WR to PRN state with FDR correction, controlled for covariate N2 stage sleep time.



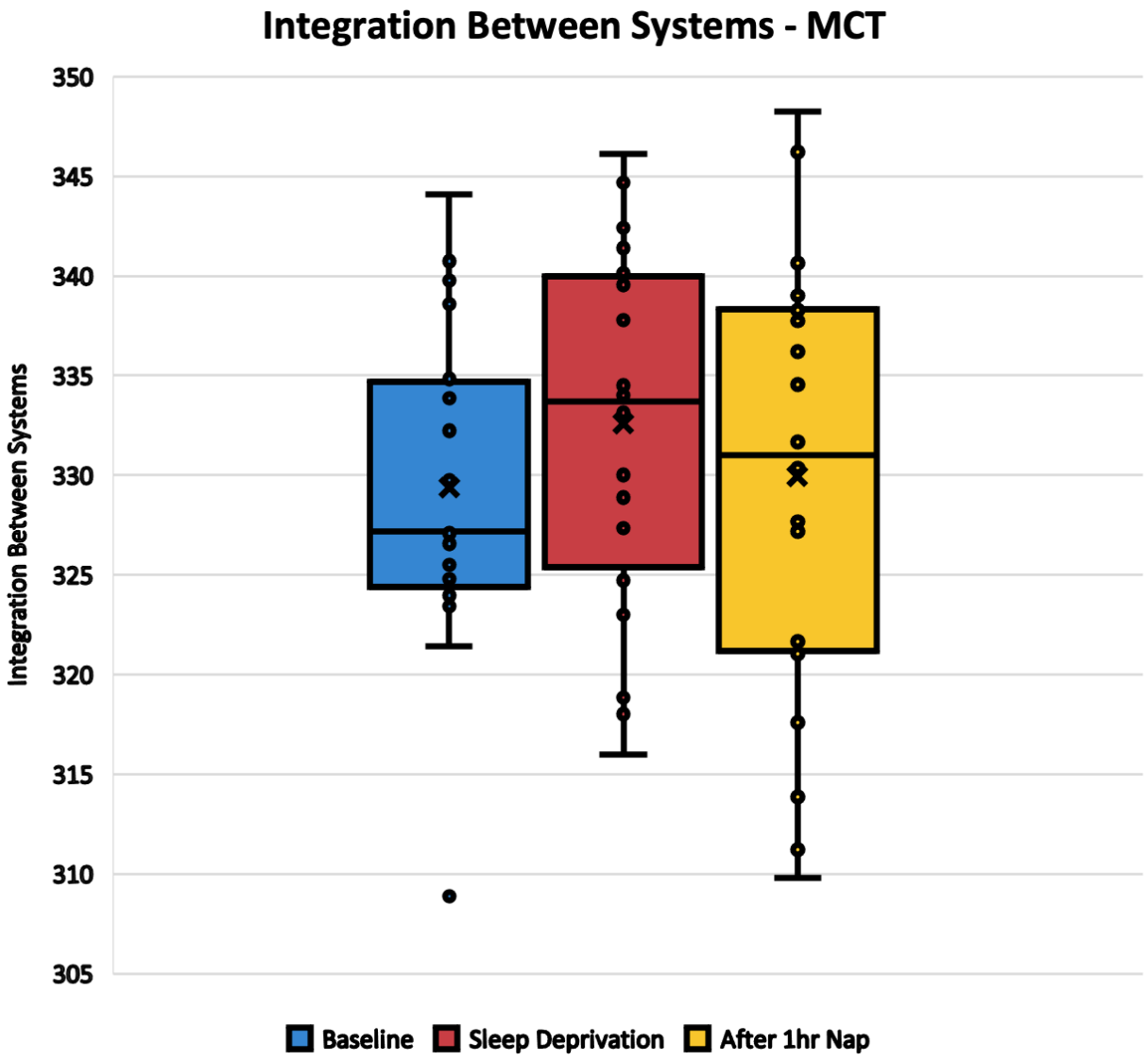
Supplementary Figure 46. Functional Connectivity during ANT Task – Changes from WR to PRN state with FDR correction, controlled for covariate N3 stage sleep time.



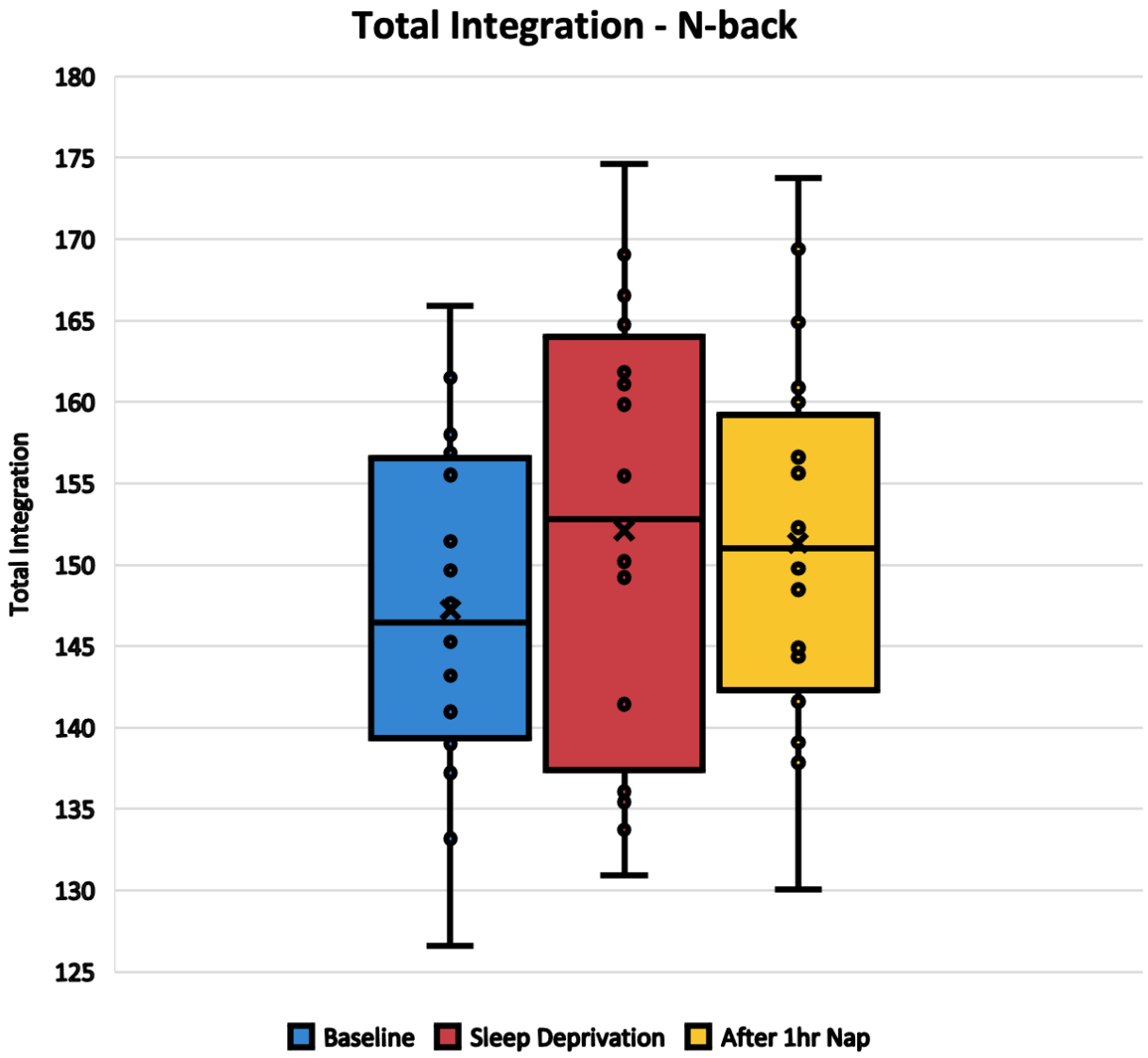
*Supplementary Figure 47. Total Integration during MCT task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*



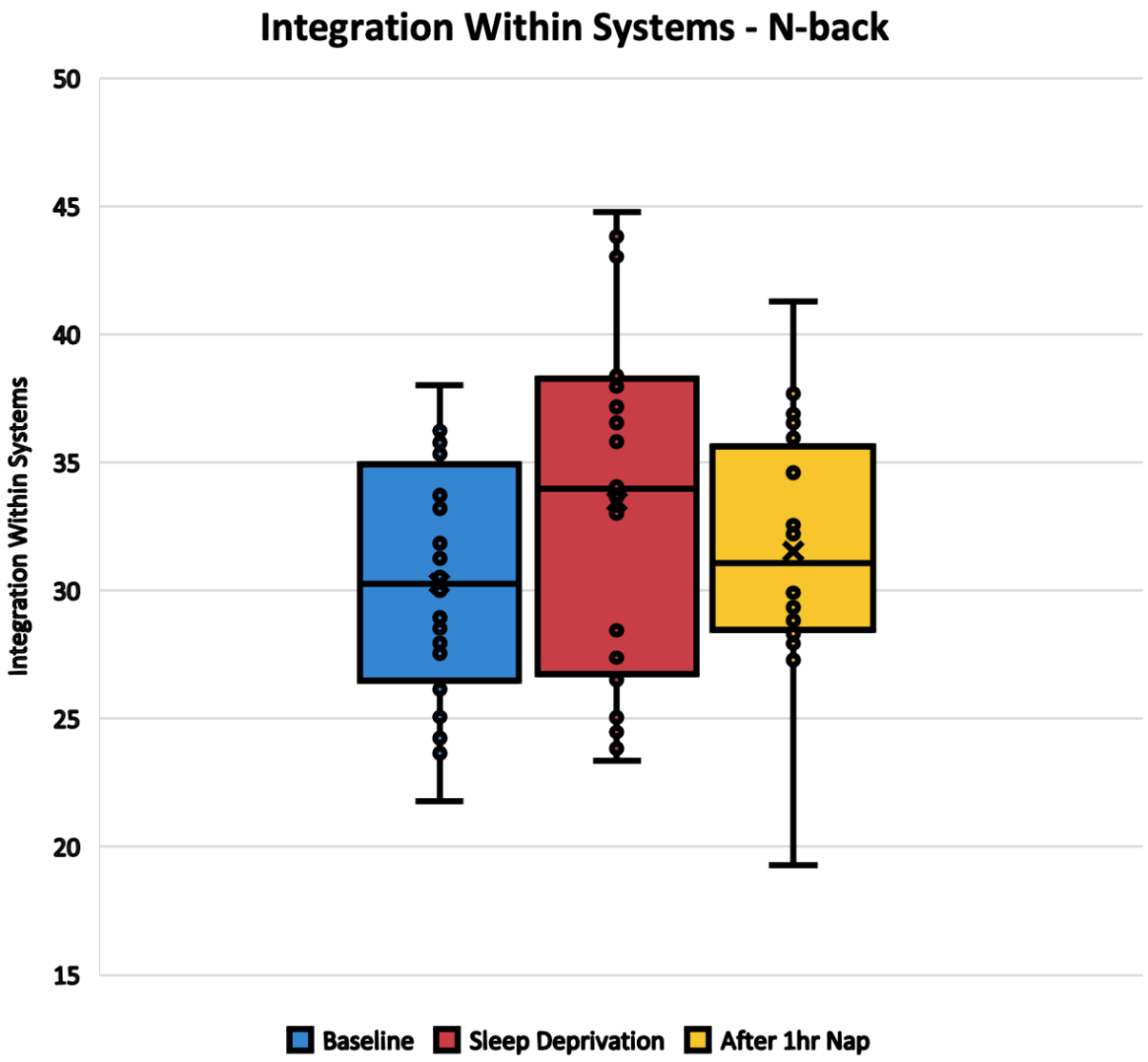
*Supplementary Figure 48. Within Systems Integration during MCT task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*



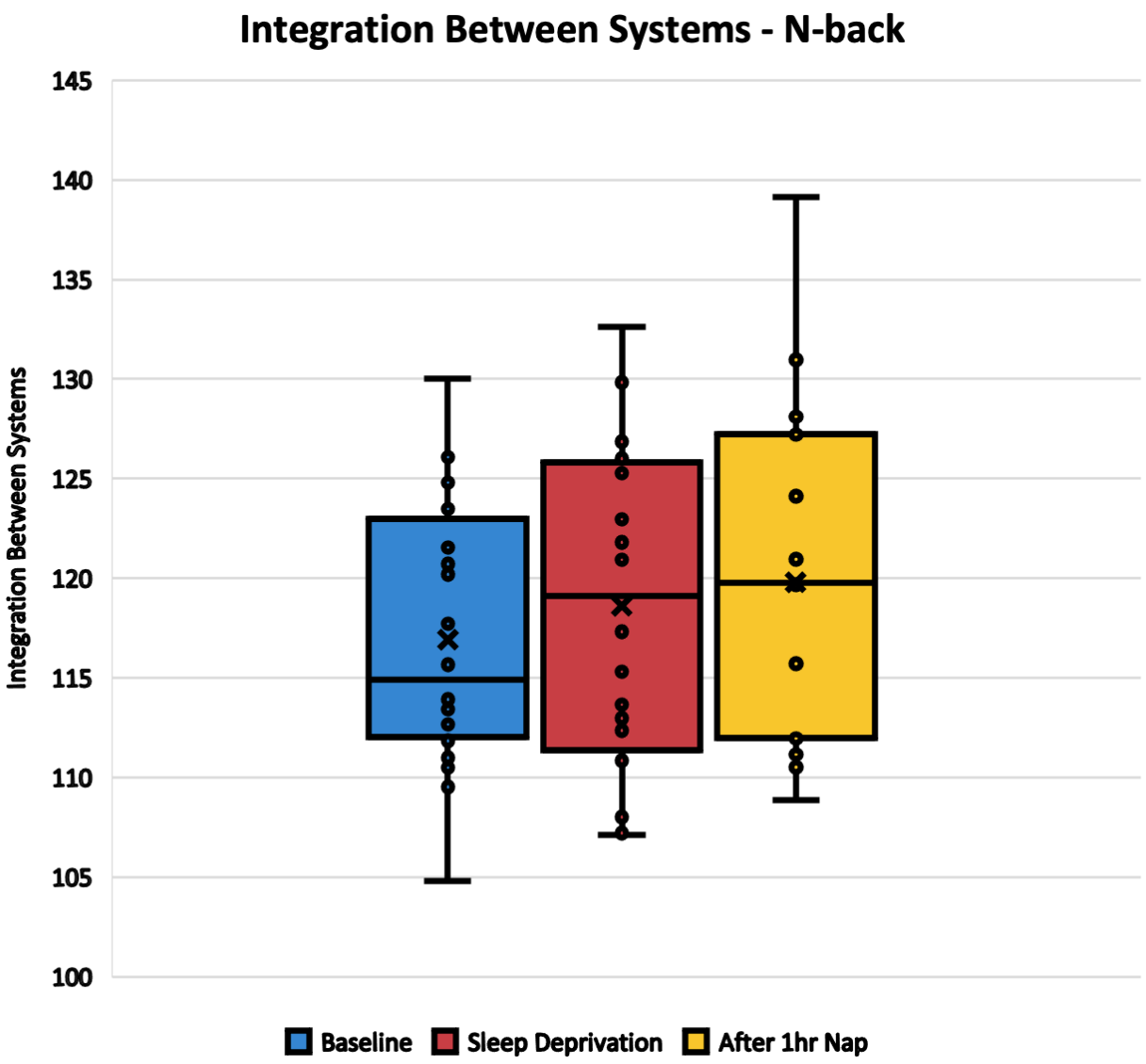
*Supplementary Figure 49. Between Systems Integration during MCT task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*



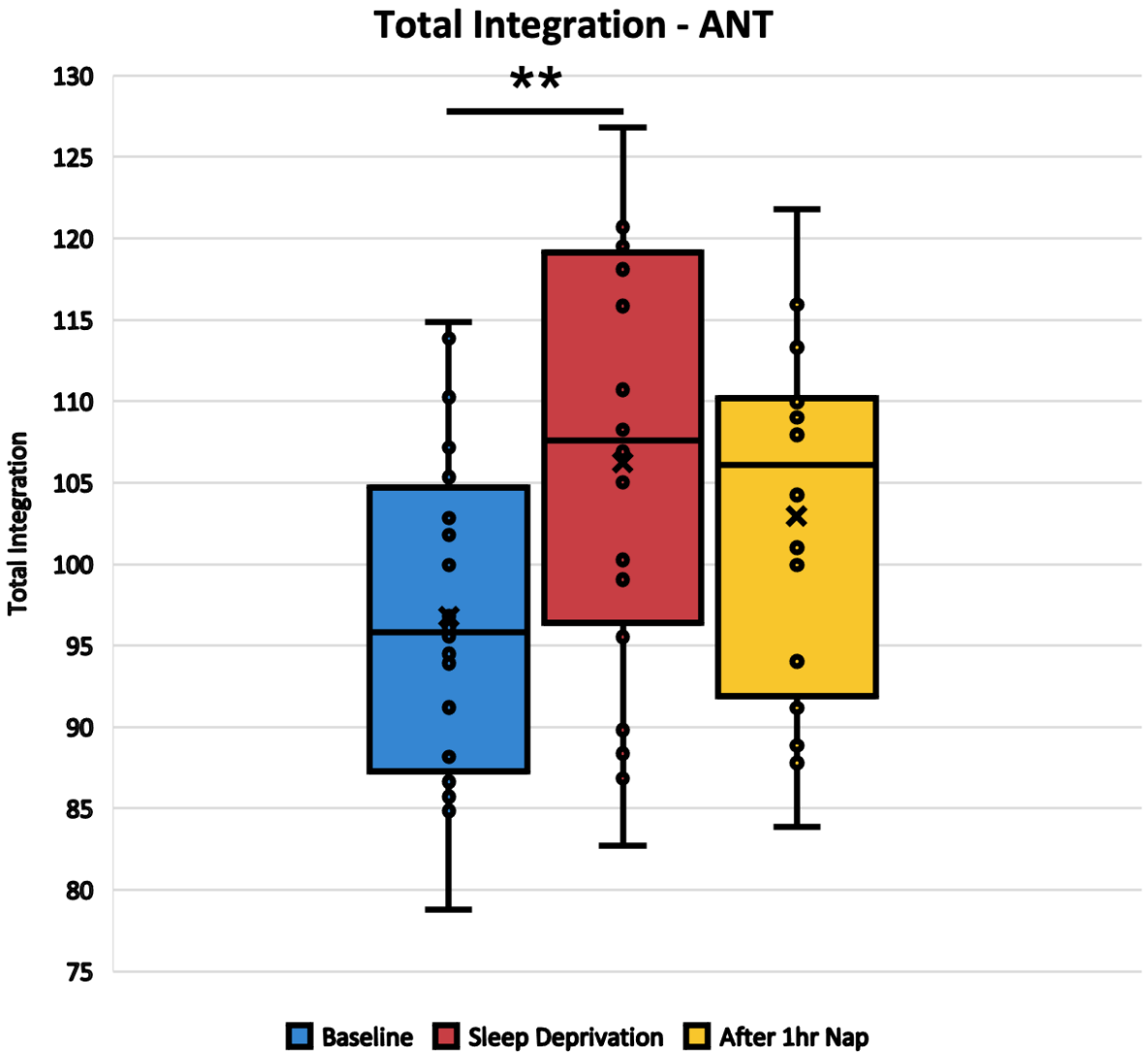
*Supplementary Figure 50. Total Integration during N-back task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*



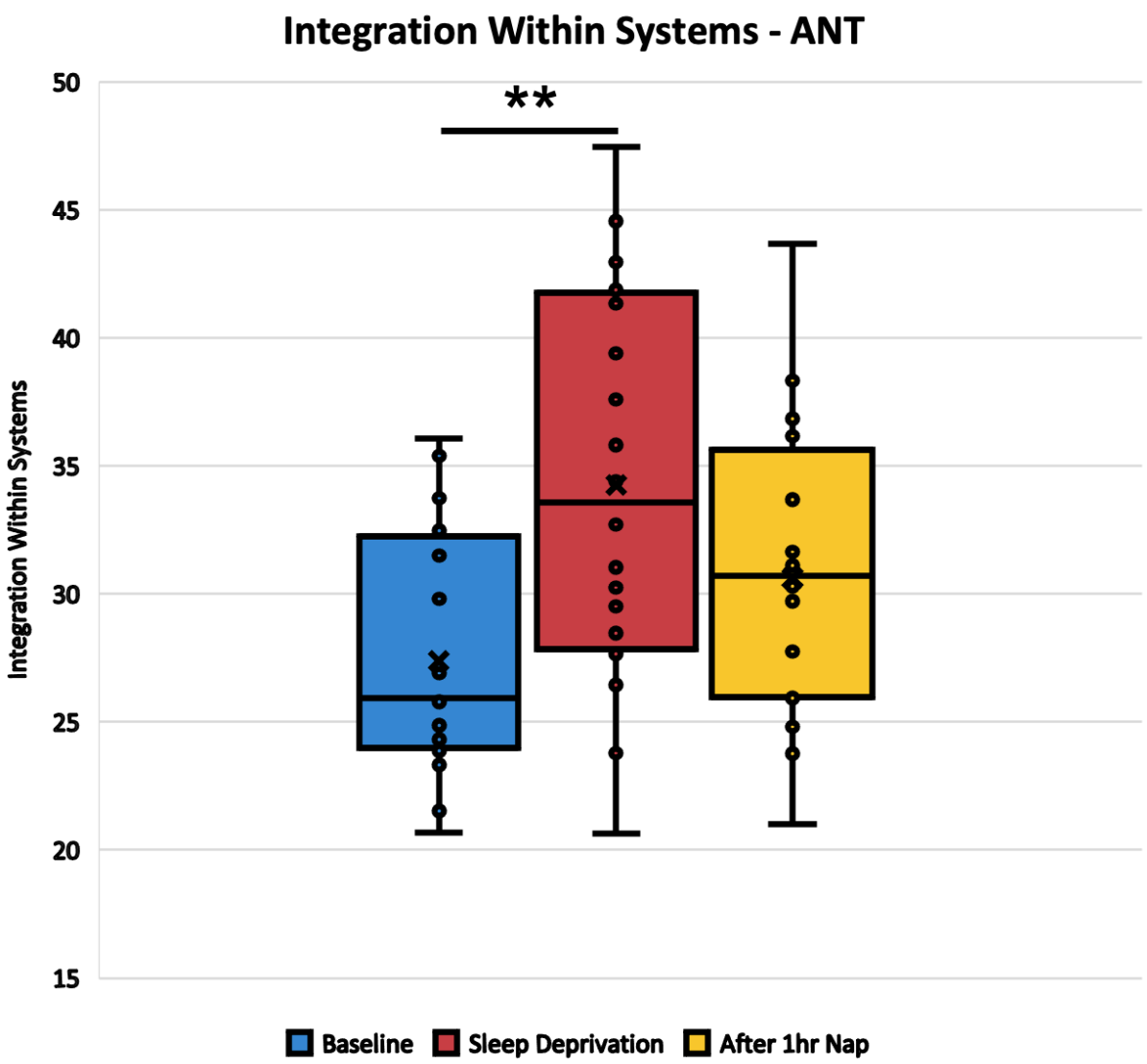
*Supplementary Figure 51. Within Systems Integration during N-back task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*



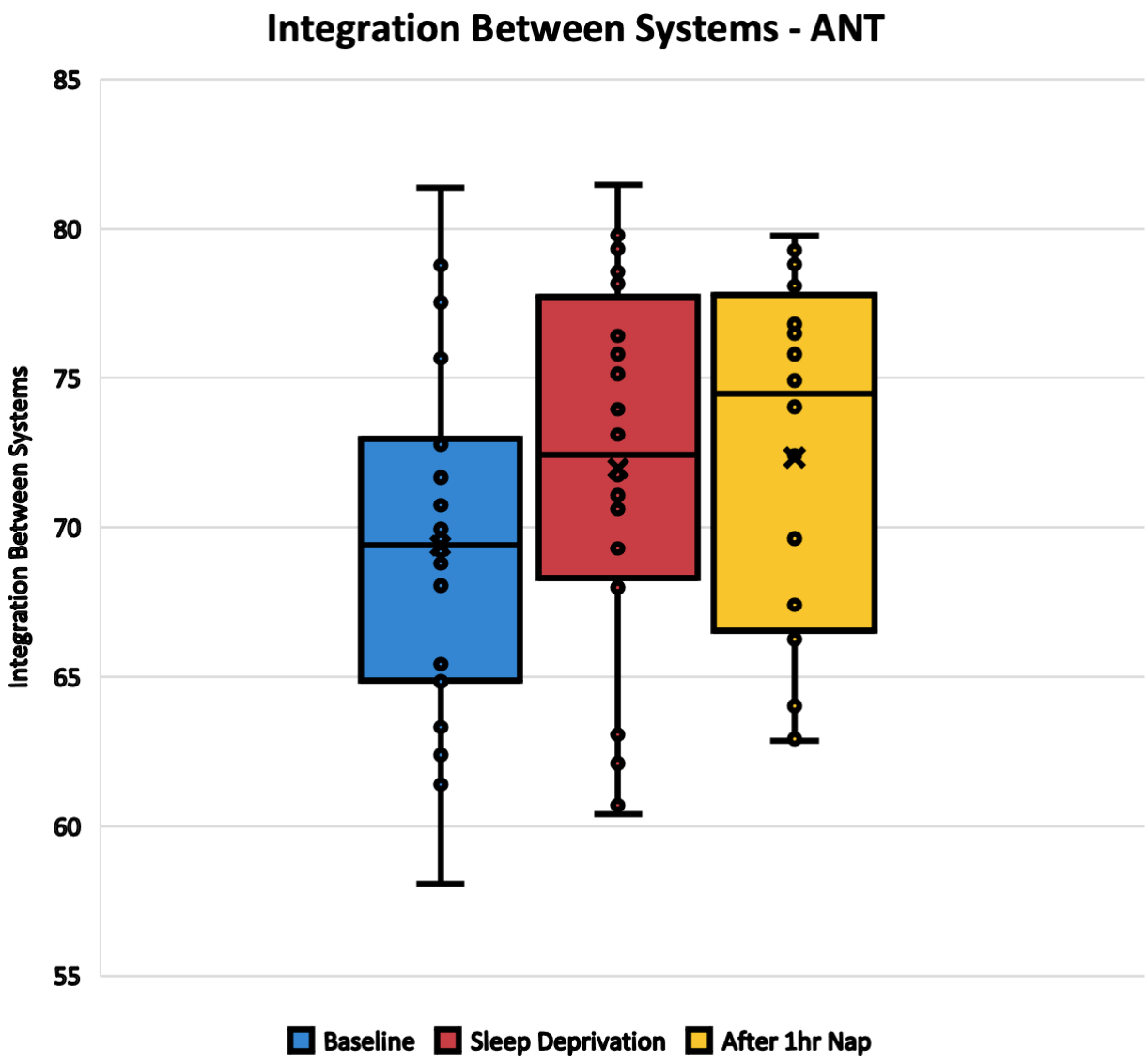
*Supplementary Figure 52. Between Systems Integration during N-back task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*



*Supplementary Figure 53. Total Integration during ANT task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*



*Supplementary Figure 54. Within Systems Integration during ANT task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*



*Supplementary Figure 55. Between Systems Integration during ANT task across 3 states (1=WR, 2=SD, 3=PRN). * = p<0.05; ** = p<0.001*