The Effect of Circadian Rhythms on BOLD Dynamics and Effective Connectivity

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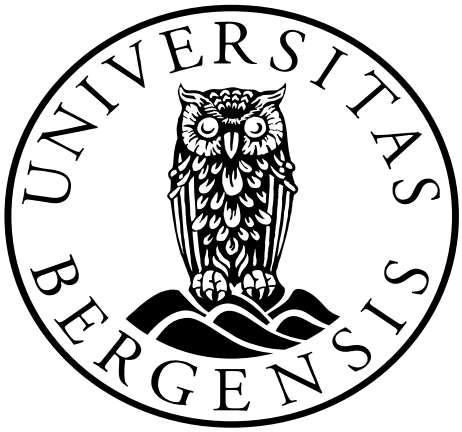

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Abstract

The field of psychology and functional neuroimaging is suffering from replication crisis. Low statistical power and validity of measures are an issue. Resting state functional and effective connectivity based on spontaneous BOLD fluctuations (>0.1Hz), which are relatively recent developments in neuroimaging lack consensus. These techniques can be used to extract large scale functional or effective connectivity networks and hemodynamic parameters describing the BOLD signal. Academic literature suggests that neuronal and hemodynamic activity throughout the day is affected by circadian rhythmicity. The current study aim is to investigate the effect of biological circadian rhythms on hemodynamic and effective connectivity parameters throughout the day. The cross spectral density dynamic causal modelling (DCM) was used to analyse the human connectome project (HCP) data distributed throughout the day. Hierarchical group-PEB found no support for changes in effective connectivity during the 09-21-hour span, whereas the hemodynamic parameters exhibited a significant circadian effect. The parameters describing the BOLD response amplitude, duration and elimination were varied on a circadian basis. The results indicate a change in relationship between neural activity and hemodynamic parameters that are reflected in the BOLD response.

Replication Crisis, Resting state fMRI, Circadian rhythms, Effective connectivity, BOLD

Sammendrag

Psykologisk felt og funksjonell hjerneavbildning har et replikasjonsproblem. Lav statistisk kraft og gyldighet av målinger er kjernen av problem. Hvilestatusfunksjonell og effektiv tilkobling basert på spontane fluktuasjoner i BOLD-signalet (> 0,1 Hz), som er en relativt nylig utviklet i hjerneavbildning, mangler konsensus. Disse teknikkene kan brukes til å trekke ut storskala funksjonelle eller effektive tilkoblingsnettverk og hemodynamiske parametere som beskriver BOLD-signalet. Akademisk litteratur antyder at nevron- og hemodynamisk aktivitet gjennom dagen påvirkes av døgnrytmer. Nåværende studiemål er å undersøke effekten av biologiske døgnrytmer rytmer på hemodynamiske og effektive tilkoblingsparametere gjennom dagen. Cross spectral density dynamic causal modelling (csdDCM) ble brukt til å analysere Human Connome Project (HCP) data distribuert gjennom dagen. Hierarkisk gruppe parametric empirical Bayes (PEB) fant ingen støtte for endringer i effektiv tilkobling i løpet av tidsrommet 09-21, mens de hemodynamiske parameterne viste en signifikant døgnrytme effekt. Parameterne som beskriver BOLD-responsamplitude, varighete og forfall varierte på basis av døgnrytmer. Resultatene indikerer en endring i forholdet mellom nevral aktivitet og hemodynamiske parametere som reflekteres i BOLD-responsen.

Preface

I participated in developing the project from the very beginning, we started with brainstorming ideas and hypothesis and got a small data sample to run a pilot study. I then collected additional data from the HCP, adjusted the scripts in collaboration with my main supervisor and performed the first and second level analysis.

I would like to thank the Re:State research group and its associates for their support of this study. I want to express my greatest gratitude to Karsten Specht and Janne Grønli for their supervision, support, and guidance during the course of this project. Lastly, I thank the Institute for Biological and Medical Psyhcology staff and Liucija Vaišvilaitė for their advice.

Table of Content

The field of psychology is suffering from irreplicable findings, where only 39% of research publications has been shown to provide replicable results (Collaboration, 2015). Studies utilizing neuroimaging techniques as method are no exception. The underlying issue of this replication rate is low statistical power in the original studies, that stems from small sample and effect sizes (Button et al., 2013; Ioannidis, 2005). Moreover, little consideration is given to inter- and intra- individual differences, that possibly negatively contributes to establishing true conclusions. Statistical power is crucial to draw valid conclusion from an experiment. Another important factor is the validity of the measure. Studies applying functional magnetic resonance imaging (fMRI) generally aim to study the cognitive processes performed in the brain. However, in the service of understanding psychological and neural processes, and the relationship between the two, the signal measured in fMRI is quite far away from the neuronal activity the method is aimed at studying.

One factors, not considered so far is natural, internal biological rhythms. One class of such rhythms is the circadian rhythm which influence time of day related variations of the participants neurobiology. There are circadian systematic changes in a myriad of parameters that influence neural activity and the signal measured by fMRI. Therefore, the aim of this thesis is to investigate the effect of circadian rhythms on neural activity and parameters influencing the measurement of this activity in resting state fMRI data. Any relationship between circadian processes, neural activity and the fMRI signal may provide a possible way to boost the validity and reliability of fMRI studies.

Biological Rhythms in The Brain

There is a long history of studying circadian rhythmicity of human and other species. The following section provides a brief history and introduces the terminology of rhythms, before discussing rhythms in biology, cognition and neuroimaging in depth.

History and Terminology of Biological Rhythms

All biological rhythms are the result of celestial bodies movement, i.e. the earth's rotation around its own axis, the moons orbital path around the earth and the earths movement around the sun. Rhythmicity in our environment has influenced the evolution of human species over the past 6-8 million years and has shaped the biology of our ancestors long before that (Smithsonian, 2018). One of the examples of rhythmicity driven cycles is the day/night cycle, which greatly affects the endogenous functions and behaviours of all species.

Jean-Jacques d'Ortous De Marian, a French astronomer, was among the first ones to describe circadian rhythmicity in early 18th century (De Mairan, 1729). De Marian observed that Mimosa plant maintained raising and lowering its leaves in isolation from light. This reported observation is one of the first evidence of endogenous circadian mechanisms.

Rhythmicity in humans and other species is largely categorized depending on the length of rhythm. Circadian rhythms (*circa* = around, *dies* = day) refers only to rhythms that oscillates on a 24 hour basis (Ungar & Halberg, 1962). However, there are several types of rhythms also present in organisms and in the human biology. Infradian rhythms are longer than 24h. Here the female menstrual cycle of 28 days is an example of a lunar rhythm (Baker & Driver, 2007). Examples of even longer rhythms influenced by the seasonal rhythms in the amount of daylight are melatonin secretion and male testosterone concentration and secretion patterns (Reinberg, Lagoguey, Chauffournier, & Cesselin, 1975; Wehr, 1997). Rhythms repeat themselves on a less than 24 hours are called ultradian rhythms, for instance the human sleep cycle that repeats itself in a 90 minute pattern during the main sleep period (Acharya U., Faust, Kannathal, Chua, & Laxminarayan, 2005). Interestingly, it has been reported that circadian rhythmicity in humans persist without exposure to natural light. A study by Aschoff and Wever observed the sleep-wake cycles of participants in light sealed chamber (J. Aschoff

& Wever, 1976). The authors discovered that after participants started to 'free run' and exhibited slightly longer circadian rhythmicity than 24h.

Light is the primary environmental cue - "zeitgeber" i.e. time giver that entrains (synchronizes) our endogenous rhythms with the exogenous environmental rhythms (Jürgen Aschoff, 1960; Pittendrigh, 1981). Secondary zeitgebers are temperature, food intake, social and physical activity. Each individual has a naturally occurring preference of sleep-wake cycle, that also affects the timing of cognitive performance, energy levels throughout the day and sleepiness. The variation in this cycle preference is called "chronotypes". The extreme ends of the phenotypical spectrum are known as "*larks*" and "*owls*", with only 0.2% of the population in the former category and 4.5% of the population in the latter category (Merrow, Spoelstra, & Roenneberg, 2005). The trait signature of *larks* is that they function best early in the morning while *owls* are at their most effective in the evening. The naturally occurring day – night shift (changes in light exposure) are detected in the retina, transmitted to the brain via the retinohypthalamic tract and processed in the suprachiasmatic nuclei (SCN). This structure is referred to as the "master clock of the brain", because it synchronizes all biological rhythms in the body and brain to a 24h rhythm.

As a result of evolutionary development both physiological and psychological factors vary on a circadian basis. Cognitive functions like processing speed, reasoning, visual search, physiological measures like blood pressure, heart rate and cortisol release are dependent on the individual circadian rhythmicity and has an effect on the signal captured by the magnetic resonance imaging (MRI) (M. Hastings, O'Neill, & Maywood, 2007; Keulers, Stiers, Nicolson, & Jolles, 2015; Monk, 2005; Natale, Alzani, & Cicogna, 2003). For example, two hours before natural awakening blood pressure starts to increase, boosting the myocardial tone and cortisol release (Krieger, Allen, Rizzo, & Krieger, 1971; Paschos & FitzGerald, 2010; Weitzman et al., 1971). Later throughout the day the cerebral blood flow velocity

increases, which highly correlates with cerebral blood flow (Conroy, Spielman, & Scott, 2005; Sorond, Hollenberg, Panych, & Fisher, 2010). As mentioned before, the suprachiasmatic nuclei (SCN) is one of the main structures involved in controlling circadian rhythmicity also affecting the decribed biological parameters. The molecular basis of the SCN will be discussed in detail in the following chapters (M. Hastings et al., 2007).

Biological Rhythms

Ronald Konopka and Seymour Benzer (1971) were the first to investigate the genetic foundation of circadian rhythms in the fruit fly "drosophila melanogaster". The duo discovered that mutations in the gene, now known as the "period" gene, in the X chromosome had significant effect on the circadian rhythmicity (Konopka & Benzer, 1971). These mutations caused either arrhythmic, shorter or prolonged activity periods. After the discovery of the "period" gene, further research investigated it in depth, establishing that it is a piece in a molecular system controlling circadian rhythm (Bargiello, Jackson, & Young, 1984; Zehring et al., 1984). The discovery and definition of the molecular processes that control the circadian rhythmicity earned Jeffrey C. Hall, Michael Rosbash and Michael W. Young the Nobel Prize in Physiology or Medicine in 2017 ('The Nobel Prize in Physiology or Medicine', 2017). The mechanisms behind the "molecular clock" is described as a transcription and translation negative feedback loop that takes place inside the cell nucleus and the cell cytoplasm. The transcription process starts with transcribing the genome that results in an inverted copy of the deoxyribonucleic acid (DNA) chain, called messenger ribonucleic acid (mRNA). Then the translation section starts when the mRNA moves to the cytoplasm of the cell/neuron where the proteins are created based on the original DNA sequence of nucleotides (a building block of DNA and RNA) (Komili & Silver, 2008; Rich &

Watson, 1954; Watson, Crick, I, & Crick, 1953). This process occurs in every cell of the human body.

The core clock genes involved in the process are CLOCK and BMAL1, which act as the activating section, where PER1, PER2, CRY1 and CRY2 are involved in encoding the deactivating sequence of the loop (Takahashi, 2017). The transcription translation negative feedback loop begins during the day by CLOCK and BMAL1 forming a macromolecular complex (heterodimer) and transferring through the nucleus membrane that initiates transcription of PER and CRY genes (Takahashi, 2017; Yoo et al., 2005; Zheng et al., 2001). PER and CRY proteins encoded by the PER and CRY genes form a complex in the cytoplasm that transfers to the cell nucleus where the PER and CRY complex compile and inhibit the transcription of their own and other genes by supressing CLOCK and BMAL1 function (Lee, Etchegaray, Cagampang, Loudon, & Reppert, 2001; Sato et al., 2006). The loop results in expression of mRNA peaks in the SCN, where PER1 peaks around 4 hours after waking, followed by PER2 and CRY1 peaks at approximately 8 hours after waking up. The BMAL1 peaks in antiphase to these in the subjective night around 16 hours into the cycle (Guilding & Piggins, 2007). The peak of protein expression is normally around 4-6 hours after the mRNA peak and is consistent in all cells.

Normally all genes are required for normal function of the loop, but in the mammalian forebrain NPAS2 can substitute CLOCK in initiating the transcription translation negative feedback loop, making the system more robust in the mammalian brain (Reick, 2001). NPAS2 can keep the circadian rhythms steady in the SCN, but not in peripheral tissue oscillators, indicating differences in central and peripheral mechanisms (DeBruyne, Weaver, & Reppert, 2007a, 2007b).

The Suprachiasmatic Nuclei. SCN synchronizes all peripheral output rhythms and is unique as the individual SCN neurons are autonomous rhythm generators, which maintain

their rhythm when isolated from the rest of the SCN network and can regain their rhythm even if suppressed for days (Welsh, Logothetis, Meister, & Reppert, 1995). The SCN consist of two nuclei located under the anterior part of the hypothalamus, above the optic chiasma and each consists of approximately 10 000 primarily GABAergic neurons (M. Hastings et al., 2007). In the SCN we can differentiate between the ventral "core" and the dorsal "shell" sections. The *core* functions as an input centre receiving information from the retino-hypothalamic tract axons and basal areas of the brainstem which are involved in entrainment, while the *shell* contains efferent neurons, which signal to brain areas that affect behaviour and other rhythmical processes in the body (Merrow et al., 2005; Reppert & Weaver, 2002). The *core* of the SCN consists mainly of neurons that contain gastrin releasing peptide (GRP) and vasoactive intestinal polypeptide (VIP), whereas arginine vasopressin (AVP) is dominant in the *shell* neurons (Welsh, Takahashi, & Kay, 2010). The structural integrity of the *core* is fundamental for maintaining function within the SCN, lesions of specific parts of the *core* disrupts circadian rhythms in locomotor activity, heart rate, body temperature, cortisol and melatonin secretion (Kriegsfeld, 2004; LeSauter & Silver, 1999).

Entrainment of the SCN is directly dependent on light exposure, by converting light to neural signals through transduction, a chemical reaction caused by the interaction of light and the photopigments in the photoreceptors of the eye (Kraft, Schneeweis, & Schnapf, 1993). The signal transmitted to SCN, was thought to be dependent on transduction by rods and cones and transmission by retinal ganglion cells. However, recently a new type of ganglion cell has been introduced - the intrinsically photosensitive retinal ganglion cells (ipRGCs). ipRGCs expresses the photopigment melanopsin, which in turn makes it intrinsically sensitive to light (Berson, 2002; Hattar, 2002). The photopigment melanopsin reacts mainly with light around 480 nm, which is in the blue end of the visible light frequency spectrum (Berson, 2002). The ipRGCs are involved in: nonvisual light processing, pupillary light reflex, sleep

and circadian rhythmicity. They primarily but limitedly project to the SCN (to other subcortical structures as well) (Schmidt, Chen, & Hattar, 2011). The rods/cone system contributes to nonvisual light processing and entrainment of the SCN through ipRGCs, which results in a more secure processing system. The presence of both melanopsin and the rod/cone system are not necessary for entrainment of the SCN, but the ipRGCs themselves are essential for transmission of neural signals to the SCN through the retino hypothalamic tract (RHT, which starts with an axonal bundle from the ipRGCs) (Freedman et al., 1999; Hattar et al., 2003; Panda, 2003, 2005; Schmidt et al., 2011).

Peripheral rhythms. Peripheral oscillatory mechanisms are present in cells and tissue throughout the mammalian body (Yoo et al., 2004). These peripheral clocks are controlled by the SCN and would be desynchronized without its input. Evidence from ablation and transplant studies provide evidence, that SCN is essential in synchronizing peripheral clocks. The results from ablation and transplant studies report that both hormonal and neuronal signals from the SCN play vital role in maintaining normal oscillatory function (Guo, Brewer, Champhekar, Harris, & Bittman, 2005; Silver, LeSauter, Tresco, & Lehman, 1996).

The efferent neuronal pathways from the SCN target mainly thalamic and hypothalamic areas. The paraventricular nucleus of the hypothalamus (PVN) transmit signals to the adrenal gland through endocrine, sympathetic and parasympathetic pathways (Dibner, Schibler, & Albrecht, 2010). Efferent projections from the SCN via the PVN influences sensitivity of the adrenal gland to adreno corticotropic hormone (ACTH) (Buijs et al., 1999; Kaneko, Hiroshige, Shinsako, & Dallman, 1980). In addition, SCN can initiate the HPA-axis (hypothalamus – pituitary – adrenal) cascade through direct connections with anterior pituitary gland neurons, and the HPT (hypothalamus – pituitary – thyroid) and HPG-axis (hypothalamus – pituitary – gonads) as well (Kalsbeek et al., 2006). The net effect of these pathways grants the SCN a great influence on the whole endocrine system.

Entrainment of peripheral rhythms. SCN regulates body temperature to entrain clocks in peripheral tissue, and temperature entrainment can by itself maintain peripheral circadian rhythms synchronized in the absence of neural stimulation (Brown, Zumbrunn, Fleury-Olela, Preitner, & Schibler, 2002; Buhr, Yoo, & Takahashi, 2010). Intrinsic communication in the SCN prevents it from being affected by temperature, allowing the SCN to remain in rhythm while resetting peripheral clocks. The changes in peripheral tissue might be driven through a transcriptional heat shock factor 1 (HSF1). HSF1 shows a circadian rhythm in the liver, and HSF1 inhibitors block the temperature initiated rhythm reset in peripheral tissue (Buhr et al., 2010; Reinke et al., 2008).

Food consumption is another important rhythmic factor that has a bidirectional relationship with circadian rhythmicity and the SCN. Academic literature reports a major shift (10h) in liver rhythm, when restricted feeding regime is introduced. However, after two days of feeding entrainment, the SCN remained phase-locked to the light-dark cycle (Stokkan, Yamazaki, Tei, Sakaki, & Menaker, 2001). Gene expression in the liver and heart show a robust circadian oscillation in 8-10% of the genes, these genes also show limited overlap between the two organs (Akhtar et al., 2002; Storch et al., 2002). Dorsomedial hypothalamus (DMH) is involved in food consumption and feeding related entrainment of the circadian system, via projections directly to orexin neurons in the lateral hypothalamus, this pathway is crucial for behavioral expression of food entrainment (Mieda, Williams, Richardson, Tanaka, & Yanagisawa, 2006). Orexin is a neurohormone released during sleep, and is expressed as mentioned in hypothalamic regions which promote appetite, where lack of orexin is associated with obesity (Funato et al., 2009).

Endocrine Rhythms. Several hormones show a repeated pattern of oscillation during the day, for example the steroid hormone cortisol which is released by the adrenal gland. Cortisol has a recognizable awakening rise in plasma concentration which peaks around 09:00

in the morning, declining slightly until midday, before it decreases further after lunch time (Kalsbeek et al., 2012; Weitzman et al., 1971). Glucocorticoids are released by the adrenal cortex, when stimulated by ACTH, which is released from the anterior pituitary gland under the hypothalamus (Dickmeis, 2009). SCN efferent neurons signal to PVN that releases CRH in the median eminence beginning the cascade from the pituitary, in addition SCN modulates adrenal gland sensitivity to ACTH through autonomic circuits (Dickmeis, 2009; Engeland & Arnhold, 2005). Cortisol plays an important role in energy metabolism and interacts with insulin, this may explain the early morning cortisol peak as a body's preparation for physical activity (Dallman et al., 1993).

Prolactin is released in a pulsatile manner every 2-3 h, with the bulk being released during REM sleep. Prolactin that mainly comes from the hypothalamus also seems to have a positive effect on REM sleep duration (Roky et al., 1995; Sassin, Frantz, Kapen, & Weitzman, 1973; Veldhuis, Johnson, Lizarralde, & Iranmanesh, 1992). Changes in seasonal photoperiod leads to adaptation of nocturnal melatonin secretion, where shorter days in winter increases and the longer days of summer decreases the nocturnal melatonin secretion (Wehr, 1991, 1997). During regular days a peak in melatonin secretion is observed around 03:00 – 04:00, but bright artificial light can suppress melatonin secretion and alter the peak of its secretion (Lewy, Wehr, Goodwin, Newsome, & Markey, 1980). Melatonin can be used to reset circadian rhythms after transatlantic flights, shift work and treating circadian disturbances in blind individuals (Arendt, Skene, Middleton, Lockley, & Deacon, 1997).

Time of day. It is plausible to reason that time of day has a likely effect on neuroimaging data, however one that could be easily controlled for. One parameter with a distinct daily variation is body temperature, which throughs around 04:00 (nadir) increasing during the day, but exhibits a 0.5 degree C dip in temperature after lunch time (Monk, 2005). This effect is called the "post lunch dip", it is not experienced by all individuals, changes in

cortisol levels and body temperature can be observed and the dip is associated with a decline in cognitive performance (Krieger et al., 1971; Monk, 2005; Natale et al., 2003). The post lunch dip occurs during the first hours after-noon, the effect may be influenced by food intake and sleep quality of the prior night (Lloyd, Green, & Rogers, 1994; Reyner, Wells, Mortlock, & Horne, 2012; Wells et al., 1996).

Time of day also affect glucose response to meals. A doubling response to identical meals has been reported when comparing same food consumption in the evening compared to morning (E. Van Cauter, Shapiro, Tillil, & Polonsky, 1992). Catecholamines (adrenaline, noradrenaline and dopamine), cortisol and growth hormone (GH) can increase the concentration levels of glucose in blood. The increase occurs through stimulating local glucose production or by inhibiting tissue uptake of glucose (Polonsky, Given, & Van Cauter, 1988; Eve Van Cauter, Polonsky, & Scheen, 1997).

Disruption of circadian rhythm seems to have an effect on the metabolic system, resulting in increased chance of cardiovascular diseases, obesity and diabetes risk (Green, Takahashi, & Bass, 2008). Lack of sleep and/or poor sleep quality over prolonged periods of time is associated with increased risk of developing diabetes, decreased energy use, increased appetite and changes in glucose metabolism. Circadian rhythms also influence glucose control, inflammation, fluid balance and vascular reactivity. Glucose metabolism levels are highly important in managing diabetes (Green et al., 2008; M. H. Hastings, Reddy, & Maywood, 2003). Literature suggests that there is a relationship between disease and poor sleep quality over prolonged periods of time (Knutson, Spiegel, Penev, & Van Cauter, 2007). In addition, psychological disorders as well as sleep disorders have been shown to correlate with alterations in SCN neural population and function (Takahashi, Hong, Ko, & McDearmon, 2008; Zhou et al., 2001).

Adenosine and Caffeine. Adenosine monophosphate is a byproduct of metabolic (glycolysis) and transportation processes. It accumulates in the extracellular space and exerts a persistent inhibitory effect on neural activity (Burnstock, 2007; Dunwiddie & Masino, 2001). Adenosine has a clear circadian rhythm, with a gradual build-up during the day and regression back to baseline during sleep (Landolt, 2008; Porkka-Heiskanen, Alanko, Kalinchuk, & Stenberg, 2002; Ribeiro & Sebastião, 2010). Overall, adenosine has a negative effect on cognitive performance and alertness (Lorist & Tops, 2003). These effects are the most likely reason why caffeine is the world's most frequently used psychoactive drug (Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999). Caffeine is an adenosine antagonist, hence the consumption of caffeine results in a generally excitatory effect on neural tissue by relieving the tonic inhibition of adenosine, which in turn increases alertness and cognitive function (Dunwiddie & Masino, 2001; Ribeiro & Sebastião, 2010). Caffeine can bind to all classes of adenosine receptors, but has a low binding rate (affinity) and is not specialized for any of the receptor types (Daly, 2007). Increases in neural activity over time leads to increased extracellular adenosine concentration upregulating the threshold for further activation in the area and can induce local energy depletion (Landolt, 2008; Porkka-Heiskanen et al., 2002).

Cognitive Rhythms

Circadian rhythmicity also affects higher cognitive functions and performance. Studies have shown that there is an observed decrease in attentional performance, variability in episodic memory recall and performance on logical reasoning tasks after total sleep deprivation (Clarisse, Floc'h, Kindelberger, & Feunteun, 2010; Drummond, Brown, Salamat, & Gillin, 2004; Hasher, Chung, May, & Foong, 2002). To assess the influence of circadian rhythm on cognitive performance curves, research has established routines to remove masking

effects, extracting the pure circadian effect without any noise (Blatter & Cajochen, 2007). An example is the constant routine, where participants are isolated from all time ques and every other entraining que is kept at a constant rate. However, the issue with these kind of protocols is that they place the research subject in a highly artificial condition, which might undermine the validity of transferring knowledge from the findings to real life conditions (Vanin et al., 2012). The constant routine find influences of circadian rhythms on our abilities to perform on tasks during the day, and a correlation with biological measures, but those factors may lost to noise normal conditions (Carrier & Monk, 2000). A fairly established decrease in cognitive performance is observed just after lunchtime (Monk, 2005), this decrease is called the "post lunch dip". It has been shown that the "post lunch dip" effect might be increased by consuming a relatively heavy lunch, suggesting the influence of food intake (Blake, 1967; Craig, Baer, & Diekmann, 1981). However, some studies have struggled to replicate the "post lunch dip" findings, reporting gender, personality and especially chronotype effects on the cognitive performance. However, it is suggested that differences in cognitive performance of larks and owls exhibit an inverted relationship curve (Christie & McBrearty, 1979; Horne, Brass, & Petitt, 1980). A more recent study found that solving insight based problems at their "non optimal" time of day increased performance, as opposed to analytical problems, this is presumably because of different cognitive processes involved in the insight and analytical tasks, where time of day seems to have a different effect on them (Wieth & Zacks, 2011). A fairly common tool to asses cognitive alertness is reaction times, which has been shown to be highly sensitive to circadian rhythmicity and sleep loss (Dinges & Powell, 1985). Usually the psychomotor vigilance task (PVT) is used to asses alertness during different time of day. The optimal performance on PVT relies on efficient activation of frontoparietal attention network and motor areas, whereas after sleep deprivation the mentioned areas exhibit decreased activation and reaction times are lower (Drummond et al., 2005).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive brain imaging technique that relies on the chemical composition of the human body, i.e. it largely consists of water, fat, and hydrogen (^{1}H) in variable amounts depending on the type of tissue. All protons have a property called spin (Uhlenbeck & Goudsmit, 1926). The ^{1}H, spin orientation is normally scattered in random directions, however when the ^{1}H protons are exposed to a powerful electromagnetic field as in an MRI scanner the proton spin orientation is aligned around the direction of the main magnetic field (B_0). The strength of B_0 determines the frequency of the protons spin (Larmor frequency), for a scanner with a 3T magnetic field the Larmor frequency of the ^{1}H proton is 127,74 MHz (Levitt & Southampton, 2001). The MRI scanner has gradient coils to manipulate the B_0 along the x, y and z axis. The gradient coils facilitate the spatial location by determining the Larmor frequency of protons in a selected slice of the brain in a predictable manner, changing the net magnetization (M) and allowing for targeting the exact slices of the brain.

Applying a radiofrequency field (B_1) of equal frequency as the Larmor frequency of ^{1}H protons in a selected area perpendicularly to B_0 causes the protons to absorb energy and a certain degree flip in M. The B_1 manipulation of targeted ^{1}H protons in a brain slice is brief, relaxation of ^{1}H protons to B_0 follows. The relaxation of ^{1}H protons to B_0 releases the absorbed energy and normalizes M. Net M relaxation happens in the longitudinal and transversal plane simultaneously. The longitudinal relaxation time (T1) is longer than the transversal relaxation time (T2), both effects depend on the tissue environment ^{1}H protons are located in. The T2 effect is defined as a time constant from natural molecular interactions, but the true transversal decay (T2*) is faster than the expected T2 due to the inhomogeneities in the magnetic field caused by vascular activity and/or an unstable magnetic field (Levitt & Southampton, 2001).

Net M relaxation difference is dependent on the type tissue it is utilized to, i.e. structural images of the brain, bone, fat, grey matter, white matter and cerebrospinal fluid (CSF) all have distinct relaxation times (Wansapura, Holland, Dunn, & Ball, 1999). The signal is manipulated by the gradient coils or an additional B_1 pulse, which is then detected by a receiver coil as it echoes or produces free induction decay (FID). The B_1 and/or gradient manipulations of longitudinal and transversal magnetization is specified to "weight" the T1 or T2 effects generating structural images focused on different parameters. The specification of this weighting, B_1, and gradient manipulation is known as a "pulse sequence". Pulse sequences can be grouped by their weighting, for instance, diffusion weighted imaging (DWI) generates image contrasts based on the random motion of water molecules (Brownian motion), highlighting areas with limited water molecule movement such as tumours (Bammer, 2003). An extension of DWI is diffusion tensor imaging (DTI), which is also based on the movement of water molecules (Brownian motion), but applied to measure tracts connecting grey and white matter in the brain (Bihan et al., 2001).

The first studies to measure an approximation of brain activity measured regional cerebral blood flow (rCBF) with positron emission tomography (PET), the a disadvantage of this method is the need to injecting the participant with a radioactive agent to generate images (P. T. Fox & Raichle, 1984; Frackowiak, Lenzi, Jones, & Heather, 1980). Neural activity was first detectable with MRI through dynamic susceptibility contrast (DSC) MRI, comparing V1 images before and after subjects were injected with gadolinium bolus while they viewed a flashing checkerboard pattern (Belliveau et al., 1991). Administration of contrast agents to detect neural activation was necessary until Seij Ogawa and colleagues developed a method (pulse sequence, gradient echo imaging) to detect and emphasize the Blood Oxygen Level Dependent (BOLD) contrast linking vascular changes with true transverse relaxation time (T2*) removing the need for contrast agents in functional MRI (S. Ogawa et al., 1992).

The brain constitutes only 2% of total human body mass while consuming around 20% of the total oxygen consumption (R. G. Shulman, Rothman, Behar, & Hyder, 2004). It has been established that neural activity has a metabolic demand, hence requires a large amount of oxygen. Oxygen molecules in the blood are carried by haemoglobin. Depending on whether the haemoglobin is carrying oxygen or not, it exhibits different magnetic properties, i.e. oxy-carrying haemoglobin is non-magnetic while deoxygenated haemoglobin is paramagnetic (Pauling & Coryell, 1936). Neural activity consumes oxygen at a higher rate, hence increasing local deoxyhaemoglobin concentration, this in turn affects the proton signal from water molecules in and around the blood vessels (BOLD contrast) (Seiji Ogawa, Lee, Nayak, & Glynn, 1990). The effect of deoxyhaemoglobin accelerates transversal magnetization dephasing (T2*) generating intensity contrasts in the MRI images (S. Ogawa, Lee, Kay, & Tank, 1990). The BOLD response exhibits an initial dip in signal intensity due to relative increase in deoxyhaemoglobin levels described above, the rCBF then overcompensates increasing the ratio of local oxyhaemoglobin resulting in a more stable magnetic environment and slower dephasing of transversal magnetization (T2*) boosting the BOLD signal (S. Ogawa et al., 1992). The dynamics of the BOLD response are explained by the balloon model taking into account the CBF, cerebral metabolic rate of oxygen ($CMRO_2$), cerebral blood volume (CBV) and neural response to the stimuli (Buxton, 2012; Buxton, Uludağ, Dubowitz, & Liu, 2004; Buxton, Wong, & Frank, 1998). By mapping the BOLD contrast in real time one can observe the changes in neural activity in the brain.

The BOLD contrast initiated an exponential increase in task based functional MRI (fMIR) research by allowing researchers to map cognitive functions to brain areas. Task based fMRI has been applied to investigate psychological diseases and help plan brain surgeries (Poldrack et al., 2013; Sunaert, 2006). Task activations is estimated to only increase energy consumption by 0.5 – 1%, while intrinsic neuronal communication and supporting structures

consume around 60 – 80% of the brains total energy expenditure (Raichle, 2010; Raichle & Mintun, 2006). A significant portion of the neuronal activity consuming large amounts of energy fluctuates in a frequency range below 0.1 Hz. These spontaneous fluctuations in the fMRI BOLD signal exhibit correlations in activity within regions responding to similar tasks (Biswal, Yetkin, Haughton, & Hyde, 1995). The initial observation by Biswal and colleagues was made in contralateral motor-cortices, where low frequency fluctuations in the BOLD signal have been verified to be caused by neural activity and can be observed in electroencephalogram (EEG) and intracranial electrocortography (ECoG) measurements supporting this (Biswal, 2012; Biswal, Deyoe, & Hyde, 1996; Biswal, Hudetz, Yetkin, Haughton, & Hyde, 1997; He, Snyder, Zempel, Smyth, & Raichle, 2008; Nir et al., 2008). Studies investigating low frequency fluctuations of the BOLD signal typically use a resting state fMRI (rs-fMRI) protocol. During the rs-fMRI the participants are instructed to lie awake in the scanner with their eyes open/closed/fixated on the fixation cross until the scan is completed.

Connectivity in The Brain

The human brain consists of roughly 85 billion neurons that each have thousands of synapses (Azevedo et al., 2009; Hawkins & Ahmad, 2016; Herculano-Houzel, 2009). The number of neuronal and nonneuronal cells in the human brain is relative to the whole body weight and size (Herculano-Houzel, 2009). There are three measures of connectivity in the human brain: structural, functional and effective connectivity. The structural connectome of the human brain would be similar to mapping the human genome, but instead of 2.91 billion base pairs we have around 85 billion neurons and up to 100 000 synapses per neuron to account for (Azevedo et al., 2009; Sporns, Tononi, & Kötter, 2005; Venter et al., 2001). Structural brain connectivity is recorded by mapping white matter fibre tracts and grey matter connections with DWI, T1 and T2 weighted imaging (Bastiani, Shah, Goebel, & Roebroeck,

2012). And finally, functional brain connectivity is defined as: ”The temporal correlation of a neurophysiological index measure measured in different brain areas” (K. J. Friston, Frith, Liddle, & Frackowiak, 1993). Functional connectivity and structural connectivity does not have a clearly defined relationship, some studies show that location, number and length of white matter structural tracts can be detected from functional connectivity or used to infer functional connectivity (Hermundstad et al., 2013; van den Heuvel & Hulshoff Pol, 2010; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). However, even though functional connectivity may reflect to some degree the underlying structural connectivity, the relationship between the two is complex, nonlinear and should not be used as a reliable estimate (Sporns, 2011).

A problematic aspect of structural and functional connectivity measures is rooted in their correlational nature, the connection and/or activation is reflected, however determining the causality of signalling is not possible. Effective connectivity is a recently reintroduced measure of brain connectivity, defined by Karl J. Friston. A significant advantage of this technique is that it allows to capture the directionality of connectivity between regions in the brain (Karl J. Friston, 2011).

The Human Connectome Project (HCP) is an initiative introduced to map the human brain. It offers a large sample of data, that can be accessed by researchers worldwide. Up to date there has been a vast number of publications, that examined the brain connectivity data from the HCP. Two of the results worth mentioned briefly, taking into account the purposes of the present project. For example, there are reported relatively large differences between genders in the structural connectome during development and differences in intra- and inter-hemispheric connectivity (Ingalhalikar et al., 2014). However, the study has been criticized for making too strong conclusions based on their data and not providing a nuanced view of the results (Joel & Tarrasch, 2014). Another study to highlight, illustrates how brain states

can be used to manipulate individual differences in functional connectivity to be more or less distinct based on analysis of task vs rest conditions (Finn et al., 2017).

Analysis of Connectivity data

There are several methodologies developed to date for analysing rs-fMRI data, to name a few: seed-based analysis, independent component analysis (ICA), and dynamic causal modelling (DMC) (Beckmann Christian F, DeLuca Marilena, Devlin Joseph T, & Smith Stephen M, 2005; Biswal et al., 1995; K. J. Friston, Kahan, Biswal, & Razi, 2014). Seed-based analysis is a hypothesis driven approach, which requires a predefined region of interest (ROI). The selected region of interest is then used to calculate correlations within the timeseries with one, multiple or all other regions in the brain. ICA is a data driven approach, where a designed algorithm is used to determine the most independent networks based in the timeseries and the number of networks requested (a good number can be estimated through a principal component analysis (PCA)) (Myoung Soo Park, Jin Hee Na, & Jin Young Choi, 2005). DCM requires a ROI, but is a data driven analysis that in addition to generating an effective connectivity measurement estimates the hemodynamic parameters that are generated based on the observed timeseries incorporating the balloon model (Buxton et al., 2004; K. J. Friston et al., 2014).

The seed-based analysis and ICA generate a functional connectivity measure. The functional connectivity measure is based on the notion that two regions work together on maintaining the same or similar function, however it does not make any inference on the directionality of relationship between the two regions. Studies indicate that there is a relationship between structural and functional connectivity, but two regions are not required to be structurally connected to be functionally connected or vice versa (Greicius, Supekar,

Menon, & Dougherty, 2009; Guye, Bettus, Bartolomei, & Cozzone, 2010; Honey et al., 2009).

DCM on the other hand, extracts effective connectivity from neuroimaging data, which estimates the effect of one region on the other, hence it is an informed analysis of the causal direction or influence from one region to another (K. J. Friston, Harrison, & Penny, 2003; K. J. Friston et al., 2014). DCM can be used with EEG, MEG, task-related and resting state fMRI data (K. J. Friston et al., 2003, 2014; Kiebel, Garrido, Moran, & Friston, 2008).The goal of using DCM is to model interactions between cortical neural populations and use that measure to draw informed conclusions about the coupling of neural regions. Bayesian framework is incorporated for examining non-linear relationship between distal brain regions to provide a deterministic value in the input-state-output system dynamic (K. J. Friston et al., 2003). DCM for task and resting state fMRI examines observed functional connectivity between regions, with an attempt to best explain the connectivity with hidden neural states (K. J. Friston et al., 2014).

Intrinsic connectivity networks

Intrinsic connectivity network/networks (ICN) are defined as a pattern of several large-scale networks that are simultaneously active at rest. The evidence of ICNs are provided by a number of studies using fMRI and PET data (Allen et al., 2011; Damoiseaux et al., 2006; Laird et al., 2011; Smith et al., 2009). There are three large scale brain networks, namely the Default Mode Network (DMN), Salience Network (SN), and Central Executive Network (CEN) that are theorized to be core for cognition and normal brain function (Bressler & Menon, 2010; Menon, 2011).

Default mode network. Shortly after the discovery of the resting-state functional connectivity, it was observed that there is a specific set of regions with lower response to task

condition in comparison to the control condition (rest). The first working definition for this phenomena was called “deactivations” to reflect the low BOLD response in task specific setting (Shulman et al., 1997). As the field of functional connectivity progressed, the “deactivations” were re-defined and led to the discovery of the Default Mode Network (DMN) (Raichle et al., 2001). The DMN is a set of brain regions that exhibits deactivation during task performance but is active during rest. DMN is a large-scale brain network that includes the following regions: posterior cingulate cortex, left and right inferior parietal cortex, dorsomedial prefrontal cortex, ventromedial prefrontal cortex, left inferior temporal gyrus, left lateral inferior frontal cortex, the medial Brodmann areas 10, 9, 8 and 32 (Raichle et al., 2001a). Brodmann area 10, 9 and 8 are in the medial frontal and prefrontal cortical regions, while Brodmann area 32 is the dorsal anterior section of the cingulate region and is connected to the former areas. The three main subareas of DMN are as follows: ventromedial prefrontal cortex (VMPFC), dorsomedial prefrontal cortex (DMPFC) and the posterior cingulate cortex (PCC) (Raichle, 2015).

The exact function of the DMN is yet unclear, but research has established that it is related to self-referential thought, emotional processing and recollection of prior experiences (Esposito et al., 2009; Raichle et al., 2001b). In addition, the DMN seems to play an important role in making simple automatic predictions based on previous memories and/or experiences (Vatansever, Menon, & Stamatakis, 2017). Functional connectivity within the DMN is affected decreased when an external cognitive demand is introduced, i.e. a precise cognitive task is performed (Gui et al., 2015). Academic literature to data, suggest that aging, neurodegenerative and psychological diseases affects or disrupts the resting state functional connectivity within the DMN.

Central Executive Network. The central executive network (CEN) is another intrinsically connected network, which is theorized to contribute to managing cognitive

resources such as working memory, attention, executive function and response inhibition (Bressler & Menon, 2010). The primary nodes of CEN are located in dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC) (Bressler & Menon, 2010; Habas et al., 2009; Seeley et al., 2007). Executive function is an umbrella term that refers to abilities such as goal formation, planning, decision-making, even though, there are slight variations in the definition of executive function within the scientific literature, the mentioned abilities reflect the core function of CEN. (Jurado & Rosselli, 2007). High functional connectivity within CEN has been associated with stronger performance in executive tasks (Seeley et al., 2007). A large part of the neocerebellum also contribute to the function of CEN, assisting in working memory and integration of information through cortico-cerebellar loops (Habas et al., 2009). Several disorders have been associated with altered functional connectivity of the CEN, such as: borderline personality disorder (decreased functional connectivity within CEN), schizophrenia (increased functional connectivity between CEN and DMN), and alcohol use disorder (decreased functional connectivity within CEN in the left hemisphere) (Doll et al., 2013; Manoliu et al., 2014; Weiland et al., 2014; Woodward, Rogers, & Heckers, 2011). Deficits in the CEN can arise from weak intra network connectivity, atypical extrinsic connectivity or defective contact with salient task-relevant stimuli (Menon, 2011). Activity in CEN is associated with response to transcranial magnetic stimulation (TMS) in treatment for depression (Liston et al., 2014).

Salience network. The network consisting of insula and the anterior cingulate cortex (ACC) is often called “The salience network” (SN). Insula participates in: bottom up detection of salient events, switching between networks, allocating attention and memory resources to salient stimuli, posterior to anterior modulation of autonomic reaction to salient stimuli and access to the motor system through strong functional connectivity with ACC

(Menon & Uddin, 2010). In addition, insula is thought to be involved in self-perception, interoception and self-awareness (Craig, 2002, 2009).

The SN has a mediatory role in switching between DMN and CEN and adjusting functional connectivity patters in response to different cognitive circumstances (M. D. Fox et al., 2005). The right anterior insular cortex plays an essential and causal role in switching between activating and deactivating respectively CEN and DMN (Sridharan, Levitin, & Menon, 2008). The right anterior insular cortex (AI) is suggested to play a coordinating role in the dynamic relationship between DMN and CEN. Activity in the right anterior insula has also been observed when participants are presented with cues for switching from rest to task conditions (Sidlauskaite et al., 2014). Evidence from studies using event related potentials in combination with fMRI indicate a modulating/top-down role of the anterior cingulate cortex (ACC) of sensory processing (Crottaz-Herbette & Menon, 2006). In addition, ACC connects the salience network to the supplementary motor cortex and midcingulate cortex, promoting response selection and motor responses (Paus, 2001; Rudebeck et al., 2008). Functional connectivity varies systematically from the rostral to the caudal section of ACC, extreme caudal regions correlated negatively with regions of the DMN (vmPFC and PCC specifically) and exhibit a positive correlation with the motor cortex (Margulies et al., 2007).

Biological Rhythms in Neuroimaging

Few studies to date have addressed the effect of circadian rhythmicity and/or time of day on spontaneous fluctuations in the BOLD signal.

Biological Rhythms in fMRI

The few published research articles investigating the relationship between circadian rhythms and functional connectivity in spontaneous BOLD fluctuations report contradicting results. One study focusing on functional connectivity in DMN and CEN reports, that FC in

the DMN gradually decreases over the course of the day specially in DMN subunits including mPFC, PCC and IPC while FC in CEN maintained stable during the day (Blautzik et al., 2013). These findings are partly supported by another study, which investigated the magnitude of cerebral blood flow (CBF) reduction during the day and FC in the DMN. The authors report, that there was a consistent decrease in DMN functional connectivity, particularly PCC, mPFC and IPL from DMN and ACC from SN exhibited reduced FC and CBF in the afternoon when compared to the morning session (Hodkinson et al., 2014). In contrast, Shannon and colleagues 2013 only found selective changes in functional connectivity throughout the day, which were observed in the medial temporal lobes, however the authors do not report any variation in metabolism or functional connectivity within the DMN when comparing morning and evening scanning sessions. On the other hand, literature focusing on early and late chronotypes report a differences between the groups in the DMN functional connectivity and throughout the day (Facer-Childs, Campos, Middleton, Skene, & Bagshaw, 2019).

There are several explanations for the individual differences in functional connectivity. Some studies indicate that the more demanding states during scanning produce elevated individual differences in FC and that CEN activity is highly dependent on the state producing increased individual differences (Finn et al., 2017; Geerligs, Rubinov, Cam-Can, & Henson, 2015; Shah, Cramer, Ferguson, Birn, & Anderson, 2016).

Plasma concentration of cortisol influences the amplitude of the BOLD signal negatively in some brain regions(Keulers et al., 2015; Lovallo, Robinson, Glahn, & Fox, 2010). Cortisol levels tend to increase under stressful conditions, however it does exabit a circadian variation as well, which suggests that it should be considered when performing fMRI scans.

A series of experiments have investigated the effect of caffeine on the BOLD contrast and spontaneous fluctuations of the BOLD signal. Task fMRI studies found that the initial dip

in the BOLD signal is reduced after ingesting caffeine equivalent to two cups of coffee (Behzadi & Liu, 2006). Caffeine also decreases the coupling between CBF and $CMRO_2$, and reduces total CBF (Cameron, Modell, & Hariharan, 1990; Chen & Parrish, 2009). In addition to that, caffeine lowers the cerebral perfusion by blocking neurovascular adenosine receptors hence affecting the BOLD amplitude depending on individual level of daily caffeine consumption (Laurienti et al., 2002). Moreover, caffeine intake speeds up the BOLD response (Liu et al., 2004), whereas functional connectivity and CBF has been shown to decrease during resting state fMRI in particular in the motor cortex (Rack-Gomer, Liau, & Liu, 2009). The temporal variability has been shown to increase after ingesting caffeine (Rack-Gomer & Liu, 2012). Academic literature suggests that caffeine generally reduces BOLD functional connectivity and global signal amplitude (Wong, Olafsson, Tal, & Liu, 2012). The decreased cerebral perfusion and increased vasoconstriction effects from caffeine reduce the baseline BOLD signal and with a normal response to neural activity gives a net increase in BOLD contrast (Mulderink, Gitelman, Mesulam, & Parrish, 2002). There seems to be an effect of caffeine on the BOLD signal and functional connectivity, that also could be time of day dependent because of adenosine. Even though the average number of participants in the studies mentioned above is relatively low (12), it is reasonable to suggest that caffeine effects vascular parameters, and given adenosines circadian variation, the effect of caffeine is most probably also dependant on the time of day. Supporting evidence have been put forward by PET study, that found an upregulating effect of prolonged wakefulness in the expression of adenosine receptors in cortical and subcortical brain areas (Elmenhorst et al., 2007). In addition, caffeine has an effect on blood pressure, which itself naturally exhibits a time of day variation with a mid-morning peak and consecutive fall throughout the day with the lowest point at 03:00 during the night (Millar-Craig, Bishop, & Raftery, 1978).

Functional connectivity

Functional connectivity in motor cortex is majorly reduced during light anaesthesia and almost absent during deep anaesthesia (Peltier et al., 2004). Whereas in higher cognitive networks functional connectivity changed only moderately during light anaesthesia (Martuzzi, Ramani, Qiu, Rajeevan, & Constable, 2010). Recent studies suggest that the DMN functional connectivity is significantly different in locked in patients compared to vegetative state

patients and can be therefore used for diagnostics of one or the other (Roquet et al., 2016). Functional connectivity between subcortical and cortical areas break down when falling sleep, while cortico-cortical functional connectivity remains normal until deep sleep (Hale et al., 2016; Larson-Prior et al., 2011; Spoormaker et al., 2010).

Alertness that peaks around 11:30 in the morning is supported by the EEG studies (Croce, Quercia, Costa, & Zappasodi, 2018). Functional connectivity in sensory areas across hemispheres is elevated during sleep (Nir et al., 2008).

Spontaneous fluctuations of slow cortical potentials (SCP) (< 4 Hz) exhibit similar patterns to spontaneous BOLD fluctuations (He et al., 2008).

Relationship between EEG and The BOLD signal

The BOLD signal has a distinct shape, normally as explained by the Balloon model (Buxton, 2012). Studies combining EEG and BOLD imaging find that "short" (<4s) stimuli elicit a disproportionally large BOLD signal compared with the expectation from underlying neural activity (Boynton, 2011; Hansen, David, & A, 2004). Meaning that the BOLD signal is not linear at short stimulate times, but increasingly linear under longer stimuli (Birn, Saad, & Bandettini, 2001).

The BOLD contrast is highly correlated with local field potentials (LFP) of EEG, which reflect incoming neural input and grey matter processing more so than the spiking output activity. This may lead to a difference in activation between fMRI experiments and certain types of electrophysiological measures (Logothetis et al., 2001). The relationship between LFP and the BOLD signal has been confirmed through intracranial electrophysiological measurements combined with BOLD measures by near infrared spectroscopy (NIRS) (Goense & Logothetis, 2008). The relationship between LFP and BOLD has been investigated in a single cortical site of monkey's brain. The authors report, that

initiated global spontaneous fluctuations in the BOLD signal had a 6 – 8 second delay (Scholvinck, Maier, Ye, Duyn, & Leopold, 2010). The coupling of the LFP and BOLD was dependent on the monkey's state, exhibiting a stronger relationship with eyes closed.

Issues arising in Neuroimaging

Relatively often research in neuroimaging incorporates low to moderate sample sizes, which in turn results in low statistical power of the results. There are several reasons why this is often the case. Firstly, fMRI research is costly and time consuming, hence given the limited time and funds for a project, the sample sizes suffer. There has been several initiatives launched over the past decade to increase the reliability of neuroimaging research. Collecting large samples of multimodal neuroimaging and making it available for free or for a relatively low fee to research community has contributed greatly to the quality of neuroimaging studies, however there is still long way to go before a consensus in the field is established. Both multisite projects as the 1000 Functional Connectome Project and unisite/protocol initiatives as the Human Connectome Project (HCP), UK biobank, the ABCD study and Midnight Scan Club offer access to their neuroimaging data for researchers to explore (Biswal et al., 2010; Casey et al., 2018; Gordon et al., 2017; Miller et al., 2016; Van Essen et al., 2013).

Hypothesis

The aim of the current study is to investigate the effective connectivity change if any during the course of day. For the scope of this project, three large scale networks were selected, namely the DMN, SN and CEN. Given the existing literature on biological rhythms in the brain, it is reasonable to expect a variability in neuronal activity depending on the time of day. Specifically, the activity of selected ICNs will be compared at 6 different timespans across the day (from 09:00 until 21:00). Taking into account the results from previous research it is likely that DMN will exhibit higher connectivity during the first hours of the day

in comparison with end of day, whereas CEN should remain relatively stable in comparison with the DMN. The global effective connectivity is expected to decrease gradually from morning to evening. Finally, the hemodynamic parameters extracted by DCM: *epsilon, transit time* and *decay*, are predicted to change on a circadian basis, and possibly in relation to the effective connectivity.

Method

Data used for this project was collected from the Human Connectome Project initiative, through their open access agreement. For the purposes of this study a recent "S1200" data release was used, for more information please see Van Essen et al., 2013 (http://www.humanconnectome.org).

Participants

The participant sample used in this study was selected from 1200 healthy adults within the age range from 22 to 35 years of age. The participants in the HCP sample were adult twins and non-twin siblings. The data was collected over the span of 3 years on a single 3 Tesla (3T) scanner. The participant pool primarily consisted of subjects living in Missouri, in families with twins. Participants with neurodegenerative disorders, documented neuropsychiatric disorder, neurologic disorders were excluded from the data sample. Furthermore, participants with high blood pressure and diabetes were consider not to meet the inclusion criteria as the mention factors might influence BOLD signal, for a complete list of the inclusion and exclusion criteria please see Van Essen et al., 2013 (Table S1)).

For the present study we selected a subsample of the S1200 release from the HCP. The scans were performed during different times of the day, mid-scan time was used to group subjects into different groups. Time of scan was extracted from supplementary data obtained from the HCP. To investigate the effect of time of day on effective connectivity in large scale

brain networks throughout the day we covered the maximum span of time possible. The sample was split into six-time spans based on the following hourly division: 09 – 11, 11 – 13, 13 – 15, 15 – 17, 17 – 19 and 19 – 21. Due to processing limitations and time constraints on the project a selection of 100 participants for each time of day group was performed. We aimed for a n = 100 in each of the time groups. The distribution of scans during the day caused the first (09 – 11) and last group (19 – 21) to lack an insignificant number of participants, respectively 4 and 2 individuals. Resulting in a total n = 594. The distribution of gender in the selected sample is adequately distributed, F = 310 and M = 284.

Procedure

Participants in the Human Connectome Project were scanned at the Washington University over a 2 day and 1-night visit. An informed consent was signed by the participants at the beginning of day 1. In accordance with previously run pilot studies a consistent scanning schedule was maintained for all the participants in the study, unless a re-scan was required, for more details see Van Essen and colleagues (2013). Before the first scanning session of a participant, a mock scanning trial with feedback on head motion was run to minimise head movement during image acquisition. The scanning sessions were scheduled once a day, one on day 1 and the second on day 2. The averaged time for each of the scanning sessions was 3 hours, the first 30 min being resting state fMRI during which the room was darkened. The participants were asked to lay still with their eyes open and fixate their gaze at the fixation cross (bright fixation cross with a dark background). Complete data collection procedure can be found in Van Essen et al., 2013.

Image Acquisition

Resting-state fMRI data collection was carried out in accordance with an optimized fMRI image acquisition protocol as determined by the HCP piloting. A custom Siemens 3T

"Connectome Skyra" scanner was used to record the data for all participants. The scanner was equipped with a 32-channel head coil, custom gradient coils and gradient power amplifiers boosting the gradient strength to 100 mT/m. Resting-state fMRI data was acquired in two sessions: first 2x15 minute runs, R/L and L/R phase encoding day one, and second 2x15 minute runs L/R and R/L phase encoding day two, a total of 1 hour resting-state fMRI. A gradient-echo multiband EPI imaging sequence was used to acquire resting-state fMRI data. Resting-state fMRI image acquisition settings were as follows: repetition time (TR) of 720 ms, echo time (TE) of 33.1 ms, 52° flip angle, field of view 208x180 mm (readout x phase encoding), slice thickness 2.0mm; 72 slices; 2.0 mm isotropic voxels and a multiband factor of 8 (for more information see Glasser et al., 2016; Uğurbil et al., 2013). In addition, high resolution T1-weighted structural images were obtained with the following parameters: TR 2400 ms, TE 2.14 ms, inversion time (TI) 1000 ms, flip angle 8°, FOV 224x224mm and 0.7 mm isotropic voxels (Uğurbil et al., 2013).

Image processing

For the purpose of this study the data was acquired pre-processed in accordance with "HCP minimal pre-processing pipeline" please see Glasser et al., 2013 for details. Standard pre-processing steps such as: correcting for distortions and spatial alignment was performed. In addition to the mentioned standard procedures the data was also corrected for spatial distortions, aligned across modalities and brought into a standard spatial atlas coordinate system. The only variation from standard pre-processing procedures was due to the bore diameter of the scanner being 56 cm, which is smaller than the standard Siemens 3T Skyra size (70cm diameter). The reduced diameter and lack of a customized patient table resulted in a higher placement of patient table in the bore and the participants head not being centred along the gradient isocentre. This means the scans have greater than normal gradient

distortions, which have been corrected for in the HCP pre-processed data used in this project, for more details see Van Essen et al., 2013.

Analysis

Time series extraction

With the interest of studying large-scale intrinsic brain networks and their activity during the day, we extracted the resting state fMRI timeseries from 8 regions of interest (ROI). Four of these regions are nodes in the default mode network (DMN): medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), right inferior parietal cortex (RIPC) and left inferior parietal cortex (LIPC) (Raichle et al., 2001b). Another two nodes of the analysis are located in the salience network (SN): anterior insula (AI) and anterior cingulate cortex (ACC) (Menon & Uddin, 2010). The final two nodes of interest are from the central executive network (CEN): dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (PPC) (Bressler & Menon, 2010). The coordinates for each ROI can be found in *table 1*.Cross spectral density dynamic causal modelling (csdDCM was used to extract and analyse the time series from the ROI) (K. J. Friston et al., 2014). The csdDCM method applied here is constrained in regard to ROI, there is a limitation to include no more than 8 regions, it was not regarded an issue in the present study as we were able to cover the primary regions of interest. Each ROI was a sphere with a 6 mm diameter which was used to specify and estimate a general linear model (GLM). In addition, one ROI from white matter and one from cerebrospinal fluid was used to regress out noise from non-grey matter sources of BOLD signals. 12 movement parameters were included to control for subject movement during the scanning session.

Table 1. Region of Interest Coordinates

Region	R/L	MNI coordinates
Posterior cingulate cortex	R/L	0 -52 26
Medial prefrontal cortex	R/L	3 54 -2
L inferior parietal cortex	L	-50 -63 32
R inferior parietal cortex	R	48 -69 35
Fronto-insular cortex	R	37 25 -4
Anterior cingulate cortex	R/L	-32 24 -6
Dorsolateral prefrontal cortex	R	45 16 45
Posterior parietal cortex	R	54 -50 50

Note. Abbreviations: MNI, Montreal neurological institute; R/L, Right and Left.

Dynamic Causal modelling

Cross spectral density dynamic causal modelling (csd-DCM) for resting state fMRI calculates the effective connectivity (A matrix) between selected brain regions based on the observed BOLD contrast (K. J. Friston et al., 2014). The observed functional connectivity (original timeseries) is converted to spectral density for each ROI and used in a forward generative model. The csd-DCM considers effects of modelled neurovascular processes and spectral noise at separate levels. Cross spectral density refers to correlation in the frequency distribution of the BOLD signal between brain regions, meaning that changes in activity per second in a region is modelled as a function of activity in another region to investigate the causal relationship between regions (K. J. Friston et al., 2012, 2014). The cross spectra (between regions) density is expressed in Hertz (Hz).

The use of Bayesian estimation requires the connectivity strength between regions to have a prior value ("*priors*"), these are designed to have minimal effect on the effective connectivity, but at the same time prevent extreme values in the results (*posteriors*). Intrinsic (self) connections in individual brain areas are limited to be negative to prevent uncontrolled

cortical activity "runaway" effects of self-excitation, for more in depth information see (Zeidman, Jafarian, Corbin, et al., 2019). Between subject variance is supplemented with fitting *priors* at all levels of the analysis. In the present study, *priors* were turned on for connections between all regions, and DCMs were specified and inverted for each resting state fMRI acquisition (2 per subject). A total of 1188 rs-fMRI acquisitions were included in the analysis. In addition to effective connectivity, DCM extracted hemodynamic parameters, α and β values.

The hemodynamic parameters of interest describe the balloon model in terms of *transit time* for each region, and as global parameter the *decay* of the signal and the relationship between neuronal activity and perfusion, also called neuronal efficacy (*epsilon*) (K.J. Friston, Mechelli, Turner, & Price, 2000). *Transit time* is calculated by dividing resting venous volume by resting flow, providing a time measure of BOLD dynamics. An increase in mean transit time would slow down the dynamics of the BOLD signal, but the shape would remain unaffected. *Epsilon* represent the increase in perfusion signal induced by neural activity and is expressed as number of transients per second. Finally, *decay* reflects the reduction of signal and can supress the post-stimulus undershoot if elevated sufficiently. The rate of *decay* is related to relaxation of arteriolar smooth muscles possibly mediated by nitric oxide (NO) (K.J. Friston et al., 2000).

The last values extracted in the csd-DCM are related to the spectral density measure. The α and β values control the amplitudes and exponents of the spectral density of the neural fluctuations (Razi, Kahan, Rees, & Friston, 2015).

The nonlinear dynamics of the BOLD signal incorporating among others the conflicting changes in blood oxygenation and rCBF (Buxton et al., 1998; K.J. Friston et al., 2000)

Parametrical Empirical Bayes

To investigate parameters at a group level a hierarchical parametrical empirical Bayes framework (PEB) was utilized (K. J. Friston et al., 2016). First level PEB was calculated group-wise to compute average effective connectivity within the time-groups (K. J. Friston et al., 2016). The second level PEB was a hierarchical group PEB fitted with different models to explain possible variations of parameter across time of day groupings. Both levels of PEB were conducted for the A-matrix (effective connectivity), for modelled hemodynamic parameters (*transit time*, *epsilon* and *decay*) and values describing spectral density (α and β). The default settings for estimation of parameters both within and across group level was followed, all connections turned on. The posterior probability threshold for reporting results was set to 95% per connection.

A set of models were implemented in the second level PEB to investigate possible time of day variability in effective connectivity, hemodynamic parameters and spectral density signature. One model was fitted for each timespan to investigate if any timespan varied significantly from the average parameter value (9-11, 11-13, 13-15, 15-17, 17-19 and 19-21). In addition, a simplistic model imitating the effect of circadian oscillations on the average parameter value measurement was specified as a sine wave, amplitude represented the level of activation. Six sine wave models were specified that differed in their phase along the time spectrum (from 09:00 until 21:00). Finally, a null model was implemented to control that the models explain the observed parameters better than simply the average across all groups. In total 13 models were implemented.

Figure 1. Circadian Rhythm Sine Wave

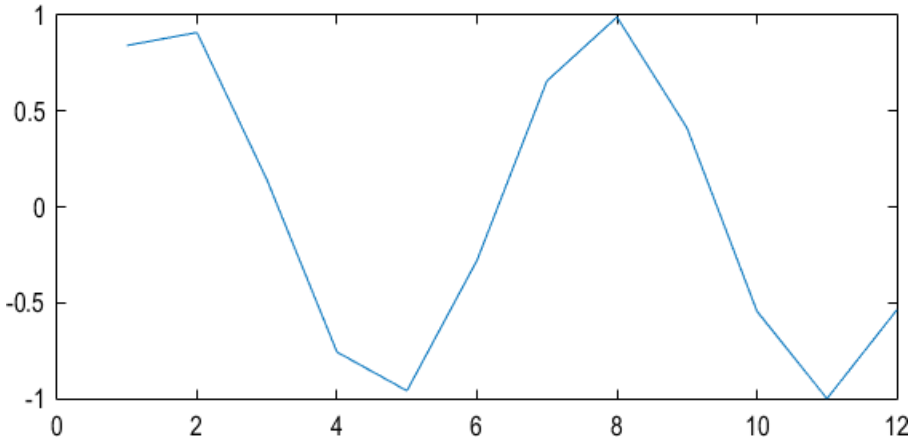

Figure 1. The rough 12-point sine wave used as a circadian model. For the CCR (circadian models) the model number represents starting location in the sine wave.

Bayesian model comparison (BMC). The best model of the underlying parameter is determined through estimating the "model evidence" of second-level PEB models and applying BMC. The model evidence is calculated by quantifying how closely the predicted timeseries corresponds to the observed data (model accuracy) minus the divergence between the *priors* and *posteriors* (model complexity). Then, the model evidence is applied in BMC to determine which model is most likely to have produced the observed data (K. J. Friston et al., 2016, 2017; Kahan & Foltynie, 2013). BMC

Results

Three different result parameters were calculated using the cross spectral density Dynamic Causal Modelling (csd-DCM) and are as follows: the hemodynamic response estimate (balloon model), the effective connectivity within and between regions of interest (A-matrix) and amplitude and exponent of the spectral density of the neural fluctuations (α and β).

First level analysis: DCM

The first level DCM analysis provided an estimate of effective connectivity, hemodynamic response and spectral density parameter for each participant separately. The

hemodynamic parameters of interest were estimated to model the balloon model and are as follows: *transit time* per ROI, *decay* and *epsilon*. Finally, α and β controlling the amplitudes and exponents of the spectral density of the neural fluctuations were extracted.

Second level analysis: PEB

Second level analysis (PEB) was used to average the values provided by the first level analysis (DCM) per defined time-spans (6 time-spans) in order to determine effective connectivity, hemodynamic response, and csd α and β value change if any across the day. In order to analyse mentioned parameters in the clustered groups a hierarchical PEB was used.

Effective connectivity. The hierarchical group PEB was used to generate predefined models that possibly could explain the actual data (variations of effective connectivity across time of day). The comparison of models was performed using Bayesian model comparison (BMC), and the results shows that the highest model evidence (model accuracy minus model complexity) was in the Null model. Figure 2 shows the effective connectivity matrix of the Null model with a posterior probability > 0.95 (pp; the updated probability of the model being true after comparison with other models). A Bayes factor of 20 in favour of model x (represents 20 times more evidence for model x than y), which can also be shown as a log Bayes factor of ln 20 = 3 which is equivalent to a pp of > 0.95 which is commonly used as a threshold for “strong evidence” in favour of model x, for more information see Kass and Raftery, 1995; Zeidman et al., 2019. The model evidence for each of the models was calculated in the second level PEB and displayed in figure 3 on a logarithmic scale relative to the least predictive model.

Figure 2. Null Model Connectivity Matrix

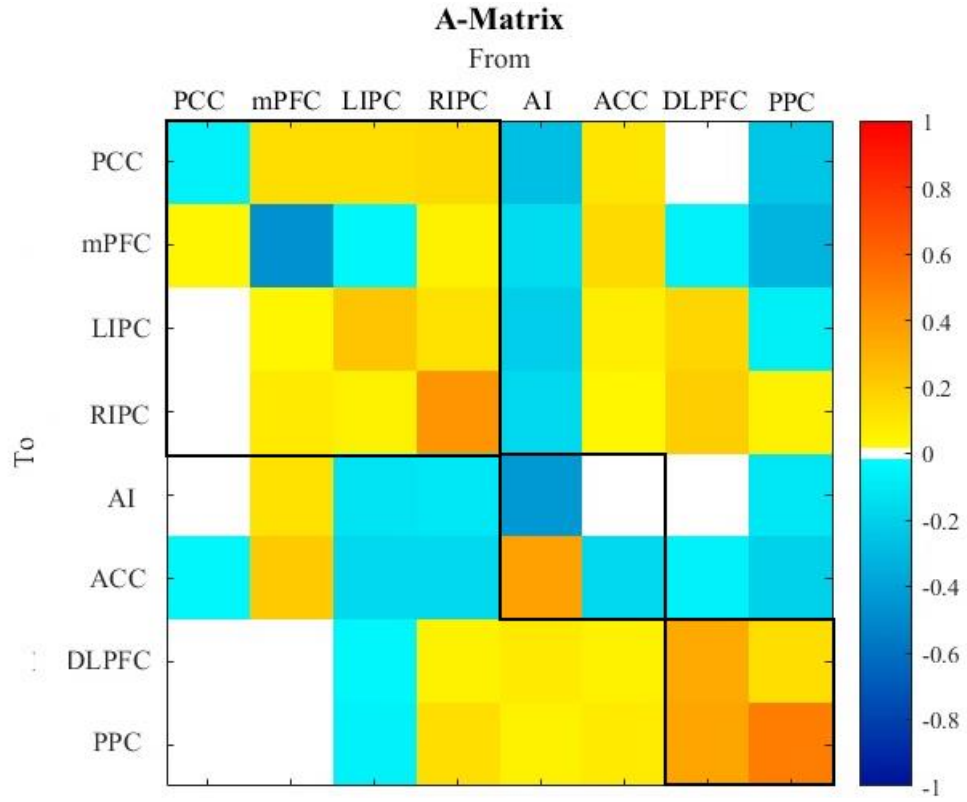

Fig 2. The estimation of effective connectivity (from columns to rows) across all subjects. The leading diagonal elements represent self-connections in logarithmic-scale relative to the prior mean of -0.5 Hz. White space represents no significant effect at > 0.95 pp.

Figure 3. Overview of Effective Connectivity Models

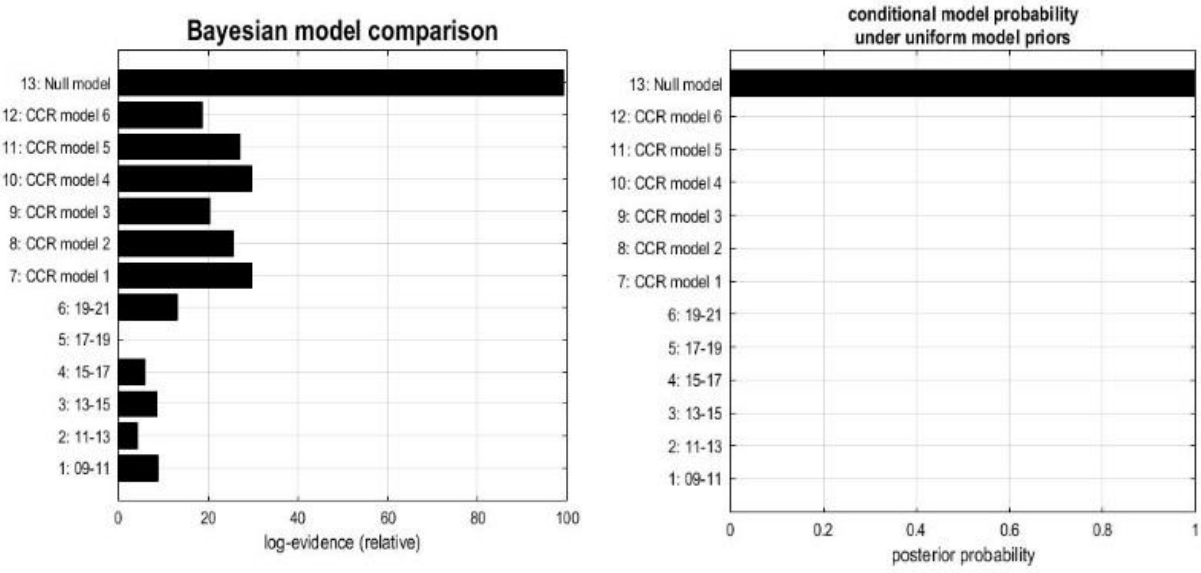

Fig 3. Abbreviation: CCR (Circadian Rhythm). **Left:** BMC model evidence calculated relative to the model with least model evidence. **Right:** The difference in model evidence converted to pp.

The BMC analysis revealed that the effective connectivity is stable throughout the day, where the Null model fitted the data best and the circadian model had a low comparability with the actual data. Even assuming the circadian models did not model an actual circadian change properly, a significantly different group would have been detected by the first six models. This means that we observed no variation during the day in terms of effective connectivity, and therefore can state that neural activity in large scale networks seems to be stable throughout the day.

Hemodynamic Parameters. The estimates of the following hemodynamic parameters: *transit time*, *epsilon* and *decay* were calculated for each time-group using PEB, then fitted with models in the hierarchical group-PEB. *Transit time* was estimated for every region while *epsilon* and *decay* were whole brain measures. Identical models to those implemented in effective connectivity were used for BMC in these parameters. Figure 4. displays the BMC for second level PEB models with hemodynamic parameters.

Figure 4. Overview of Hemodynamic Models

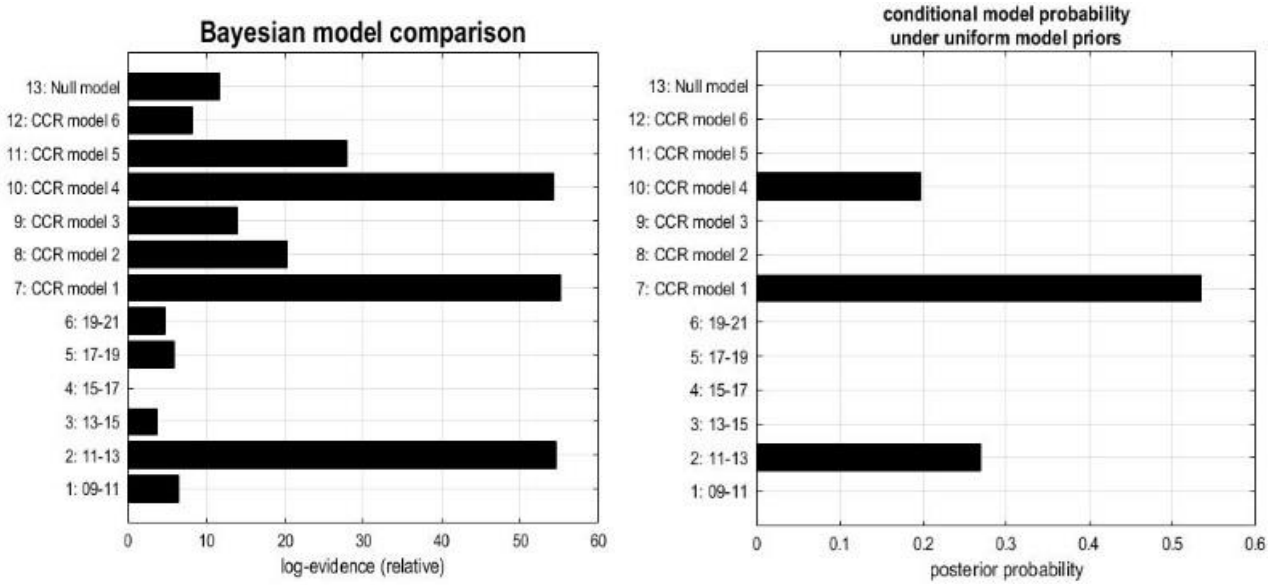

Figure 4. Abbreviation: CCR (Circadian Rhythm). **Left:** BMC model evidence calculated relative to the model with least model evidence. Models 1-6 each weighted time of day increase in effective connectivity. **Right:** The difference in model evidence converted to pp.

Display of the change in posterior parameters relative to the fitted model is seen in figure 5. The posterior values seen in figure 5 represent the level of parameter movement in accordance with the model shape (+) or the inverted shape of the model (-). The model with highest model evidence and pp is model 7, which predicts an initial increase in parameter value followed by a decrease throughout the day and a minor surge in the evening. The t*ransit* time in several areas, and *decay* are significant at a high pp level and follow the modelled path, while *epsilon* exhibit a negative relationship with model 7. This translates to an increase in *transit time* and *decay* from morning to post midday (13), followed by a decrease through the remainder of the day with a slight increase in the evening (19-21).

Figure 5. Estimated Posterior Parameters

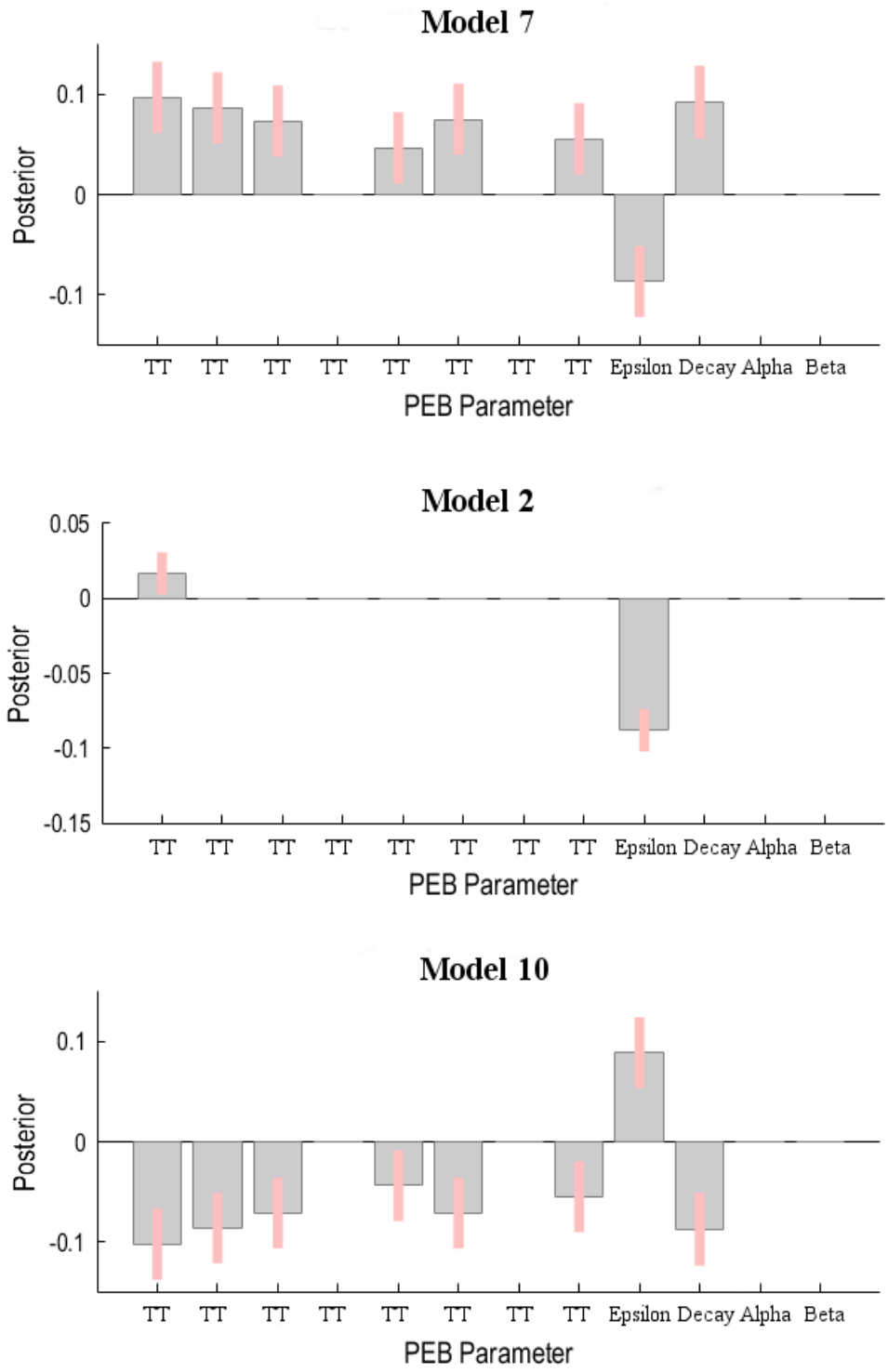

Figure 5. Abbreviation: TT (*Transit Time*, per ROI in the following order: PCC, mPFC, LIPC, RIPC, AI, ACC, DLPFC, PPC). The posterior parameter estimates representing the hemodynamic and spectral density variation across the day with > 0.95 pp. White space represent no effect at this pp level. Models are sorted from highest to lowest model evidence (7, 2, 10). Narrow red bars showing 90% confidence interval (i.e. Bayesian credible intervals).

An inverse pattern is seen for *epsilon* in model 7, where *epsilon* also exhibits a significant decrease at 11-13 in model 2. Model 10 predicts the opposite form in comparison to model 7 and generates approximately the inverted values for all parameters of model 7, further supporting the circadian movement of hemodynamic values during the day. The changes in *transit time* can be seen for all regions of large scale intrinsically connected networks, however there are no significant circadian changes observed in RIPC and DLPFC regions.

Spectral Density Parameters. The influence of time of the scanning session was analysed for the amplitude and exponent of spectral density in the entire brain. The α and β values were modelled, which did not display an effect throughout the day at > 0.95 pp. level.

Discussion

The aim

The aim of this thesis was to investigate if effective connectivity changes throughout the day in large scale intrinsically connected networks. We applied cross spectral density DCM to 594 subject data obtained from the HCP. The extracted effective connectivity and hemodynamic response parameters were compared across 6 timepoints by applying a hierarchical group-PEB fitted with time of day and circadian models. The results did not support the main hypothesis as the null model (no change throughout the day) explained the observed effective connectivity best. However, a clear circadian effect was observed in the hemodynamic parameters extracted from the DCM. All three classes; *transit time, decay and epsilon* displayed a significant relationship with the circadian model (7) at the level of > 0.95 pp, where only the *transit time* from RIPC and DLPFC was found not significant.

Findings

Primary Hypothesis. To the best of my knowledge there are no currently published research that addresses possible change in effective connectivity across during the course of day. The primary hypothesis was not supported -brain activity is dependent on circadian rhythms. There are several possible reasons for this, firstly the research was carried out on open access data, hence unable to account for internal biological time and/or chronotype. As was established by previous research different chronotypes have distinct responses to certain points of time during the course of day such as the post lunch dip and morning rise in cortisol levels, that are reasoned to influence the effective connectivity based on time of day groupings (Merrow et al., 2005; Weitzman et al., 1971). Given the previous research it could be suggested that since *larks* and *owls* exhibit inverted variation in time of day effects, comprising participants of distinct chronotypes in a single dataset might result in non-significant findings.

Where a milder difference between chronotypes could also result in a large variation within the groups, resulting in large diviation hence providing support for the null hypothesis. In fact, functional connectivity differences between early and late chronotypes have been observed in the DMN (Facer-Childs et al., 2019). Furthermore, functional connectivity differences in large scale brain networks are distinct across individuals, especially in the CEN (Finn et al., 2015). When controlling for chronotype and sleep duration and quality, previous research has reported significant differences in functional connectivity in the DMN when comparing different time of day sessions (Blautzik et al., 2013; Shannon et al., 2013). However, these studies utilized repeated measures design, meaning that the same participant was scanned several times, the findings might be the result of repeated measures design and brain imaging pre-processing pipelines increasing the likelihood of observing a statistically significant difference between groups compared. This approach improves the signal to noise

ratio drastically, by practically removing the interindividual differences. Given described limitations it is plausible to theorize that differences in effective connectivity are not distinct as distinct as reported by the mentioned study.

Secondary Hypothesis. Circadian variation in the hemodynamic response. The findings from current study provide support for the secondary hypothesis. These results if true are highly intriguing and a possible concern for the fMRI community. The hemodynamic parameters *transit time, decay and epsilon* all exhibited a significant relationship with the circadian model (7) fitted in the hierarchical group-PEB. *Epsilon* represents the number of evoked transients per second, which can be interpreted as the efficacy of the neuronal activity in eliciting the BOLD signal (K.J. Friston et al., 2000). This means that an increase in *epsilon* boosts the amplitude of the BOLD signal response and undershoot. The significant relationship between model 7 and *epsilon* value indicates a systematic change in BOLD amplitude throughout the day. There is a negative relationship between *epsilon* and model 7, as expressed by the negative value of the posterior parameter of *epsilon.* This means that there is a decrease in BOLD amplitude from timepoint 1 to 2 and then an increase throughout the day with a slight decrease between the last timepoints. The midday decrease in *epsilon* can be seen in both model 7 and 2, where the *transit time* for PCC, mPFC, LIPC, AI, ACC and PPC all exhibit a positive relationship with model 7. *Transit time* is resting venous volume divided by resting flow and predicts the dynamics of the BOLD signal. An increase in *transit time* would slow down the dynamics of the signal, but the shape would remain identical. Lastly, the *decay* parameter reflects the rate of signal elimination. An increase in this parameter reduces the rCBF and can supress the BOLD undershoot. The *decay* parameter and model 7 exhibits a positive relationship. *Transit time* and *decay* exhibit a peak in parameter values from 9-11 until 11-13, then a decrease throughout the day, while *epsilon* exhibits the inverted pattern. In relation to the biological circadian clock, there is a decrease in blood pressure,

heart rate, cognitive abilities and the daily bottom of CBF(V) around 11-13, whereas, cortisol is still high. The daily changes in blood parameters provides support for the described change in *transit time*.

It is reasonable to observe a slower BOLD response with the reduced CBF. And it is likely that the *decay* is dependent on vascular signalling and relaxation time (K.J. Friston et al., 2000). Interestingly *epsilon* exhibits a reduction in amplitude around midday, which is completely not in line with the circadian slope of CBF(V) (Conroy et al., 2005). This decrease in CBF(V) should have facilitated an increase in BOLD amplitude (*epsilon*) due to reduced baseline signal. This is supported by studies on caffeine and fMRI signal that report a significant fMRI signal increase when the CBF(V) is decreased (Cameron et al., 1990; Mulderink et al., 2002).

Rhythms. When taking into consideration the circadian rhythmicity of temperature, blood pressure and cortisol, the first data points analysed in the data set were relatively late (9-11) (Conroy et al., 2005; Millar-Craig, Bishop, & Raftery, 1978; Weitzman et al., 1971). This possibly could explain why model 7, had a starting point almost at the peak of the sine wave. Since the data sat was distributed from 09:00 until 21:00 it does not have coverage of the early morning surge. With this in mind it is plausible, that the second group of 11-13 becomes the peak of most values (Merrow et al., 2005; Millar-Craig et al., 1978; Weitzman et al., 1971). As we have seen there is a molecular mechanism in every cell of the body that oscillates on a 24 hour basis, a key component of this mechanism is PER1 (Lowrey & Takahashi, 2011). PER1 is part of the deactivating section of the feedback loop, generally there is a peak of PER1 protein expression around 11-13 which synchronizes well with the post lunch dip that influences temperature, alertness and cognitive abilities (Guilding & Piggins, 2007; Monk, 2005).

As it was described in the introduction, the PER1 is a key component in the molecular clock that maintains the rhythmicity of every cell in the body (Lowrey & Takahashi, 2011). PER1 is part of the deactivating section of the feedback loop, which reaches its peak of PER1 protein expression around 11-13. This in turn, synchronizes well with the post lunch dip that influences temperature, alertness and cognitive abilities (Guilding & Piggins, 2007; Monk, 2005). The BOLD signal is based on several hemodynamic parameters that have been approximated in models as the balloon model (Buxton, 2012). Several of the parameters as CBF, $CMRO_2$,

Temperature is utilized by the SCN to entrain peripheral brain areas and tissue in the body, the SCNs intrinsic organization renders the SCN immune to entraining effects of temperature (Merrow et al., 2005). The bottom of the temperature curve "nadir" is around 05:00, which is 6 hours before the CBF minimum point. This correlates with the time it takes from mRNA peak to protein expression peak (in phase with BMAL1) (Guilding & Piggins, 2007). In addition, daily changes in temperature would affect the Larmor frequency of the 1H protons in different tissues and could affect brain imaging data. Unexpected differences in Larmor frequency due to temperature changes could lead to spatial anomalies both in structural and functional MRI (Levitt & Southampton, 2001). The potential amplitude difference of 0.5 degrees of Celsius during the post lunch dip could significantly impact imaging spatial validity (Monk, 2005). Even if the effect would likely be minor, it could prove important in clinical cases or experimental setting, if the variation would happen to be systematic between groups.

EEG experiments provide support for effective /functional connectivity changes during the day (Croce et al., 2018; Goense & Logothetis, 2008; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001).

Limitations

There are several limitations, that could possibly be addressed in future studies. First and foremost, the data obtained from the Human Connectome Project, even in high quality, was not collected in order to address the connectivity differences across the time of day. Given that, the study did not account for individual chronotype differences, quality of sleep before and between the scanning sessions. Secondly, the analysis method used in the present study (DCM) differentiates between the hemodynamic response and brain activity measures, however no additional parameters, that have been shown to influence the BOLD signal were accounted for (for instance, blood pressure, cerebral blood flow, levels of cortisol). Finally, the study relied on between subject design, i.e. different subjects were randomly assigned to the time-spans, whereas in order to obtain a truly comprehensive understanding of the circadian rhythmicity, a repeated measure (within subject design) would be best, where the same participant would undergo scanning at each time-span.

Further Research

Given that the body of academic literature on circadian rhythmicity and resting-state functional connectivity is rather limited, future studies should aim and replicate the findings of the current research. The confirmation of the current findings would provide the research community with a deeper understanding of circadian rhythm impact on brain connectivity. The future studies should take into account the chronotypes of the participants and control for individual differences, which has been shown to affect resting state connectivity (Facer-Childs et al., 2019). Furthermore, if the current findings, while controlling for individual chronotype differences are confirmed, more research is needed to understand the dynamic effective connectivity during the day. The use of dynamic causal modelling in future studies, could possibly explain the true nature of relationship between BOLD signal and neural

activity. These future achievements would heavily contribute not only by bringing consensus in circadian rhythmicity and resting state connectivity research, but also for in depth understanding of brain activity. The findings could be applied in both academic and clinical research.

Conclusion

In summary, the results from the current study contribute to the limited body of literature on circadian rhythmicity and resting state functional connectivity. The findings suggest, that even though there is an observed variability during the course of day in the hemodynamic response, which is captured by fMRI, the neuronal activity remains stable. The changes in the hemodynamic response, possibly reflect the circadian rhythmicity influence on different time-spans used in this research, whereas the lack of differences between time-spans in effective connectivity suggests that the measurement used to capture neuronal activity, i.e. the BOLD signal, is more susceptible to exogenous parameters than the brain activity itself. These findings urge the need of further separation between the hemodynamic response and neural activity, since the relationship between the two might not be direct. Naturally, these findings, before taken as proof, should be replicated in future research.

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