"THE CORTEX IS BOTH CHAOS AND ORDER, AND THEREIN LIES ITS STRENGTH."

GERHARDT VON BONIN (1890–1979)

Cortical thickness and neuropsychological applications: Morphometric differences in cortical thickness associated with cognitive variances in ageing and circadian chronotypes

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ABSTRACT

Although rapidly emerging, the field of Neuroscience is still in its infancy. With in-vivo imaging rapidly emerging and novel analysis methods being developed and improved all the time, the neural substrates of behaviour and cognition can be observed like never before. A relatively new method in the anatomical analysis of neuroimaging is cortical thickness analysis. A sensible and intuitive measure of brain morphology and cytoarchitecture, the thesis explores which role cortical thickness measurements can take, when combined with neuropsychological methods. This thesis examines several approaches to neuropsychology with traditional face to face assessments like the Wechsler Scales, to more modern computerised testing, like CANTAB, through to novel approaches and psychometric testing. Whilst combining neuroimaging with neuropsychological methods, this thesis will also account for two of the most inevitable confounding factors in neuropsychology - Ageing and diurnal sleep preference.

Though cortical thickness, much like comprehensive neurocognitive batteries like the WAIS and its overall summary score FSIQ, is often expressed through a single composite measure (e.g., global cortical thickness, or mean cortical thickness), this thesis will examine the complexities in developmental trajectories and differences across the brain, when interpreting cortical thickness analysis and explain why the key is really in the detail. This thesis closely examines possible new modulating factors in neuroscientific research, namely circadian chronotype, the role of neuropsychology as a gold standard in the evaluation of cognition, the importance of choosing the correct assay, and how caution must be exercised as brain imaging methods and their measurements are more dynamic than previously thought.

DEDICATION

Dedicated to:

My parents, Claudia & Stefan Höfig, whose unwavering support, and love has made this possible.

Danke für Eure uneingeschränkte Unterstützung und Euren Glauben in mich. Worte werden nie genug sein.

&

My late husband Parminder Ruprai, without whom I would have given up along the way. *I wish you were here to see it.*

La tristesse durera toujours.

„WEGE ENSTEHEN DADURCH, DASS MAN SIE GEHT“

FRANZ KAFKA

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LIST OF ABBREVIATIONS

A	Afternoon
ACC	Anterior Cingulate Cortex
ANOVA	Analysis of Variance
BA	Brodman Area
bankssts	Banks of the superior temporal sulcus
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAT	Computerised Adaptive Testing
CFT	Cluster Forming Threshold
CWP	Cluster-wide-probability
CMAT	Chrono-Memory Attention Test
CSF	Cerebrospinal Fluid
CT	Cortical Thickness
CWP	Cluster-wide probability
DASS	Depression Anxiety Stress Scale
DK	Desikan-Killiany (Atlas – Parcellation)
DKEFS	Delis-Kaplan Executive Functioning System
DTI	Diffusion Tensor Imaging
E	Evening
ECT	Early Circadian (Pheno-)Type
EEG	Electroencephalography
eTIV	estimated total Intracranial Volume

ESS	Epworth Sleepiness Scale
F statistic	ANOVA F test statistic
FDR	False Discovery Rate
fMRI	Functional magnetic resonance imaging
FS	Freesurfer
FSIQ	Full Scale IQ
g	General intellectual ability Factor
gC	Crystallised Intelligence (Verbal Ability)
gF	Fluid Intelligence (Reasoning Ability)
GLM	General Linear Model
GM	Grey matter
GMV	Grey Matter Volume
GUI	General User Interface
IAP	Intracarotid Amobarbital Procedure
IPC	Information Processing Capacity
IQ	Intelligence Quotient
lh	(pertaining to) Left Hemisphere
M	Morning
MC_S	Monte-Carlo Simulation
MCTQ	Munich Chronotyping questionnaire
MEQ	Morningness-Eveningness questionnaire
MEG	Magnetoencephalography
MNI (space)	Montreal Neurological Institute (space)
MPFC	Medial pre-frontal cortex
MR	Magnetic resonance

MRI	Magnetic resonance imaging
MSF	Mid sleep phase on free days
MSF_{sc}	Corrected Mid Sleep on free days
ns	not significant
ONS	Office for National Statistics
p	Significance value
p^a	Significant at Monte-Carlo Simulation level $p<0.01$
p^b	Significant at False Discovery Rate $p<0.05$
p^c	Significant in SPSS for main/interaction effects, $p<0.05$
p^d	Significant, when Bonferroni corrected, $p<0.05$
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
POMS	Profile of Mood States
PSI	Processing Speed Index
PSQI	Pittsburgh Sleep Quality Index
PVT	Psychomotor Vigilance Task
QDEC	Query-Design-Estimate-Contrast Program
REM	Rapid eye movement sleep
RF	Radiofrequency
rGMD	regional Grey Matter Density
PET	Positron Emission Tomography
PRI	Perceptual Reasoning Index
Rh	(pertaining to) Right Hemisphere
ROI	Region of interest

SCN	Suprachiasmatic nucleus
SD	Standard deviation
SEM	Standard error of the mean
SPM	Statistical parametric mapping
SRT	Simple Reaction Time
STM	Short-term Memory
T	T test statistic
tGMV	Total Grey Matter Volume
TOD	Time of day
tp	timepoint
VBM	Voxel-based Morphometry
VCI	Verbal Comprehension Index
WADA	Alternative name for intracarotid amobarbital procedure
WAIS	Wechsler Scale of Adult Intelligence
WM	White matter
WMI	Working Memory Index
WMS	Wechsler Memory Scale
WTAR	Wechsler Test of Adult Reading
WMV	White Matter Volume
1.5/3T	1.5/3 Tesla
Z_{OP}	Estimated effect size between Observed and Predicted values

INTRODUCTION

"MAN IS THE MEASURE OF ALL THINGS"

PROTAGORAS (485-411BC)

PART I

Humans are capable of higher order cognition, abstract thinking and, perhaps most importantly, language, unparalleled in the animal kingdom. In comparison with other mammals, however, humans neither have the largest brain, either relatively, or absolutely, nor do they rank first in gyrification. In fact, anatomically compared to its closest evolutionary relatives, the human brain is strikingly similar to non-human primates and entirely unremarkable. Despite around 86 billion neurons and at least twice as many glial cells, the human brain, incredibly, is not at all extraordinary, when scaled up against other brains, primate, or non-primate (see review Herculano-Houzel, 2012). From an evolutionary point of view, it is clear that high levels of intelligence can be realised in a variety of cortical architectures and that it is a precise combination of neuronal packing density, overall neuron size, transmission velocity and processing capacity (Dicke & Roth 2016). Humans appear to have taken a qualitative, rather than quantitative, leap and this thesis will examine how the underlying morphology of cortical thickness relates to cognition, through the analysis of various neuropsychological assays.

Whilst normative data is an accepted key benefit of standardised neuropsychological testing, neither normative procedures (Maclaren et al., 2014), nor normative data for neuroimaging measurements have been agreed upon (Potvin et al. 2017), in particular relating to cognitive functioning, despite anatomical size of cortical areas grossly correlating to the complexity of the function it primarily supports (Bigler 2015).

The primary impetus of this thesis therefore seeks to assess cortical thickness as an informative measure, indicative of brain structure and health, which can be correlated to cognition, on both a global and region-specific scale, and in relation to important mitigating factors, such as ageing, circadian chronotype and time of day.

1. THE BIRTH OF NEUROPSYCHOLOGY

Neuropsychology, by definition, is the study of the relationship between the brain and behaviour. Where cognitive psychology emphasises the 'mind', neuropsychology focusses on establishing a direct causal link between anatomical substrates, behaviour, and cognition. It seeks scientific explanations for complex mental processes, such as vision, memory, language and thinking, but also higher-level processing skills, such as problem solving and reasoning (Parkin 1996, p.3).

Before the advent of neuroimaging, as we now know it, detailed insight into the human brain, in particular in vivo (from within), was sparse. Case Studies outlining newly attained deficits in line with the acquired brain trauma, were often the only way to link a specific skill or behaviour to a localised area (Coltheart 2001, p.3, Lassonde et al. 2006). Whilst neuroimaging has contributed much to the field of neuroscience, the traditional neuropsychological method has clear advantages. Lesion studies can establish causality with certainty, as there remains little doubt between the link between cognitive skill and cortical area. Long before anatomical variances were discovered, neuropsychology established physiological differences between hemispheres through the observation of cognitive deficits in stroke patients, for example (The Lancet, 1986).

From lesion studies, assessing cognitive dysfunction to draw conclusions on the cortical and subcortical distribution of healthy function, the field quickly expanded into the neuropsychological patterns of neurodegenerative disease, such as Huntington's Disease, Parkinson's Disease, Multiple Sclerosis or Alzheimer's Disease. But it also examined the detrimental effects of other psychological disorders or conditions, such as depression, anxiety, post-traumatic-stress-disorder (PTSD), healthy ageing or sleep deprivation.

The introduction of epilepsy surgery, in particular, heralded a distinct change in neuropsychology. The discipline owes much of its early developments to the assessments of epileptic patients, which were available for detailed assessment before and after surgery. This allowed neuropsychologists a much more controlled environment, in which to study the effects of induced discrete surgical lesions (Baxendale & Thompson 2010).

Whilst we now know much about the cognitive effects of many diseases, progressive development and change through healthy ageing, this will be further explored in Chapter 4, as well as the importance of sleep for cognition, in Chapter 5.

(1.2) Measuring Cognitive Function

The applications and goals for neuropsychological testing are now manifold and execution depends entirely on the circumstances in which it is used and the individuals it assesses. In some ways, molecular or cellular processes underlying cognition are entirely irrelevant, because the only thing that truly matters is whether brain functioning is optimal to allow for independent daily living. However, understanding the mechanisms which facilitate cognitive functioning at its most basic level is crucial in

the recognition, early intervention, and successful treatment of many neurological diseases. Understanding compensatory processes within the brain has given invaluable insights into cortical plasticity, for example. The brains of epileptic patients, or those who sustained traumatic brain injury at an early age, can often show abnormal lateralisation for speech (Springer et al. 1999, Müller et al. 1999), or functional reorganisation to compensate for the lesions. Despite sub-optimal conditions with injuries to previously thought crucial functional modalities, these patients often demonstrate near-normal or normal performance (Kleim & Jones 2008, Mikellidou et al. 2017). This effect was observed even where an early hemispherectomy was performed. Brain plasticity can allow for compensatory reorganisation to take place, resulting in cognitive performances on the normal spectrum, with only one remaining hemisphere, with deficits often only apparent in very specific and detailed examinations. This process appears to favour functions essential for independent living, in particular, such as linguistic and visuospatial skills, in particular (Odgen 1989, Mariotti et al. 1998).

The search for biological explanations and a thorough understanding of underlying processes therefore becomes of particular importance, when we seek ways in which to influence, rehabilitate or medicate them. Some applications of neuropsychological testing stem from its origins in identification and localisation of brain lesions and their behavioural and functional consequences (Goldstein 1992), whilst others are relatively new in a discipline that is only starting to come into its own.

(1.3) Common Uses of Neuropsychological Assessment

The most common uses of neuropsychological assessment are summarised below, though this list is not intended to be exhaustive (Adapted and Consolidated from Goldstein 1992, p.8, Lezak et al. 2004, pp 4-11, Winiarsky & Whitaker 2015, p.722, 725, Zuchella et al. 2018, Lezak et al. 2004, pp.128-129,757, Slick et al., 1999):

(1.3.1) Diagnosis:

A common aim, when conducting a neuropsychological evaluation in a clinical setting, is to provide a differential diagnosis that can prioritise treatment (Schroeder et al. 2019). Despite the development of neuroimaging methods, only thorough neuropsychological evaluation can show the extent of cognitive aptitude or dysfunction. Sensitive imaging tests for several conditions e.g., Autism, Attention Deficit Hyperactivity Disorder (ADHD), do not yet exist, and imaging methods cannot provide differential diagnosis for e.g., Alzheimer's Disease vs. frontotemporal dementia, psychiatric vs. neurological disorder/symptoms, neurodegenerative disease vs. mood disorder.

Diagnosis is usually made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (currently in its 5th Edition, DSM-5). A diagnosis for autism spectrum disorders (ASD), for example, requires thorough examination through various disorder specific batteries, e.g., the Childhood Autism Rating Scale (CARS, Rellini et al. 2004) and the Autism Diagnostic Interview revised (ADI-R, Schopler et al. 2010). Assays used for diagnosis often differ between hospitals or medical centres, based on which tests Practitioners are trained in, and which specific tests a centre has acquired based on clients' needs.

(1.3.2) Clinical Treatment planning, remediation, monitoring, evaluation

Neuropsychological assessment can provide an in-depth account of current cognitive functioning and highlight aptitudes and deficits alike. This can serve as a baseline, monitor for decline, effects of treatment (e.g., pharmacological effects) and inform patient care, treatment, and rehabilitation. It can provide valuable insights into a patient's capacity for self-care and self-management of, for example, financial affairs and highlight whether additional safeguards, or support ought to be put in place. Neuropsychological testing can provide global performance scores, as well as domain specific information, e.g., about verbal fluency (Harvey 2012). This is important for those with focal stroke or small localised acquired brain injury, who may have largely unaffected global functioning, with very specific functional deficits (e.g., semantic category fluency (Luteijn & Barelds 2004, GIT-II).

(1.3.3) Neurosurgery:

The combination of neuropsychological assessment and neuroimaging, clinically, is most likely of most significance in the realm of neurosurgery.

Neuropsychological assessment and evaluation play a vital part in the pre- and post-surgical assessment, and planning for patients eligible for neurosurgery (e.g., epilepsy or brain malignancies, such as gliomas) or deep brain stimulation (e.g., Parkinson's Disease). Information gained from imaging, such as lesion, or glioma infiltration site, and cognitive evaluation can guide the surgeon's decision on which areas to resect or spare, depending on which areas of cognitive functioning are implicated. This is sometimes done through navigated transcranial magnetic stimulation (nTMS), to map the language areas of the cortex, prior to surgery (Picht et al. 2013, Lehtinen et al.

2018). Language mapping can also be done via intra-operative language production tasks, evaluating repetition and object naming abilities (DuLIP, De Witte et al. 2015). These test not only region-specific capabilities, e.g., Broca's area, which broadly hosts the grammatical and articulation facilities of a patient, but also network specific functions, such as the verbal ability network localised on the arcuate fasciculus. The arcuate fasciculus is a white matter bundle, which plays a critical role in phonological processing and links frontal, temporal, and parietal areas (Sierpowska et al. 2017).

Post-operative assessment of cognitive functioning is an important part of mapping recovery. Where possible, baseline testing provides information about the level of cognitive decline following re-assessment, and any improvements following recovery. As cognitive disruption is further mediated by post-operative intra cortical inflammation (Hoven et al. 2014), neuropsychological testing is repeated several times to track longitudinal outcomes.

(1.3.4.) Clinical Trials:

Assessing possible cognitive side effects of investigational medicinal products is a vital part of the monitoring process in any clinical trial. Many approved medications have known cognitive side effects, such as antiepileptic drugs, which can be associated with slowed reaction time or increased drowsiness, verbal fluency, and visuospatial skills (Vijayakumar et al. 2018), or antipsychotic drugs, which have been known to induce serious metabolic side effects, such as type 2 diabetes or dyslipidemia, which impede on cognitive functions (MacKenzie et al. 2018).

With clinical research in the UK underpinned by Good Clinical Practice principles (GCP), as set out by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and

regulated by formal legislation under the EU Directive 2001/20/EC, trials involving new drugs and human subjects require close monitoring. In trials where cognitive or psychological impairment may be anticipated, e.g., in trials for a new psychoactive drug, cognitive function must be continuously examined to detect any unexpected adverse effects or reactions (Ramana et al. 2020).

(1.3.5) Research:

The use of established neuropsychological batteries is vital to many studies investigating brain-behaviour relationships (e.g., Tsatali et al. 2021, establishing discriminant validity of the WAIS-R Digit Symbol Substitution Test in mild cognitive impairment of Alzheimer's Disease, Sweeney et al. 2000, assessing neurocognitive impairment of uni- and bi-polar mood disorders with CANTAB).

But research also plays an integral part in validating neuropsychological batteries and establishing normative data (Nielsen et al., 2019), validating existing batteries in additional languages (Romero et al. 2018) or specific populations (e.g., Dassanayake & Ariyasinghe 2019, CANTAB in Sri-lankan Adults, Flinn et al. 2018, forensic normative data for the WAIS-IV). Research also facilitates the development of novel cognitive tests, e.g., to establish early patterns of cognitive decline (Liew 2019, Schweiger et al. 2003).

(1.3.6) Longitudinal Studies:

Collecting information on neuropsychological functioning at various points throughout the lifespan, has been crucial to our understanding of brain development and cognitive functioning throughout the lifespan. Cross-sectional age-related studies have helped to create normative samples for many widely accepted neuropsychological tests and

provide invaluable insight into healthy cognitive processing at different stages of life (e.g., Schnack et al. 2015). Longitudinal research has provided valuable insight into disease progression, possible prognosis predictors and disease trajectories over time (Hinrichs et al. 2017, Tang et al. 2018, Riddle et al. 2017).

(1.3.7) Forensic and Medico-legal:

Forensic mental health assessments (FMHA, Heilbrun et al., 2003) can answer questions pertaining to mental capacity, fitness to stand trial, or provide explanations for criminal behaviour. Their primary purpose is to provide expert opinion, or testimony to a legal professional, pertaining to capacity, capability and / or intent. Whilst diagnostic or therapeutic assessments rarely enter legal proceedings, and thus practitioners are unlikely required to give testimony, FMHA are commissioned in anticipation of giving evidence at a later date. Principles of FMHA are similar to diagnostic neuropsychological assessments, though the process differs significantly, as reports are written to specific requirements set by e.g., a judge, and with the purpose of informing a legal third party (Heilbrun 2001, Heilbrun et al. 2014). Special attention must be paid for evidence of malingering, in particular for those seeking to claim unfitness to stand trial on grounds of 'insanity'. Neuropsychological assessments may also be required in civil litigation cases, driving competency assessments or insurance claims / compensation claims. If there is an incentive for intentional poor performance e.g., in compensation claims, where an exaggeration of cognitive symptoms may lead to a greater compensation sum, attention must be paid to malingering.

(1.3.8) Education:

Even though specific educational issues are usually assessed by an educational psychologist, it is not unusual for assessments to cross over into neuropsychological terrain. Through medical advances more and more infants are now surviving, despite premature birth, birth trauma, congenital disease, or illness, leading to infant mortality rates decreasing steadily (currently at their lowest since records began in 1980, ONS 2021). However, this leads to an increase of children entering the educational system with additional educational and health needs, requiring specialist neuropsychological assessment and support to maximise educational attainment (MackKay 2005).

Furthermore, a child with sickle cell anaemia, for instance, may be referred for poor academic performance, including poor attention and comprehension, for an underlying cause of silent strokes to be discovered as the root cause of these problems. Neuropsychological evaluation can also help with the instatement of IEP's (Individual Educational Plans), EHCP (Education, Health & Care Plan) or social security benefits on the grounds of learning disabilities.

(1.4) Selecting a Neuropsychological battery

There is a vast array of neuropsychological tests to choose from and suitability depends entirely on the reason for the referral or assessment and what the patient stands to gain from it (Winiarsky &Whitaker, 2015).

The Wechsler Scales (WAIS III/IV, WMS III/IV, WTAR, Wechsler 2008) are some of the most widely used measures to assess compound constructs of intelligence (Rabin et al. 2016) and are discussed in broader detail in Chapter 3. A notable disadvantage to the Wechsler scales is the administrative effort required to administer and score the test and the time required for both the patient and the Neuropsychologist

conducting testing. Computerised testing, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, 2012), can make this process much more time efficient. Whereas the Wechsler scales at a minimum require some manual scoring and inputting of raw data to make it useable and interpretable, data from computerised testing can be accessed and extracted easily and quickly from the program itself (Bilder & Reise 2018), though newer versions of the Wechsler scales allow for administration via IPad for administration comfort, also (Young 2020). Computerised adaptive testing (CAT) can increase efficiency and accuracy in neuropsychological testing in the region of 50-95%, without compromising quality (Choi et al. 2012, Ebesutani et al. 2012).

CANTAB (Cambridge Cognition 2012) is discussed in further detail in Chapter 4, where it is the method of choice, when comparing samples of younger and older participants. CANTAB, whilst being computerised, also includes a normative database for guidance. Whilst there are logical benefits to using a well validated, trusted battery, introducing new and novel items is necessary to further the development of research. By basing new tests on objective and quantifiable constructs, based on previous literature, new experimental content should not be problematic (Bilder & Reise 2018). Chapter 5 examines the well-known Psychomotor Vigilance Task (PVT, Dinges & Powell, 1985), but also introduces novel psychometric testing (https://www.profilingforsuccess.com).

(1.5) Scope of Neuropsychology

(1.5.1) Key benefits of standardised testing

One of the most compelling reasons to use standardised tests, such as the Wechsler Scales or CANTAB, are their well-documented validity, reliability, and available normative data, making them widely useable and easily interpretable (Rabin et al. 2016, Bilder and Reise 2018).

Standardised tests contain normative data which allows for easy contextualisation of individual performance in relation to peers of comparable age and / or educational attainment (Wechsler 2008, Cambridge Cognition 2012). Tests which have been translated and validated in additional languages (e.g., Wechsler Scales) provide culturally and linguistically valid tests of cognitive abilities, comparable across countries.

Ecological validity is one of the biggest difficulty's neuropsychologists face, when determining test suitability (Rabin et al. 2016). Is the test battery reflective of the real-world construct it proposes to examine? Do the methods approximate to the actual neuropsychological paradigm it intends to measure (Brewer & Crano 2014, pp. 11-26)? Neuropsychological methods are increasingly used in research with healthy participants, whereas many tests were developed with patients in mind, so how do they relate and translate to patient populations and vice versa?

In the clinical patient population, neuropsychology is used to gain information about a single individual and aid further clinical investigations, treatment, or rehabilitation (e.g., Winiarsky & Whitaker 2015, p.722, 725 & Zuchella et al. 2018). Normative data, which exists for most established assays, serves as guidance to approximate overall

functioning range, and indicate areas of concern, but fully recognises that each patient is individual and unique, with relative strengths and weaknesses.

(1.5.2) Normative Data in Neuroimaging

The combination of behavioural and clinically acquired data and segmentation software has the potential to make MRI a powerful screening tool in clinical applications (Maclaren et al., 2014), though normative comparative procedures have not yet been universally agreed upon. Robust normative data for neuroimaging measurements does not yet exist (Potvin et al. 2017), in particular in relation to cognitive functioning, something which will be explored further in Chapter 3.

In order to utilise neuroimaging methods to predict cognitive deficits and triage and tailor neuropsychological testing, methodologies need to be agreed upon, as well as compared to and validated against standardised tests (such as the Wechsler Scales). Potvin et al. (2017) produced a database which allowed a direct comparison of an individuals estimated total intracranial volume (eICV), relative to age, sex, and MRI scanner specifications, but more research is required to reliably map variations in brain morphology to cognitive functioning. Chapter 3 examines the existing literature in relation to cognitive links to their underlying anatomical substrate, in particular in relation to intelligence. It compares the morphometric measurement of cortical thickness with a more traditional measurement of voxel-based morphometry and extrapolates whether the two are directly comparable in the results they yield when correlated to cognitive functioning.

Brain morphometry measures are now known bio markers in neurodegenerative disease, such as Alzheimer's disease, and could benefit from utilising a wider range of imaging methods (Dubois et al. 2007, Schuff et al. 2009) besides

neuropsychological tools, to inform disease trajectory or risk markers, that could predict cognitive outcome.

(1.6) MRI and Neuropsychology

In the era of neuroimaging, neuropsychology has gone beyond mere localisation and has assumed a role in the clinical evaluation of pre-and post-operative neurosurgery patients, partakes in the rehabilitation of those suffering traumatic brain injury (Baxendale & Thompson 2010) and serves as the foundation for functional imaging paradigms.

(1.6.1) Lateralisation of language

Neuropsychological evaluation plays an important role when interpreting imaging data, for instance, in the lateralisation of language. Traditionally, this is only achieved to a satisfactory standard by the Wada procedure, in particular in the presurgical evaluation of epilepsy patients (Lassonde et al. 2006). The Wada or intracarotid amobarbital procedure (IAP), named after its creator Juhn Wada, involves the unilateral, sequential anaesthetisation of each hemisphere, by way of sodium amytal injection into the carotid artery, to induce a temporary lesion, artificially creating language and memory deficiencies. People naturally differ in their language localisation and lateralisation, with an increasing variability in sinistrals (Henninger 1992, pp148-150). This is even more relevant in patients with epilepsy and those with brain lesions acquired at an early age, who often show atypical presentation of language, with bilateral or right-side dominant presentation (Springer et al. 1999, Müller et al. 1999). Language lateralisation is an important factor to consider when

deciding which areas to spare, for the sake of a positive cognitive outcome following surgery (Henninger 1992, pp148-150). However, in recent years (Bauer et 2014, Szaflarski et al., 2017) research has been conducted to reduce, or replace the use of IAP altogether, because of its invasive, potentially distressing nature (Meador & Loring, 1999) and associated morbidity. As fMRI is now an accepted, trusted, and matured tool in neuroscience, it has been used increasingly to inform surgical decisions, even though this is not yet clinical standard (Rutton & Ramsay 2010). Meta-analysis (Bauer et al.2014) and a recent practice guideline summary (Szaflarski et al. 2017) have found that fMRI could be a 1st triage tool, with IAP only being utilised if fMRI findings are ambiguous. Applications such as above show the clinical potential when combining neuropsychological assessment with imaging methods and how it can inform diagnosis and treatment.

(1.6.2) Combining Neuropsychology and Neuroimaging

Combining neuropsychological methods and findings with neuroimaging techniques has many benefits and is a promising direction for further neuroscientific research. Foremost, a wider spectrum of information is covered, and a single issue is being investigated from various angles. Second, it allows an insight into anatomy whilst utilising clinical tools for the assessment of specific brain structures subjected to damage, in a clinical population, such as epileptic patients, or chronic sleep disorders, such as insomnia, as well as control subjects.

MRI lends itself to both research and clinical applications, because of its better resolution (when compared to Computer Tomography, for instance) and anatomical clarity (Uzzell 1994). The brain comprises different tissue types, which give rise to unique signals when obtaining structural MRI. Grey matter comprises neuronal cell

bodies, which are higher in water content, whereas myelinated axons, the basis of white matter, are fattier (Houston et al. 2013). Relating imaging measures to underlying cellular and molecular events is challenging and changes in cortical thickness may reflect a combination of processes, only one, or none of the suspected ones at all, though unlikely. Some researchers caution, that, although tempting, one should refrain from linking MRI to neurobiological or cellular processes, as evidence is limited (Paus et al. 2008), whilst others are more confident that the dynamic changes observed on MRI may arise from any number of processes, etc. myelination, synaptogenesis, neurogenesis, gliogenesis, altering dendritic structure and vasculature etc. (Zatorre et al. 2012, Houston et al.2013). The development of underlying brain structures will be further discussed in Figure 1.7. This thesis will concern itself with structural imaging methods only. MRI physics and the details of utilised methodology is discussed further in Chapter 2, and more specifically in (2.2).

Many well validated clinical batteries utilise normative data, providing a reference point for results, and allowing researchers to draw conclusions about the neural substrates underlying these cognitive modules. The aim should be to conduct both areas of research equally well, to benefit from the information they provide and the strengths in design they offer. Combining neuropsychological tools with MR images combines the ability to gain a comprehensive picture about an individual's cognitive strengths and weakness, whilst also gaining an insight into the architecture which facilitates it. Applying this clinically would allow for a comprehensive picture of individual capacity, whilst in research applications whole cohorts of groups could be compared. It is rarely ever a single mode of study, driving an entire discipline forward, and so, whilst it is difficult to gain much insight into human neuronal activity and how this facilitates cognition in vivo, much has been learned from rat studies (e.g., Xie et al.

2013) and applied to models in humans. Information from animal research (Van der Worp et al. 2010, Van Essen & Glasser 2018), histological data from tissue samples following neurosurgery (Annese et al. 2004, Cardinale et al. 2014) post-mortem autopsy (Huttenlocher and Dabholkar, 1997, de Brabander et al. 1998), and a variety of techniques such as EEG (Huber et al. 2006), MEG and (f)MRI, have contributed to the much more cognisant view on the processes involved in human cognition. The emergence of advanced imaging and investigation methods has led to a quantum leap in neuropsychological research, by providing neuroscientists and neuropsychologists with many new tools to study the many facets of cognition and its principal brain mechanisms (Lassonde et al. 2006).

(1.6.3) Principles across functional and anatomical architecture

Where neuropsychology and structural imaging methods are being combined, the framework relies on several principles. For example, we are relying on the assumption that functional and anatomical architecture is grossly the same across the cohort being examined.

When testing for language functioning, for example, one would expect grammatical and articulation facilities to be locatable in familiar regions (Tremblay and Dick 2016). Aside from the lateralisation of language (see 1.7.1), localisation of specific language centres is important in pre-surgical patient assessment. Whilst brain mapping is relative to the individual, mapping techniques such as ‘navigated transcranial magnetic stimulation’ (nTMS) rely on an approximate knowledge of the brains underlying modular architecture (Narayana et al. 2017).

Although traditional modular architecture models, such as the language localisation 'Wernicke-Lichtheim-Geschwind model' (Geschwind 1970), have evolved to current 'dual-stream- (Tremblay and Dick 2016), or 'neural network models' , even components of complex network theories, are modular in their most basic elements (Ferdinando 2001, Huang 2021). We therefore must, at least at a basic level, trust the modular architecture of the brain, on order to make predictions when combining structural MRI and Neuropsychological assessments. Some of the relevant principles are outlined below:

(1.6.3.1) Similarity Principle

Functional and anatomical modularity and uniformity across the population are the most basic premise in Neuropsychology. It is assumed that cognitive systems are based on modular architecture, and that cognitive modules correspond to anatomical modules. Based on these assumptions, we can consider observations made from regional brain injury reflective of the cognitive function it controls (Coltheart, 2001, pp. 9-11). Neuropsychology further assumes that the functional architecture and its neural substrates are homogenous across people, to draw generalised conclusions. When considering the application of modern neuropsychology in research, these assumptions are seen in a broader context. The notion of 'normality' is relative in almost all scientific disciplines, as 'normal' usually falls within a prescribed, wider spectrum of what is considered acceptable, and what is not. Modern neuropsychology still relies on a similarity principle (Bigler 2015).

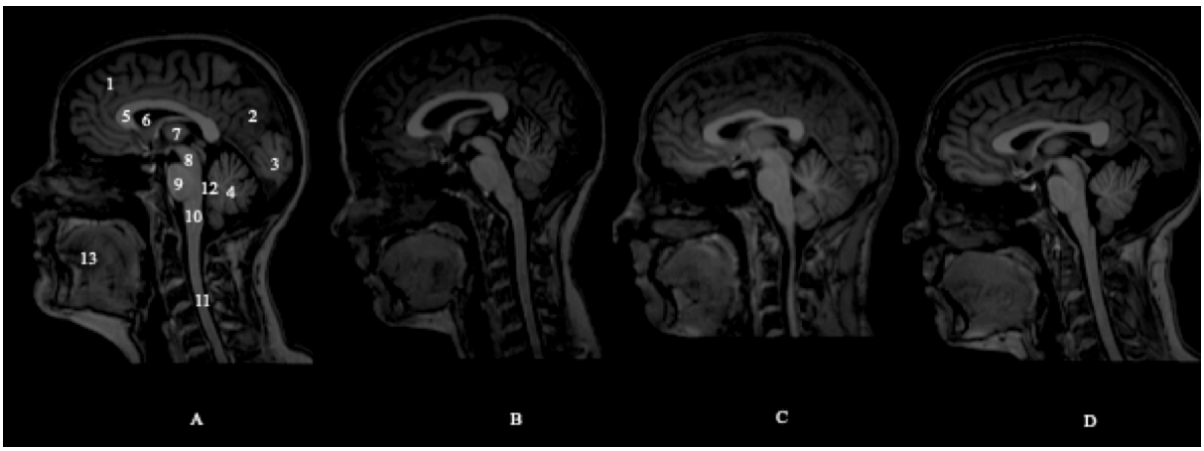


Figure 1.1. Midsagittal T_1 of four participants. Recognisable structures across 'normal' brains have been modelled on participant A. 1=Frontal lobe, 2=Parietal lobe, 3=Occipital lobe, 4=Cerebellum, 5=Corpus Callosum, 6=Lateral Ventricle (Body), 7=Thalamus, 8=Midbrain, 9=Pons, 10=Medulla, 11=Spinal Cord, 12=4th ventricle, 13=Tongue.

Healthy 'normal' brains have a shared neurotypical appearance. Although the brains in Figure 1.1. differ, with the corpus callosum (5) for example, presenting uniquely shaped for each person, they are all similar and identifiable. Landmark structures like the corpus callosum, thalamus, midbrain, pons and cerebellum are recognisable in all individual scans. We might consider a clinical population of epilepsy sufferers homogenous in the way they collectively deviate from the normal and healthy, by exhibiting seizures, in the same way we consider healthy individuals homogenous for the absence thereof. Whilst in a control population homogeneity is assumed, based on the above principle, patient groups often require careful selection, matching syndromes, or lesions, as closely as possible (Parkin 1996, pp14-17).

(1.6.3.2) Symmetry Principle

Neuropsychology also considers the cortex to be symmetrical, in such a way, whereby a patient sustaining a unilateral lesion could be their own control subject, when assessing the severity of the injury (Bigler 2015). Figure 1.2 show the comparison between what would be considered a symmetrical brain, and a brain with atypical symmetry. The abnormality in participant B was an incidental find and subsequently

determined to be a benign cyst, which had no impact on the general functioning of the participant.

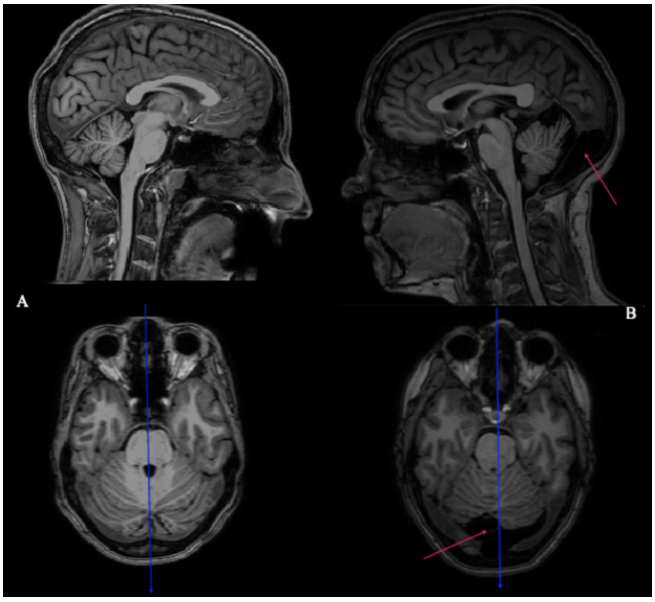


Figure 1.2 Comparison between neurotypical healthy brain (A) and atypical healthy brain (B). The benign cyst (red arrow) found in (B) was an incidental find as part of research participation. Both subjects completed neuropsychological batteries and performed within the normal range without areas of concern.

Whilst both hemispheres are almost identical in macrostructure, the left is associated in 95-99% of dextrals with language function (Corballis 2014), making it the most lateralised of human brain functions (Riès et al. 2016). Homogeneity in a sample would mean to accept that most individuals have a left centred language system, whilst accepting that their language capabilities or skills may differ. Similarly, one would expect the primary sensory area, or primary auditory cortex, to be in comparable regions across a population.

(1.6.3.3) Size-Normalcy, Size-Function and 'Just-right' Principle

Outliers in any population can be expected, cortical thickness measurements congregate within a range of expected values, depending on its underlying cortical structure and varying with age. Average cortical thickness is in the region of 2.5mm, with its highest values around 4.5mm and its lowest 1.5mm. Agranular areas, like the

motor cortex are amongst the thickest cortical regions, whilst primary sensory, calcarine or polar cortex are amongst the thinnest (Solari & Stoner 2011). Global thinning of the cortex can be present as early as middle age but becomes particularly noticeable in the fifth decade of life (Salat et al. 2004). Healthy ageing is associated with a degree of atrophy, whilst neuron numbers remain relatively stable (Morrisons & Hof 1997, Peters et al. 1998). The relationship between cortical thickness, cognition and healthy ageing will be explored in more detail in Chapter 4.

The 'size function rule' relates to the biological principle of allometry. Body size accounts for 97% of brain size, but the size of individual structures within the brain have developed according to the function they serve (Rilling 2006). As stated in the first paragraph, the human brain is not at all remarkable anatomically, and yet cognitively capable of so much more than nonhuman primates or other mammals (Herculano-Houzel 2012). When the human pre-frontal cortex is defined cytoarchitectonically, it is shown to be larger than expected for a primate of our size (Brodman 1912, Passingham 1973, Rilling 2006). The human frontal lobes appear to have specialised in higher order functioning, which resulted in a unique modification on a cellular level (Passingham 2002). Cellular complexity is significantly higher in humans than other non-human primates, with Brodman area 10 approximately twice as large as in great apes (Semendeferi et al. 2001, Rilling 2006). Higher order association cortices have expanded beyond allometrical predictions, suggesting that this disproportionate development aided the evolution of higher-order cognition and language amongst humans, whereas primary sensory and motor areas of the brain have only evolved minimally (Rilling 2006). Whilst the human sense of smell has a far worse reputation than it deserves, and its relative size compared to the rest of the

brain is very small (0.01% of the overall volume), human olfactory abilities are actually excellent (McGann 2017) and subject to remarkable plasticity in congenital or early blindness (Araneda 2016), with increased volume and enhanced functioning seen in individuals with early blindness (Rombaux et al. 2010).

Whilst overall brain volume in adults is positively associated with cognitive ability (Lange 2010), which will be touched upon in chapter 3, lower volumes in the anterior cingulate, and lateral prefrontal cortex, part of the executive control and default-mode network, are associated with Attention-Deficit/Hyperactivity disorder (ADHD) (Kessler 2014). Anatomical size of a given brain region, is therefore grossly connected to the function and complexity of the function it supports (Bigler 2015).

When considering the size of the cortex or cortical regions, the size-function principle does not mean, the bigger the better. As the size-normalcy principle implies, individuals congregate within a range of expected values, usually normally distributed on a bell curve. Though developmental trajectories for different structures within the brain differ (Shaw et al. 2008) brain development outside of the expected range is considered abnormal (Bigler 2015). Microencephaly is brain growth -2 to -3 Standard Deviations (SD) below the expected mean, with -3 SD usually associated with severe cognitive dysfunctions (Pavone et al. 2017), whilst Macrocephaly (+2 SD) and Megalocephaly (<+2SD) refer to brain growth, above the expected range (Tan et al. 2018), which, depending on which underlying cause resulted in the brain overgrowth, is also associated with a range of symptoms (Biran-Gol et al. 2010). The normalcy principle reflects the “just-right” principle, in relation to expected developmental trajectories (Bigler 2015).

(1.7) Limitations combining MRI and Neuropsychology

There is an intrinsic difficulty in translating gross anatomical information conveyed in neuroimaging, into cognitive terms. As Chapter 2 will explore in more detail, MRI imaging is an indirect measurement of brain structure, which makes it susceptible to many variables, such as hydration (Walker et al. 2011). When combining two or more methods, there will inevitably be some sort of interference and noise, both known and unknown, that may affect the results and make their interpretation much more difficult. Some issues may arise from the methodologies used to interpret images, such as voxel-based morphometry (VBM) which is based on the grey matter distribution in the brain. The value at each voxel in the tissue segments can be thought of as representing a proportion of the corresponding tissue in that voxel (Hutton et al. 2009) and in a group cohort may identify areas of grey matter loss, and give insight into subtle structural changes, which may not be easily identifiable in a single patient (Focke et al., 2008). Voxel-based morphometry assessments in patients have shown abnormalities on a standard MRI, but the clinical utility of VBM analysis is constrained by the need to balance sensitivity and specificity and data must be interpreted cautiously (Salmenpera et al. 2007) and may be unlikely because of the lack of robustness in individual comparison (Keller & Roberts 2008). Chapter 3 will take a closer look at voxel-based morphometry in comparison with cortical thickness measurements in relation to an extensive neuropsychological battery.

More issues arise at the interpretation stage. As more and more becomes known about how the brain functions, it is becoming increasingly clear that entire networks, rather than single modalities, are responsible for cognitive function (Ito et al. 2020). As research advances and function-structure models, due to the involvement of neuronal

networks, become progressively complex, interpretation of such models also becomes increasingly difficult.

(1.7.1) Confounding variables in Neuroscience

Whilst at one end of the spectrum, brain pathology and disease affect neuropsychological functioning in the most obvious way and much has been learned from lesion studies, many other non-pathological factors such as lifestyle choices, sleep (Fallone et al.2001), diet (Leidy et al. 2015) or ageing can affect functioning. A major problem with the interpretation of neuropsychological performance is knowing which confounding variables modulate cognition, whether there are interaction effects between two or more factors and whether they reserve any impact to only one cognitive domain, several, or all. Anything that affects the brain on a structural level has the potential to disrupt or alter cognition. Healthy functioning is potentially affected by many variables – more than could ever be reasonably be accounted for in any study.

Aspects of nutrition, such as polyphenols and polyunsaturated fatty acids, are thought to affect adult neurogenesis and play a role in preserving cognition in ageing (Poulose et al. 2017), which may be highly relevant in the context of identifying risk marker and risk mitigators in age related cognitive decline.

Lifestyle choices such as recreational drug use (Liakoni et al. 2015), e.g., cocaine and amphetamines, or soft enhancers, such as energy drinks, caffeine tablets or herbal drugs (Maier et al. 2013), can also affect cognition on a short- and long-term basis. Biological or social factors, such as genetics (for review, see Savitz et al. 2006), socioeconomic background (Noble et al. 2006), social class and birthweight (Jefferis

et al. 2002) can affect, influence, or direct the trajectory of educational attainment. Transient states of anxiety e.g., test anxiety (Maloney et al. 2014) or anxiety because of workload demands or stressors (Heath 2018) can negatively impair cognition and lower performance levels (Gass & Curiel 2011).

Disorders such as clinical anxiety (Generalised Anxiety Disorder, GAD) (Eysenck et al. 2007), major depression (Bora et al. 2013) or post-traumatic stress disorder (Brandes et al. 2002), have also been shown to impair cognition, in particular memory and attention, however it is prudent to point out that there is a high level of comorbidity in these conditions (Spinhoven, et al. 2014) and evidence shows that coexistence of more than one of these disorders can lead to poorer long-term outcome in terms of cognitive deficiency (DeLuca et al. 2005).

Substances such as caffeine (e.g., Kamimori et al. 2015, Temple et al. 2018) and sugar (e.g., Beilharz et al. 2018) have been shown to affect cognitive aspects such as vigilance and attention, which is an important mitigating factor in sleep or attention research.

With age and sleep being two of the most important extraneous variables, this thesis will examine their effects on both cognition and cortical thickness. There is a marked correlation between cognitive abilities and development throughout the lifespan (Bartzokis et al. 2001, Shaw et al. 2006, Schnack et al. 2015) as well as a wealth of research looking at the effects of sleep deprivation, sleep debt (Lin and Dinges 2008). Identifying the structures most affected by cortical ageing, as well as those most affected by individual sleep preference, will be the focal point of this thesis.

PART II

This thesis aims to examine two of the most inevitable and fundamental variables of cognition; ageing (Chapter 4) and innate diurnal sleep preferences (Chapter 5), in their context to cortical thickness and neuropsychology. The following section intends to give a brief overview over the function of sleep and the known cognitive deficits experienced upon sleep loss, whilst the cognitive impact of ageing will be discussed in Section (1.12), where the developmental trajectories of cortical maturation will be examined in more detail.

(1.8) Sleep

With humans spending almost a third of their lives asleep, it is clear that sleep is not only a necessary, but also a time-consuming function. A far cry from ancient views, proclaiming sleep kin to death and linking it to 'forgetting', we now know, that the opposite is true. Sleep is not only a major component in the consolidation of memories and aids remembrance; without it, we could not survive (Sara 2017, Vaccaro et al. 2020).

For many years little attention was paid to the impact of sleep, but with sleep disorders and the cognitive impact of chronic sleep loss becoming a major public health problem in many of the industrialised countries (Roenneberg & Merrow 2016, Grandner 2017, Gulia & Kumar 2018), research has grown increasingly interested (Dai et al. 2019). Despite rising attention, scientists have yet to conclude the primary function of sleep and its impact on human health. Whilst research now recognises its vital importance on the well-being of individuals (Dijk & Sheldon 2015), our 24/7 society has very little regard for it, perhaps due to its failure to understand it (Lockley & Foster 2012, p.1,

40). In addition, the willingness to sacrifice sleep in favour of additional time at work, in particular, is perceived favourably by society, as well as employers (Grandner 2017). With societal attitudes at odds with basic biological needs of the human body, at the expense of human health, more needs to be done to challenge unhealthy behaviours that have a major cognitive and physiological impact.

From an evolutionary and survival standpoint, sleep comes at a risk to the individual and begets major vulnerabilities (Schönauer & Pöhlchen 2018). This is particularly true for those who are not sheltered from the elements, predators, and other dangers, in secure housing. The huge cost associated with sleep, and its ubiquitous nature across all living organisms, however, suggest that there is an overarching adaptive value to it (Lockley & Foster 2012, p.47).

There are various theories which seek to explain the function of sleep and some which suggest that sleep may serve a variety of functions. Neurochemical hypotheses for example, focus on the role of synaptic neurotransmitters in sleep and arousal (Assefa et al. 2015), whilst the essence of recuperation theories is based on wakefulness disrupting the homeostasis of the body and sleep being required to restore it (Hauglund et al. 2020).

Circadian theories of sleep focus on when we sleep, rather than why (Pinel 2003, p.356) and form the basis of chapter 5, which investigates intrinsic sleep preferences and differences in their neural substrates, more specifically morphometric differences in cortical thickness in association with cognitive variances.

Whilst modern humans don't sleep less than our ancestors or those in pre-industrial societies (Youngstedt et al. 2016), present day sleep schedules are often at odds with

individual diurnal sleep preferences (Yetish et al. 2015), to suit the demands and pressures of modern life. This, however, comes at a significant cost to the biological 'inner' clock, which is unable to effortlessly switch between the variable and often unnatural schedules demanded today.

Human beings naturally fall on a spectrum of circadian chronotypes. In pre-industrial societies this likely aided the uninterrupted running and safety of communities. Someone would be awake at all hours during the night, to ensure the protection of the camp, tend to young children or fires (Ekirch 2016). Primitive lighting, such as fires, lamps or candles have long been used to manipulate light exposure and extend the day (Dijk & Skeldon 2015) and allow selected activities to take place past sundown (Ekirch 2001), but with the rise of the incandescent electric lighting, a new era began. Light activation is a major determiner of human sleep and circadian rhythm control (Yetish et al. 2015) because it entrains the inbuilt Master clock (the suprachiasmatic nucleus), and in turn affects all peripheral clocks (e.g., other organs, digestive rhythms, etc.) (Roenneberg & Merrows 2016, Figure 1.4).

Circadian Chronotype is a classification, which defines an individual's genetic predisposition to specific diurnal sleep timing. Some are naturally predisposed to rise early, whilst others fall on the other end of the spectrum and present extreme 'night owl' tendencies (Roenneberg et al.2003), going to bed late, and rising later in the day. Although Chronotype distribution is derived from polymorphisms in clock genes (e.g., CLOCK, Bmal1, Cry1/2, PER1/2/3 & casein kinase /d/e, Brukamp 2009), sleep preferences and requirements also change based on developmental age and environmental factors (Roenneberg & Merrow 2016).

The phase reference point for sleep, is the midpoint between sleep onset and waking (Benoit et al. 1981), as midsleep has been reported as the best phase anchor point for melatonin production (Terman et al. 2001).

Human circadian rhythm control is partially mediated by the effect of light on the melanopsin system, and peripheral body-clocks develop a phase relationship to the suprachiasmatic nucleus, based on the light environment and phase of entrainment (Roenneberg & Merrow 2016).

(1.8.1) Biorhythms and Biological Clocks

Biological clocks are usually divided into Ultradian, Circadian or Infradian oscillators (Brukamp 2009). Ultradian rhythms occur more than once daily (<20 hours e.g., Sleep cycles), Circadian rhythms once daily (20-30 hours e.g., Core Body temperature) and Infradian Rhythms less than once daily (>30hours e.g., Menstrual cycle) (Rosenberg et al. 2014).

Almost all biochemical, physiological, and behavioural processes display a degree of need for homeostasis and rhythmicity, though the sleep-wake-cycle is the most obvious, of the circadian rhythms (Pinel 2003, pp.357-358). The sleep-wake homeostasis is an internal biochemical process which results in an inbuilt propensity to generate a steadily increasing sleep drive following prolonged wakefulness (Porkka-Heiskanen et al. 1997), balanced against and countered by the circadian drive for arousal, until the onset of melatonin production prepares the body for sleep (Moore 1996).

Biorhythms are usually synchronised by exogenous stimuli, such as light, or endogenous, naturally occurring, inherent mechanisms (Foster & Kreitzman 2017, pp.2-3). A key pacemaker in the circadian rhythm, utilising light as its external stimuli,

is the suprachiasmatic nucleus (SCN, see Figure 1.3), which is the body's 'internal biological clock'. The SCN receives afferent fibres directly from the retina via the retino-hypothalamic tract (Brukamp 2009, p.37-38, Foster & Kreitzman 2017, p.53-55) and orchestrates rhythmicity throughout peripheral 'clocks' in the body. The SCN drives the sleep-wake rhythm but is also a driver of the endocrine-(Morris et al. 2012), insulin sensitivity- and glucose rhythms (Poggiogalle et al. 2018), amongst other.

(1.8.2) Circadian Rhythm, Entrainment and Zeitgebers

Daily life is structured by three clocks (Figure 1.3): The solar clock, the social clock and the inherent biological clock (the SCN, Roenneberg et al. 2003). External events producing bio-rhythmicity are called Zeitgebers (German for "Time-Giver") and the circadian clock is usually entrained to the 24h of the solar clock. However, even in the absence of external temporal cues, humans usually manage to maintain all of their circadian rhythms and the circadian cycle ends up at around 25 h (Moore 1999, Roenneberg et al. 2003). In the absence of exogenous cues e.g., natural light, other Zeitgebers, such as social interaction, or structured mealtimes, can entrain and maintain the circadian cycle (Mistlberger et al. 1996, Roenneberg & Foster 1997, Rajaratnam & Arendt 2001).

The absence of all exogenous cues usually only occurs in laboratory conditions (i.e., in constant routine experimental protocols). In natural circumstances the social clock is generally not strong enough to advance the circadian clock, or phase of sleep, alone. The phase of entrainment therefore also depends on the strength of the zeitgeber. Light intensity as perceived by the human eye, is measured in luminous flux (lux). Prior to artificial lighting, humans were exposed to either high (>300lux) or dim (<30 lux) light intensities.

Today intermediate light intensities are more common ranging between 30-300 lux (Phillips et al. 2019). Whilst mid-day light intensities outdoors range from 10 000 lux upwards, indoor environment are generally below 400. Various studies (e.g., Okudaira et al. 1983, Savides et al.1986, Rimmer et al. 2000, Gronfier et al. 2004) have shown that longer exposure to outdoor light produces phase advancement of the sleep period. Likewise, light intensities as low as 6 lux have been shown to disrupt melatonin onset by around 50% (Zeitzer et al. 2000, Phillips et al. 2019). The importance of the light environment, and the timing of light exposure can therefore not be understated.

In a natural light-dark cycle the peripheral organs develop a characteristic phase delay to the SCN rhythm. Cortisol and melatonin and body temperature are peripheral rhythms, that have been extensively used as markers for the circadian phase of the suprachiasmatic nucleus (Moore et al. 2013), but methodologies for measuring these biomarkers are based on onerous protocols and requiring a high level of participant compliance (Roenneberg & Merrow 2016, Dijk & Duffy 2020).

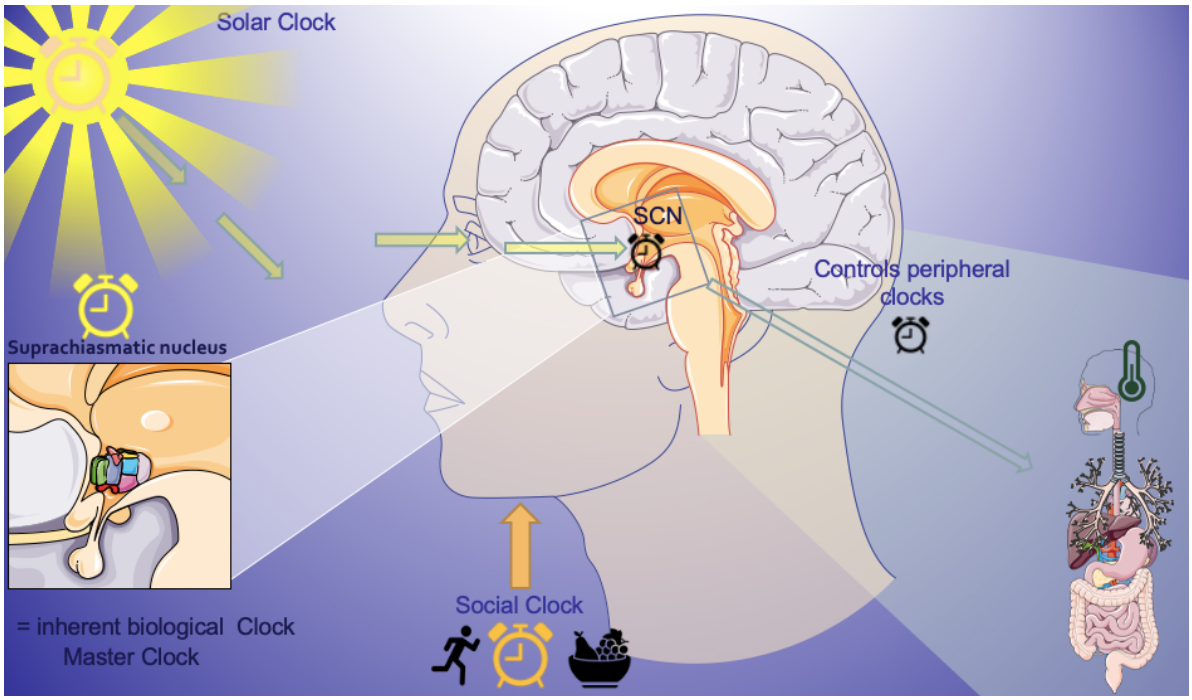


Figure 1.3 The 3 clocks of daily life. The suprachiasmatic nucleus receives light stimuli directly from the retina and serves in a hierarchical structure, as the body's 'Master Clock', sending information to other 'clocks. Peripheral oscillators, e.g., other brain areas, heart, kidney etc. adopt internal phase relationships based on the information from the SCN (Roenneberg & Merrow 2016).

(1.8.3) Circadian rhythmicity and Human Health

The relationship between individual health and wellbeing and the circadian clock is complex and encompasses more than just simply satisfying the basic need for sleep. Nearly all organs, peripheral tissues and cells exhibit some circadian rhythmicity. It therefore makes sense that optimal health requires the synchronisation of all internal clocks (Lockley & Foster 2012, pp.127-128).

Whilst sleep may be the suspension of most conscious physical activity, it is not a state of neural quiescence. Many essential activities such as cellular repair, removal of toxins (Assefa et al. 2015, Jessen et al. 2015, Hauglund et al. 2020), memory consolidation (Wei et al. 2016, Sara 2017) and information processing, occur during this vital rest period and neural recordings and functional brain imaging have shown that neuronal activity only decreases by about 10%, compared to waking (Hobson et al. 1998). Brain function and the maintenance of consciousness is associated with high metabolic cost, of up to $1/5^{th}$ of the overall body metabolism (DiNuzzo & Nedergaard 2017). The metabolic cost of sleep only decreases to around 85% during non-Rapid-Eye-Movement (non-REM) sleep (Stender et al. 2016), whilst Rapid-Eye-Movement sleep has been shown to be as costly as wakefulness (Wehr 1992).

(1.8.4.) Sleep Stages and Sleep Quality

'Sleep' is characterised as a heightened anabolic state and thought to aid the rejuvenation of the body. It is broken down into 5 distinct stages, which consist of both rapid-eye-movement and non-rapid-eye movement sleep (Hellier 2015, p.965). From a state of wakefulness (W) humans cycle between non-rapid eye movement stages N1, N2 and N3 / N4 (Slow Wave Sleep) and the rapid-eye-movement stage (REM).

Sleep stages are distinguished by brain wave activity, or synchronised oscillations, where neurons release their action potential in a coordinated manner, which can be measured with an electroencephalogram (EEG) (Memar & Faradji 2018).

Wakefulness / Pre-sleep

During wakefulness, brain activity shows alpha and beta waves. Eye-open wakefulness is characterised by predominantly beta-waves, which signal alertness and focus, which changes to an alpha rhythm as individuals become drowsy and close their eyes (Hellier 2015, p.966, Memar & Faradji 2018).

Non-rapid eye movement stage N1

Stage 1 in the lightest stage of sleep and characterised through more than 50% of the alpha rhythm. This stage accounts for about 5% of a single sleep cycle lasting about 90-110 minutes. During this stage brain wave activity slowly transitions into theta waves.

Non-rapid eye movement stage N2

N2 is categorised by theta waves, with random short bursts of increased frequencies, called ‘sleep spindles ‘. During this stage both body core temperature and heart rate drop. The sleep spindles which characterise this stage are thought to inhibit complex processing, reducing arousal from external stimuli and thus ensuring sleep tranquillity (Lachaux et al. 1999). They are also thought to assist with sleep-based memory consolidation (Hellier 2015, p.967). Adults spend most of their ‘sleep’ in N2 (Malik & Wu 2018).

Slow Wave Sleep (SWS) Non-rapid eye moment stage N3 / N4

N3 and N4 are considered the ‘deep sleep’ or ‘slow wave sleep’ stage, and characterised by theta waves transitioning to delta waves, which are lowest in frequency, and highest in amplitude, when compared to alpha, beta and theta wave oscillations. This stage has the greatest arousal threshold, and the sleeper is generally less responsive and non-reactive to external stimuli. Being awoken during this stage of sleep will lead to sleep inertia or mental fogginess (Hellier 2015, p.968). Delta oscillations are associated with the release of a growth hormone necessary for the process of healing (Van Cauter et al. 2000, McGinty & Szymusiak 2005).

Rapid-Eye-Movement Sleep (REM)

REM sleep, associated with dreaming, is characterised with the brain wave oscillations of a relaxed, awake individual, however, most muscles are atonic, with the exception of eye and diaphragmatic breathing muscles (Della Monica et al. 2018). REM sleep accounts for approximately 25% of sleep in adults and appears to be a physiological requirement for most mammals (Hellier 2015, p.968). Exposure to stressful situations or deliberate deprivation of REM sleep, for example, leads to an increased amount of time spent in this stage during the next sleep cycle (Beersma et al. 1990, Sucheki et al. 2012).

Sleep requirements and mechanisms change over the course of the lifetime. Whilst newborns require between 12-18 hours of sleep, often entering REM sleep directly, and spending approximately 50% in this phase, adults only require around 7-8 hours,

progressively entering deeper sleep, whilst cycling through sleep stages N1, N2 and N3 (non-rapid eye movement sleep) into REM sleep, spending most of their time in stage N2. (Zajak et al. 2010). As people enter old age, they tend to spend less time in Slow wave sleep N3 and increasingly more time in N2.

Whilst sleep quantity is important, the specific characteristics of individual sleep stages make it clear that sleep quality is of equal importance ensuring that enough time is spent in each sleep stage, depending on developmental age (Ohayon et al. 2017).

Research has consistently shown that accumulated sleep pressure, caused by prolonged wakefulness or accumulated sleep debt, impact upon the validity of neuropsychological findings (Yoo et al. 2007) in otherwise healthy individuals, through impaired cognition in almost all areas of task performance (Krause et al. 2017, Akers et al. 2018), decreased attention, performance, mood (Dinges et al.1997) and impaired memory consolidation (Karni & Sagi 1993, Stickgold et al. 2001, Halassa et al. 2009). Moreover, 20% of car accidents are attributed to sleepiness, as the main or a major contributing cause (Mittler et al. 1988) and sleepiness was also linked to increased accidents in a simulated driving task amongst professional drivers (Russo et al. 2003).

Sleep disorders are also often intrinsically tied to neuropsychological disorders seen clinically (Waters & Bucks 2011), with approximately 90% of patients with depression also complaining of sleep impairments (Jannson-Frojmark & Lindblom 2008), but comorbidities also present in almost all major psychiatric and neurological conditions, such as schizophrenia (Lee & Douglass 2010, Fleming 2018 pp. 99-107), showing a connection between low mood and poor sleep.

It is important to point out that chronic sleep restriction, accumulated through fewer than 6 hours of quality sleep per night, has been shown to produce cognitive impairments, equivalent to those seen after 2 nights of total sleep deprivation (Van Dongen et al. 2003, Dai et al. 2018). Sleep debt, social jetlag and long sleep inertia times can therefore have serious consequences on performance, health and well-being (Fallone et al. 2001).

For the purposes of this thesis, the term sleep debt is used as an umbrella term describing the state of having sustained a loss of sleep through e.g., shift work, sleep disorders or jet lag. The term sleep debt is intended to define an accumulation of sleep loss over a period of time. Sleep debt may occur when sleep onset time is consistently delayed, whilst sleep termination time remains constant, or when sleep termination occurs before a full night's sleep has been achieved (Van Dongen et al. 2003). Sleep debt can result as a consequence of social jetlag. Social jetlag occurs when there is a marked difference between diurnal sleep behaviour on workdays versus free days. If one's natural sleep propensity is at odds with the social requirements dictated by working hours, for example, a social jetlag occurs, whereby the internal clock fails to effortlessly switch between, and the body becomes desynchronised (Roenneberg & Merrow 2016). If desynchronisation prevails over a prolonged period of time, sleep debt becomes a chronic, because sleep behaviour on free days is unable to shift the internal sleep rhythm enough to recover sufficiently.

(1.9) Sleep loss and Cognition

Poor sleep quality and overall accumulation of sleep debt have been strongly associated with adverse health outcomes (Grandner 2017). Accumulative and chronic sleep deprivation been associated with weight gain (Markwald et al 2013), cardiovascular disease (Klein et al 2004), a 33% risk increase for diabetes (Eckel 2001, Patterson et al. 2004), osteoarthritis (Patterson et al. 2004), and cancer (Callee et al. 2003) as well as raised inflammation markers, hypertension, and hypercholesterolemia (Grandner 2017). Aside from associations with a variety of physical ailments, chronic sleep loss has also been associated with varying degrees of cognitive deficits. Though not intended to be exhaustive, the below list aims to provide an overview over the cognitive deficits associated with sleep deprivation:

(1.9.1) Executive Function

Executive functions are higher order cognitive processes such as working memory, forward planning, decision making and problem solving and are commonly associated with the pre-frontal cortex (Kerr & Zelazo 2004, Poletti 2010), although a prominent executive functioning centre is also located in the anterior cingulate cortex (ACC) (Peterson & Posner 2012). Executive functioning is one of the most fundamental processes in the brain, as it relies on vigilance and attention (Lim & Dinges 2008). It is divided into several components summarised below:

Working Memory:

With working memory being subdivided into the phonological loop, the visuospatial sketchpad, the episodic buffer, and the central executive system (Baddeley 2000), the effect of sleep deprivation on working memory

performance appears to depend on which underlying system is being tested (Alhola and Polo-Kantola 2007). Tasks requiring a lower level of vigilance or concentration, appear to be affected more, than those, more complicated and engaging in nature. Whilst working memory tasks, such as delayed digit recall tasks in Frey et al 2004 and Pilcher et al 2007, showed an overall decreased response time and reduced accuracy, more complex working memory e.g., n-back task in Tucker et al 2010, verbal working memory or visuo-spatial working memory tests in Nilsson et al. (2005) and Quigley et al. (2000), remained largely unaffected.

Lim and Dinges (2008) proposes that this is due to basic working memory relying far more on attention, than working memory, which requires more executive functioning components to work effectively (Turner et al. 2007).

Inhibition:

Behavioural inhibition i.e., the ability to inhibit a pre-potent response (e.g., GO-NO GO task) is affected in sleep loss (Stenuit & Kerkhoff 2008), with omission and commission errors increasing with time spent awake (Drummond et al. 2006, Harison, Jones & Waterhouse 2007). This was further evidenced by abnormal modulation of pre-frontal and anterior cingulate gyrus activity (Drummond et al.2006).

Verbal Fluency:

Deficits in verbal fluency following sleep loss is common, with reports of fewer words and preservation of incorrect responses on tasks of semantic and phonetic fluency (Patrick & Gilbert 1986, Harrison & Horne 1997, 1998). Recent studies were unable to replicate these results, however (Tucker et al. 2010).

Problem solving, creative thinking and planning:

Sleep loss tends to result in longer response times, together with increasing commission errors (Killgore et al. 2008). Anatomically this appears to be linked to the frontal lobes and the anterior cingulate cortex (Waters & Bucks 2011).

Mental Flexibility and Task Switching:

Trail making, and symbol digit modality tests have shown to be negatively affected with decreased performance speed, in relation to poor sleep (Stenuit & Kerkhoff 2008).

(1.9.2) Memory:

There is increasing evidence that sleep in important for learning and memory consolidation of newly learnt skills and words (Waters & Bucks 2011, Sara 2017). Performance appears to be generally affected through lower overall functioning, lower recall (Compos-Morales et al.2005), slower list, prose and paired learning, as well as poorer semantic memory (Drake et al. 2001). Memory appears to be affected by the time spent awake and showed dysfunctional hippocampal activation during memory encoding in sleep deprived subjects (Yoo et al.2007). Verbal learning was impaired following sleep deprivation, with simultaneous abnormal prefrontal and parietal lobe cortex activation, and reduced temporal lobe activation, being observable on MRI (Drummond et al. 2000).

Short term memory:

Literature findings on the impact of poor sleep on STM have been mixed. Some studies report impaired digit recall performance (Frey et al 2004) and spatial memory impairment of around 5-10% (Ferri et al. 2001), whilst others are unable to replicate these findings (Quigley et al. 2000). Functional imaging

studies have been more insightful with sleep deprivation being linked to reduced intraparietal sulcus activity and reduced memory capacity (Chee & Chuah 2007).

(1.9.3) Language:

Skills relying on the retrieval of existing and previously acquired knowledge, appear largely unaffected by sleep disruption. Participant performance on the Wechsler Test of Adult Reading (WTAR), sentence completion, reading comprehension, logical reasoning, and grammatical reasoning, remain intact (Pilcher et al. 2007, Waters and Bucks 2011).

(1.9.4) Mental Arithmetic:

Arithmetic skills are affected by sleep deprivation, evidenced by slower performance, and increased errors (Frey et al. 2004), though performance is also susceptible to time spent awake (Stenuit & Kerkhofs 2008). Structurally, sleep loss in relation to mental arithmetic was observed through decreased activation in the bilateral prefrontal cortex and abnormal activation in the parietal lobe (Drummon et al. 1997)

(1.9.5) Motor Performance and Visual-Spatial Skills:

Motor performance shows a decrement by approximately 30% in terms of speed and accuracy (Williamson & Freyer 2000) in sleep disrupted participants. Accidents in simulated driving were linked to deficits in saccadic eye movements and smooth eye pursuit in sleep deprived individuals (Russo et al. 2003).

(1.9.6) Reaction Time:

Insufficient sleep produces decrements in simple reaction time (SRT) speed, as well as in complex reaction time (Stenuit & Kerkhof 2008), though speed was more affected than accuracy (Koslowsky & Babkoff 1992).

(1.9.7) Social Cognition:

Emotional decision making (Killgore, Balkin & Wesenstem 2006), social and interpersonal functioning (Killgore et al. 2008) and moral judgment (Killgore et al. 2007) were all found to be significantly impaired in sleep deprived individuals.

(1.9.8) Summary:

Both, total sleep deprivation, as well as accumulated sleep debt over time, result in impaired cognitive performance. Areas of cognition requiring greater amounts of attention and vigilance are impaired disproportionately as general processing capacity is reduced (Alhola & Polo-Kantola 2007). Inadequate sleep leads to insufficient restorative and rejuvenating activity which would normally occur during restful sleep. This disrupts inter-neuron communications, through slower neuron response time, weaker action potential and slower transmission rates, leading to slower processing speed, lower processing capacity and mental lapses in attention and visual perception (Nir et al. 2017).

Whilst the exact function of sleep is not yet fully understood, it is clear that it is of vital importance at any developmental stage to facilitate optional cognitive potential.

PART III

From an anatomical standpoint, this thesis primarily assesses cortical thickness measurements following macro anatomical landmarks and examines how they relate to neuropsychological data and in relation to common nuisance factors. Cortical thickness is defined as the measured distance in mm, between the white matter surface i.e., the interface between grey matter and white matter, and the pial surface i.e., the interface between the grey matter surface and cerebrospinal fluid (CSF) (Figure 1.5). Cortical thickness reflects the size and morphology of the encephalon and thus, informs indirectly of its composition, as it is considered to reflect packing density of neurons (Sowell et al.2003).

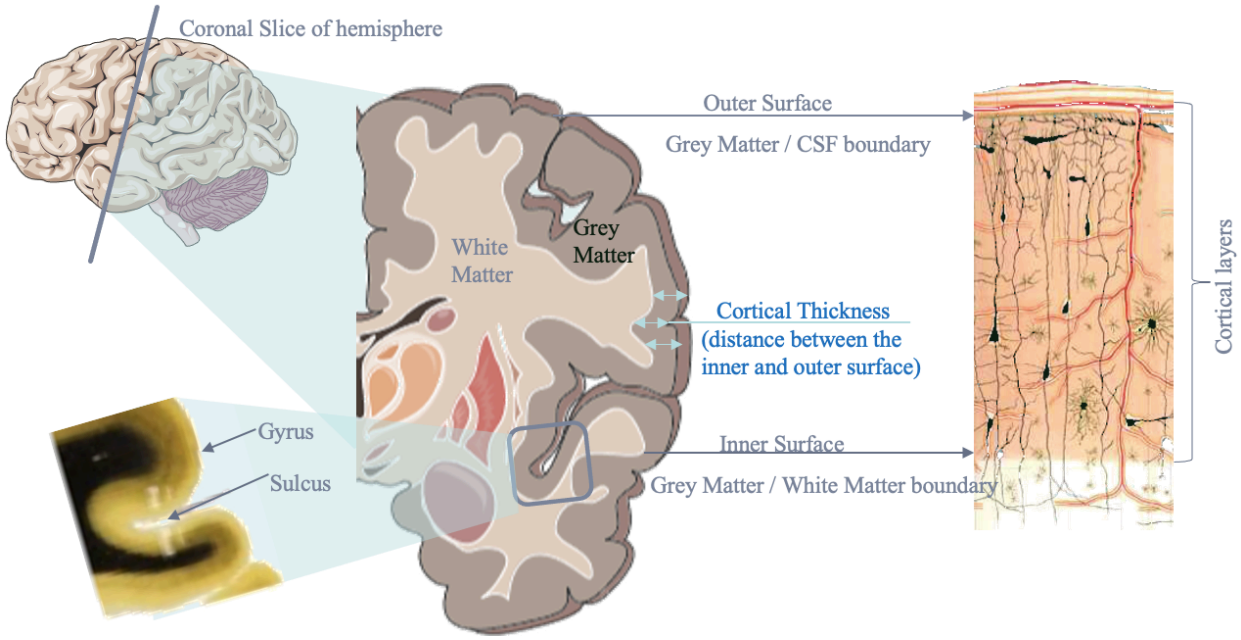


Figure 1.4 Illustration of cortical thickness measurement in relation to the whole brain and its underlying composition (concept based on Dahnke et al. 2012)

(1.10) Cortical thickness as a trajectory to behaviour

Cortical thickness analysis is a relatively new neuroimaging method for assessing brain morphology, offering complementary information for understanding brain anatomy in a biological and topologically meaningful manner. It purports to measure a tangible physiological construct relating to brain morphometry and may therefore be a much more sensible measurement in relation to underlying neural processes than voxel-based measurement type approaches, for instance.

Several studies suggest that cortical thickness relates to cognitive ability more closely than other morphometric measurements (Haier et al.2004, Luders et al., 2009, Narr et al. 2007, Karama et al. 2009, Choi et al. 2008, Colom et al. 2009). Point estimates of the thickness in a given region are likely able to reflect on neuronal and structural organisation (Narr et al. 2009), rather than simply indicating the density of grey matter tissue within the search space. Whilst voxel-based morphometry (VBM), for instance, is a somewhat arbitrary measure, cortical thickness directly relates to cortical gyrification and physiology. This has been verified with histological measurements by Cardinale et al. (2014) who compared actual brain tissue with cortical thickness measurements obtained by Freesurfer (http://surfer.nmr.mgh.harvard.edu/). Cortical reconstruction of individual cortices can be computed in Freesurfer with great precision and therefore shows immense promise in clinical application, for example in pre-surgical planning.

In validation studies where manual and automated measurements were compared, results agreed to within 0.2mm (mean difference 0.077 mm), showing high levels of reliability (Cardinale et al. 2014).

Previous research has verified cortical thickness measurements against histological analysis, manual measurements, and voxel-based thickness estimation methods (Annese et al. 2004, Cardinale et al. 2012, Clarkson et al. 2011) and the advantages of such in vivo measurements are obvious.

Manual measurements, in particular those pertaining to synapse counts or packing density of neurons, are time consuming and difficult. Availability of fresh post-mortem brains, in particular developing brains, is limited and studies are often restricted to a relatively small number of samples, posing difficulties for statistical power and overall representativeness (Huttenlocher & Dabholkar 1997, Paus et al. 2008). Though post-mortem studies have contributed and continue to contribute much to the field of neuroscience, investigating functioning brains in vivo, through neuroimaging, is invaluable to research. In order to understand cortical thickness as a measure and interpret it in the most sensible manner, one needs to understand the development and underlying architecture of the brain.

(1.11) The cytoarchitecture of cognition

The maturation process of human brain morphometry is closely related to an individual's intellectual development, but the correlation between cortical thickness and intellectual ability is not linear throughout the lifespan and closely related to age (Chastelaine et al. 2019). This section intends to inform on the critical events in this timeline, indicative of the developmental trajectory of an individual and to demonstrate that the relationship between cognition and cortical thickness is dynamic. A neuropsychological assessment, as discussed above, is a snapshot in time, of an individual's abilities and must take into account several factors, which may impact on

performance. Cortical thickness, likewise, is a dynamic marker and must be interpreted with other factors in mind, most notably age. Whilst the construct of intelligence in relation to cortical thickness is investigated further in chapter 3, the topic of ageing is further explored in Chapter 4.

(1.11.1) Intelligence

The construct of intelligence (g) is defined as an individual's general information processing capacity (IPC), or mental manipulation abilities (Hofman 2012), which is determined by a combination of relative neuron numbers, relative packing density and relative axon transmission velocity (Dicke & Roth 2016). Not all brain regions are correlated with intelligence and different constructs of intelligence develop and peak at different times Hartshorne and Germine (2015). Two of the most cited concepts of intelligence are those of gC- crystallised intelligence and gF – fluid intelligence (Grey et al. 2003, Choi et al. 2008, Goriounova & Mansvelder 2019). Whilst gF, defined as perceptual reasoning skills, tends to reach its peak in early adulthood, gC goes on to develop until well into adulthood, with average vocabulary peak performance around 50 years of age.

Furthermore, the visual, auditory and limbic cortices, are known to myelinate early and show a more linear pattern into ageing, whilst following a cubic trajectory over span of the entire lifetime (Sowell et al. 2003). Table 1.1 summarises the developmental trajectories in relation to their underlying cortical structures, whilst Table 2.1 (Chapter 2) links these to the regions of interest, according to the Freesurfer Desikan Killiany (DK) atlas. Figure 1.5 illustrates the differences in the underlying cortical structures summarised in Table 1.1. Regions without predictive value are e.g., the precentral cortex (agranular), postcentral cortex (granular), transverse and temporal cortices (granular), pericalcarine cortex (granular). Those with no prominent correlation to

intelligence are e.g., the entorhinal cortex (agranular transition cortex), and limbic structures (agranular) which tend to be heterotypical, whilst association cortices are associated with homotypical isocortical regions. Underlying cortical structures therefore appear to match broadly with developmental trajectory and intelligence construct.

(1.11.2) Early Development

Postnatal brain maturation involves dynamic changes, which are temporally and regionally specific. Between childhood and early adulthood grey matter volumes decrease and white matter volumes increases, however maturational and developmental trajectories are distinct between more primitive brain structures than phylogenetically new ones (Sowell et.al. 1999a, b, 2004, Houston et al. 2013). Figure 1.5 shows a brief outline of the relative phylogenetic age of brain structure and gives a summary of interchangeable nomenclature for each distinct part (Basma et al. 2020).

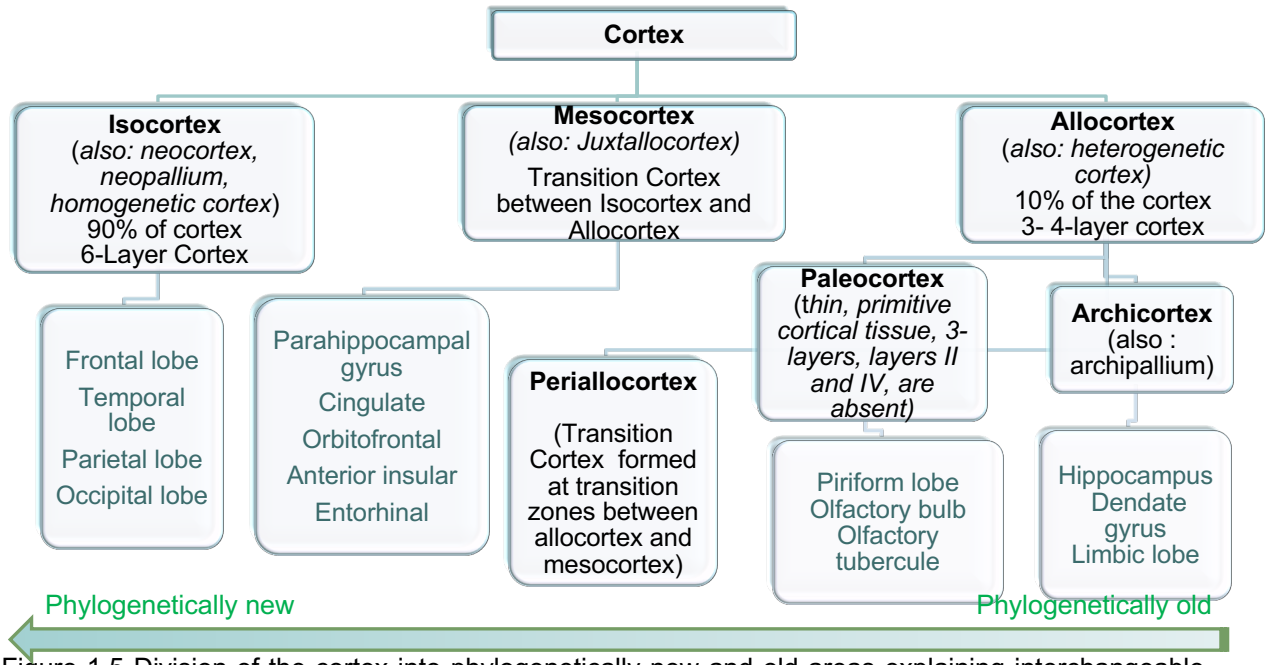


Figure 1.5 Division of the cortex into phylogenetically new and old areas explaining interchangeable terminology (based on Solari & Stoner 2011, Basma et al. 2020)

In early adolescence thinning is apparent on large areas of the dorsolateral frontal, bilateral occipitoparietal and anterior & posterior temporal cortices, where rates of loss are in order of 0.1-0.3mm per year, whereas thickening is restricted to the left anterior and posterior perisylvian regions, that correspond remarkably well with traditional concepts of Broca's and Wernicke's areas, gain around 0.05-0.2 mm per year (Sowell et al. 2004). This shows how cortical thickness developmental trajectories for regions reasoning tasks, differ. gF (abstract reasoning) tends to follow a logarithmic or cubic development over time (see also Table1.1 Shaw et al. 2008), whereas gC aspects, such as verbal comprehension, increase over time, with acquired knowledge, influenced by education and experience, and tend to follow a quadratic development over time (Choi et al., 2008).

Following pre/early adolescent cortical thickness peak, formation, and usage dependant selective elimination of synapses (Huttenlocher & Dabholkar 1997), helps create and sculpt neural circuitry, including those supporting cognitive abilities (Hensch 2004). Newer information suggests that cortical adulthood does not exist, but rather, that the cortex continues to change and develop throughout the lifespan, in particular in individuals with a higher IQ (Schnack et al. 2015).

Figure 1.9 demonstrates how the neuroanatomical expression of intelligence is dynamic, across the lifespan (Shaw et al. 2006) and how the relationship between intelligence and cortical regions varies according to developmental stage. Whilst short term memory function peaks around 20 years of age, working memory function usually peaks around 30 years of age and emotion recognition ability around age 40. A peak in total myelin volume has been observed around age 30, decreasing by 10% per decade thereafter (Dennis & Thompson, 2013).

(1.11.3) Early Adulthood

Though the dynamics are not fully understood yet, a connection between developmental trajectories and cognitive function has been found. Between adolescence and early adulthood, a thinner cortex points to advanced biological development (Sowell et al. 1999). Cortical thinning in the frontal lobes, in particular, appears to be part of maturational events, such as synaptic pruning and continued myelination (Sowell et al. 2001). In addition, the cortices of children with differing intellectual aptitude, demonstrated different rates of maturation. In the frontal and temporal regions, in particular, a higher IQ was associated with a thinner cortex, in younger subjects, though this relationship reversed in adolescence (Shaw et al. 2006). Table 1.1 illustrates how cortical thickness trajectories in different brain regions appear to change in relation to their underlying morphology and structural organisation (Shaw et al. 2008). Maturation of the human cortex through cortical thinning has been associated with 2-3-fold reduction in synapses during adolescence and young adulthood, possibly reflecting dynamic reorganisation of the synaptic circuitry during development (Huttenlocher & Dabholkar 1997). In addition, ongoing intra-cortical myelination is responsible for vigorous thinning in the visual cortex, for example (Natu et al. 2019). By 20 years of age, males have a total of approximately 176.000 km of myelinated axons compared to approximately 149.000 km in females.

Post-mortem studies have shown that myelination, synaptic pruning continues into adulthood, in the third decade of life and perhaps beyond (Huttenlocher & Dabholkar, 1997).

Since brain morphology and cortical thickness are dependent on the relative neuron packing density of the underlying cortical structure, assessment of cortical thickness in relation to relationship to cognition is sensible.

Table 1.1 is a brief overview categorising cortical regions, by developmental trajectory, underlying cortical type/ structure and Brodman area. 'Trajectory' defines the developmental curve of cortical thickness over the lifetime: 'Cubic' shows an initial childhood increase, followed by adolescent decline, then stabilisation in adulthood. 'Quadratic' shows an increase, then decrease, but no stabilisation, whereas 'Linear' shows a steady decline (Solari & Stoner 2011). Broadly speaking, homotypical granular isocortical regions, e.g., pre-frontal regions, have a cubic developmental trajectory, whereas transitional areas either follow a quadratic (e.g., agranular heterotypical cingulate cortex) or linear (e.g., entorhinal cortex) decline with age (Sowell et al.2003).

(1.11.4) Adulthood (Midlife)

Decline in gray matter volume becomes apparent between early adulthood and old age, whereas white matter volume increases between 19 and 40, but declines thereafter (Bartzokis, et.al.2001). During adulthood the cortex continues to change, forming and optimising long range connections by age 30, reflected by initial thickening in some regions (Schnack et al. 2015) e.g., areas of the right cingulate cortex (Habeck et al. 2020) anterior cingulate and medial orbitofrontal / subcallosal cortex (Salat et al. 2004). Brain plasticity may therefore be another indicator of lifetime developmental trajectory of cognitive function, since cortical adulthood, per se, does not seem to exist, in particular in high functioning individuals (Schnack et al. 2015). Education level, and ongoing education has been shown to moderate age-related atrophy and protect against the risk of Alzheimer's Disease (AD) incident. With learning actively impacting on the length of the distal branches of neuronal cells, some interindividual variation may therefore be explained by the level of education received (Jacobs, et.al., 1993).

According to Jacobs et al. (1997) dendritic neuropil remaining relatively stable after 40 years of age, only "*underscore the importance of lifelong commitment to a cognitively invigorating environment*".

As described in early cortical development, high and low functioning individuals appear to take moderately different cortical developmental trajectories throughout their lifetime. Additionally, patterns of thickening and thinning in adulthood are not only related to age and education level, but also relative to individual cortical thickness. High functioning individuals, for instance, show thickening in the right posterior and isthmus cingulate, which is correlated to an incidence of thinning in the right superior temporal and temporal pole area (Habeck et al. 2020).

Further, in adulthood, higher intelligence is also associated with more pronounced thickening in regions corresponding to gF and postpone thinning of specific areas of the cortex (Brans, et.al.2010). Large changes of CT over time, in particular, are associated with a higher IQ, whilst the cortex changes less drastically in those with a lower Information Processing Capacity (IPC). There is also evidence suggesting that high IQ individuals use their brains more efficiently (Neubauer & Fink, 2006), through increasing the efficiency of existing networks over development (Bullmore & Sporns, 2010). Plasticity of the brain may therefore be as important to the construct of intelligence as brain structure itself (Schnack et al. 2015). This could be a key point in the evaluation of cortical thickness in relation to cognition and predicting cognitive outcomes, depending on developmental trajectory.

(1.11.5) Late Adulthood

Although, healthy ageing is generally associated with overall cognitive decline, verbal fluency and verbal comprehension abilities go on to develop until age 50 -60 (Hartshore & Germine 2015, Schnack et al. 2015, Goriounova et al.2018).

The healthy ageing process is characterised by an overall decline in total brain weight, global cortical thinning and gyral atrophy (Kemper 1994, Raz 2003, Salat et al. 2004). Mean cortical thickness values decline steadily with age, and cortical thinning is present as early as middle age and apparent within the third decade of life. The ageing process then accelerates dramatically during the sixth and seventh decade, with atrophy unrelated to initial thickness (Fischl and Dale 2000).

Neuron numbers in humans (and other mammals) remain relatively preserved in old age. Studies have found comparable neuron counts between younger and older subjects (Morrisons and Hof 1997), suggesting that programmed cell death is unlikely the main cause of age-related atrophy (Giannaris and Rosene 2012, Tower 2015).

Following dynamic changes in the cortex and continuous thinning throughout the lifespan without inevitable cognitive decline, old-age related changes must relate to different alterations in neuronal morphology (Vidal-Pineiro et al. 2020).

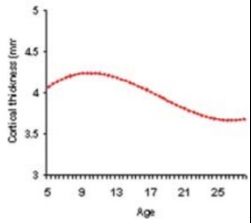
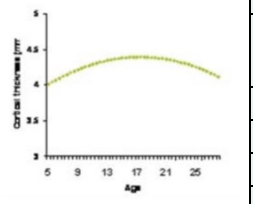
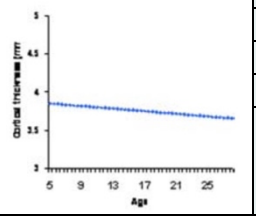
Trajectory	Cortical Region	Cortical Type	BA	CS
CUBIC 	Lateral orbitofrontal	Homotypical granular	10, 11,12	**2**
	Medial/ lateral frontal pole	Homotypical granular	10, (9)	**2**
	Lateral prefrontal (Superior, middle and inferior gyri)	Homotypical granular	9,45	**2**
	Anterior cingulate (Dorsal supracallosal part)	Heterotypical agranular	24, 32	**1**
	Precentral Motor area	Heterotypical agranular	4,6	**1**
	Somatosensory area	Heterotypical granular	3,1,2	**5**
	Posterior Parietal	Homotypical granular	7	**2**
	Posterior Insula	Homotypical granular	13	**2**
	Auditory area	Heterotypical granular	41,42	**4**
	Lateral Temporal	Heterotypical granular	21	**2**
	Polar / Calcarine occipital	Heterotypical granular	17	**4**
	Lateral Occipital (Superior middle, inferior gyri)	Homotypical granular	19	**3**
QUADRATIC 	Posterior Orbitofrontal	Transition Cortex	10,11,47	**2,3**
	Right Parahippocampal	Heterotypical agranular	27,34	**1**
	Anterior cingulate (Ventral supracallosal part)	Agranular/Transition Cortex	32,33	**1**
	Body of Insula	Homotypical/Dysgranular	13, 16	**2**
	Anterior superior temporal	Homotypical granular	22	**3**
	Left temporal Polar	Homotypical granular	38	**2**
	Right Entorhinal / perirhinal	Transition Cortex	28,34	**1**
LINEAR 	Posterior orbitofrontal	Transition Cortex	47	**2,3**
	Frontal Operculum	Transition Cortex	43	**1,2**
	Subgenual Cingulate	Transition Cortex	25	**1,2**
	Anterior Insula	Agranular/Transition C.	33	**1**
	Medial occipitotemporal	Transition Cortex	37	**2,3**
	Left Entorhinal / perirhinal	Transition Cortex	28,34	**1**

Table 1.1 Summary of Developmental Trajectory in relation to underlying cortical structure. **Cortical structure** indicates 1=Agranular, 2=Frontal Granular, 3=Parietal Granular, 4=Calcarine/Polar Granular 5=Granular and relates to Figure 1.7 (Adapted and merged from, Shaw, et.al. 2008, Solari &Stoner, 2011, and Brodman, 1909.)

Intra-cortical myelination is the main driver for early developmental thinning (Whitaker et al. 2016, Natu et al. 2019), with individual gene expression of marker genes for pyramidal cells, astrocytes and microglia, in particular, responsible for inter-regional variations (Shin et al. 2018). In healthy ageing, however, cortical thinning appears to be mainly caused by neuronal, cellular and dendritic shrinkage (Morrison and Hof 1997), whereas global thinning in pathological ageing e.g., Alzheimer's Disease, is influenced by neuronal loss (Terry et al. 1991, Esiri 2007).

Age related changes have been found to be both region (Uylings & de Brabander, 2002) and cortical layer specific (De Brabander, et.al., 1998). The largest degree of regional atrophy in the healthy ageing brain can be found in the inferior prefrontal, precentral and supramarginal region (Salat et al. 2004), with grey matter loss being most discernible in the insular and superior parietal gyri (Good et al. 2001).

(1.12) Ageing and Cognition

With only temporal regions relatively spared in the healthy ageing brain, overall cognitive decline seems an obvious consequence to atrophy. The next section will provide a brief overview of the cognitive consequences of healthy ageing, whilst chapter 4 will focus in more detail on cognition in ageing, in particular in relation to cortical thickness measurements.

(1.12.1) The prefrontal cortex and age

As evident from neuroimaging studies (Salat, et.al., 2004), a lot of structural decline seems to be present in the frontal or prefrontal regions of the cortex e.g., Raz, 2000; Crawford, Bryan, Luszcz, Obonsawin, & Stewart, 2000; Schretlen et al., 2000; Souchay, Isingrini & Espagnet, 2000, Andres & van der Linden, 2001. Frontal lobe

decline may therefore play a significant role in age related cognition (Salthouse, Atkinson and Behrish, 2003).

(1.12.2) Executive Function

Due to the marked thinning observed in the pre-frontal cortex, atrophy in this region in particular, appears to contribute to the age decline in executive functioning tasks, such as working memory (Salat et al. 2002a). Overall deficits in executive functioning performance have been observed in older adults, when compared to younger adults (Verhaeghen 2011).

(Divided) Attention:

Whilst sustained attention in older adults is comparable to younger adults (Berardi et al. 2001), divided and selective attention is affected by age related cognitive decline, evidenced in particular through slower performance (Verhaegen et al. 2003, Van Gerven & Gurreiro 2016).

Working Memory:

Working Memory has been repeatedly shown to be affected negatively by aging, most prominently, through the work done by Baddeley and colleagues (Baddeley 1986, 2003). Decline has been shown to be following a linear trajectory and reportedly begins as early as young adulthood (Brockmole & Logie, 2013)

Inhibition:

Some studies (Goh et al. 2012, Adolfsdottir et al. 2017) have shown age related decline in inhibition tasks, whilst a meta-analysis (Verhaeghen 2011) did not support age related deficits.

(1.12.3) Memory:

Memory abilities are both spared and affected by the healthy ageing process, depending on their underlying processes. Memory processes requiring executive control, for instances, are affected negatively by ageing, whilst those linked to verbal knowledge tend to remain stable (Oschwald et al. 2019).

Semantic Memory:

Memories pertaining to language e.g., vocabulary, semantic information or factual verbal knowledge have been shown to increase until around the age of 55 (Rönnlund et al. 2005) and can remain stable up to the age of 90 (Park et al. 2002). This is in line with verbal intelligence (gC) and language abilities developing and accumulating throughout the lifetime and then remaining relatively stable in healthy ageing, as discussed previously.

Prospective Memory:

Prospective memory is required in the execution of pre-planned activities, such as recurring events like taking one's medication at a specific time. When this ability is tested under laboratory conditions older adults perform worse than younger adults (Kliegel et al. 2016), especially when the task is deemed more challenging (Ihle et al. 2003). Interestingly, however, in real world settings older adults not only perform comparable to younger ones, but at times also superior (Schnitzspahn et al. 2011). This phenomenon has been linked to higher motivation through real-life incentives/rewards and self-management flexibility (Schnitzspahn et al. 2011).

Episodic memory:

Episodic memory, referring to one's ability to remember past events, is vulnerable to diminishing performance. Several studies have investigated episodic memory in older adults and found pronounced differences in performance, when compared against younger people (Salthouse 2004). On the contrary bilingual individuals were observed to have better episodic recall, compared to monolinguals, (Schroeder & Marian 2012). Bilingualism, more specifically the early acquisition and extensive practise of at least two language may therefore act as a protective factor for episodic memory function in older adults (Schroeder & Marian 2012).

(1.12.4) Language:

Language cortices mature relatively late, when compared to other cortical areas. Anterior language areas, such as Broca's area are found to mature and decline earlier, than the more posterior language cortices. This means, generally that language proficiency develops until later adulthood and is less vulnerable to ageing (Sowell et al. 2003).

The understanding of whole sentences has been linked to fronto-parietal language regions, which extend into Wernicke's area, spilling over into the inferior-parietal lobule (Mesulam et al. 2015), whilst posterior temporal lobe structures are more concerned with language comprehension skills and less vulnerable to ageing, than other regions. Reading ability, seated in the anterior temporal region (Mesulam et al. 2015), remains largely unaffected by healthy ageing (WTAR, Wechsler 2001) and NART (Nelson & Willison 1991)

(1.12.5) Processing Speed:

Processing speed is one of the first fluid (gF) cognitive faculties to decline in healthy ageing, which is likely a major driver of poorer cognitive performance in older people (Schaie 2005). With an individual's processing speed capacity linked to overall mental manipulation capacity and overall cognitive performance (IPC, Hofman 2012), decline in processing speed is likely impacts other fluid cognitive domains (Robitaille et al.2013).

(1.12.6) Motor Performance:

There is a general decline in motor performance and sensory-motor control in older adults. Causes are manifold and involve cognitive decline, as much as they do central – and peripheral nervous system decline, and overall muscle atrophy. Overall decline leads to slower and less accurate fine motor control, and affects gait and balance, which is a major driver for ongoing independence in older adults (Seidler et al. 2010). Dual task motor-cognitive control also becomes more problematic with increasing age, due to decreasing mental resources, in particular limited processing ability (Beauchet et al. 2003, 2005).

(1.12.7) Reaction Time:

Older adults have significantly slower reaction time, when compared against younger adults (Kerchner et al. 2012). With overall physical ability generally declining with age, and the risk of falls increasing with age, reaction time has been shown to be a predictive factor in fall risk assessments in the elderly (Kim et al. 2017).

AIM OF THE THESIS

The aim of this thesis is primarily to combine neuropsychological methodologies with cortical thickness analysis. Neuropsychology is, and likely will remain, the gold standard of cognitive assessment. However, by combining validated neuropsychological assays with structural neuroimaging data, the combined approach may shed further light on the underlying morphometry of structural and cognitive developmental trajectories of healthy ageing and in response to diurnal sleep preference.

Cortical thickness was selected, as the method of choice, as a sensible and interpretable measure of brain morphology and underlying cortical structure. And its context to lifetime development, underlying cell structure and relation to cognition has been explored in this chapter. This thesis will now explore functioning in relation to cortical thickness measurements in a small healthy control population, comparing traditional voxel-based morphometry data, underpinning the working model for the structural basis of intelligence. It will trial a case study approach for combining normative cortical thickness data with a cognitive assay and it will assess this approach and in relation to two inevitable variabilities when assessing cognition: Ageing and Sleep preferences.

Chapter three examines neuropsychology from the perspective of the time intensive pen and paper type assessment, having tested a small group on an extensive pre-surgical battery. Additionally, it tests how cortical thickness related to voxel-based morphometry, one of the more traditional methods in neuroimaging studies, and accounting for a vast amount of research prior to cortical thickness analysis. It further tests, in a small case study, whether a combined methodology could provide a clinical

framework in the pre surgical and/or clinical evaluation by testing relatively new approaches to anatomical normative data.

Chapter four explores cortical thickness against a standardised computerised neuropsychological battery comparing a cohort of younger and older participants, whilst experimental Chapter six examines diurnal sleep preferences and cortical thickness in relation to cognitive performance. By taking a closer look at two of the most inevitable and common nuisance factors in neuropsychological research i.e., ageing and sleep, it is hoped that valuable insight into the meaningfulness of cortical thickness as a tangible measurement in brain morphology underlying cognitive function can be gained.

Ultimately, although the scientific community has an understanding of how the brain works and the mechanisms involved in neurotypical and pathological functioning, ongoing research may lead to new way to understand the underlying causes of many variables and diseases affecting cognition.

CHAPTER TWO

METHODS AND MATERIALS

"SOMEWHERE, SOMETHING INCREDIBLE IS WAITING TO BE KNOWN"

CARL SAGAN (1934-1996)

(2.1) Neuroimaging

Throughout this thesis there will be a reliance on structural Magnetic Resonance Imaging (MRI) data and analysis thereof. This will be done particularly through Freesurfer (https://surfer.nmr.mgh.harvard.edu/), which calculates cortical thickness and other volumetric measurements. The datasets and participants are unique to each chapter, as are the neuropsychological assays utilised. This chapter will focus in more depth on MRI data and cortical thickness analysis.

(2.2) Magnetic Resonance Imaging (MRI) Physics

The most widely used MRI relies on hydrogen (H) reactivity with an external magnetic field. Since the human body comprises approximately 75% of water (H_2O), presenting a relative abundance of hydrogen, its magnetic properties lend themselves to investigations via MR (Roth & Faulkner 2013, p. xi). Hydrogen nuclei behave like tiny magnets by aligning themselves with the strong external magnetic field inside the MRI scanner. Most hospitals use 1.5 Tesla (T) machines, whilst research centres often use 3T (or even 7T). The strength of the magnetic field can determine the quality of the imaging, with a higher magnetic field aligning more hydrogen nuclei and hence

increasing the potential signal (Barker & Cicchetti 2012, p.140). MRI involves the pulsing of radio frequency (RF) energy at the resonance frequency of the hydrogen nuclei. This evokes a response from those nuclei (O'Shea 2005, p.25), leading them to absorb the RF energy and tip away from alignment with the external magnetic field. The MR image is created from the re-emitted RF energy, with additional magnetic field gradients used to encode spatial location.

As touched upon in the General Introduction, different cortical structures give rise to distinctive signals. Primarily, this results from their consistency, with grey matter being higher in water (H_2O) content, since it is composed of neuronal bodies, whereas white matter contains myelinated axons, which are fattier in content. (Houston et al., 2013). Because of the relatively small density differences between white and grey matter, neuroimaging methods must be able to sensitively differentiate between them (Nolte 2009, pp112-117). MRI is known for its superior properties in soft tissue imaging in the human body, compared to other neuroimaging methods.

RF energy, used as part of the scan sequences, alters the orientation of the hydrogen ions in such a way, that their change back to their aligned orientation is detectable (Barker et al., 2008, pp.114-115). This determines the image acquired (Roth and Faulkner, 2013, p. xii). Displaced protons align themselves after each RF pulse, and the rate of alignment along with other features, including proton density, gives information about the physical properties of the tissue, most notably its water content (Ginsberg 2005, p53). Structural MRI can produce several image contrasts, with T_1 & T_2-weighted images being the most commonly used and most important in clinical applications. T_1-weighted images were utilised in this thesis (Nolte 2009 pp.112-117). T_1 reflects the time constant during which the nuclei return to alignment with the static field following the RF pulse, whereas T_2 represents the time constant during which

nuclei lose alignment with one another (i.e., become out of phase). Tissue parameters reflect differently in T_1 or T_2-weighted images, and the image acquired influences the appearance of different structures. In a T1 image cerebrospinal fluid (CSF) appears hypo intense to (darker than) fat and brain tissue, while white matter, entwined with fat and protein, appears hyperintense (lighter than). These properties appear inverted in a T_2-weighted image. T_1-weighted images are primarily used to assess anatomical structures, whereas T_2s are required for pathological evaluations (Nolte 2009, pp.112-117, Roth & Faulkner 2013, p.213, 61).

(2.3) Limitations of Magnetic Resonance Imaging

MRI is inherently noisy and a claustrophobic experience, which not all patients will tolerate. There are also strict exclusion criteria for those with metallic magnetic material in their bodies, such as pacemakers. Movement during scanning can cause major artefacts and may therefore preclude those who may be unable to tolerate scanning easily, such as young children (Barker et al. 2008).

MRI, as any other neuroscientific method, is not immune from noise or confounding factors. Scanner-related performance can cause issues (Johansen-Berg, 2011) when comparing data across studies, an issue which is addressed in more detail in Chapter 3. As scanner manufacturing type and field strength can affect measurements, consistency within datasets is important (Han et al. 2006, Kruggel et al. 2010, Govindarajan et al. 2014, Potvin et al. 2016). To account for some of the more common limitations when using MRI, participants in all three experimental chapters of this thesis were scanned in the same scanner, by the same scanning operator, utilising the same equipment.

Head or overall subject motion (Pierpaoli 2011) and different head positions during image acquisition can drastically alter the image and result. Depending on hardware artefacts can cause more or less significant problems, with smaller grey matter estimates, for instance (see MRI artefact review by Erasmus et al. 2004). Images can also be confounded due to inhomogeneities in the B1 field, which can change over time (Draganski and Kherif 2012),

Some confounding variables are controlled by using the same imaging protocol and software for data processing of all participants' images. Other variables, such as participant positioning, and field of view selection are harder to control and not consistent between scans. More recently there has also been a suggestion that there is variability within the brain in a single day (Trefler 2016). Though the origin of this phenomenon has not yet been conclusively explained, it could result from differences in hydration (Duning et al. 2005, Kempton et al. 2011), in response to the menstrual cycle (Hagemann 2011), because of seasonal differences (Miller et al. 2015) or because of neuronal use in the time since waking (Nakamura et al. 2015). Differences in "Time of Day" are addressed in more detail in Chapter 5.

Above all, it is important to note that MRI provides an indirect measurement of brain structure only, which makes it susceptible to confounds due to motion, hydration or cardiac pulsation (Walker et al. 2011). This also means that results must be analysed and interpreted with caution. The areas of interest and significance shown in this thesis result from statistical comparisons between experimental and control conditions, or from assessments of differences between target groups, but not from direct changes in volumetric brain measures during these assessments themselves.

(2.4) MRI Acquisition

Study protocols for Chapters 3, 4 and 5, with associated scanning permissions, received ethics approval from the University of Birmingham STEM ethics committee. Participation in MRI scanning required prospective participants to familiarise themselves with the provided MRI scanning information sheet and complete and return a safety screening form which highlights implications and exclusion criteria for MRI scanning (such as pacemakers or metal pins.). Upon successful completion of the MRI screening, participants were invited for scanning at Birmingham University Imaging Centre (BUIC). On arrival, subjects underwent another safety check, and signed an ethics consent form. Participants of all experiments received another briefing about the procedure before completing their MRI scan. The high-resolution T1-weighted images ($1mm^3$ isotropic voxels, TR = 8.4 ms, TE = 3.8 ms, flip angle = 8, matrix = 288 × 288, 175 slices), forming the basis of this thesis, were acquired using a 3T Philips Achieva MRI scanner with the same sequence used in all cases. T1 weighted imaged were acquired by measuring spin-lattice relaxation, using a short repetition time (TR = 8.4ms) and echo time (TE=3.8ms).

(2.5) Cortical Thickness

All Cortical Thickness (CT) measures were derived from T_1 images, through cortical reconstruction and volumetric segmentation by applying the methods outlined in Dale et al. (1999), Dale and Sereno (1993) and Fischl and Dale (2000) utilising the freely available Freesurfer (FS) image analysis suite (http://surfer.nmr.mgh.harvard.edu/),

which is the main source for information for Freesurfer use, including all user manuals or Wiki. Further citations and research can be found there.

All data were processed with Freesurfer V6.0.0., in line with suggestions by Gronenschild et al. (2012). The anatomical resolution for T_1 weighted images needs to be around 1mm. Clinical MRIs can be used in FS processing if the resolution does not exceed 1.3mm, as the accuracy of cortical thickness estimation decreases with voxel size (as per Freesurfer guidelines).

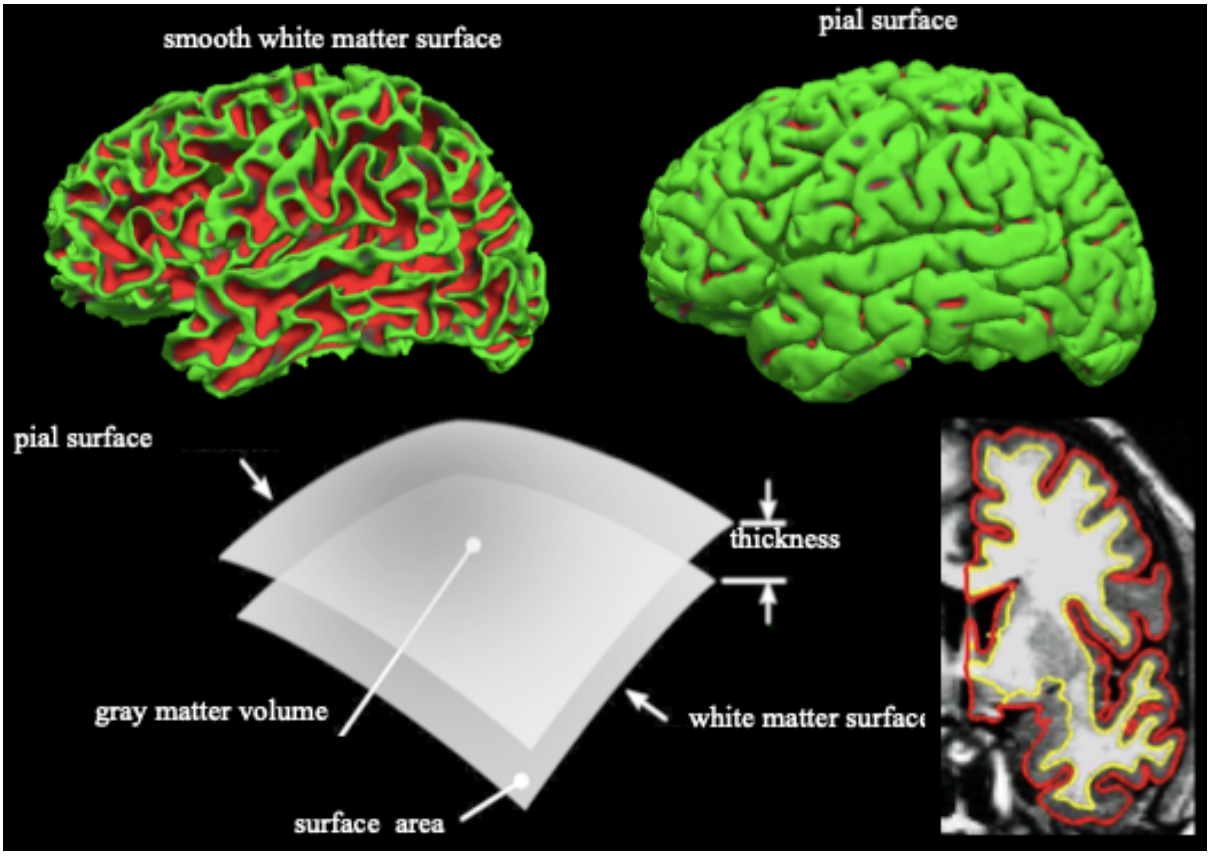


Figure 2.1 Illustration of cortical thickness measurement - White matter and pial surface reconstruction in an individual subject to visualise cortical thickness measurements. Smooth white matter surface displayed on the top left, pial surface to the top right, with green indicating a gyrus and red a sulcus. Adapted from Winkler, et al. (2010), with cortical reconstructions computed in Freesurfer https://surfer.nmr.mgh.harvard.edu

A mesh of triangles in tessellations of over 160 000 vertices per hemisphere represents the reconstructed cortical surface. The T1 intensity gradient, which reflects the difference between white and grey matter determine vertex positions. The pial

surface represents the top of the outer grey matter surface of the brain (Marie et al. 2016). Surfaces near the medial wall of the temporal lobe, hippocampus and amygdala do not always accurately follow the structure and are not always reliable for analysis, especially if this is intended for Region of Interest (ROI) analysis. There are several potential reasons why it could be difficult to generate pial and white matter surfaces in the medial temporal lobe area for example, one of which is that this region tends to be the farthest from the coils receiving the RF signal, and hence suffer from low signal to noise. Processed images were visually inspected to ensure that all Freesurfer areas were accurately generated.

(2.6) Quality control of MRI images and Freesurfer data

All MRI images were visually inspected for gross distortion and, or artefacts, including movement. The quality of segmentation was inspected visually, and all images were found to be of decent quality. Further processing of the data included steps such as motion correcting, averaging, and smoothing, which is intended to deal with common extraneous factors affecting MRI.

Output reports were inspected for all subjects to ensure all Freesurfer regions were adequately generated. Cortical thickness and volumetric measurements were exported for further statistical analysis and visually inspected by region.

(2.7) Pre-processing of Cortical Thickness Data:

Anatomical MRI (i.e., T_1) scans were processed via the standard Freesurfer processing pipeline by applying the recon-all script to all applicable scans in the group

subject data. This script processes the raw data in several steps (Figure 2.2). The process includes motion correcting and averaging (Reuter et al., 2010), removal of non-brain tissue using a surface deformation procedure (Segonne et al. 2004), automated Talairach transformation, segmentation of subcortical white and grey matter structures (e.g. hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002, Fischl et al. 2004a), intensity normalisation (Sled et al. 1998), tessellation of grey/white matter boundaries, topology correction (Fischl et al. 2001, Segonne et al. 2007), and surface deformation following intensity gradients (Dale & Sereno, 1993, Fishl et al., 2001).

Once cortical models are created, further data processing or analysis may commence, including surface inflation (Fischl et al., 1999a), matching of cortical geometry across subjects (Fischl et al. 1999b), automatic parcellation (Figure 2.2 Desikan et al.2006, Fischl et al. 2004b, Winkler et al. 2010) and creation of surface-based data based on curvature and sulcal depth.

Cortical thickness is calculated as the closest distance from the grey matter / white matter boundary to the grey matter / cerebrospinal fluid boundary, for each vertex on the tessellated surface (Fischl and Dale, 2000) (http://surfer.nmr.mgh.harvard.edu/).

To make output data executable in QDEC* for statistical comparisons the data must be cached for further surface smoothing, and the recon-all script run with the –qcache command, and at 10mm full-width half maximum (FWHM), which is FS's standard option and commonly used.

(2.8) Cortical parcellation within Freesurfer

Freesurfer offers automatic parcellation of the human cortex according to three pre-programmed atlases: The Desikan-Killiany Atlas (2006), the Destrieux Atlas and the Desikan-Killiany-Tourville (DKT) Atlas. Cortical thickness values for each region of these atlases are readily found in the subject directory for each participant in the processed data set. Atlas choice and parcellation is an important part in neuroimaging analysis which can impact the final results. There are a variety of parcellation protocols, some based on the underlying cytoarchitectonic structure, others based on microanatomy or landmarks (Yaakub et al. 2020). Although there is no universally agreed parcellation system that is right for every approach, Freesurfer atlases have been independently validated against other mapping systems and manual labels (Heckermann 2010, Makowski et al. 2018).

The Desikan-Killiany (DK) atlas is the one most widely used in existing cortical thickness studies and forms the basis of the cortical thickness analysis used in this thesis. Desikan et al. (2006) identified 34 cortical regions of interest (ROI) in each hemisphere of the cerebral cortex based on anatomical landmarks (e.g., gyri) and validated this against manual procedures showing high reliability. Manual tracing defined structures from the depth of one sulcus to another, thus incorporating the gyrus within. Whilst the definition of these regions therefore follows macro-anatomic and not cytoarchitectonic landmarks, there is evidence that there is substantial overlap between them (Fischl et al., 2007). One should note that exclusionary criteria determined the frontal pole, as other frontal lobe regions were determined first, and the remaining portion termed 'frontal pole'. That is, the frontal pole is not actually a measure of the frontal pole, but rather the remaining portion of frontal lobe, once other structures had been defined (http://surfer.nmr.mgh.harvard.edu/).

The DK-atlas is the most commonly used and has thus been selected as the atlas of choice, for ease of comparisons with existing literature.

(2.9) Comparison between parcellation systems

As Freesurfer uses a different parcellation system to other programs e.g., VBM, as utilised in chapter 3, regions were often compared to or annotated by Brodman area (BA). In part, the reason Brodmann Areas (1909) are still of relevance more than a century after their development, goes beyond their ability of cytoarchitectonic localisation, and include their integration of histological information with functional localisation. Cortical parcellation systems are manifold and there isn't one universally accepted model that fits every single requirement (for review, see Zille & Amunts

2010). Brodmann areas, however, are an almost universally accepted way of comparing different parcellation methods through a traditional segmentation method. Brodman areas were defined as in Zilles and Amunts (2010).

Table 2 is a comprehensive amalgamation of these Freesurfer regions with their corresponding Brodman areas (Brodman, 1909), underlying cortical type (Shaw, 2008), and cortical structure (Solari &Stoner, 2011), as well as expected developmental trajectory (Shaw, 2008). Agranular Structures e.g., Primary Motor cortex, are amongst the thickest, with up to 4.5mm in healthy individuals, whereas Association Cortices (Frontal, Parietal, Calcarine) denote homotypical or transition cortices with an average thickness of around 2.5mm. Granular Structures underlying the Primary Sensory Cortices are amongst the thinnest with a cortical thickness of around 1.5mm (Solari & Stoner, 2011, Triarhou, 2013). There is thus considerable natural regional variation in cortical thickness, determined by underlying cellular structure.

(2.10) Freesurfer Output

All Freesurfer output from the 'recon-all -all' pre-processing stream is located in the individual's "Subject Directory" .Cortical thickness measurements for the 34 regions defined by the Desikan-Killiany atlas parcellation are found in the rh.aparc.stats and lh.aparc.stats. Aseg.stats contains output from subcortical segmentation and provides information about the estimated intracranial volume.

Freesurfer output is given for each hemisphere and data files generally include a version for the left hemisphere (lh) and the right hemisphere (rh). Global mean cortical

thickness (bh) i.e., thickness combined across both hemispheres, can be calculated through:

$$\text{bh.thickness} = \frac{\big((\text{lh.thickness x lh.surfarea}) + (\text{rh.thickness x rh.surfarea}) \big)}{(\text{lh.surfarea} + \text{rh.surfarea})}$$

Average cortical thickness data for each participant within the pre-defined regions was manually extracted for further statistical analysis in external programs (SPSS, Excel), where statistical analysis through FS's QDEC indicated significant suprathreshold regions, or for Regions of Interest (ROI) (Bruehl et al., 2013).

(2.11) Cortical thickness measurements and Freesurfer Validation

As there are no universally agreed methods for measuring cortical thickness, other approaches exist, e.g. voxel-based-cortical thickness (Hutton et al., 2008), or cortical thickness measurements from minimum line integrals on soft-classified tissue (Aganj et al., 2009) or cortical thickness analysis via Brain Voyager (https://www.brainvoyager.com). However, Freesurfer is the method of choice for this thesis.

Freesurfer reliability has been established (Tae et al., Jovicich et al.2009, Lehmann, 2010) and validity has been tested and successfully compared against histological analysis (Rosas et al. 2002, Cardinale et al., 2014) and manual measurements (Kuperberg et al., 2003, Salat et al. 2004). Morphometric measurements show good test-retest reliability across scanner-types and field strengths (Han et al. 2006, Reuter et al., 2012).

Wagstyl et al. (2015) have shown that there is a strong relationship between cortical thickness and laminar differences in the estimated position for visual, auditory, and somatosensory cortices.

Table 2.1 Freesurfer Desikan-Killiany Regions (2006), with Brodman (1909) Area (**BA**) Reference, Isocortex Cortical Type annotation (Shaw, et.al.2008), Cortical Structure reference, **1**= Agranular, **2**=Frontal Granular, **3**=Parietal Granular, **4**=Calcarine/Polar Granular **5**=Granular, denoting minimum and maximum cortical thickness (Solari & Stoner, 2011) and Developmental Trajectory (Shaw et.al., 2008) indicating what measurements to expect from each region when discussing results.

Division	Aspect	Freesurfer Label lh/rh	BA	Cortical Type (Isocortex)	Cortical structure	Developmental Trajectory
Frontal Cortex	Superior	superiorfrontal	4, 6, 8	Homotypical	2 (1)	Cubic
	Middle Frontal Gyrus	rostralmiddlefrontal	9,10,46	Homotypical	2 3	Cubic
		caudalmiddlefrontal	23,31	Heterotypical	1 (2)	Cubic
	Inferior frontal gyrus	precentral	4			Quadratic
		parsorbitalis	47	Homotypical	2 3	Quadratic
		parsopercularis	44 Broca's Area	Transition	2	Linear
		parstriangularis	45	Homotypical	2	Cubic
	Orbitofrontal	lateralorbitofrontal	10, 11, 12	Homotypical	2	Cubic
		medialorbitofrontal	10 11 47	Homotypical	2	Linear
		paracentral	4 (precentral motor area)	Agranular	1	Cubic
		frontalpole	9 10	Homotypical	2	Cubic
Parietal Cortex	Superolateral	superiorparietal	5,7	Homotypical	2	Cubic
		inferiorparietal	39	Homotypical	3	
		supramarginal	40	Homotypical	3	
	Inferior/ Medial	postcentral	3, (primary somatosensory cortex) 1, 2	Granular	5	Cubic
		precuneus	7	Homotypical	2	Cubic
Temporal Cortex	Lateral	superiortemporal	22/ Wernicke's Area, 38	Homotypical	3	Quadratic
		middletemporal	21	Homotypical	2	Cubic
		inferiortemporal	20	Homotypical	2	Quadratic
		bankssts		Homotypical	3	Quadratic
		transversetemporal	41, 42 / Auditory Cortex (Heschls Gyrus)	Granular	5 (4)	Cubic
	Medial	fusiform	37	Homotypical	2	Linear
		entorhinal	28	Transition	1 2	Linear
		temporalpole	27, 28, 34, 35, 36	Homotypical	2	Quadratic
		parahippocampal	27, 34	Heterotypical	1	Quadratic
Occipital Cortex	Superolateral	lateraloccipital	18, 19	Homotypical	3	Cubic
	Medial/ Inferior	lingual		Homotypical	2 3	Linear
		cuneus		Homotypical	4 5	Cubic
		pericalcarine	17 (V1, Primary Visual)	Granular	4 5	Cubic
Limbic	ParahippocampalGyrus	entorhinal	34	Transition		
	Cingulate Cortex	rostralanteriorcingulate	24, 32, 33	Agranular	1	Cubic
		posteriorcingulate	23, 31	Transition		
		isthmuscingulate	26, 29, 30	Allocortex & Neocortex		
		caudalanteriorcingulate	23 24	Agranular	1	Quadratic
	Limbic Integration Cortex	insula	13	Homotypical/ Agranular	1	Quadratic

Cortical thickness and neuronal density have been linked (la Fougere et al., 2011, Collins et al., 2010, Cahalane et al., 2012) and can reliably be associated with intracortical connectivity such that lower neuronal density is associated with increased dendritic arborisation (Elston, 2003, Cullen et al., 2010). As such, Freesurfer output is considered to be a reliable summary of the anatomy, which can then be compared with other data.

(2.11.1) Limitations of Cortical Thickness data

Cortical thickness is a complex measure given its variance due to underlying cell structure, genetic predisposition etc. (Brouwer et al. 2014). Due to its computation from T_1 images it is susceptible to the same possible confounding variables as the images themselves. Additionally, cortical thickness undergoes drastic changes during the lifespan and developmental trajectories change depending on region and underlying structure (see Table 1.1). Cortical thickness measurements must be interpreted taking into account the sex and age of the subject, as well as regional variants depending on which variable is being assessed. It is not a static measure and requires circumstantial interpretation.

(2.12) Statistical Analysis and Thresholding

Statistical Analysis was carried out with FS QDEC and IBM SPSS Statistics 24 and statistical thresholds, unless otherwise indicated, pertain to these. QDEC, Freesurfer's graphical user interface (GUI) driven statistics engine, allows the user to design and execute an analysis of the morphometry data outputted by the Freesurfer pipeline. It can execute General Linear Models (GLM) for up to two groups and two

continuous variables. The ‘mri_glmfit’ command-line tool has more extensive GLM capabilities and is utilised in Chapter 5 with further explanation there.

QDEC’s primary input source for data is via a text file named 'qdec.table.dat’ which includes subject IDs as specified in the recon-all command stream, to link demographic and behavioural data to the processed T_1s. The target surface for data analysis is ‘fsaverage’ by default and must be located in the group file containing individual subject directories. ‘fsaverage’ is dependant for each cohort of participants/patients analysed and is created automatically during pre-processing. QDEC has several pre-sets to build a design for analysis. It completes each analysis for one hemisphere at a time, with options to select independent and dependent variables.

FS QDEC conducts separate linear regressions across 155000 points on the surface of the brain to analyse associations between groups or in relation to variables (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysis_freeview). QDEC allows separate group analyses and regressions, with or without co-variate factors. Each regression produces a regression plot and an associated p-value.

To account for multiple comparisons, results at Monte-Carlo Simulation (MC_S) level, with $p^a<0.01$ were aimed at. MC simulation is QDEC’s most conservative statistical threshold is achieved through 10 000 Monte-Carlo style permutation simulations (Menary et al. 2013). MC_S are carried out at a vertex-wise cluster-forming threshold (CFT) of 2.0, equivalent to $p^a<0.01$, which indicates that all vertices in a cluster are of the same value. The masking threshold is specified as absolute/unsigned (abs) by default, meaning that any voxel, regardless of sign (positive or negative), exceeding the threshold will be displayed. FS output data also specifies other properties of

regions of interest (ROI); such as surface area, coordinates relative to MNI305 space (which is discussed in further detail in chapter 3) and a cluster wise probability value (CWP), which signifies the probability of seeing a cluster that size or larger during simulation. Freesurfer instructions recommends setting the CWP threshold at <0.05 for significance. A confidence interval for the CWP is also computed. The CWP threshold is a post-hoc statistical test, after $p^a<0.01$ has been applied. Where the p^a threshold for MC_S could not be reached, analysis with the FDR (False Discovery Rate) method (Genovese et al.2002, Karama et al. 2011) was used. Applying an FDR value of $p^b<0.05$ implies that 5% of all cortical points having a t-value above the FDR threshold are false positives. FDR rates of 0.05 are commonly accepted as sensible thresholds for statistical significance (Karama et al.2011).

Specific statistical tests utilised in SPSS are indicated separately (e.g., Analysis of variance = ANOVA, t-test) and referred to by test used. 'F" denotes statistics derives from ANOVA's, 't', from t-tests. Results were considered significant at an overall α=.05 criterion for each pairwise comparison in SPSS statistics. Interaction and main effects were therefore considered significant at $p^c0.05$ for main or interaction effects, and Bonferroni corrected at $p^d<0.05$, to account for multiple comparisons. Significant results are specified as p^*, whilst non-significant results are specified as "not significant" or "NS".

(2.13 Images)

Images utilised from other sources are cited, where applicable. Figures from experimental chapters and novel results were created using QDEC, IBM SPSS 24, Z-Charts Maker, Prism GraphPad 8 and Paint S. Images in novel schematics (e.g.,

Figure 1.4), were sourced through Servier Medical Art by Servier, under a Creative Commons Attribution 3.0 Unported License (https://smart.servier.com).

(2.14) Neuropsychological Assessments

The datasets and participants are unique to each experimental chapter (Chapter 3, 4 and 5), as are the neuropsychological assays utilised. A broad discussion on the selection of neuropsychological methods can be found in the general introduction (Chapter 1) and further reasoning for each method utilised will be given in their respective chapters.

Although it would have been advantageous to utilise the same battery throughout, to draw direct conclusions across all experimental chapters, the assays differ in each chapter primarily due to accessibility and availability issues. Whilst this makes it a little more challenging to draw inferences from the thesis as a whole, it meant that the approach of combining a neuropsychological battery with cortical thickness data was applied across a broader range of data.

CHAPTER THREE

STRUCTURE- BEHAVIOUR RELATIONSHIP WITH VOXEL-BASED MORPHOMETRY AND CORTICAL THICKESS IN RELATION TO THE WECHSLER INTELLIGENCE SCALE

"EVERY BEHAVIOUR HAS AN ANATOMY"
GESCHWIND, M.D. (1975)

(3.1) Introduction

With neuronal cells being the building blocks to every cognitive process within the brain, even the slightest change in action potential kinetics or factors affecting efficiency in information processing and transfer, may result in innate differences in mental ability (Goriounova et al. 2018).

Human intelligence is associated with neuronal complexity, action potential kinetics and efficiency in information transport. Larger dendritic trees facilitate pyramidal neurons to track the activity of synaptic inputs faster and with greater precision. Neuron size and complexity may constitute the variation in cortical thickness, and thus, variation in neural function and cognitive proficiency.

The cellular basis of intelligence appears to be a combination of relative number of neurons, packing density and axon transmission velocity (Dicke & Roth, 2016). These factors combined determine the general informative processing capacity (IPC) which is linked to general intelligence (g), as defined by mental manipulation abilities (Hofman 2012).

(3.1.2) Neuropsychological assessment

As the field of neuropsychology has expanded and its application are now manifold, the scientific concept of dependability becomes of increasing importance. As neuropsychological assessment has moved beyond a pure healthcare assessment tool (see Introduction 1.4), its reliability, dependability and validity have been increasingly challenged (Lezak et al. 2004, Russell et al. 2005).

Clinically, the use of neuropsychological batteries is to create a comprehensive thorough assessment, allowing a diagnosis of cognitive dysfunction to be made and / or treatment choices to be made confidently because of findings (Russell et al. 2005). Clinical test batteries can be time consuming and onerous on both the patient, as well as the clinician administering them, however, it also allows for a prolonged period of observation, which may influence clinical judgment.

The Wechsler scales are considered the gold standard in neuropsychological assessment, and specifically in intelligence testing, and novel measures of intellectual ability are often measured against these well validated assays (Hall et al. 2010, p.132). The Wechsler Adult Intelligence Scale in the method of choice in this chapter, largely due to its large amount of normative data and high test-retest reliability (Wechsler 1998). Neuropsychological assessments, and large standardised batteries are common in the presurgical evaluation of epilepsy patients. But whilst they are being applied to surgical candidates, those ineligible for surgery, do not routinely, or consistently benefit from neuropsychological knowledge, despite its potential implication on treatment choices and therapeutic decision making (Helmstaedter & Witt 2017).

(3.1.3) MRI and Cognition

Some of the reasons why volumetric measurements derived from MRI may be useful in offering complementary information, helpful in understanding the basis of human cognition, have been discussed in the general introduction. Cortical thickness is thought to be a tangible and sensible measurement of brain morphometry and considered to reflect the packing density of neuronal cells (Sowell et al. 2003), which in turn are thought to reflect the basis of intelligence. Though brain imaging measures are macroscopic, cortical thickness aims to capture the essence of underlying brain structure (Goriounova & Mansvelder, 2019). With packing density of neurons and relative number of neurons reflecting human intelligence at least in some significant way, it is clear why cortical thickness is an important measurement to consider.

Voxel-based-Morphometry (VBM) is a commonly used method in neuroscientific research (Wright et.al.1995, Bullmore et.al.1999, Ashburner & Friston, 2000, Good et.al. 2001) and a relatively fast and straightforward method for quantifying the amount of grey matter within a voxel. VBM is as well establish a tool in neuroimaging, as the Wechsler Scales are in neuropsychology (Hidese et al. 2020). However, VBM ostensibly measures something very different to ‘cortical thickness’ and thus, this chapter wants to examine what complimentary information Freesurfer can add to what VBM traditionally provides.

(3.1.4) Normative data and the application of cortical thickness in a clinical setting

When assessing individuals on their neuropsychological performance, data is almost always compared and validated against normative scores. Whilst normative data exists for most established and validated neuropsychological assays, there are almost

no examples of robust normative measurements in neuroimaging. With Neuroscience still in its infancy normative data allowing for robust comparisons between neuropsychological data and its anatomical substrate is sorely missing.

Potvin et al. (2017) attempted to address this gap with normative data from 2713 healthy individuals aged 18-94, accounting for age, sex, estimated total intracranial volume, scanner manufacturer and field strength. The derived formulas allow the assessment of individual cortical thickness measurements, against a normative sample, denoting the extent of deviation. Further research into this field would allow extended use of cortical thickness measurements, and could inform, for example, pre-surgical evaluation in suitable candidates.

Cortical thickness maps are helpful in localising the central sulcus and the reconstruction of the pial surface can aid the surgical planning or stereotactic implantation of intracerebral electrodes and resection. It could be further useful in the presurgical workup of focal cortical dysplasia (FCD) patients (56% of FCD patients have thickness values greater than 6mm whereas normal range does not normally exceed 4.5mm) or in the assessment of abnormal language distribution, as a less invasive method than the Wada procedure (see introduction, Cardinale et al. 2014).
BA 38 or the superior temporal gyrus, located in the anterior end of the temporal lobe, for instance, is one of the earliest regions affected in Alzheimer's Disease and could serve as a valuable biomarker to premature thinning of the cortex. It is also one of the earliest involved regions at the start of temporal lobe seizures in epileptic patients (Goriounova et al., 2018).

(3.1.5) Conceptual Background

The relationship between IQ and cognition to regional brain structure and function is well documented (Colom et al. 2006, Deary et al. 2006, Jung & Haier 2007). So much so, that the Parieto-Frontal Integration Model (P-FIT) was derived, forming a framework for the biological basis of intelligence, able to predict individual differences in IQ and reasoning ability (Jung & Haier 2007). Though the P-FIT model is still utilised and considered valid, it is predominantly based on VBM data (Karama et al. 2010).
Cortical thickness is a newer method of analysis and based on a more intuitive measure of underlying brain morphometry. Since it also aims to measure volumetric as well as structural changes, it makes sense to test its usefulness in offering complementary information, in comparison it to a more traditional method. Early studies investigating the comparability of cortical thickness measurements and voxel-based morphometry were e.g., Hutton et al. (2009), who concluded that results were comparative, but that (voxel based) cortical thickness measurements were more sensitive to age related decline. They concluded that voxel-based morphometry likely gave a value taking into account grey matter changes, surface area, folding and thickness and proposed that VBM should be routinely combined with cortical thickness data for optimal data acquisition.

VBM is an extensively researched neuroimaging tool to analyse neuroanatomical correlates and assessments in patients have shown abnormalities on standard MRI. VBM was originally designed to detect cortical thinning, in a way that previous volumetric analyses could not, unconfounded by other morphometric variables and sensitive to the different types of brain tissue, e.g., grey matter and white matter. VBM is a well-validated and pragmatic measurement to characterise small scale differences

in focal differences, which respond well to voxel wise testing, but also volumetric differences, such as grey or white matter density changes (Ashburner & Friston, 2001). The clinical use of VBM analysis, however, is constrained by the lack of robustness in individual cases, and because of its somewhat arbitrary correlation to underlying brain structures (Salmenpera et al. 2007, Chen, et al. 2008). Discrepancies in the results between voxel-based morphometry (VBM) data and cortical thickness (CT) data derived from the same cohort are likely due to the discrepancy in the neuroanatomical location of VBM and CT. The difference in registration targets requires not only a conversion between atlases, but also between volume and surface space (Voets et al., 2008, Blankstein et al. 2009).

Table 3.1 Summary of relation between IQ and cortical thickness across the different Freesurfer regions. ⬆indicates a positive relationship or correlation, whereby a thicker cortex is indicated with a better task performance. ⬇indicates a negative relationship/correlation , whereby a thinner cortex is indicated with improved task performance. Legend : lh = left hemisphere, rh = right hemisphere, CT= Cortical thickness, FSIQ = Full Scale IQ score, VC – Verbal Comprehension, g = General Intelligence

Division	Freesurfer Label lh/rh	Brodman Area	Relation to IQ	Comments	Study
Frontal Cortex	superiorfrontal	4 6 8	**lh, rh** rostral aspect ⬆CT=⬆g score	Prefrontal regions tend to support gF rather than gC	Menary et al. 2013 Schnack et al 2015
	rostralmiddlefrontal	9 10 46	**lh** large surface area ⬆processing speed **rh** ⬆CT ⬆g		Hartberg et al. 2011 Menary et al. 2013
	caudalmiddlefrontal	9 23 31	**rh** ⬆association with CT		Choi et al 2008
	Precentral gyrus	4 6	Precentral motor area, Agranular cortex (up to 4.5mm)		
	Pars Orbitalis	47			
	Pars Opercularis	44			
	parstriangularis	45			
	lateralorbitofrontal	10 11 12	Lh rh ⬆FSIQ CT	Referred to as biological centre for intelligence	Narr et al 2007
	medialorbitofrontal	10 11 47	Lh rh ⬆FSIQ CT. rh ⬆sig after 4th decade		Schnack 2015
	paracentral	4			
	frontalpole	9 10			
Parietal Cortex	superiorparietal	5,7, 19	**lh** Posterior, lateral aspect ⬆CT = ⬆g score **rh** rostral aspect +CT	Block Design predicted by rh parietal lobe CT (spatial recognition) Lateral parietal cortex ⬇ Fronto=parietal network reflects gF	Menary et al. 2013 Zink et al. 2018
			lh ⬇association VC- CT		
	inferiorparietal	30, 31, 39	**lh** medial aspect ⬆CT = ⬆g score **lh rh** ⬆FSIQ CT		Menary et al. 2013 Narr et al 2007
			rh ⬇association VC – CT		
	supramarginal	31, 40	**rh** ⬆association with Block Design (spatial recognition)		Menary et al. 2013 Zink et al. 2018
			lh ⬇association VC – CT		

	postcentral	1 2 3 6	Primary somatosensory cortex, Granular cortex (1.5mm)		
	precuneus	7, 39	**Lh, rh** ⬆CT = ⬆g score		Menary et al. 2013 Schnack et al 2015
			rh ⬇ association VC -CT		
Temporal Cortex	superior temporal	21 22 38	**lh** posterior aspect +CT **rh** anterior aspect ⬆CT=⬆g **lh** anterior temporal ⬆	Many temporal regions show slight increase between second and fifth decade before decreasing	Menary et al. 2013 Choi et al.2008 Potvin et al. 2017
			rh ⬇ association VC-CT	-BA 38 exclusively involved in gC	Goriounova et al. 2018
	middletemporal	21	⬆auditory processing & language	-Mean ct value of temporal lobe ⬆ association with IQ	Goriounova et al. 2018
	inferiortemporal	20	**lh** ⬆correlation with IQ		Choi et al. 2008
	bankssts				
	transversetemporal	41 42	Auditory Cortex, Granular Cortex (early myelination)		
	fusiform	37	**lh, rh** ⬆CT =⬆g **lh rh** ⬆FSIQ CT	-Participates in the analysis of visual form, motion and representation of objects	Hartberg et al. 2011 Narr et al. 2007
	entorhinal	28	Transition Cortex, Agranular (up to 4.5mm)	-Minor predictive value - Most highly influenced by environmental factors in terms of surface areas and thickness	Potvin 2017 Panizzon et al. 2009
	temporalpole	27 28 34 35 36		Variations in laminar thickness influence visual analysis abilities central to cognitive processes esp. IQ testing. Minor predictive value	Narr et al. 2007 Potvin 2017
	parahippocampal	27 34	Lh rh ⬆FSIQ CT lh⬇association VC – CT		Menary et al. 2013
Occipital Cortex	lateraloccipital	18 19	Rh ⬆CT =⬆g		Menary et al. 2013
	lingual	37			
	cuneus				
	pericalcarine	17 18	V1 primary visual, Granular cortex (early myelination)		
Limbic	entorhinal	34			
	rostralanteriorcingulate	24 32 33	⬆thickness in the **rh** rostral anterior cingulate is related to ⬇working memory performance, larger cortical surface area in the **lh** related to ⬆working memory performance		Hartberg et al. 2011
	posteriorcingulate	23 31	Agranular cortex (up to 4.5mm)		
	isthmuscingulate	23			
	caudalanteriorcingulate	23 24			
	insula	13			

Studies which have compared VBM and cortical thickness data against cognition, e.g., Pereira et al. (2012) or Karama et al. (2010), have usually done so with limited neuropsychological batteries (Nestor et al. 2015, Green et al. 2018), or whilst looking at a-priori Regions of Interest (ROI).

Hidese et al. (2020) were the first to utilise the WAIS (III) in an adult population for whole brain analysis, investigating all of the WAIS indices, whilst comparing traditional VBM data with more novel approaches (Diffusion Tensor Imaging). They found Verbal IQ to be significantly correlated to the left anterior cingulate gyrus, left posterior insula, and left superior and middle frontal gyri but no other significant correlations between their methodological approaches.

Table 3.1 summarises several studies on the relationship between cortical thickness and cognition, in particular in relation to intelligence and collates it to form a coherent picture between brain region and relationship between cortical thickness and cognition. The table highlights an important trend showing that whilst a higher Full Scale IQ is generally related to increased cortical thickness in the denoted areas, whereas better verbal comprehension abilities appear to be associated with lower cortical thickness values.

(3.1.6) Aims

Cortical thickness and voxel-based morphometry are two ways of analysing T1 anatomical data, however there have been few direct comparisons between the two, in particular in relation to neuropsychological data. This chapter aims to do a systematic comparison, by translating the coordinates of significant regions found in

VBM and cortical thickness analysis, respectively, into a universal space. This chapter will focus on combining anatomical data with the WAIS. Due to the clinical uses of WAIS and its potential for providing clinically useful information a case study aims to demonstrate the usefulness of cortical thickness analysis in clinical patient workup.

This chapter first aims to compare cortical thickness to voxel-based morphometry results from correlations against WAIS indices, by translating their differing coordinates into a single space to see if this might account for the discrepancy in the neuroanatomical location of VBM and CT.

It further seeks to test, whether the combination of cognitive data with cortical thickness data, derived from standard MRI, and Z-scored calculated from a normative database, might offer complimentary information, which could inform clinical decision making and perhaps aid triaging of cognitive testing to focus on predicted strengths and weaknesses.

(3.2) METHODS

(3.2.1) Subjects

9 healthy control subjects were recruited (mean age of 24.6 years, ranging from 21 to 30 years of age, 5 female) with the inclusion criteria of not having a significant neurological medical history (e.g., history of seizures) or any other neurological deficit. Subjects were required to have a good level of English language (native standard) and had to meet the general inclusion criteria for MRI scanning. Subjects underwent approximately 4 hours of neuropsychological testing, approximately one hour in the scanner and were paid for their participation (£20).

(3.2.2) Neuropsychological Testing

Neuropsychological testing, due to its time-consuming nature, was preferably done prior to scanning and on a separate day. Subjects were tested on a comprehensive neuropsychological battery of tests comprising the Wechsler Adult Intelligence Scale (WAIS).

Neuropsychology Test Battery:

The *WAIS* (except optional subtests) was chosen for a general indication of intellectual ability. The WAIS-III consists of several subtests measuring different aspects of intellectual functioning. Participants were tested on Picture completion, Vocabulary, Digit Symbol Coding, Similarities, Block Design, Arithmetic, Matrix Reasoning, Digit Span, Information, Symbol Search and Letter Number Sequencing. The sub tests create four major sub scores, a Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), Processing Speed Index (PSI). The four sub scores combined produce the overall Full-Scale IQ (FSIQ). (Wechsler, D., 1998).

The 9 subjects tested in this study have been tested with two versions of the WAIS. The old version WAIS-III was used with 4 subjects and the newer version WAIS-IV was used with 5 subjects. This was based on availability of the battery at the time of testing, rather than due to methodological decision. The WAIS-III and IV are intrinsically very similar. They yield a main score which is the FSIQ. However, in the WAIS-III the FSIQ is made up from two primary sub scores, calculated from four secondary sub scores: The Verbal IQ (VIQ, made up from VCI and WMI) and the Performance IQ (PIQ, made up from PRI, and PSI). The WAIS-IV has been simplified in terms of these sub scores and only reports the VCI, PRI, PSI and WMI. Figure 3.3 illustrates the hierarchical structure of the WAIS and its indices and subtests.

WAIS Testing:

The WAIS composite, indices and sub scores are indicated to reflect the following:

The Full-scale IQ (FSIQ) score from a Wechsler adult intelligence scale is one of the most reliable and traditionally most reported score. The FSIQ should be interpreted alongside its percentile rank, and taking the combined information of the VCI, PRI, WMI and PSI into account. If discrepancies between indices are too large, caution is advised and closer attention to individual subtests must be paid. The FSIQ represents a broad score indicating the examinee's general level of intelligence, by tapping into several cognitive skills across the brain. Table 3.1 shows cortical areas associated with g and with the WAIS in particular, across the brain. A higher composite FSIQ indicates a higher level of intelligence, when compared to normative data. IQ scores are normally distributed on a bell curve (Figure 3.4) and represented with scaled composite scores, a qualitative description, and a percentage, e.g., the average IQ range is between 90-109, which is approximately 50% of the population.

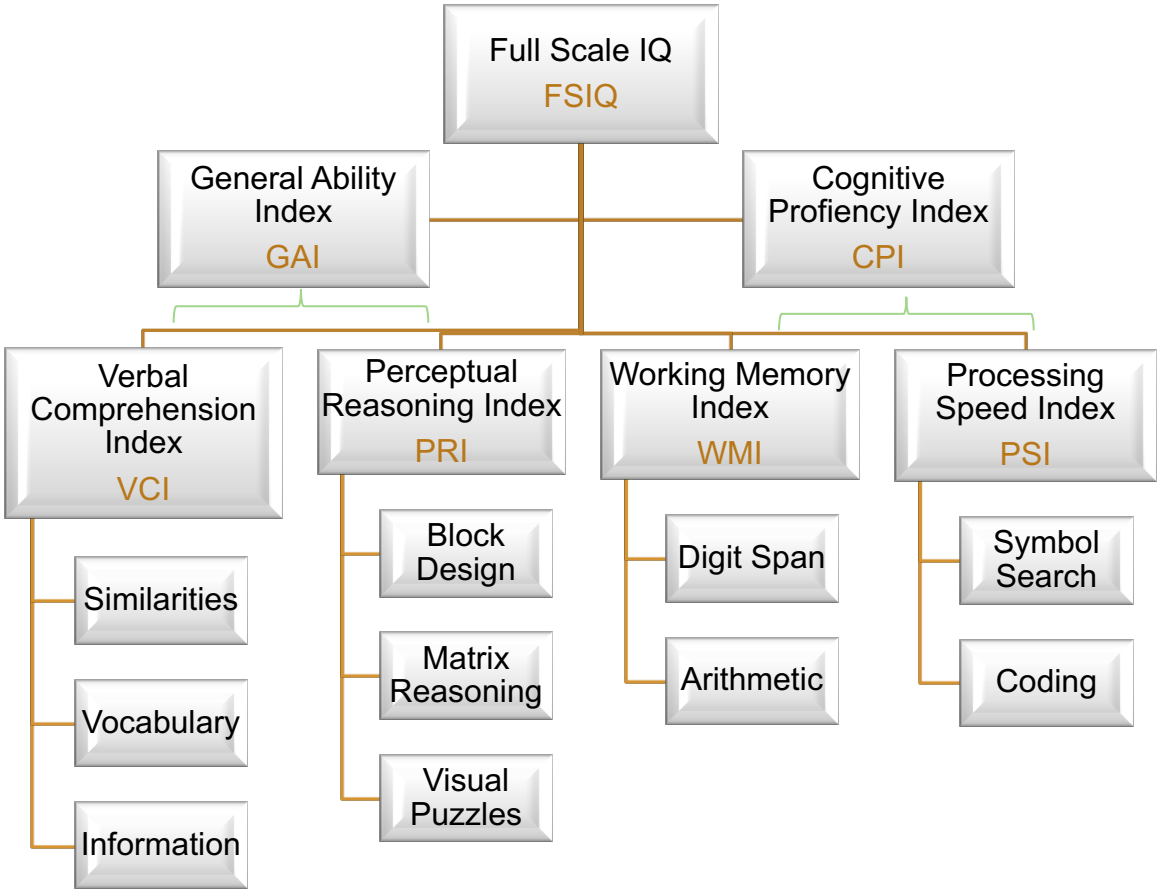


Figure 3.1 Wechsler Scale Flowchart to show subtests and composite Indexes

The VCI is a measure of verbal concept formation, verbal reasoning and acquired knowledge. Though it is correlated with the PRI, it is dependent on environmental factors, such as education. The PRI measures perceptual non-verbal reasoning skills and visual motor integration. WMI measures the examinees' ability to retain information and mentally manipulate or reproduce it. WMI requires attention, concentration, mental control, and reasoning and is an essential component of higher order cognition.

The PSI assesses how quickly the examinee can evaluate simple information or carry out simple tasks. Index scores are estimates of overall functioning in a specified domain

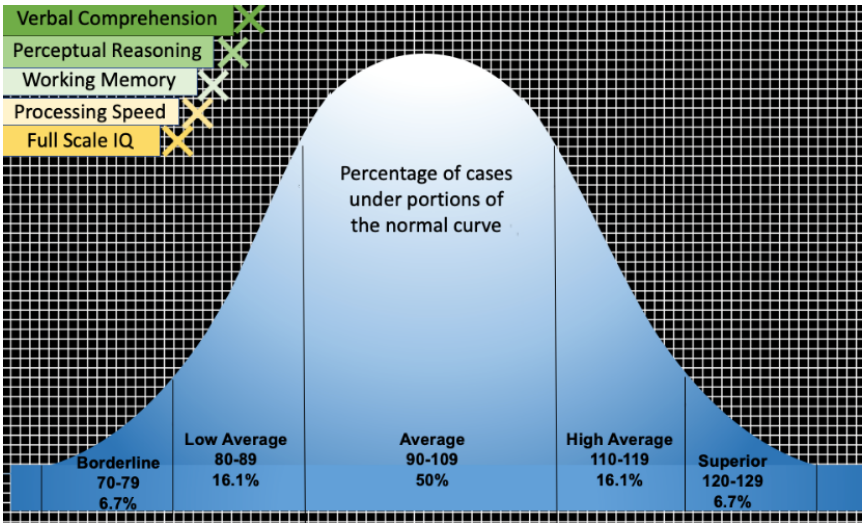


Figure 3.2 Bell Curve demonstrating normal distribution of IQ scores

(3.2.3) MRI Acquisition:

T_1 acquisition, preparation and analysis are discussed in detail in the overall Methods Chapter (2). After brief initialisation scans, a T1-weighted high-resolution anatomical scan (1mm^3 isotropic voxels) was acquired. This T1 scan formed the basis of the analysis included in this report.

(3.2.4) VBM Data

T_1 scans also formed the basis of Voxel based Morphometry analysis.

All scans were normalised, segmented, and smoothed prior to analysis. Spatially normalised images were resliced to isotropic 1mm voxels. Images underwent segmentation of grey matter (C1), white matter (C2) and cerebrospinal fluid (CSF) using the standard options of SPM8 (Wellcome Department of Imaging Neuroscience, UCL, UK). They were then smoothed with a 10 mm (FWHM 10_10_10) isotropic Gaussian kernel to minimise variability amongst subjects. This creates images which

are more normally distributed and permits voxel wise analysis (Bonilha et al. 2004). Following pre-processing, statistical analysis for the Wechsler Scale commenced.

Statistical Analysis VBM Data

A standard VBM analysis comparison of each of the 9 subjects' T1 image and their WAIS scores was performed, using a one sample t test with 2 contrasts (0 1 -1) in SPM8 to detect regions of interest. Group differences were analysed as follows: Regions were considered significant when corrected for multiple comparisons with the family-wise error (FWE) rate set at p-0.05. Secondly an uncorrected level of p = 0.001 with an extent threshold of a minimum cluster size (k) of [100], was applied, in the event that multiple comparison correction failed to detect differences. (Dai et al. 2018, Didelot et al. 2008, Kim et al. 2003, Cho et al. 2003).

An analysis was carried out with the same parameters for each of the WAIS subtests and results appear in a parametric map of the t statistic (t) which is corrected for normal distribution.

(3.2.5) Freesurfer Cortical Thickness Data

Chapter 2 discusses the methods used to acquire cortical thickness data in detail. In brief, measures were achieved by applying the methods outlined by Fischl and Dale (2000) and previous publications such as Dale, Fischl, &Sereno (1999) and using freely available Freesurfer software (http://surfer.nmr.mgh.harvard.edu). In this part of the analysis an FDR threshold of 0.05 was applied, rather than the more stringent Monte Carlo threshold, given the small number of subjects.

(3.2.6) Comparisons of VBM and FS-CT Coordinates

The analysis for regions of interest in SPM8(for VBM data) and Freesurfer (for cortical thickness data) was carried out separately and suprathreshold regions correlating to WAIS scores were then regionally compared.

As briefly discussed in Chapter 2, many different systems exist, and there isn't one universally accepted approach. Regions may be labelled stereotaxic, i.e., by coordinates, such as the Talairach atlas (Lancaster et al. 2000), depending on microanatomy, i.e., reflecting microscopic features of the brain such as the Brodmann atlas (Brodmann 1909), or macroanatomical, that is, in relation to the gyri and sulci of the cortex, such as the Freesurfer DK atlas (Desikan et al. 2006).

SPM8 and Freesurfer use different reference spaces. One of the most common systems for reporting neuroimaging coordinates used to be the Talairach atlas, utilised for example in the freely available 'Talairach daemon' web application (Lancaster et al. 2000). However, more recent non-linear registrations cannot be used to map individual brains onto the Talairach space, due to the absence of an actual Talairach image (Lacadie et al. 2008a). One of the most common currently used reference 'space' for mapping individual brains, is the Montreal Neurological Institute (**MNI**) space (Evans et al. 1993). However, there isn't a single MNI space either, and SPM, for instance, has used a variety in the past, for example the MNI305, the Colin27, the MNI152linear and newer versions such as the MNI152 NLIN 6th generation or MNI152 NLIN2009 (for a review on functional localisation see Brett et al. 2002).

The current MNI space for SPM8, which analyses the VBM data is the ICBM152 linear as defined by the International Consortium of Brain Mapping (ICBM, Ashburner et al. 2013, pp47-48). The ICBM152 linear is based on 152 normal T_1's matched to the MNI305 (Brett et al. 2002).

Freesurfer uses its own cortical parcellation atlas, as discussed previously (Ch2) and reports 'Talairach' coordinates in QDEC. However, those coordinates are not true Talairach coordinates, but rather, coordinates based on Matthew Brett's MNI305 space (for a review on brain templates see Mandal et al. 2012, for information on Freesurfer coordinates see http://surfer.nmr.mgh.harvard.edu/fswiki/CoordinateSystems).

To compare the coordinates obtained from both VBM and FS cortical thickness analysis, coordinates were entered in a freely available online tool which is part of the Yale BioImageSuite (https://bioimagesuiteweb.github.io/webapp/). MNI to Talairach information are based on Lacadie et al. (2008a) and allows the user via a GUI webapp (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html) to translate MNI coordinates, as well as traditional Talairach coordinates into a single space, and then overlay Brodmann areas (Lacadie et al. 2008b). Brodmann areas were then used to compare between the two different analyses, in table form as well as visually, with the coordinates mapped on a template brain.

(3.2.7) PART II CASE ANALYSIS WITH NORMATIVE DATA

In addition to a comparison between VBM and cortical thickness measurements, a case study example utilising normative data has been completed.

A qualitative case study is commonly used to explore a concept through various data sources, and thus reveal multiple facets of the investigated phenomenon (Baxter & Jack 2008)

The normative calculator, which is freely available (Potvin et al. 2017) requires estimated intracranial volume (eTIV, or ICV), found in aseg stats, and observed values found in the lh.aparc and rh.aparc for Desikan Killinary regions. Output from the calculator provides normative data, taking account of age, gender, eTIV, scanner field strength and manufacturer. Z scores for each of the Freesurfer regions for each hemisphere show how much the observed values deviate from the mean, taking into account the above factors.

Assessments on correlations between test scores and brain regions were made according to the information given in table 3.1, which contains an overview over the cortical areas most relevant in cortical thickness intelligence research.

OO was selected at random, from the very small sample, because his profile highlighted both strengths and weaknesses, allowing a demonstration of the proposed methods.

(3.3) RESULTS PART I - GROUP ANALYSIS

The sample yielded the neuropsychological scores illustrated in Figure 3.4. They had a mean Full-Scale IQ of 108.2 (SD 8.1), Verbal Comprehension Index of 108.3(SD 12.4), Perceptual Reasoning Index of 117.6 (SD 12.5), Working Memory Index of 96.2 (SD 13.5), and Processing Speed Index of 107.2 (SD 18.01). Scores were distributed normally.

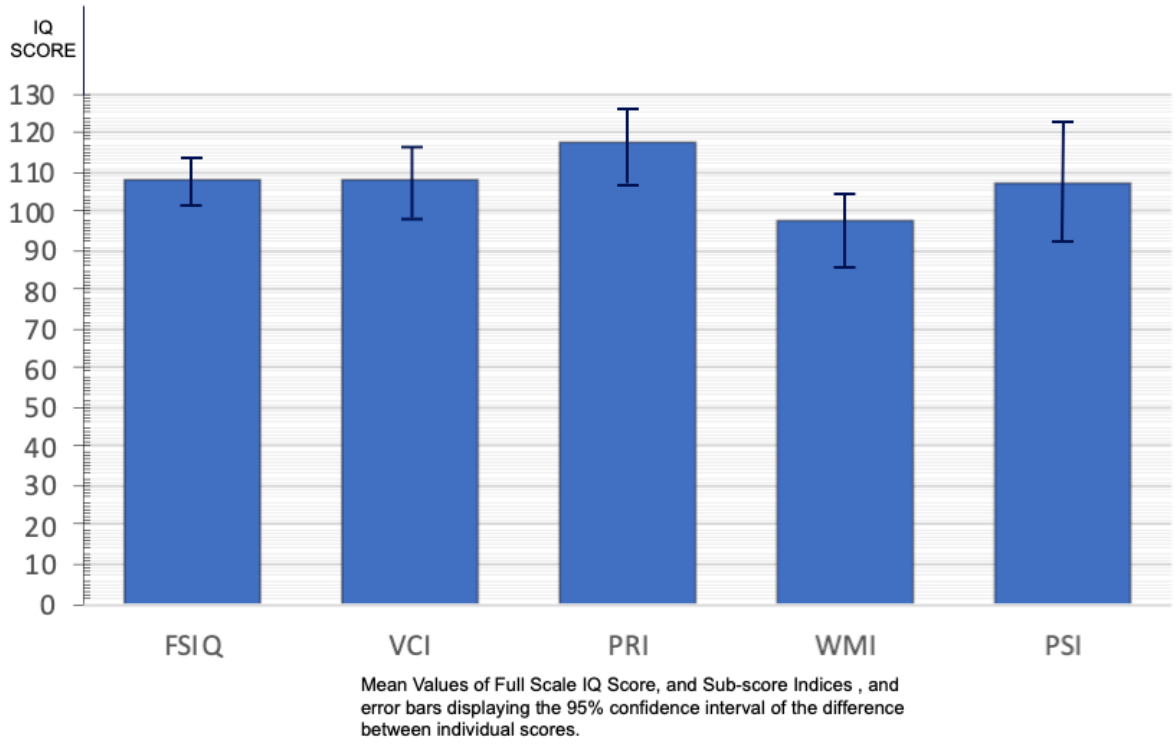


Figure 3.3 Summary of WAIS Full-Scale Intelligence Quotient (FSIQ) and Sub-scales, Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and Processing Speed Index (PSI).

Comparison between VBM and Cortical Thickness

When comparing the regions that overlapped between VBM and Cortical thickness analysis, when correlation MRI data with WAIS scores, the most significant overlap was found in Brodman area 19 for the Full-Scale IQ score, which was associated with the occipital subgyral (VBM) and lateral occipital, and fusiform region (FS Cortical Thickness). There was a further overlap in BA 23, though this was significant for the Processing Speed Index for VBM analysis and Full-Scale IQ in FS Cortical Thickness analysis. Regions of interest for the FSIQ were the left occipital subgyral region, left inferior temporal gyrus, right medial frontal gyrus, and right anterior cingulate cortex. VCI was associated with significant regions in the left precentral gyrus, left medial frontal gyrus and right parahippocampus. Regions associated with PRI were the left precuneus and precentral gyrus, as well as the right transverse temporal gyrus. The PSI only showed significance in a small area of the left cingulate gyrus. No significant relation to the WMI was found. Regions and their coordinates can be found in Table 3.2.

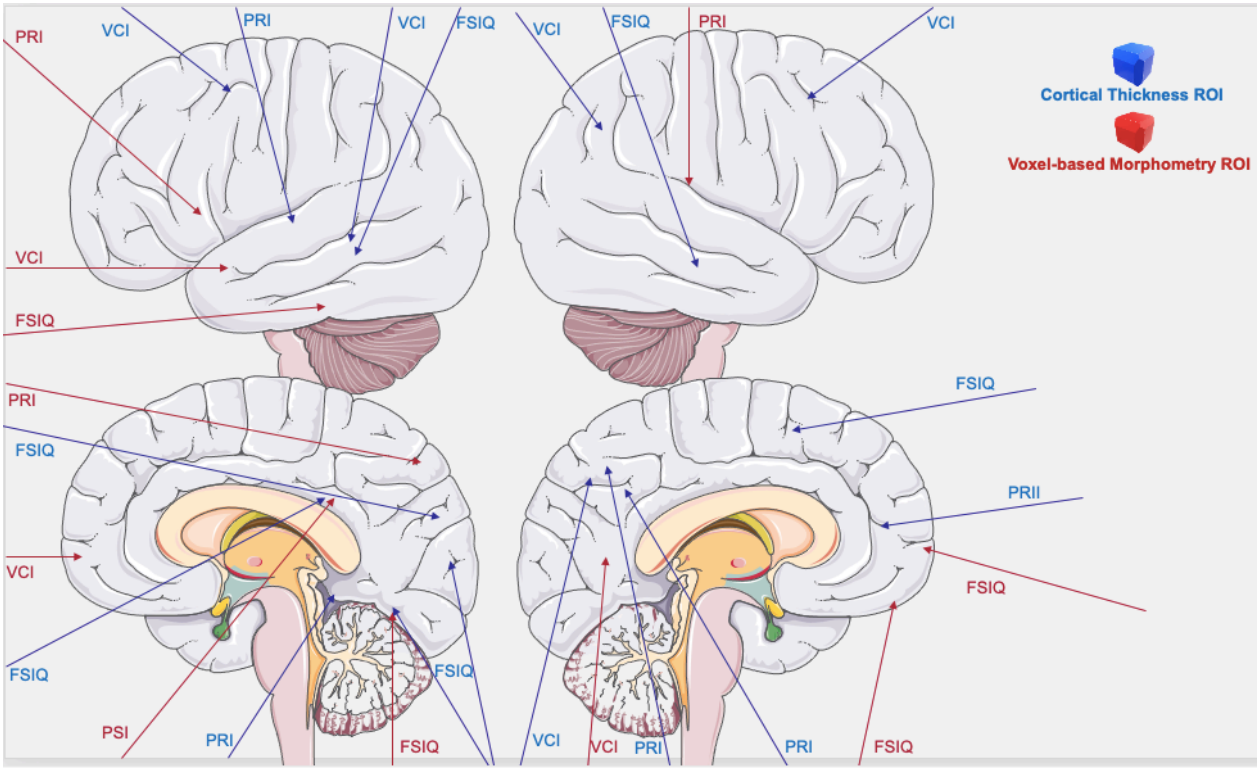


Figure 3.4 Visual illustration of VBM vs Cortical thickness data, with coordinates having been plotted approximately onto a representative sample of a standard brain. FSIQ, denotes corresponding areas to the Full-Scale IQ, VCI, to the Verbal Comprehension Index, PRI, to the Perceptual Reasoning Index, and PSI to the Processing Speed Index. Results from Cortical Thickness analysis are marked in blue, and those marked in red indicate regions of interest derived from voxel-based morphometry.

	Full Scale IQ		Verbal Comprehension Index		Perceptual Reasoning Index		Processing Speed Index
	LH	RH	LH	RH	LH	RH	LH
Voxel Based Morphometry	Occipital subgyral region -27 -74 1 Inferior temporal gyrus -41 -15 -20	Medial frontal gyrus 13 61 -4 Anterior cingulate gyrus 17 31 -24	Precentral gyrus -54 7 -14 Medial frontal gyrus -7 54 -12	Parahippocampal gyrus 30 -54 -4	Precuneus -14 -71 45 Precentral gyrus -45 11 9	Transverse Temporal gyrus 62 -15 12	Cingulate gyrus -4 -41 26
Cortical Thickness	Middle temporal gyrus -55.6 -39.4 -4.0 Isthmus cingulate gyrus -10.2 -38.3 31.6 Lateral occipital gyrus -23.8 -86.4 16.4 Fusiform gyrus -32.7 -71.5 -8.8	Superior frontal gyrus 7.3 10.6 56 Middle temporal gyrus 63.7 -29.0 -7.3	Precentral Gyrus -39.5 -4.9 46.5 Pericalcarine gyrus -10.6 -79.4 46.5 Banks of the superior temporal sulcus -47 -46.4 8.1	Caudal middle frontal gyrus 35 9.4 33 Superior parietal gyrus 24.2 -57.4 43.9 Inferior parietal 46.1 -51.3 33	Transverse temporal gyrus -33.3 -28.1 11.3 Fusiform gyrus -31.7 -40 -16.9	Precentral gyrus 27.7 -14.4 60.2 Precuneus 9.4 -50.8 47.8 Rostral anterior cingulate gyrus 6.6 35.6 15.8	

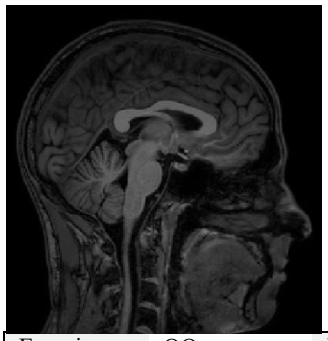
TABLE 3.2

Where regions vastly exceeded the number of VBM regions per subtest, the highest supra-threshold regions were selected for comparison against SPM analysis. Once suprathreshold regions were recognised in FS, the global maxima for each was selected for their coordinates, which are summarised in Table 3.2, alongside their corresponding BA areas. For FSIQ, VCI and PRI Freesurfer was able to identify a number of regions in addition to those identified by VBM. A total of 12 areas were identified as related to FSIQ, with the top four on the left hemisphere being middletemporal gyrus, isthmuscingulate, lateral occipital cortex and fusiform gyrus.

The right hemisphere yielded 9 clusters in total, with the top two being superiorfrontal gyrus and middletemporal gyrus. VCI showed significant associations in the left hemisphere for precentral gyrus, pericalcarine cortex and the banks of the superior temporal sulcus (bankssts), whilst the caudal middle frontal gyrus, superior parietal cortex and the inferior parietal cortex were significant in the right hemisphere. The PRI was associated with the transverse temporal cortex and fusiform gyrus on the left and the precentral gyrus, precuneus cortex and the rostral anterior cingulate on the right. Neither WMI nor PSI reached the significance threshold. Table 3.2 summarises the analyses and highlights the only overlap across Brodmann areas, which is BA 19 in relation to FSIQ. Because the comparison via Brodmann area alone was not as clear as was anticipated, coordinates were also mapped onto a BA example area. The main overlap between VBM and CT could be observed for area 19 in relation to FSIQ, but also for its sub scores. There was some further overlap in area 23 though it was identified in relation to PSI in SPM and FSIQ in QDEC. Illustration 3.5. maps the coordinates identified in each analysis into its approximate area.

(3.3.1) PART II - REPORT, CONTAINING MORPHOMETRIC DATA

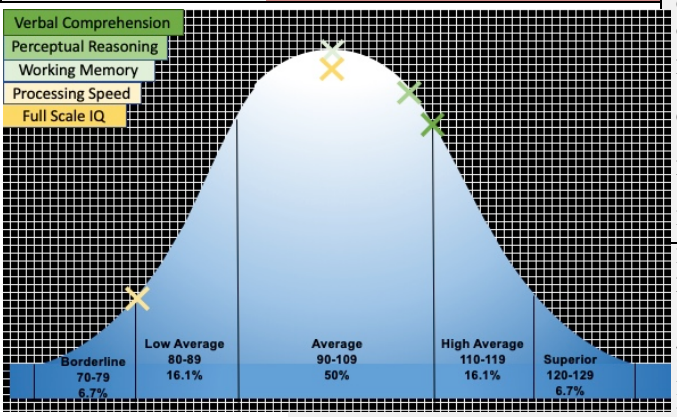
Participant ‘OO’ was assessed on a range of neuropsychological tests and underwent MRI testing, in line with voluntary research study participation. The following report and its contents are for exploratory research purposes and not intended as a clinical evaluation. The report took the template format as provided alongside the Wechsler clinical scales (Wechsler, D., 1998) titled “Sample Report”, but includes morphological information obtained from Freesurfer. The report aims to assess the feasibility of combining neuropsychological data with volumetric data from MRI scanning.



Overview

Examinee ID	OO	Examiner ID	DR
Age at Testing	23	Native Language	English
Gender	Male	Handedness	Right
Ethnicity	White British	Level of Education	Undergraduate
Estimated Intracranial Volume	1639277mm^3	Testing Site	BUIC
Field Strength	3T	Manufacturer	Phillips

Verbal Comprehension	110	high average	75th %tile
Perceptual Reasoning	107	average	68th %tile
Working Memory	100	average	50th %tile
Processing Speed	74	borderline	4th %tile
Full Scale IQ (FSIQ)	100	average	50th %tile
General Ability Index	109	average	73rd %tile
Cognitive Proficiency Index	83	low average	13th %tile



Volumetric Measure Overview
Z score map scale

Maximum	**4.9**
Middle	**0.0**
Minimum	**-1.9**

Region	Surface L	Surface R	Thickness L	Thickness R	Volume L	Volume R
Temporal lobe						
Superior temporal gyrus	1.3	3.2	1.6	1.1	3.1	3.5
Middle temporal gyrus	1.8	1.4	-0.2	0.2	1.1	1.5
Inferior temporal gyrus	4.5	1.4	0.3	1.0	4.9	2.2
Transverse temporal gyrus	0.5	1.7	-0.1	0.2	0.3	1.7
Banks of the superior sulcus	-0.1	1.0	0.9	0.4	0.0	1.0
Entorhinal cortex	3.4	0.9	-0.7	0.5	2.6	1.6
Parahippocampal gyrus	-0.1	-0.5	0.7	1.0	0.2	0.7
Fusiform gyrus	0.9	0.3	0.2	0.1	1.1	0.3
Temporal pole	2.9	1.1	-0.5	0.8	1.5	1.5
Frontal lobe						
Superior frontal	3.8	1.5	-1.6	-1.6	2.2	0.2
Rostral middle	1.6	0.4	-0.2	-0.9	1.7	-0.3
Caudal middle	1.6	2.7	-0.5	-0.2	1.3	2.9
Pars opercularis	-0.9	0.3	-0.1	-1.1	-1.0	-0.2
Pars triangularis	-0.8	-0.4	0.2	-0.5	-0.7	-1.0
Pars orbitalis	0.7	3.4	0.7	-0.7	1.0	2.6
Lateral division	1.5	1.5	-0.7	-1.0	1.5	1.6
Medial division	1.3	2.0	-0.5	-1.1	0.7	0.8
Precentral gyrus	2.4	2.8	0.1	-0.5	2.0	2.1
Paracentral lobule	1.7	0.8	-0.6	-0.6	1.1	0.6
Frontal pole	2.8	0.2	0.2	-1.2	2.6	-0.7
Cingulate cortex						
Rostral anterior	1.3	0.9	-0.6	-0.5	0.8	1.4
Caudal anterior	-0.4	2.6	-0.5	-0.8	-0.5	1.8
Posterior	-0.5	1.7	-0.8	-1.9	-1.0	0.6
Isthmus	-0.2	0.3	-1.0	-0.8	-0.6	0.7
Parietal lobe						
Postcentral gyrus	2.0	3.2	0.3	0.6	1.6	2.6
Supramarginal gyrus	2.6	1.3	-0.5	0.1	2.2	1.5
Superior parietal lobule	1.4	0.6	0.2	0.4	1.6	0.9
Inferiorparietal lobule	1.9	1.4	-0.5	-0.3	1.4	1.2
Precuneus	1.6	2.1	-0.5	-0.9	1.2	1.3
Occipital lobe						
Lingual gyrus	-1.3	1.2	0.5	1.4	-0.8	1.8
Pericalcarine cortex	-1.1	-0.7	0.5	1.6	-0.7	0.0
Cuneus cortex	-0.8	0.9	1.2	1.2	0.0	1.4
Lateral occipital cortex	2.0	1.6	1.8	1.3	3.5	2.7
Insula	0.6	0.5	0.1	-0.8	0.9	0.3
Whole cortex	2.6	2.5	0.0	-0.1	3.0	2.7

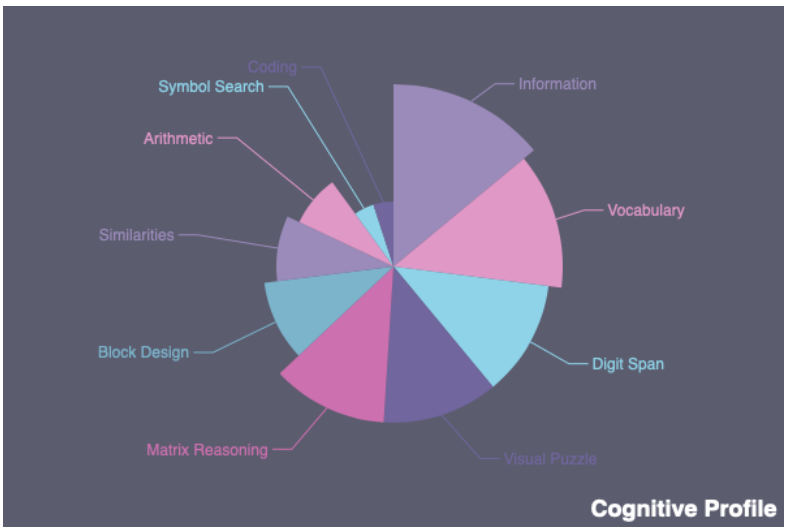
OO is a 25-year-old Caucasian male, studying for his undergraduate Bachelor of Science degree, at the time of testing. OO reported no history of neurological or psychological trauma or illness and no other significant medical history. He is not taking any regular medication.

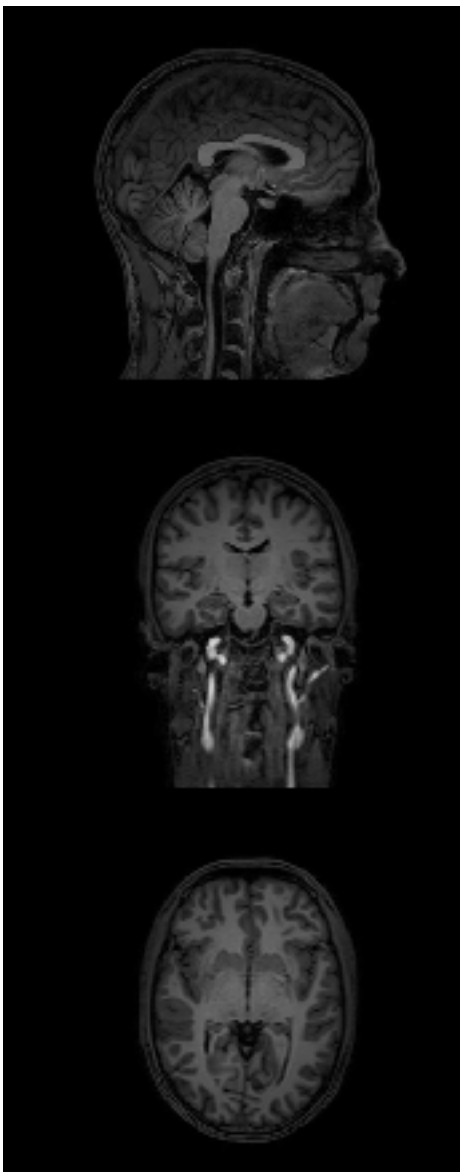
Test Session Behaviour

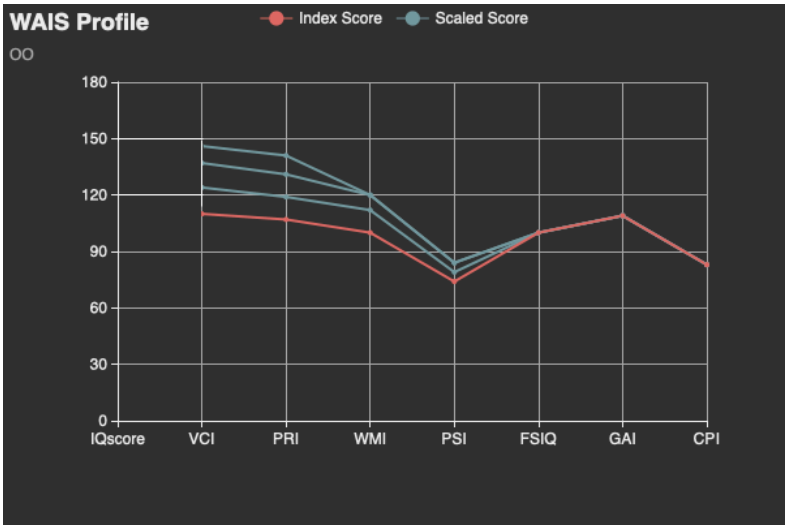
OO arrived unaccompanied and of neat appearance for testing. He was oriented to person, place, time and situation. OO was compliant with instructions and took part with interest and enthusiasm. He was open to conversation and establishing rapport. MRI scanning, which took place on a separate date, was uneventful. OO reported no problems during testing, though he found certain tasks difficult, which is reflected in his test scores.

General Overview

OO's performance on the Wechsler Adult Intelligence Scale- Fourth Edition showed a strength in his verbal comprehension (VCI) and perceptual reasoning ability (PRI) and a weakness in his processing ability (PSI). Volumetric measures calculated from his MRI scan are between average and up to 3 Standard Deviations above normative, when age, gender and estimated intra-cranial volume are taken into account. His Full-Scale IQ is in the average range with a standard score of 100, placing him on the 50th percentile. Perceptual Reasoning places him on in the 68th percentile and above approximately 68% of his peers, with a standard score of 107. His verbal comprehension ability is a clear strength with an above average performance on the 75th percentile, whilst his working memory is average with a composite score of 100. Processing speed is a clear weakness with OO scoring above only 4% of his peers.







Morphometric examination of the MRI in relation to cognitive ability

OO's overall cortical thickness is as expected for his age and gender. However, there is a trend towards significance in regions known to be associated with Verbal Comprehension, in particular Vocabulary. OO displays a SD-1 in this area, below what would be expected for his age and eICV. The cortical thickness of the right precuneus has been shown to have a negative correlation with Vocabulary, with a thinner cortex in this area, indicative of higher verbal ability.

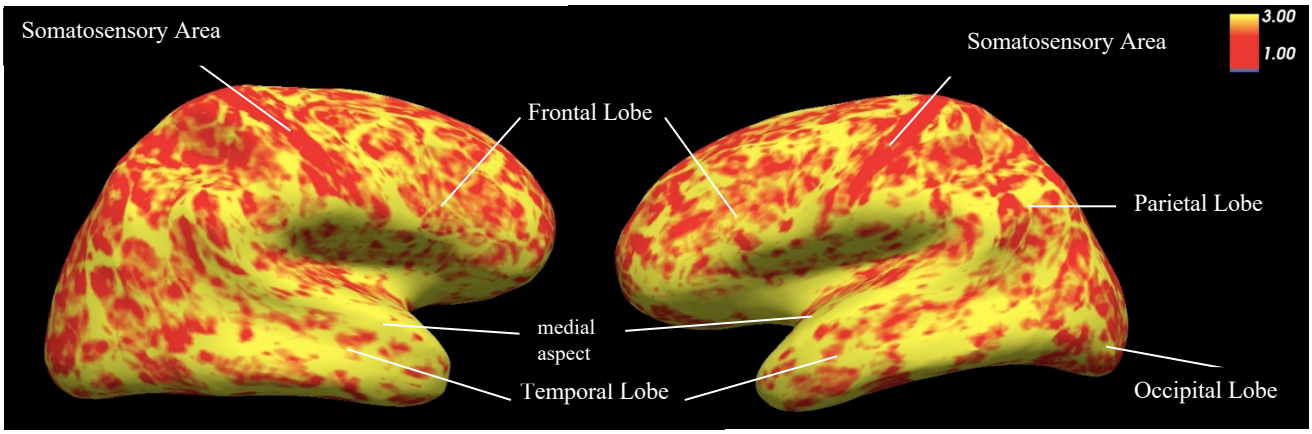


Figure 2 is showing OO's reconstructed Cortical Thickness Map on an inflated brain. It shows fluctuations in thickness on a colour scale of red to yellow. Red is indicative of a thinner cortex and yellow of a thicker cortex relative of OO's individual values. The map shows clearly where OO's somatosensory area is located, indicated as one of the thinnest areas in the cortex. It also shows the relative thickness of the temporal lobe, compared to the other cortical areas. The Frontal lobes with an average thickness of 2.5mm are representative of the rest of brains thickness and overall profile of a slightly mixed profile between thinner and thicker areas. The occipital lobe has a slightly thinner profile, compared with to the remaining cortex, and its average thickness is approximately 2-2.1mm, compared to an average whole brain thickness of around 2.5. This is largely due to the Primary Visual Areas (V1 and V2) being located in the calcarine fissures of the occipital lobe; however the lateral occipital cortex appears to have some predictive value over cognition, with OO's lateral occipital cortex being lh1.8SDs and rh1.3SDs above what would be expected.

Cortical thickness has been largely associated through a positive relationship in the frontal lobes, where OO tends to trend below his peers. Frontal regions also tend to support fluid intelligence characterised through working memory, reasoning and processing speed, which is below average in OO supported by an overall lower profile of cortical thickness Zscores.

(3.4) DISCUSSION

Voxel based morphometry and Freesurfer's cortical thickness exhibit fundamental differences in methodology. Both approaches did show an overlap in BA19 for FSIQ and BA 23 for the PSI(CT) and FSIQ(VBM), with both regions being comparable to those identified in previous studies (e.g., Choi et al., 2008, Menary et al., 2013, Zink et al., 2018 & Hidese et al. 2020). When comparing VBM results against a study conducted by Colom et al. (2002), there is a substantial amount of overlap. Colom et al. looked at correlations in clusters generated from g generated for Block Design (BD) and Vocabulary (VOC). Clusters were found in lh BA10, 11, 46, 47 and rh BA 8, 10 in the frontal lobes, which overlaps with the clusters found for the FSIQ (rhBA10 and VCI lhBA10). In the parietal lobes Colom et al. (2002) found clusters in lhBA7, 19, 40 and rhBA40, which overlaps with findings for PRI (lhBA7, rhBA40) and FSIQ (lhBA19). Further comparable areas were found in lhBA20 for FSIQ, lhBA19 FSIQ, and BA19 for VCI scores. The same study, along with others (e.g., Duncan et al., 2000, Menary et al. 2013, Narr et al. 2007) showed similar areas to the FS-CT results of this study in rhBA8 for VCI, lhBA21 FSIQ, lhBA37 for PRI and as reported for cortical thickness only, in Table 3.1.

The main areas to compare between analyses in this study BA19 and BA 23 relate functionally to the WAIS. The Cingulate Cortex is attributed to motivation, anticipation of tasks, attention, and error detection (Nieuwenhuis et al. 2001, Posner & DiGirolamo,1998, Bush et al. 2000), which makes particular sense in terms of the WAIS and the sub scores that comprise the FSIQ. BA23, from its cognitive relation to the WAIS, has also been identified as having the highest local functional connectivity

density (Tomasi &Volkow 2010) which is interesting considering that research is showing more and more that it is networks across the brain that facilitate higher order cognition, rather than singular areas alone (Laughlin & Sejnowski 2003).

Whilst in direct comparison VBM and CT did not show comparative regions in all areas identified in each respective analysis, all regions have previously been linked to the WAIS and discrepancies could be explained, because the analyses approach their measurements in a different way, as well as working in a different MNI space.

(3.4.1) Technical Considerations and Limitations

Whilst FS seemed to be able to get more information from the data and identified more suprathreshold regions than SPM, applying the coordinates from the FS output to a generic brain for comparison via Brodmann areas was more difficult at times, with some coordinates resulting in nonsensical regions, outside of the brain, or in the cerebellum, for example. This was particularly true for regions closer to the surface, such as the fusiform gyrus, the lingual gyrus, inferior temporal gyrus and lateral orbitofrontal cortex. Whilst MNI spaces were discussed earlier, there does seem to be an issue taking FS generated coordinates and inputting these unaltered elsewhere, because the FS brain is reconstructed and aligned to its own version of the cortex (see Methods Ch2), as well as to an average brain which is made up from the subjects within the group cohort. Though it is meant to be co-registered to a similar MNI space as SPM8 VBM, it does cast some doubt on the reliability of comparisons when looking at coordinates alone.

Another problem, when comparing the results, is that VBM essentially measures regional grey matter density via voxel wise comparison, with density relating to the relative amount of grey matter and the concept of voxels being somewhat arbitrary. A

voxel represents the grey matter density of itself and its neighbours, smoothed to a template to allow for comparison with other MRI data (Ashburner & Friston, 2000, 2001). FS purports to measure the actual packing density of neurons based on the mm measurement between the white matter surface and pial surface, as well as surface area and volume. Whilst both analysis methods originate from basic MRI, which clearly has limitations, CT analysis seems to provide a lot more volumetric data than VBM. Though in recent years additional toolboxes have allowed more comprehensive volumetric analysis in SPM (e.g., CAT12 toolbox, see comparison with FS Seiger et al. 2018). VBM is a relatively quick statistics tool and doesn't require time consuming pre-processing, whereas the initial pre-processing time of FS data alone can take approximately 8 hours or more, depending on the size of the dataset.
Other studies encountered similar difficulties when comparing SPM-VBM and FS-CT (e.g. Grimm et al. 2015) and noted that the systematic comparison between VBM and FS would require the alteration of many technical parameters, which has not yet been done, aside from whole brain volume (Klauschen et al. 2009) and might be a future direction for research.

Given the initial explorations of morphometric data in this chapter, cortical thickness should certainly be considered in the analysis of individuals, as well as in clinical assessments. Clinically neuropsychological assessments are often used in candidates with cognitive symptoms affecting day-to-day functioning, or in those with conditions which may necessitate surgery to improve their quality of life. Cortical thickness is an interesting measure to consider in this context, because it has already shown itself to be a sensitive biomarker for a variety of conditions and diseases. For example Attention Deficit Hyperactivity Disorder (ADHD) is linked to reductions in the anterior cingulate cortex (Bledsoe et al. 2013) and now classed as a neurodevelopmental

disorder, which results in changes in brain maturation responsible for the observed symptoms (Xiao et al. 2016). Cortical thickness is also known to have specific characteristics in conditions such as bipolar disease (see review Hanford et al. 2016) schizophrenia (Takayanagi et al. 2011), developmental dyslexia (Williams et al. 2018) and epilepsy (Butler et al. 2012). Despite this, CT is not yet routinely used in clinical investigations, even though the measures of cortical thickness in the region of interest, have a much more straightforward neurobiological interpretation, as opposed to other analyses.

Since FS-CT is a relatively new tool, changes in cortical thickness in relation to intelligence have not yet been studied in longitudinal designs, despite the fact that changes clearly do occur over the course of a lifetime (Schnack 2015). In order to establish sensible biomarkers, more longitudinal designs following adults over several decades are needed.

(3.4.2) Potential Applications and Clinical Use

As discussed in the general introduction (CH1) language lateralisation plays an important role in the evaluation of presurgical candidates, and alternative procedures to the traditional IAP or Wada (Lassonde et al. 2006) should be aimed for to avoid the associated mortality rate, as well as other related side effects experienced by patients. Language lateralisation is clearly an important factor to consider, for the sake of a desirable outcome post-surgery, but other aspects of cognition should also play a key role when planning surgery.

Volumetric brain MRI has the potential to become a powerful screening tool in clinical applications, if future studies focus on developing more robust normative data relative to well validated neuropsychological assays. Aside from informing early on possible

disease trajectory, and thus prompting possible intervention early, it could also aid the informed decision making about whether surgery is in the best interest of the patient.

Recent studies indicate that epilepsy patients with thinning in the frontal cortex may have poorer surgical outcomes than those without, which suggests that CT data as part of pre-surgical evaluation may help identify those at risk of surgical failure (Kamson et al. 2016).

An example of what an evaluation containing both comprehensive neuropsychology, as well as information on normative volumetric data could look like, is included in Part II of the results. This is clearly a prototype and not necessarily indicative of what a clinical report would look like, once methodology has been refined. Given the fundamental differences between cortical thickness measurements and voxel-based morphometry these data should be viewed as complimentary to one another, as comparison is complex.

In the context of this chapter, normative data comparing and correlating cortical thickness with performance in a widely used clinical tool, e.g. the WAIS, could allow for a triaging of problematic areas of cognition and thus allow for targeted testing and or intervention.

The concept of normative data in neuroimaging is relatively new even though it is established in many other sciences, most notably in context, neuropsychology. The Potvin et al. (2017) data is a good start and provides a much-needed normative counterpoint to the wealth of information extracted from FS, but more needs to be done in this area for data to become of clinical use.

What could be helpful in the study of how underlying brain morphometry relates to neuropsychological data, is to create a big data set of participants undergoing the same comprehensive neuropsychological battery to draw conclusions about relative

correlation plots in specific brain regions. Defining these regions more specifically might be necessary to really pinpoint the precise areas of where cognitive functions may be subserved, or at least where the underlying brain morphometry has an impact on it. To apply morphometry data to the individual in a normative context, much more needs to be known about specific functions and specific tests relate to specific brain regions.

Whilst normative data at this point might tell us something about the developmental trajectory an individual might take, or explain some innate differences in cognitive function, based on the brain's individual capacity, not enough is known to draw real conclusions about the relationship between very specific functions and specific areas. Although the information in table 3.1. begins to paint a picture of how a cortical thickness profile is correlated with cognitive functioning, it is pieced together by various studies, with different definitions of intelligence, utilising various sub-tests from various batteries.

In terms of identifying or predicting performance on the basis of volumetric data, in particular cortical thickness, the WAIS sub scores have not been as extensively researched as the FSIQ, or VCI and PRI as comparative measures (examples are Block Design, Zink et al. 2018, or selective sub test analysis in Lee et al. 2016). Specific research for those variables is therefore lacking and is something future research should be concerned with, in particular in relation to normative data. Correlation plots in a larger scale study, between task performance on specific tasks in relation to cortical thickness, are desirable, to be able to interpret normative volumetric data. There is also a potential that once normative volumetric data can be interpreted with greater precision, this could be a screening tool to inform

neuropsychological assessment with greater specificity. In the WAIS, tasks for PSI and WMI are limited. However, if normative volumetric assessment points to memory and processing speed difficulties, for example, the WMS and BMIPB (BIRT Memory and Information Processing Battery) alongside an abbreviated version of the WAIS (WASI- Wechsler Abbreviated Scale of Intelligence, & WTAR – Wechsler Test of Adult Reading) may be a better choice of assay, to really pinpoint where difficulties present themselves, rather than following a standard range of assays.

One aspect of difficulty when combining neuroimaging and neuropsychology, was the vast amount of data, both the complete neuropsychological battery, as well as standard the FS analysis yields.

The WAIS alone has various interpretable values, the complete battery as discussed in the methods part had an almost overwhelming amount of data, to be compared to neuroimaging data. This meant that only part of it would be analysed to test the methods and see whether the model would produce not only significant, but sensible results.

It is also important to point out that every individual will display strengths and weaknesses. In particular in the context of assessing healthy individuals, it is prudent to state that, inevitably there will be a range of abilities and capabilities. In relation to the underlying brain anatomy and microanatomy, individuals may simply have a limited capacity at which their brain is able to operate, or the maximum they can achieve, particularly in view of gF (Hampshire, et al. 2012).

This chapter set out to compare voxel-based morphometry and cortical thickness by translating the coordinates they yield, into a universal space. This was not without difficulty and the overall conclusion drawn is that VBM and CT are fundamentally

different measurements. Though the results yielded from comparative analysis are similar and in-line with previous research for both methods of analysis, respectively, they should be viewed as complimentary methods of analysis, rather than comparative. Research focussing on cortical thickness measurements should therefore be cautious when relying on older studies using VBM as their method of choice.

Large normative datasets correlating cortical thickness maps with cognitive data, show real potential promise for clinical application, given the relative ease with which cortical thickness maps can be calculated,

Neuropsychological methods will remain the gold standard for assessing cognitive ability and functioning, however their application remains lengthy and somewhat onerous on both the patients and the practitioners.

Being able to triage the most prudent tests, based on areas most likely in need of intervention, may ease the process somewhat on the patient, in particular.

CHAPTER FOUR

AGE RELATED CHANGES IN CORTICAL THICKNESS ASSOCIATED WITH COGNITIVE DECLINE

"AGEING IS NOT LOST YOUTH, BUT A NEW STAGE OF OPPORTUNITY AND STRENGTH"

BETTY FRIEDAN (1921-2006)

(4.1) An ageing society

In a society with increasing life expectancy, healthy ageing and the detection of age-related diseases at pre-symptomatic stages, is of growing focus. Thanks to advancements in medicine and healthcare, and an overall rise of living standards in the industrialised nations, in particular, society is 'getting older' (Oschwald et al. 2019). Birth rates have fluctuated in the past century, with spikes observed in 1920, 1947 and in the 1960's. Progressively decreasing mortality rates, alongside those spikes in births have resulted in a large number of people now in their late 90's, 70's and 50's (Storey 2020, Office for National Statistics, ONS).

Life expectancy is forecasted to increase further. Those born in 1981 are anticipated to enjoy a cohort life expectancy of around 84 years. This increased to 89 years for those born in 2010 and is expected to rise to approximately 91, by 2030 (Thurley, et al. 2011, House of Commons).

Measuring the ageing of society is often done by calculating the proportion of people aged 65 or over. In England, this is expected to increase in all areas from 18.2%-

20.7% in the next decade (2018-2028) (Nash 2020, ONS). Additionally, birth rates are falling, which provides logistical challenges for the adult social care sector, in particular, and local authorities, as they are expected to plan for a rise in the need of formal care for the elderly (Storey 2020, ONS).

With an extending lifespan, it is thus becoming increasingly important to ensure that extra years are spent in good health and with a good quality of life. The World Health Organisation (WHO, 2015) acknowledged this global challenge of healthy ageing and urged changes in health and social care policies, to positively influence this inevitable change in demographics.

(4.1.2) Ageing and Cognition

Chapter 1 has already provided some information on the main cognitive challenges in healthy ageing (1.12). In summary, healthy ageing seems to be associated with an overall decrease in processing speed (Hofman 2012). However, as pronounced as cognitive differences between the young and old, in laboratory settings are, these findings do not always translate into real-world scenarios with seniors often able to live fulfilling and independent lives into their 70s or beyond (Salthouse 2012).

Although even relatively early research demonstrates how cortical thickness declines globally with age, and how cortical thinning is present as early as middle age, in the third decade of life (Salat et al. 2004,), the relationship between cortical thickness, thinning and cognition is more complicated than a simple equation of ‘the thicker the better”.

Previous research has very clearly established that a degree of thinning occurs inevitably with age, however, postmortem studies found that brain weight remains relatively stable until age 40, after which there is a gradual decline until reaching lowest value around 86, by which time mean brain weight is 11% less than at around 19 years (Dekaban, 1978)

As previously discussed in this thesis, both increases and decreases of cortical thickness and surface area could be interpreted as continuing regional development (Schnack et al.2015). Cortical thickness reduction is non-linear, as it becomes more pronounced after the 6th decade if life with a drop of more than 3Standard Deviation points over the course of adulthood (Potvin et.al., 2017). Areas of significant thinning, when comparing younger and older participants, were found in particular in the inferior prefrontal, precentral, and supramarginal regions (Salat, et.al., 2004), but also in the superior, middle, and inferior frontal gyri, superior and middle temporal gyri, precuneus, inferior and superior parietal cortices, fusiform and lingual gyri, and the temporo-parietal junction (Fjell, et.al., 2009), as well as smaller age-related differences in the volume of the fusiform, inferior temporal and superior parietal cortices (Raz, et.al., 1997). Figure 4.1 shows the developmental trajectory and thickening and thinning of some of these regions (Vidal-Pineiro et al. 2020).

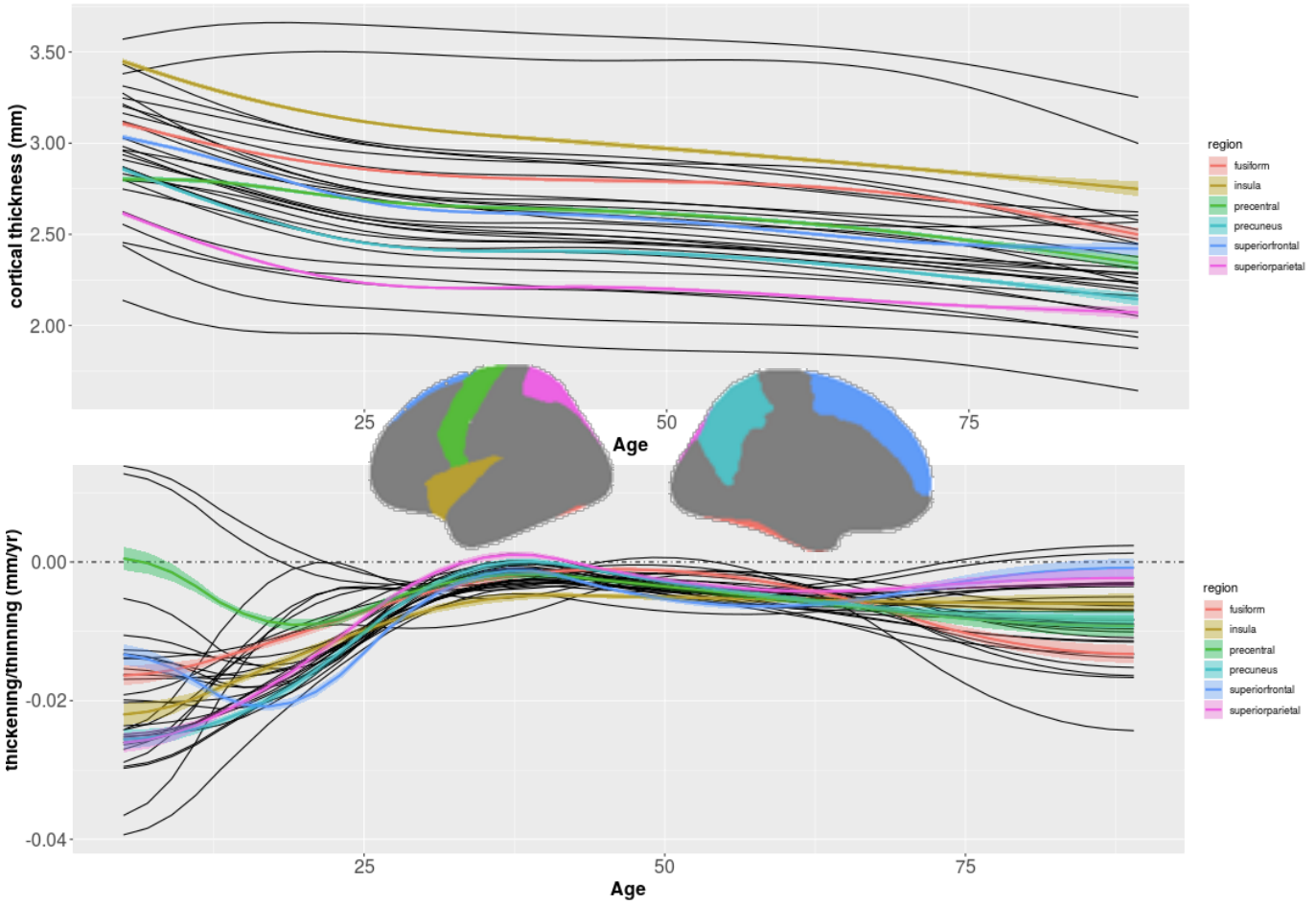


Figure 4.1 Illustration of trajectory for thinning and thickening of individual regions for fusiform (red), insula (yellow), precentral (green), precuneus (blue), superior frontal (violet) and super parietal (pink). Figure created with https://athanasiamo.shinyapps.io/Virtual_histology_2019 from Vidal-Pineiro et al. 2020. Black lines represent other brain regions, not specifically mentioned.

Figure 4.1 demonstrates the complex relationship between cortical thickness and development, with different regions showing different offset points and lifetime thinning/thickening trajectories (Vidal-Pineiro et al. 2020).

Joint utilisation of neuroimaging and neuropsychological tools further allows for the assessment of how specific cognitive functions, e.g., processing speed, memory functioning, or executive functioning, relate to precise areas in the brain or to interactions within distributed brain networks. This can be used to assess the aptitude and ability in healthy subjects, as well as patients. Structural markers in symptomatic patients in relation to neuropsychological profiling can allow for a detailed diagnosis

and prognosis and allow predictions for recovery or long-term implications, in particular in comparison with normative data derived from a healthy population.

Predicting risk markers for cognitive decline in relation to anatomical structure and potential loss of grey matter or overall brain volume, may in future help to address significant problems before they arise with adequate intervention, or help manage them more acceptable. The CANTAB paired associate learning (PAL) subtest, for example, has shown promise in early Alzheimer's Disease screening (Junkkila et al. 2012). However, a combination of neuropsychological tests and neuroimaging could potentially not only identify those at risk of cognitive decline in ageing, but also offer avenues for treatment, currently not available.

(4.1.3) Cortical thickness and Ageing

Cortical thickness offers complementary information for understanding brain anatomy by way of an index of cortical morphology, which reflects size, density and arrangements of neurons in a biological and topological meaningful way (Parent &Carpenter, 1995). Analysis, however, is relatively complex, and standardised measures and techniques are not yet universally agreed upon (Perlman, 2007). Cortical thickness measures distribution and quantity of grey matter, and can provide meaningful insight into grey matter loss (Voets, et.al., 2008, Winkler, et.al., 2010). Previous research has verified cortical thickness measurements against histological analysis and manual measurements (Rosas, et.al., 2002, Kuperberg, et.al., 2003, Salat, et.al., 2004). In particular on the topic of healthy aging cortical thickness leads to sensible insights, such as age-related alteration of global morphometric properties, gyral atrophy and overall loss of cortical volume and mass (Kemper, 1994).

It is clear that changes to brain morphology appear to be widespread, across most areas of the cortex, and as such similar results are expected from this study, albeit its small sample size.

(4.1.4) Contextual background

Ziegler et al. (2010) compared a cohort of younger people with a cohort of older people to assess whether changes in cognition could be attributed to underlying changes in brain morphometry. Cortical thinning was found in widespread regions, bilaterally in the superior frontal gyrus, precentral gyrus and banks of the central sulcus, as well as the calcarine sulcus, cuneus, lateral pre-frontal and inferior parietal cortex. Although this study did aim to assess a correlation between cortical thickness in a priori Regions of Interest, and composite cognitive scores, none were found.

A similar study investigated changes in cognition across the lifespan but also failed to discover any significant associations between cognitive ageing and cortical thinning (Cox et al. 2018). Ritchie et al. (2019) utilised CANTAB in a longitudinal design correlating cortical thickness to cognitive performance and found that overall higher intellectual abilities were related to higher cortical thickness, but results were not found to be predictive of cognitive development between the ages of 14-19. Frangou et al. (2020) confirmed cortical thickness decline in a large-scale study of 17075 individuals aged 3-90 years, suggesting that normative variance may assist in detecting abnormal deviations in cognitive outcomes.

The aim of this study was to analyse data in relation to a cohort of younger and older adults, in relation to its relevance to cortical thinning and cognitive ability. Previous research has shown that atrophy is significantly prevalent in older adults, over the age

of 50-55, and that these differences in cortical volume and thickness are widespread across the brain. Research has also shown that cognitive decline is a widespread phenomenon across the aging population and as such, a comparison using cortical thickness data, as well as neuropsychological testing of the same cohort would be advantageous to show this link. CANTAB is a widely used and well validated neuropsychological tools, and has previously been utilised in ageing research, with the Paired Associates Learning task (PAL, CANTAB, Cambridge Cognition) shown to be particularly sensitive to mild cognitive impairment associated with early Alzheimer's disease, or in those who fit early criteria for Alzheimer's disease.Widespread differences in cortical thickness are expected, in line with previous research, and areas of significance are expected to correlate to a difference in cognitive performance. Regions of interest identified based on Suprathreshold analysis are expected to correlate significantly with group performance.

(4.2) METHODS

The data in this chapter was collected as part of a separate project and study and has been made available for further analysis of the wide range of information and data collected.

(4.2.1) Subjects

Twenty younger (M= 27 ± 3 years, 10 male) and twenty older (M=74 ± 4 years, 9 male) subjects were recruited for this study. In addition to the test battery outlined below, older participants were also required to complete the Advanced Mini-Mental State Test (3MS) (Teng & Chui, 1987), to screen for cognitive impairments and allow for preselection of suitable candidates, if applicable.

(4.2.2) Neuropsychological and cognitive testing

Neuropsychological and cognitive testing took place both before and after MRI scanning, on two separate occasions during the study. Subjects were required to visit the lab twice, 14 days apart, to complete the study. Participants were screened on their first visit for their suitability for participation, both cognitively and according to scanning safety procedures.

Subjects were tested on a comprehensive battery of tests comprising the 3MS (Older participants only), National Adult Reading Test (NART, Nelson & Willison, 1991), and a series of subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB,Cambridge Cognition, discussed in more detail below). Computerised testing was carried out in a quiet testing room, on an 11” Samsung tablet (XE700T1C; Intel 1.7GHz i5 processor, 4GB RAM, 64-bit Windows 7).

(4.2.3) Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition).

CANTAB is a computerised method of language independent cognitive assessment. Up to 25 Subtests measure a wide range of neuropsychological functions such as visual memory, working memory, semantic and verbal memory, executive function, planning, attention, decision-making, response control and social cognition. Tests can be run independently, allowing researchers or clinicians to select them by relevance to their particular area of interest.

A subset of CANTAB tests were chosen for the original study, namely Cambridge Gambling Task (CGT), Intra/Extra Dimensional Shift (IED), Paired Associates Learning (PAL) and Simple Reaction Time (SRT), and their relevance in relation to age was investigated.

The chosen CANTAB subtests were pre-selected in relation to their relevance to the already known effects of ageing, to be able to reliably study other aspects of cognition and neuroimaging for the relatively small cohort.

CANTAB tests were run in “clinical mode”, which allows comparisons in relation to already available normative data. Output measures in relation to normative data are not relevant to this study, as data is compared between two groups, and as such will not be reported or discussed below.

Cambridge Gambling Task (CGT)

The Cambridge Gambling Task falls into the Decision Making and Response Control Category of CANTAB. Unlike other 'Gambling' tasks, CGT dissociates risk taking from impulsivity, because in the ascending bet condition the participant who wants to make a risky bet has to wait patiently for it to appear (Manes et al, 2002). The likely neural substrate for this task is the orbitofrontal prefrontal cortex. Specifically, this test measures impulse control and risk-taking in decision making.

Subjects are presented with a choice of boxes across the screen, coloured either red or blue, and asked to guess whether a yellow token is hidden behind a blue or a red box. This task requires no learning element, or information retrieval over consecutive trials, as all relevant data is presented upon each stage of the task. The CGT is made up of five stages and as the task progresses participants are asked to choose a stake and place a bet on where they suspect the token to be hidden. The participant must try to accumulate as many points as possible.

The Cambridge Gambling Task outcome measures assessed in this study are:

CGT Quality of decision making

This score indicates the proportion of trials the subject gambled on the most likely outcome, with a higher score representing a better decision-making behaviour.

CGT Risk Taking

This score indicates the proportion of points that were gambled when the most likely outcome was bet on. It is a more complex outcome measure with a lower score representing greater self-control.

Intra/Extra Dimensional Shift (IED)

The Intra/Extra Dimensional Shift Task Measures Executive Function, Working Memory and Planning abilities, as well as rule acquisition and attentional set shifting. It features visual discrimination and attentional set formation and is primarily sensitive to the fronto-striatal areas of the brain. This test is a computerised analogue of the Wisconsin Card Sorting test (WCST).

Subjects are presented with Simple Stimuli, of either colour filled shapes, or white lines, or Compound Stimuli, consisting of both, white lines overlaying filled shapes. Participants must learn a set of criteria to identify the 'correct' stimuli by progressing through the test. In the second Block of this Task the rules are reversed, and the previously correct stimulus is incorrect.

The IED outcome measures assessed in this study are:

IED Total Errors Adjusted

This score represents a measure of efficiency. It takes account of the fact that subjects may pass through to all 9 Stages of this task but commit a large number of errors whilst doing so. It is further adjusted to account for the fact that finishing the task prematurely through failure to progress, means there is

less opportunity to make errors, compared to subjects who complete all 9 stages. It is an overall representative measure for this sub-test.

Paired Associates Learning (PAL)

This subtest measures visual memory, new learning ability and working memory, and is primarily sensitive to medial temporal lobe functioning. It is a useful tool for assessing individuals with questionable dementia, Mild Cognitive Impairment, Alzheimer's Disease, and age-related memory loss.

Over a total of 8 Stages the subjects are shown a number of boxes which are opened one at a time, in a randomised order, with one or more containing a pattern. After all boxes were opened, patterns are then displayed in the middle of the screen, and the participant is asked to touch the boxes originally containing them. Up to six or ten attempts are granted, with patterns being re-presented to serve as a reminder to subjects when an error is made. When all locations have been remembered correctly, subjects proceed to the next Stage. If a Stage cannot be completed correctly, the test terminates prematurely.

The PAL outcome measures assessed in this study are:

PAL Total Errors Adjusted

This score represents the total errors committed at Stage 8, with an adjustment being made if subjects did not reach this stage due to failure to progress. The CANTAB user manual describes this measure as the most specific for participants' performance. It is descriptive of performance on the most difficult stage of the PAL task, and thus more insightful into subject ability, and most

commonly used as the outcome measure of choice for measuring memory and new learning ability in high functioning individuals.

PAL First Trial Memory score

This memory score measures participants ability to correctly locate the patterns after the first trial, across all stages (0-26 in clinical mode), with a higher score indicating better memory performance. First Trial Memory is described as the most meaningful of the memory scores.

Simple Reaction Time (SRT)

The Simple Reaction Time Task is part of the Attention Sub-Group of the CANTAB test battery. It measures simple reaction time in response to a single known stimulus and is similar to the Psychomotor vigilance Task (PVT).

Subjects are asked to press a button as soon as they see a square on the screen. Simple Reaction Time comprises 3 Blocks. Block 1 being a practise stage of 24 trials and Block 2 and 3 being the assessment stages with 50 trials each.

The SRT outcome measures assessed in this study are:

Simple Reaction Time (*algorithm*) latency

This measure allows for customised options to be applied in the “Results Manager Summary” of this cognitive test. For Simple Reaction Time, the Mean latency score was selected as the most meaningful measure of reaction time speed between groups.

(4.2.4) Pre- Processing of CT Data

Anatomical data was obtained following the procedures set out in the general Methods Chapter 2. Cortical thickness measures were achieved by applying the methods outlined by Fischl and Dale (2000) and Dale, Fischl, &Sereno (1999), Dale & Sereno (1993), Fischl, et.al (2002), using the Freesurfer software (http://surfer.nmr.mgh.harvard.edu).

(4.3) RESULTS

Cognitive Data

NART

Results for the mean scores in the National Adult Reading Test (NART) were significantly different between younger (M FSIQ=114.6, SD 7.6) and older participants (M FSIQ=119.9, SD 6.3), t (Df=36) =-2.348, p=0.023. The equivalent Full-Scale IQ as calculated by the NART, was higher in older participants, compared to younger ones, as were the resulting equivalent sub-scores for the verbal IQ (Young, M=112.6, SD 7.03, Older, M=117.5, SD5.7) and the Performance IQ (Young, M=113.4, SD 6.7, Older, M=118.3, SD 5.6).

CANTAB

Independent sample t -tests comparing the means for cognitive performance scores, between younger and older participants found significant differences. In the intra-Extra Dimensional Shift Task (IED) younger participants (M=16.6, SD 17.84) committed significantly fewer errors, when compared to older participants (M=29.5, SD20.9), t (Df=37.1) =-2.096, p=0.043. Younger persons (M=5.1, SD 5.2) also outperformed older persons (M=22.4, SD 22.6) with fewer errors in the Paired Associates Learning task (PAL Errors), t (Df=21.015) = -3.343, p=0.003.Younger Participants were also able to remember pattern locations more accurately in the Paired Associates Learning Task assessing Memory performance (PAL Memory) (M=20.2, SD 2.3), than older participants (M=17.2, SD 4.7), who performed comparatively worse, t (Df=32.979) = 3.421, p=0.002. Equal variances were not assumed for the IED, PAL Error and PAL Memory task, as Levene's test for equality of variance was significant with p>0.05. Results were reported accordingly.

Mean Latency for the Simple Reaction Time Task (SRT) was lower in young participants (M=253.9, SD 52.5), when compared to older participants (M=307.9, SD 85.7), who took longer on average to respond to a simple stimulus presented on screen, t (Df=38) = -2.415, p=0.021, equal variances assumed. Figure 4.2 shows a visual representation of error measures (PAL errors and IED) between groups.

The Results for the Cambridge Gambling Task (CGT) were not significantly different between groups.

To ensure that lower and overall less efficient task performance was not the result of slower reaction time, scores from the Simple Reaction Time Task were correlated against performance in other CANTAB measures. No significant correlations were found.

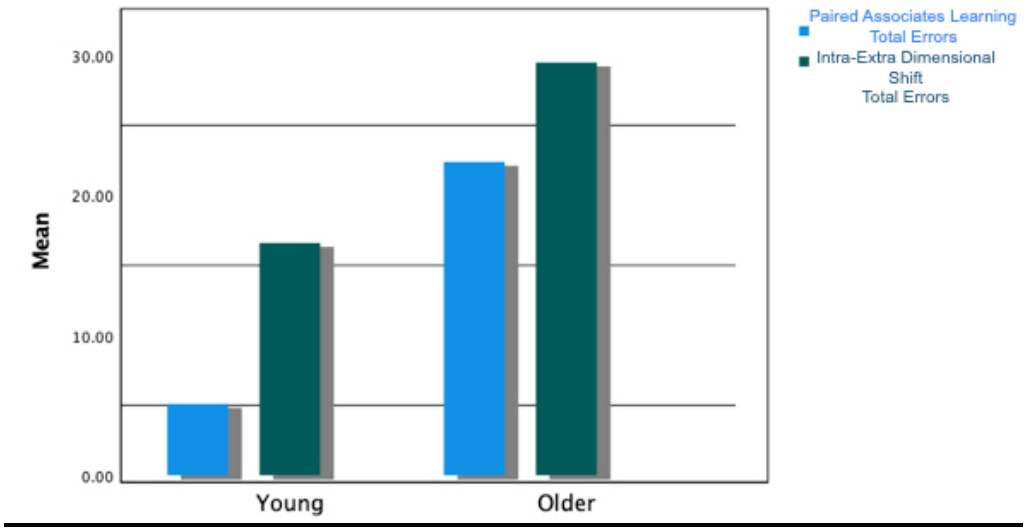


Figure 4.2. Illustration showing difference in young vs older in Paired Associates Learning total Error commission (Blue) and Intra-Extra Dimensional Shift Task total Error commission (Green). In the intra-Extra Dimensional Shift Task (IED) younger participants (M=16.6, SD 17.84) committed significantly fewer errors, when compared to older participants (M=29.5, SD20.9). Younger persons (M=5.1, SD 5.2) outperformed older persons (M=22.4, SD 22.6) with fewer errors in the Paired Associates Learning task (PAL Errors).

(4.3.2) Differences in cortical thickness when comparing MRI's of Young vs. Old

Widespread differences between Young and Old, necessitated a Montecarlo Null Simulation, to narrow down regions of interest. Montecarlo Null Simulation is the most conservative test QDEC allows for.

Figure 4.3 shows an overview over the regions of differences in average cortical thickness between young and old participants, on the left and right hemisphere, respectively. Table 4.1 summarises these findings by showing the global maxima of suprathreshold regions and their coordinates.

Cluster Name	Size(mm^2)	TalX	TalY	TalZ	Cluster-wide-probability
Left insula	44883.66	-31.5	6.8	7.7	P= 0.00010
Left precentral	461.24	-31.5	-17.7	40.7	P= 0.00910
Left superiorparietal	375.96	-32.5	-38.8	48.6	P= 0.03120
Right superiorfrontal	43480.59	11.4	44.7	14.5	P= 0.00010
Right fusiform	2966.49	29.6	-39.6	-15.2	P= 0.00010
Right precentral	438.70	32.4	-17.9	40.1	P= 0.01400

Table 4.1 Global Maxima of Suprathreshold regions, and their coordinates given in Freesurfer Talairach Coordinates (Tal) x, y, z

Further comparisons in QDEC, assessing the task performance – age – cortical thickness relationship, did not survive the False Discovery Rate threshold, set at $p<0.05$. Supra-threshold regions were extracted for further analysis in SPSS.

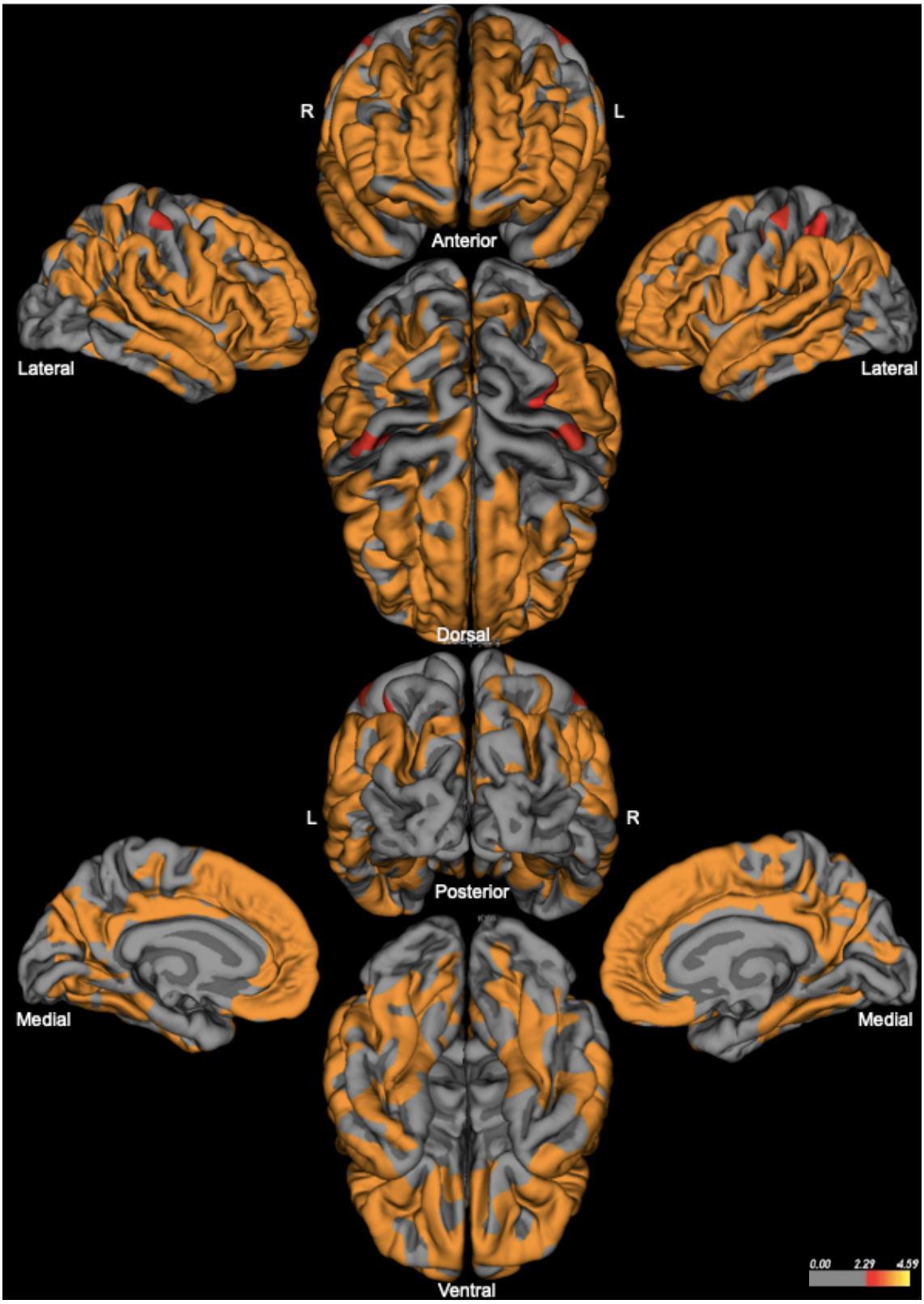


Figure 4.3 Overview over areas where the cortical thickness is significantly (MCs =p<0.01) different between younger and older participants. The figure shows widespread, global differences in cortical thickness between the two cohorts.

(4.3.3) Further Statistical Analysis

Mean Cortical Thickness correlated significantly with task performance on the Cambridge Gambling Task (r=+.323, p<0.05), Paired-Associates Learning total errors (r=-.447, p<0.01) and Paired-Associates Learning (Memory) (r=+.395, p<0.05).

Regions of interest were correlated against task performance. Correlations were carried out between groups, as well as separately in each group, to avoid reflection of a group difference, only. Table 4.2 summarises significant correlations between groups, by task and region.

Total error commission on the Paired Associates Learning task between groups was correlated with cortical thickness in the left insula (r=-.361, p=0.022). This correlation was particularly prominent in younger participants (r=-.571, p=0.009), where a thicker cortical thickness value was correlated with fewer errors.

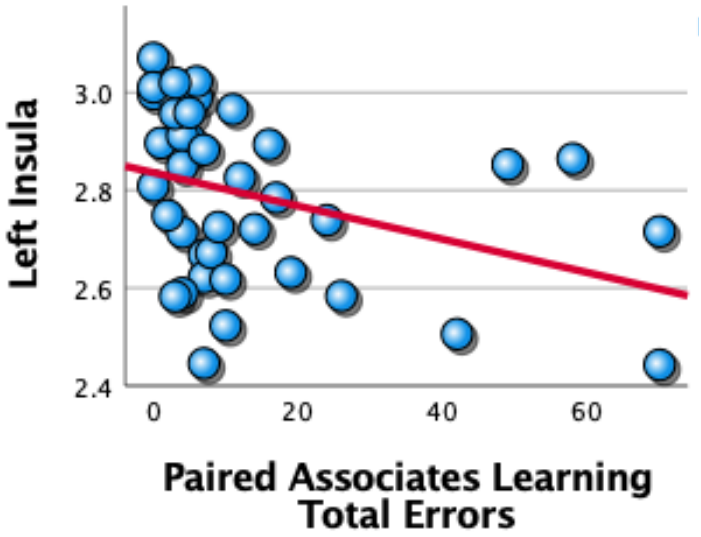


Figure 4.4 Figure illustrating the correlation between thickness in the left insula and total errors in Paired Associates Learning.

There was also an apparent correlation between the Cambridge Gambling Task and the left precentral gyrus (r=.326, p=0.04), as well as the right superior frontal gyrus (r=0.357, p=0.02).

		Left Hemisphere			Right Hemisphere		
		Precentral	Superior Parietal	Insula	Superior Frontal	Fusiform Gyrus	Precentral
Paired Associates Learning (Errors)	Correlation	-.399*	-.389*	-.361*	-.402*		-.379*
	Significance	.011	.013	.022	.010		.016
Cambridge Gambling Task (Quality)	Correlation	.326*			.357*		
	Significance	.040			.024		
Intra- Extra Dimensional Shift (Errors)	Correlation	-.321*					-.342*
	Significance	.043					.031
Paired Associates Learning (Memory)	Correlation	.322*		.411**	.353*		.318*
	Significance	.043		.008	.026		.046
Simple Reaction Time (Mean)	Correlation				-.325*		
	Significance				.041		

Table 4.2. Summarising significant correlations between groups , by task and region.

There was a recognisable trend between thickness in the right fusiform gyrus and performance in the paired associates learning task. However, this did not reach statistical significance.

(4.4) DISCUSSION

QDEC analysis yielded very definitive results on global differences in cortical thickness measurements between the younger and older cohort, even after a montecarlo null simulation was performed. These results were expected, and are not surprising, given that healthy aging, even in high functioning older adults results in noticeable cognitive decline, based on overall brain volume loss, cortical thinning, and gyral atrophy (Kemper, 1994).

Five regions were identified as being statistically significant in this cohort of younger and older people. The precentral gyrus, identified on both the left and right hemisphere, has been previously identified as being affected by age decline (Salat, et.al., 2004), and is thus in keeping with previous research findings, as well as the superior parietal cortex (Good et al. 2001, Raz et al.1997). The insula, superiorfrontal and fusiform were all previously identified in healthy aging studies, and as such are expected and in line with other studies conducted in this field, despite the relatively small cohort size (Good et al. 2001, Fjell et al. 2009)

Correlations between age and cortical thickness for both hemispheres show a very visible and pronounced group effect, and underline the prominent global difference, in cortical thickness between groups. This part of the analysis yielded the expected results and provides further evidence for the widespread cortical differences in the aging brain.

Younger participants showed significantly higher cortical thickness measurements, both on average globally, but also in individual suprathreshold regions, as opposed to

older participants, who showed a significantly thinner cortex. This is again, in keeping with previous research findings, and a confirmation from the QDEC analysis.

The CANTAB Intra Extra Dimensional Shift task, IED Total Errors Adjusted measure yielded significant results with $p<0.05$. A lower score in this subtask means fewer errors overall, which in turn means better task performance. Younger participants performed statistically better than their older counterparts, with fewer Total Errors, and thus greater efficiency in performing the Intra Extra Dimensional Shift (IED). Since IED is a measure of executive function, Working Memory and Planning abilities, it is unsurprising that Younger Participants performed better overall, as Working Memory is affected by the aging process (Baddeley,1986, 2003, Salat, et.al., 2004). Paired Associates Learning Total Errors Adjusted (Stage 8)
This outcome measure also yielded significant results with $p<0.003$. This measure is also a subtest for visual memory, new learning ability and working memory, and is primarily sensitive to medial temporal lobe functioning, and thus, a significant result is in-keeping with previous research (Baddeley,1986, 2003, Salat, et.al., 2004). Younger participants also had a higher mean Paired Associates Learning _1st Trial Memory score ($t(38)=21.500$), than older participants, which yielded a significant outcome with $p<0.002$). It is therefore concluded that Age has a significant effect on the Paired Associates Learning Task, 1st Trial Memory score.
Younger participants *also* had a lower mean Simple Reaction Time Latency score than older participants. This was significant with $p<0.02$. It is therefore concluded that Age impacts significantly on participants ability to react rapidly to presented stimuli.
Although reaction time differed significantly between younger and older participants, reaction time did not account for the difference in cognitive scores, that is, older

participants did not perform worse in the other CANTAB sub-tasks due to simple reaction time effects.

Interestingly, however, in real world settings older adults not only perform comparable to younger ones, but at times also superior (Schnitzspahn et al. 2011). This phenomenon has been linked to higher motivation through real-life incentives/rewards and self-management flexibility (Schnitzspahn et al. 2011).

Older adults are often shown to perform worse than younger counterparts in laboratory tasks relating to prospective memory for example (Kliegel et al. 2016), but showed comparative or superior performance, in real-life settings (Schnitzspahn et al., 2011). This raises some questions on the specific populations used in ageing studies. Are younger participants, for example, largely university undergraduates with a high level of computer literacy, whereas older adults in the same study are less computer literate and thus in an uncomfortable situation, affecting performance?

Is CAT testing situation too novel for older adults, requiring a large level of attention and working memory, because of a strange and unfamiliar situation, and thus artificially lowering their performance abilities? Whilst certain tasks, if performed in a real-life setting, make more logical sense to older adults, because it is contextualised within a required task.

Overall Young participants were shown to have higher values of cortical thickness across large regions of the cortex and it makes sense to conclude that overall thinning is related to some of the observed cognitive decline.

CANTAB measures were statistically significant with the exception of the CANTAB Gambling Task. A higher Global cortical thickness value meant better task

performance across all tasks, whether significant or not, be that by lower scores, through less commission of errors, or by faster reaction times.

Although individual suprathreshold regions did not yield significant results in QDEC, due to not meeting the FDR threshold, mean global Cortical Thickness correlated significantly with task performance on the Cambridge Gambling Task (Quality) ($r=+.323$, $p<0.05$), Paired-Associates Learning (Errors, Figure 2) ($r=-.447$, $p<0.01$), Paired-Associates Learning (Memory score) ($r=+.395$, $p<0.05$). Results were largely expected, despite small sample size, and further reinforce the dramatic effects of aging on both cortical thickness as well as cognitive performance.

This study sought to confirm that cognitive differences between younger and older participants, could be explained through differences in cortical thickness. Matched groups of younger and older participants showed the expected widespread differences in overall cortical thickness, as well as overall differences in cognitive performance. Though CANTAB is a well-validated tool in ageing research, it had not been utilised with a matched group of younger participants before, in relation to cortical thickness measures.

Larger samples are likely required to predict which regions might lead to the decline in cognitive functioning observable in the older cohort.

Additionally there may be other extraneous variables at play that were not considered in this study.

It is known that sleep is an important variable when cognitive functioning is being assessed (see Chapter 1, e.g., Lin & Dinges, 2008 and Siddiqui, 2008) and that the sleep needs between older and younger people differ (Woodward 2012). In particular , older people are known to require less sleep than younger people, diurnal sleep

patterns may change and older people may be prone to sleep difficulties, affecting cognition (Gulia and Kumar 2018). It is possible that the sleep differences between the older and younger cohort, namely overall sleep obtained, per night, or quality of sleep, affected the results, beyond what has been analysed here.

The next chapter will take account of sleep as a variable to cognition. It is possible that diurnal sleep preferences and sleep quality, as well as the time-of-day MRI scans were obtained, affect data. Chapter Five will look at whether innate differences in diurnal sleep preference and internal clock time affect cognitive performance, and whether research may need to be reconsidered in light of this.

CHAPTER FIVE

VOLUMETRIC BRAIN DIFFERENCES IN CIRCADIAN CHRONOTYPES IN RELATION TO COGNITIVE PERFORMANCE AND TIME OF DAY

"TO EVERY THING THERE IS A SEASON,
AND A TIME TO EVERY PURPOSE UNDER THE HEAVEN"
ECCLESIASTES 3:1, KING JAMES BIBLE

(5.1) Introduction

In an increasingly 24-hour society, where almost every need, want or desire can be addressed around the clock, there is also an ever-increasing demand to provide human resources to deliver this continued availability (Lockley & Foster 2012, p.1, 119).

These societal changes are relatively new in human evolutionary development and experienced a surge with the advent of the electric incandescent lighting, at the end of the 19th Century, without which many nocturnal activities would not be possible. Our ancestors would have had a biological sleep-wake pattern, more closely related to the natural light-dark- and diurnal temperature cycle (Yetish et al. 2015, Dijk & Sheldon, 2015, Ekirch 2016). With the ability to light the night, came the capacity to manipulate light exposure (Dijk & Sheldon 2015) and rising desire to extend the 'day' (Lockley & Foster 2012, p.119).

Whilst sleep duration, per se, has not changed significantly over the past 50+ years (Youngstedt et al. 2016), diurnal sleep patterns have changed to adapt to modern schedules (Yetish et al. 2015, Ekirch 2016). This chapter will explore whether the

cognitive cost of this infringement is associated with morphometric changes, between different types of circadian types and whether these changes can be observed throughout the day.

(5.1.2) Social Jetlag, Circadian Disruption and Chronotypes

Shift workers are known to experience sleep problems as a result of frequently desynchronising their sleep from normal circadian phase, in order to accommodate work commitments (Dijk & Duffy 2020). But aside from sleep difficulties, shift work and circadian disruption is also associated with a significant incident of health issues, ranging from poorer mental health, diabetes, cardiovascular disease, gastrointestinal complaints, to fatigue and even an increased risk of certain cancers (Lockley & Foster 2012, pp.127-128) Health risks associated with circadian disruption are most likely linked to misaligned light exposure at night and chronic sleep restriction (Lockley & Foster 2012, p.129).

With cognitive effects of sleep deprivation extensively studied (e.g., effects on vigilance, Lin & Dinges, 2008, executive function, Siddiqui, 2008 or short-term memory, Frey et al. 2004, see also Chapter 1), research turned to other factors affecting daily sleep schedules. It became evident very quickly, that further consequences occurred when sleep debt accrued over a period of time, because individual diurnal sleep preferences, expressed through circadian phenotypes, are disrupted through conflicting social schedules (Waters & Bucks 2011).

Roenneberg and colleagues studied sleep timing of individuals extensively, and developed the Munich Chronotype Questionnaire (MCQT, Roenneberg et al. 2003), which is now considered the best assessment tool for Circadian Chronotypes,

because it defines Chronotypes by their Mid Sleep Phase on free (MSF) days (Foster & Kreitzman 2017, p.17).

Sleep on free days is thought to be a true representation of chronotype, however, accrued sleep debt during workdays may lead to a propensity to oversleep on free days. The MCQT therefore determines circadian chronotypes by their corrected mid-sleep time on free days, after accounting for accumulated sleep debt (Roenneberg 2012, Roenneberg et al. 2007, 2012).

Even though Chronotypes vary with age (Monk et al.1997), with endocrine factors thought to be involved in these age dependent changes (Roenneberg et al. 2003), the MCQT gives the best available estimate of Circadian Types and is the tool utilised in this study, to distinguish participants and their intrinsic preferences. The MCQT has also been validated against several biochemical and physiological biomarkers for chronotypes, such as melatonin and cortisol (Facer-Childs et al. 2019, Ghotbi et al. 2020) or activity acrophase (Santisteban et al. 2018).

(5.1.3) Chronotype and Cognition

As discussed above, that artificial sleep deprivation leads to a range of cognitive impairments, usually most apparent through reduced responsiveness to external stimuli, decreased vigilance, performance deficits, and thus poorer task performance (Ferrera et al. 1999, Fallone et al., 2001). Besides sleep deprivation, lifestyle and occupational factors, such as shift work, increased societal stress and increased caffeine and alcohol use, can lead to decreased sleep duration and quality in as much as 30-40% of the general population (Ban & Lee 2001, Hublin et al. 2001, Krueger & Friedmann 2009). Accumulated sleep debt through superimposed societal schedules

incompatible with inherent chronotypes and sleep inertia times are also known to decrease cognitive abilities (e.g., Dinges et al. 1997, Karni & Sagi 1993).

When zeitgebers change rapidly, the internal clock cannot adjust quickly enough to consolidate exogenous cues with endogenous ones, leading to desynchronization and disruption of circadian rhythmicity. Jet lag occurs when zeitgebers are changed and exogenous cues are shifted through phase advance, in eastern travel, or phase delays, in western travel.

'Social Jetlag", which is the desynchronisation between internal and external phase, as the natural sleep-wake cycle is disrupted due to imposed routines (Pinel, 2003), can be just as pronounced as travel induced jetlag. LCT's show a large discrepancy between individual sleep preferences and normal work schedules, which leads to a significant sleep deficit during the working week (Roenneberg et al. 2003). The same is true for ECT's in shift work, leading to reduced productiveness and increased procrastination (Kühnel et al. 2018), fatigue and safety considerations (Sadeghniiat-Haghighi & Yazdi 2015).

Wittman et al. (2006) found that Late Circadian Types (LCT), experienced a chronic functional jetlag in comparison to Early Circadian Types (ECT**)**, because the inherent circadian cycle does not fit conventional schedules. Internal clock confusion caused tiredness and a degree of disorientation, with LCT's feeling more worn out and tired in the evening when following a standard social schedule. These impacts are more significant and typically found in a younger age group (14-25-year-olds), particularly in relation to sleep quality and mental balance in the evening, most probably because school and work schedules are likely to interfere with natural diurnal sleep preferences (Wittman et al. 2006).

Chronic Jetlag (e.g., in aviation workers) produces temporal lobe atrophy, leading to spatial cognitive deficits (Cho 2001). By analogy, chronic social jetlag, produced through accumulated sleep debt, or socially incompatible sleep preferences therefore may also produce functional deficits.

Haraszti et al. (2014) found that Time of Day (ToD) was a significant variable in individual Chronotype performance, with LCT's having higher odds for achieving low performance in the morning and ECT's having higher odds for achieving low performace in the afternoon. The influence of circadian type on cognitive performance was found to be strongly exacerbated by social jet lag, and that social jetlag beyond Chronotype was a negative predictor of performance outcomes.

Average optimal times for cognitive activities, have been gathered in a range of studies. Logical reasoning, for example appears to be peaking around 1000-1200hrs (Foster & Kreitzmann, 2017, p.15), Long term memory is most efficient in the afternoon (1600hrs, Estaki, 2014, p.69) and Simple Reaction Time (SRT) has been shown to be at maximum efficiency in the early evening (1700-2000hrs, Pöppel, 1970). It is clear, however, that individuals vary, and that time since waking is not always considered when optimal times are discussed.

Social jetlag showed a negative effect on average grade in college students during the highly regulated term time schedule, most likely to interfere with LCT's, whilst Mid sleep phase on free days (MSF) negatively correlated with academic performance in the subset of morning test takers of the same cohort, during exam times (Haraszti, 2014).

(5.1.4) Neurocognitive testing sensitive to sleepiness and homeostatic sleep drive

A wide variety of neuropsychological tests have been used to assess states of wakefulness and sleepiness, though not all of them have proven suitable. As neuro-

behavioural integrity changes dynamically throughout the day, cognitive testing must be able to reliably reflect this variable performance. Cognitive capacity is sensitive to time of day, time since waking, acute total or chronic partial sleep loss, so neuro-cognitive arrays must be suitable for repeated administration, without substantial inter and intra-subject variability (Dorrian et al. 2005). Measuring the extent of functional impairment as a result of any type of sleep loss or increasing homeostatic sleep drive, is dependent on parameters such as task complexity (Wilkinson, 1964, Lamond &Dawson, 1999), duration (Dinges & Powell, 1988, Dinges and Powell, 1989, Findley, et.al., 1999) and response rate (Williams and Lubin 1967). Further criteria for suitable assays are therefore; brief task duration, preventing extraneous factors, such as lack of interests from altering performance negatively (Bohlin 1971), simplicity, with a minimal learning curve to avoid aptitude effects (Horne & Wilkinson 1985) and allows for repeated administration without the underlying psychometric properties changing (Dorrian et.al. 2005). These aspects are important for both clinical, as well as experimental testing. Assessing the level of cognitive impairment induced by acute sleep deprivation, or chronic sleep loss is relevant in order to understand the importance of sleep.

As the pre-frontal cortex (PFC) is thought to be particularly sensitive to sleep loss, tasks in recent years, have targeted this neural substrate in particular (Harrison et al. 2000). Horne and colleagues have contributed vastly to a frontal lobe hypothesis, proposing that sleep loss in particular uniquely affects the PFC. This was demonstrated in non-verbal-planning tasks (Horne 1988), temporal memory (Harrison et al. 2000) and working memory tasks (Abi-Dargham et al. 2002), indicating that the latter, in particular, depends on the dorsolateral-pre-frontal cortex (Cools et al. 2002). As working memory is dependent on the central executive attention system (Baddeley

1992, Baddeley 2001) and attention is one of the major neural constructs affected by sleep loss and homeostatic sleep drive, it can be said that working memory function is predictive of other cognitive arrays, under such circumstances, also (Engle 2002). Underlying executive attention and executive function is therefore vitally important on any neurocognitive measure, reflecting a fundamental aspect of waking function, and thus sensitive to sleepiness (Dorrian et al. 2005). Even though the terms “Executive Function” and “Frontal Lobe Function” are often used synonymously, it is important to point out that not all functions of the pre-frontal-cortex are inherently ‘executive’ (Siddiqui, et.al. 2008), nor is “executive function” exclusively contained to the frontal lobe. The executive network spreads around the cortex with several regions involved in higher order cognitive skills (Hunter, et.al.2012b).

Short-Term Memory is a critical component of working memory (Baddeley 2000, Cowan 2008). Though working memory and short-term memory (STM) are often used interchangeably (Aben 2012), there is a distinction between short-term memory, which denotes the capability of memory maintenance, only, whereas working memory represents the capability to maintain *and* manipulate information (Davidson et al. 2006, Jenson et al. 2007). The pre-frontal cortex, in particular the dorsolateral pre-frontal cortex, has been repeatedly linked to short term memory function (Kessels et al. 2000, Gazzaniga et al. 2009), whereas long-term memory retrieval has been linked to the posterior parietal cortex instead (Postle 2005). Short-term memory is therefore an executive function and thus reliant on the executive attention network and suitably sensitive to sleepiness and sleep drive propensity (Bergman et al. 2016). In other studies, simple auditory and visual STM tasks, were shown to be particularly sensitive to diurnal fluctuations, with a decline in performance, depending on time since waking (Esteki & Sadeghi 2010).

(5.1.5) Neural Substrates of Chronotypes

Takeuchi et al. (2015) demonstrated an association between 'morningness' (Early Circadian Types) and 'Eveningness' (Late Circadian Types, as assessed by the Morningness-Eveningness Questionnaire, MEQ) and lower regional Grey Matter Distribution (rGMD) in the precuneus and adjacent areas, in the left posterior parietal cortex and adjacent areas and a higher rGMD in the bilateral orbitofrontal cortex. 'Morningness' was associated with a higher rGMD in bilateral hypothalamic clusters around the bi-lateral coordinates closest to the suprachiasmatic nuclei. As these regions are highly relevant in the physiological facilitation of sleep, underlying structural differences for the diurnal preferences of sleep timing and differentiated cortical profiles seem logical. Cortical thickness differences between Chronotypes will form part of the investigations in this chapter.

Takeuchi et al. (2013) investigated regional grey matter and regional white matter volume in relation to executive functioning. Previous studies (e.g., Takeuchi et al. 2010, Takeuchi et al. 2011) had already shown associations between regional grey matter volume and regional white matter volume and other cognitive functions. Results were showing a positive effect on regional grey matter volume in the posterior medial part of the orbitofrontal cortex and a negative main effect of executive dysfunction in the left working memory area of the superior temporal sulcus and middle temporal sulcus, as well as the right hippocampus and right para-hippocampal gyrus.

As previously discussed in this thesis, when assessing cortical thickness, one cannot always assume that higher values correlate with better functioning or increased task performance, as increasing evidence shows the contrary. This is especially true, when talking about younger cohorts, as maturational events in normal cortical development,

such as synaptic pruning and continued myelination, are characterised by cortical thinning. The frontal lobes in particular thin the most during late adolescence and early adulthood (Sowell et al. 1999, 2001).

Grey Matter density reduction and brain growth in the superior frontal regions that primarily control executive functions (Shaw et al. 2006) therefore may lead to positive correlations between task performance and lesser regional grey matter volume in relevant regions (Takeuchi, et.al., 2013). Moreover, white matter microstructure underlying the frontal lobes has been previously associated with disturbances in motor movements and cognitive function, e.g., attention (Kiernan and Hudson, 1994).

Rosenberg, et.al. (2018) qualified chronotype as a modulating factor in brain imaging and recommended it be taken into consideration as routinely as e.g., gender. Vertex wise cortical thickness analysis showed ECT's to have significantly lower grey matter volumes bilaterally in the lateral occipital cortex, as well as lower GM volume in the right lingual gyrus, occipital fusiform gyrus and occipital pole, when compared with LCT's. Cortical thickness was shown to be of lower grey matter volume in the left anterior insula, precuneus, inferior parietal cortex and right pars triangularis in ECT's than LCT's. These findings reveal that Chronotype differences are associated with specific neural substrates of cortical thickness, surface area and folding.

(5.1.6) Time of Day effect

In addition to reported differences in neuropsychological performance in relation to Time of Day (ToD), growing number of studies report ToD differences and diurnal changes in T_1 derived brain structures. Neuroimaging methods are now able to detect brain volume changes, as small as 0.1% (Caramanos et al. 2010). Such small changes are usually expected permanently, through the healthy ageing process over a 1-year

period but appear to also result from physiological fluctuations such as hydration, or hormonal changes. However, there also appears to be a 'Time of Day' effect that results in structural changes within a single day. Ventricular volume, for example, has been shown to be correlated with ToD (Maclaren et al. 2014).

Maclaren et al. (2014, n=3) showed a significant positive correlation between ToD and ventricle size change and noted that their data indicated that maximum observed changes in ventricle volume, was of similar magnitude as those observed in other studies, where subjects underwent a dehydration protocol (Kempton et al. 2009, 2011, Nakamura et al.2014).

A much larger study (Miller et al. 2015, n=404) examined how seasonal differences in the length of a day accounted for differences in hippocampal volume. Nakamura et al. (2015) showed a decrease in brain volume from morning to evening, at a rate of -0.4% per day, of -0.09%-0.2% per 12 h of intracranial volume. Trefler et al. (2016) investigated the same phenomenon in a smaller sample (n=19) and found a highly significant effect of Time of Day on total brain volume, with as much as 0.1mm of intracranial volume reduction per 12hours. Behavioural training appeared to attenuate this effect.

Cerebrospinal fluid (CSF) volume appeared to be most affected, with a significant increase in total CSF of 0.17% per 24h, whilst GMV and WMV significantly decreased by -1.85 and -0.49% per day, respectively. There also appeared to be a significant decrease of cortical thickness as a result of ToD, of 0.1 mm per 12h, with frontal and temporal lobes disproportionately affected compared to others.

(5.1.7) Reasoning for this chapter

Previous neuropsychological studies have shown clear links between sleep loss and cognition, accumulative social sleep debt and cognition, as well as differences in task performance and circadian chronotype. Neuroimaging studies have revealed how diurnal sleep preferences results in different neural substrates, and how the brain can change, within a single day. However, no study to date, has combined all these elements to investigate a connection between cortical thickness, circadian chronotypes, time of day and task performance. This chapter aims to investigate these issues and the questions examined and tested in this chapter are as follows:

(I) Does the average cortical thickness differ between Circadian Chronotypes, ECT and LCT? As Late Circadian Types frequently show lower task performance, cortical thickness measurements are expected to be lower than in Early Circadian Types.

(II) Are there differences in cortical thickness in relation to Time of Day? Previous research has shown that Time of Day can impact intracranial volume, so this effect would be expected again.

(III) Are Time of Day differences in cortical thickness impacted by chronotype? Are these differences based on “Clock Time” or “Internal Time”? With Early and Late Circadian Types operating on a different internal schedule, based on preferred sleep schedule, a difference between groups depending on Time of Day is expected.

(V) Are Time of Day Differences in Cortical Thickness, between Circadian Chronotypes be linked to Task performance? Can this be corrected for internal time? With Early and Late Types reaching peak performance at different times in the day,

due to time elapsed since waking, it is expected that performance could be corrected by matching task performance to internal time.

(VI) Do the results change, if mental health variables, as measured by the DASS, are taken into consideration.

(5.2) METHODS

Psychological tests and procedures not described in this study, were performed together with those explained in this chapter. These provided the basis for other studies, investigations, and publications (e.g., Facer-Childs, et.al., 2019). The data examined here were acquired as part of other projects (http://etheses.bham.ac.uk//id/eprint/8300), and as such some methodological selections had already having taken place.

(5.2.1) Pre-selection Criteria

Participants were recruited for research via email. Those interested were required to answer questions about relevant medical history, MR Safety screening (as discussed in overall Methods (2)) and the Munich Chronotype Questionnaire (MCTQ). Prior or current sleep disorders, neurological or psychiatric conditions, medication affecting sleep and left handedness were exclusion criteria.

(5.2.2) Assessment of Circadian Types

For the purposes of this thesis the terms Circadian Type, Circadian Chronotype, Late Circadian Type / LCT and Early Circadian Type / ECT are used interchangeably.

Chronotype	Group Size	Age (mean ± SD)	MSFsc Score (mean ± SEM)
Early Circadian Types	N=16	24.7 ± 4.6	02:24 ± 00:10
Late Circadian Types	N=22	21.3 ± 3.3	06:52 ± 00:17

Table5.1 Corrected Mid Sleep Scores for initial Categorisation

The MCQT is currently considered the best assessment tool for categorising circadian types, because they are defined by their mid sleep phase on free days (Foster &

Kreitzman, 2017, p.17). Corrected mid sleep on free days (MSF_{sc}) was calculated by adding half of the sleep duration to sleep onset time. Those with a MSF_{sc} below or equal to 4.00 were categorised as Early Circadian Phenotypes (ECT) and those with a MSF_{sc} above or equal to 5.50. were categorised as Late Circadian Types (LCT).
As all participants were asked to follow their preferred diurnal sleep routine, the effects of sleep deprivation, sleep debt or prolonged sleep inertia were therefore removed from all but the earliest test session at 8:00h for LCTs. Chronotype specificity is extremely complex and not yet fully understood in its entire neural and genetic depth (Rosenberg et al. 2014), therefore a combination of multiple assessment techniques to verify circadian phenotyping is always desirable (Hofstra & deWeerd 2008). Initial categorisation using the MCQT was verified through additional cortisol and melatonin samples, sleep start and wake up times collected and automatically calculated through actigraphy analysis (see Facer-Childs et al. 2019 & http://etheses.bham.ac.uk//id/eprint/8300, for more details).

(5.2.3) Testing Times

Times are presented as hh:mm. Testing occurred at 14:00 h or 'afternoon' (A), 20:00 h or 'evening' (E) and 08:00 h or 'morning' (M),. Once categorised by chronotype, participants are not only distinguished by being an Early (ECT) or Late (LCT) circadian chronotype, but also by the time at which their scan and test score was obtained. ECT_M, for instance refers to Early Circadian Types in the Morning, whereas LCT_E refers to Late Circadian Types in the Evening. Table 5.2 gives an overview over the abbreviations commonly used in this chapter.

Circadian Type / Time of Day		Early Circadian Type	Late Circadian Type
		ECT	LCT
Afternoon (14:00hrs)	A	ECT_A	LCT_A
Evening (20:00hrs)	E	ECT_E	LCT_E
Morning (08:00hrs)	M	ECT_M	LCT_M

Table 5.2 Abbreviations for chronotypes at different times of day

(5.2.4) Neuropsychological Testing

As part of their study participation, participants were required to complete a battery of tests and questionnaires; MCTQ, Epworth Sleepiness Scale (ESS), Karolinska Sleepiness Scale (KSS), Depression, Anxiety and Stress Scale (DASS), Profile of Mood States (POMS), Pittsburgh Sleep Quality Index (PSQI), CMAT (Psychomotor Vigilance, Stroop, Memory Test, Executive Function test) and Isomotor Grip strength, some of which were used to assess inclusion and exclusion criteria, others to assess cognitive function (see Facer-Childs et al. 2019 & http://etheses.bham.ac.uk//id/eprint/8300, for more details) . Only the MCTQ, KSS, DASS and CMAT tasks of Psychomotor Vigilance, Memory and Executive Function, will be explained and investigated in this chapter.

Karolinska Sleepiness Scale (KSS)

The KSS assesses subjective situational sleepiness at the time of administration of the test (Shahid et al. 2011). It was first developed by Åkerstedt and Gillberg (1990) and requires participants to rate their sleepiness on a 10-point scale, from “Extremely alert” (=1), “Neither alert nor sleepy” (=5) to “very sleepy, fighting sleep” (=9) and “can’t keep awake” (=10). Due to being situational and self-assessed, it is sensitive to fluctuations and varies throughout the day, but validity studies showed a high correlation between KSS, EEG and behavioural variables (Kaida et al. 2006, Kaida et al. 2007). It is difficult to assess test-retest reliability as the KSS is depending on

exogenous factors and has a high variability depending on e.g., earlier sleep or effects of drugs. The KSS has shown a strong correlation with Time of Day and Time since waking (Shahid et al.2011).

Depression Anxiety and Stress Scale

The DASS was first described in 1983 by Lovibond, S. and later published in a detailed account in the DASS manual by Lovibond S. and Lovibond P. in 1993 as a self-administered questionnaire (Lovibond and Lovibond 1995). The DASS aims to provide measures of general negative affective syndromes whilst discriminating between three main emotional syndromes – Depression, Anxiety and Stress. Whilst the syndromes do correlate moderately high (in particular Stress with Anxiety) the Scale is able to distinguish them successfully (Lovibond and Lovibond 1995). The DASS42 consists of 42 questions, whilst an abbreviated version, the DASS21, consists of 21 items. The shortened version, DASS21, was utilised in this study. The items of the DASS21 were selected so that scores for the short version can be converted to DASS42 full scale scores, by multiplying by 2 (Lovibond and Lovibond 1995). 7 DASS items, correspond to the Depression scale (Dysphoria, Hopelessness, Devaluation of Life, Self-depreciation, Lack of Interest, Anhedonia, and Inertia), 7 items to Anxiety (Autonomic Arousal, Skeletal musculature effects, Situational Anxiety and Subjective experience of anxious affect) and 7 items to Stress (Difficulty relaxing, Nervous Arousal, easily upset, Irritable, Impatience). A four-point scale of “Did not apply at all” (=0), “Applied to some degree” (=1), “Applied to a considerable degree” (=2) and “Applied most of the time” (=3) was applied to questions like “ I felt down and blue” or “I felt I was close to panic”, and scores above 21 infer severe depression, anxiety (>15) and stress (>26)

(Lovibond and Lovibond, 1995). DASS42/21 forms and scoring templates are freely available online (http://www2.psy.unsw.edu.au/dass//).

Cognitive Performance (Chrono-Memory-Attention-Task)

Prior to formal testing sessions, participants were required to complete the CMAT on at least three separate occasions, to familiarise themselves with the tasks. Due to participants being asked to complete the CMAT multiple times during their participation in this study, trials were randomised to avoid learning.

Testing sessions were conducted in a designated room. Participants were required to complete the cognitive tasks on a desktop computer (DQ67OW, Intel® CoreTM i7-2600 processor, 4GB RAM, 32-bit Windows 7).

The CMAT is available on an online platform (https://www.profilingforsuccess.com) and was designed by 'Team Focus Limited', an occupational psychology firm (https://www.teamfocus.co.uk/psychometric-tests/memory-and-attention/). The CMAT includes measures of sustained attention by measuring reaction time through the Psychomotor Vigilance Task (PVT), Reaction Time through interference, by way of the Stroop task, Short-Term Memory function, through a matching pairs task, and compound executive function, through a novel complex psychometric task, requiring the participant to follow instructions as quickly and accurately, as possible.

The variables used in this thesis are PVT, Short Term Memory (STM) and compound executive function (CEF) and are described further below.

Psychomotor Vigilance Task (PVT)

The PVT was originally developed in 1985, as a measure for sustained attention (Dinges & Powell 1985). It is the most widely used cognitive performance test in sleep

and circadian research (Blatter and Cajochen 2007), due to its sensitivity to sleepiness in both clinical experiments, but also in operational contexts (Dorrian et al. 2005). In addition to sleepiness, the PVT has also shown to be sensitive to work schedules (Caldwell et al.2003), naps (Dinges et al.1987), age (Philip et al. 1999), bright light and caffeine (Wright et al. 1997), amongst others.

Participants are required to respond to the incidences of stimuli, on an otherwise blank screen and indicate the presence of a stimuli with the click of a button, as quickly as possible (Dinges & Powell 1985). Omission errors or lapses, i.e., the absence of a response in the presence of a stimuli, Commission errors or false responses, recorded as 'false starts', i.e., a response in the absence of a stimuli, and reaction time of responses in relation to a stimulus, are measured (Dinges & Powell, 1985). Less omission and commission errors, as well as a faster reaction time in response to stimuli, indicate a better performance, and better sustained attention, whilst slower reaction time and increase in errors indicates a poorer performance. Slow reaction times are responses greater than 2.0 seconds after the stimuli, whilst fast response times are around or below 1.0 seconds, following presentation of the stimuli (Drummond et al.2005).

Short Term Memory Task

In this study, participants were asked to complete a matching pairs task. A 6x6 block containing 36 squares was presented (Figure 5.1). Upon clicking on the squares, participants were able to uncover the picture hidden beneath the white square. Two pictures at any time were able to be selected and if a matching pair was discovered these images would remain uncovered. However, if a matching pair was not

discovered both images would disappear again. Time until completion of the task was used as the measure of short-term memory efficacy, with shorter time indicating better performance, and longer duration indicating poorer performance.

Figure 5.1 Paired associates' task for measuring short-term memory

Compound Executive Function Task

To test these processing skills, the final task of the CMAT required participants to follow complex instructions, retain and process information, and correctly act on the increasingly complicated rules. Participants were shown shapes on a screen (Figure 5.2) and asked to select shapes based on certain criteria:

"Before each set of screens is shown, you will see some instructions telling you which of the shapes you should select. The purpose of this test is to follow these instructions as quickly and as accurately as possible. The instructions will become harder as you progress through the test."

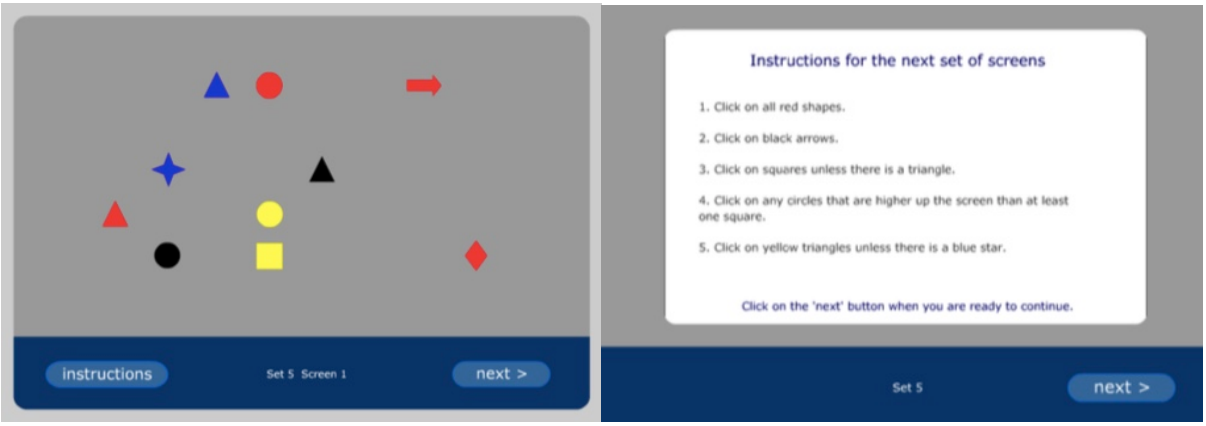


Figure 5.2 Compound executive function task example.

Over 25 trials, there were a total of five different rules with five trials each to be completed. Rules included requests like: “Click on yellow triangles unless there is a blue star”, or “Click on squares unless there is a triangle”. Participants were judged on accuracy and speed, with a higher percentage of accurate responses and faster completion time indicating better performance of compound executive function.

(5.2.5) Neuroimaging Data Acquisition

The T_1, anatomical MRI scans required for cortical thickness analysis were acquired as part of fMRI data acquisition utilised in other studies. T_1 acquisition, preparation and analysis is discussed in detail in the overall Methods Chapter (2).

(5.2.6) Cortical Thickness Analysis

Cortical thickness measurements were calculated and extracted following the protocol and procedure described in the General Methods (2), using Freesurfer (http://surfer.nmr.mgh.harvard.edu/,e.g. Fischl and Dale, 2000; Fischl et al., 200, Reuter et al. 2010, Reuter et al. 2012).

Primary analysis was carried out in Freesurfer as in chapters 3 and 4. However, Freesurfer’s GUI driven statistical engine “QDEC” cannot be used with more than two

groups and more than two continuous variables, so is unable to compare all three time points in one statistical model.

(5.2.6.1) DODS approach

Freesurfer offers the option of a “command line” analysis stream to set up a General Linear Model (GLM). The GLM model allows for two different designs, DODS (Different-Offset, Different-Slope) and DOSS (Different-Offset, Same-Slope). This type of design is unique to Freesurfer and interpretation can be complicated. The statistical design for the full set of data, i.e., comparing LCT and ECT at their 3 time points (A, E & M), is DODS, but can be modified to ‘ask’ specific statistical questions. DODS assumes that, cortical thickness values at the offset (A) are different between early types and late types, and changes at a different rate (different slope), whereas DODS assumes the relationship is linear or on the same slope.

Whilst QDEC can automatically create a design matrix, analyses in the command stream require a Freesurfer - Group Descriptor File (FSGD), which stipulates this. As the design is testing an interaction between two groups and three time points (Circadian Type and Time of Day) this can only be tested with a DODS model.

(5.2.7) Data Analysis

(5.2.7.1) Partial Correlation Model

If the effect of the covariate needs to be regressed out (*e.g., is there a difference in average thickness between Circadian Type accounting for Time of Day, see Figure 5.3)*, then a DODS model for an interaction will be run first, followed by a DOSS model to test for a different offset (Hendrickson et.al., 2017, Greve, D. 2018).

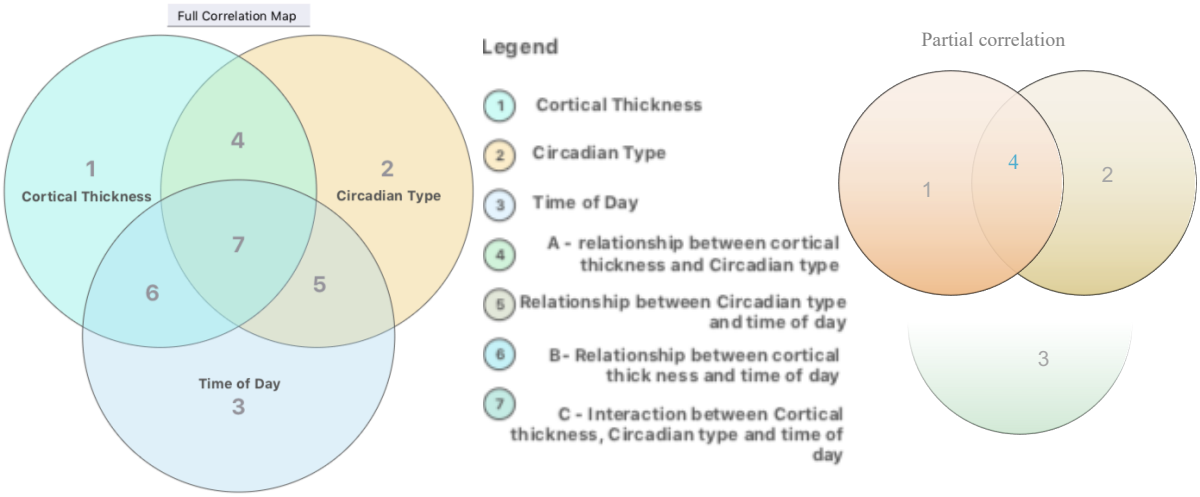


Figure 5.3 Visualisation of accounting for a factor through partial correlation: One of the full correlation maps in this study design includes cortical thickness – circadian type – time of day. Part of the relationship between average thickness and chronotype is due to time of day (7), because participants were repeatedly measured at three time points. To find out the relationship between chronotype and cortical thickness time of day must therefore be accounted for and partialled out of the design. The partial correlation design on the right now shows that if the influence of time is taken into account but removed from the design (7), 4 alone represents the correlation between 1 & 2 (Dancey and Reidy2004).

Where the command-line GLM indicated that no main interaction or main effect in the full model was found, QDEC was utilised in favour of command-line stream due to the relative ease of the GUI option QDEC allows.

Therefore, several comparisons were carried out in QDEC between groups (ECT – LCT) at the same point, e.g., ECT A – LCT A, between groups at different time points, e.g., 'ECT A and LCT E' and within groups at different time points, e.g., ECT A – ECT E, in a pairwise comparison model.

QDEC

Results meeting the cluster forming threshold (CFT) after a Monte Carlo (MCs) Null simulation threshold of $p^a<0.01$ (Log (10) p=2), are considered significant for the purposes of this chapter, where groups were compared at two time points and thus included more data points (e.g., ECT_A_E vs LCT_A_E).

MC_S $p^a<0.01$ is a very conservative threshold for pairwise comparisons and the most stringent test FS QDEC allows, so for completeness results at a false discovery rate (FDR) of $p^b<0.05$ are also given. An extent threshold of 0.05 (Log (10) p= 1.3) is applied to the suprathreshold regions, for visual purposes, showing only those vertices above the threshold.

SPSS

Additional statistical analysis was carried out in SPSS. General linear models (GLM) in the form of repeated measures ANOVAs were carried out, to assess interactions between circadian types, at different time points (Afternoon, Evening, Morning). *Cortical regions of Interest* (ROI) as established with Freesurfer's QDEC, were used in SPSS when comparing behavioural scores with cortical thickness. Prior to each ANOVA assumptions of multivariate normality, homogeneity of variance-covariance and sphericity were assessed. Unless otherwise indicated, these assumptions were not violated, and no further corrections were necessary. Box's Test of equality of covariance matrices was considered significant at p=0.05, with p<0.05 indicating a violation. Mauchly's test of sphericity indicated that the sphericity assumption is met if p >0.05. In the event of a violation, results were corrected with Greenhouse -Geisser Epsilon (Field 2013, Howell 2002).

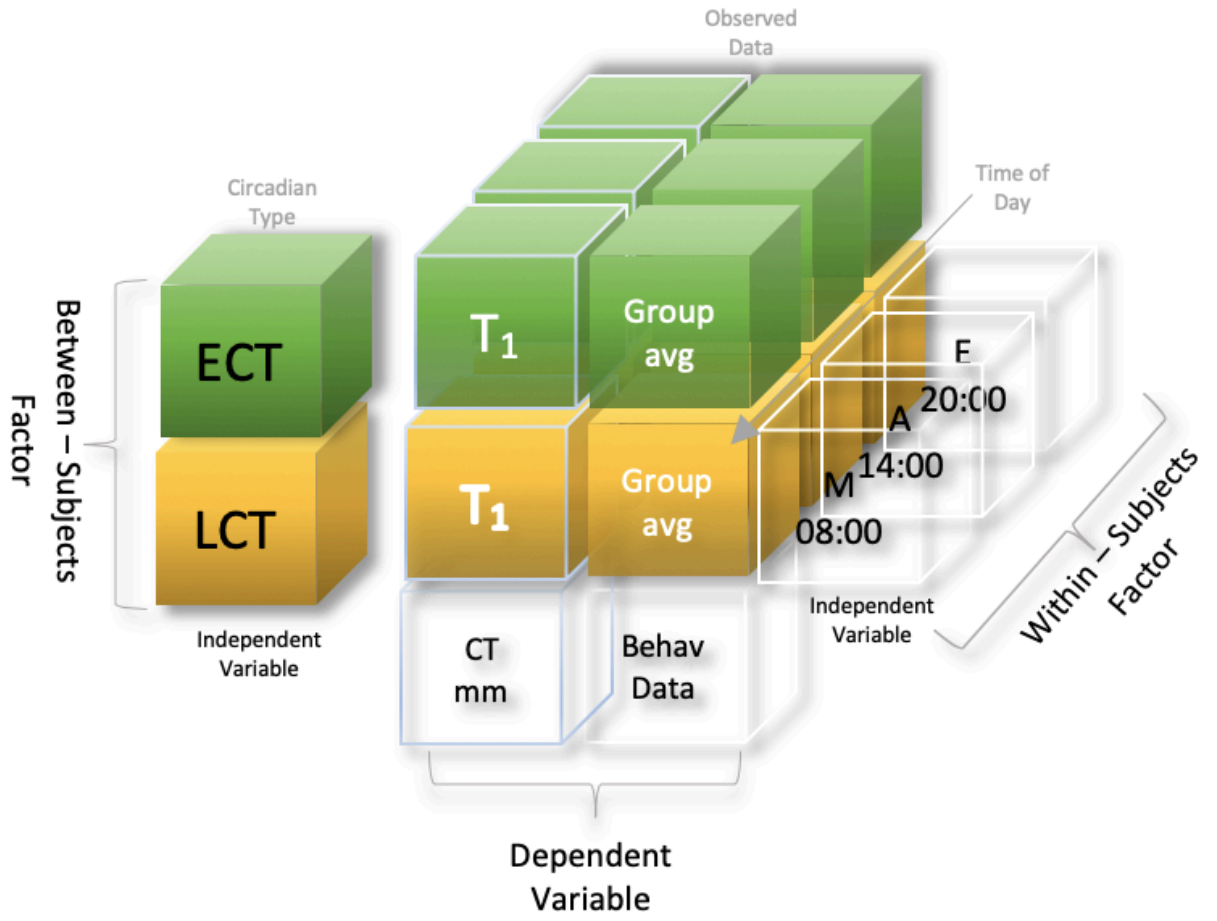


Figure 5.4. General Linear model / ANOVA set-up for comparisons of cortical thickness (CT, derives from T_1)- behavioural data (Behav.Data, e.g., group average of executive functioning), interactions between groups (circadian types ECT/LCT), at different times of the day (M=Morning, A= Afternoon, E= Evening).

(5.3) RESULTS

Behavioural data for compound executive functioning, short term memory and psychomotor vigilance tasks were compared between circadian types (ECT, LCT) and at three different time points (Afternoon, Evening, Morning). Figure 5.6 a) shows visualisation of the data compared between ECT and LCT, and b) estimated marginal means for different times of day.

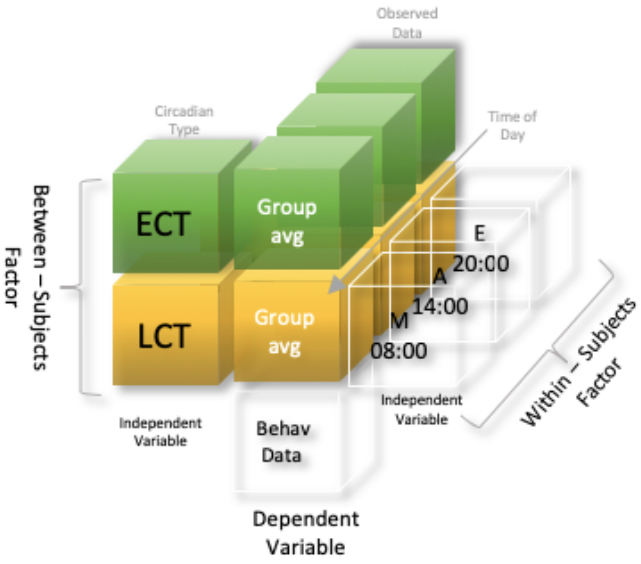


Figure 5.5 Circadian Type - Time of Day - Functioning Model

A repeated measures ANOVA showed a strong main effect of time of day for compound executive functioning performance ($F(1,36) = 5.028$, $p^c=0.009^*$), and a trending interactive effect between time of day and circadian type for compound executive functioning ($F(1,36) = 3.071$, $p=0.052$). Performance differed significantly throughout the day, and between participants, with ECTs showing a shorter time until completion, than LCTs.

Analysis further showed an interaction effect between time of day and circadian type for PVT. Mauchly's test of sphericity showed that the assumption of sphericity was violated ($p=0.022^*$), so results were corrected, and a main interaction was found with Greenhouse-Geisser ($F(1,36) =4.774$, $p=0.02^*$). ECT and LCT differed significantly in their PVT performance with a mean difference of ±0.032, $p=0.043^*$, Bonferroni corrected for multiple comparisons. ECT's had an overall shorter reaction time, which denotes a better performance on the PVT, overall.

(5.3.1) Does average cortical thickness differ between Early Circadian Chronotypes (ECT) and Late Circadian Chronotypes (LCT)?

A general overview between groups shows only a marginally higher whole brain thickness in ECT's (2.41mm) when compared against LCT's (2.40 mm) and a marginally higher volume in LCT's (465899.48mm^3) compared to ECT's (463584.38mm^3). When averaged over the whole brain this difference is not significant, for circadian phenotypes or at different times of day. A comparison between circadian phenotypes for cortical thickness, whilst accounting for Time of Day (ToD), was carried out in Freesurfer's QDEC (http://surfer.nmr.mgh.harvard.edu) to identify individual regions of interest. After Monte Carlo Null Simulation (MC_s) at a vertex wide cluster forming threshold (CFT) of $p^a<0.01$, suprathreshold regions for each hemisphere were identified.

Early circadian types (ECT) differed from late circadian types (LCT) through a larger average thickness in the left lateral occipital cortex (x -28.6, y -87.3, z 0.6, cluster-wide-probability (CWP) p=0.0005*) and right lateral occipital cortex (x 33.1, y -85.1, z 3.3, CWP p=0.0001*) , right supramarginal gyrus (x 51.6, y -35.9, z 25.7, CWP p=0.0007*) right precuneus (x 20.8, y -63.4, z 29.4, CWP p=0.002*) and right lingual gyrus (x 27.5, y -50.2, z -2.1, CWP p=0.0001*). LCT's showed a thicker cortex in the left superior frontal gyrus (x -7.0, y 34.0, z 42.4, CWP p=0.0001*), left medial orbitofrontal cortex (x -11.6, y 37.1, z -10.1, CWP p=0.0003*) and left caudal anterior cingulate cortex (x -5.6, y 16.2, z 27.2, CWP p=0.003*). Figure 5.7 illustrates these differences across the whole brain.

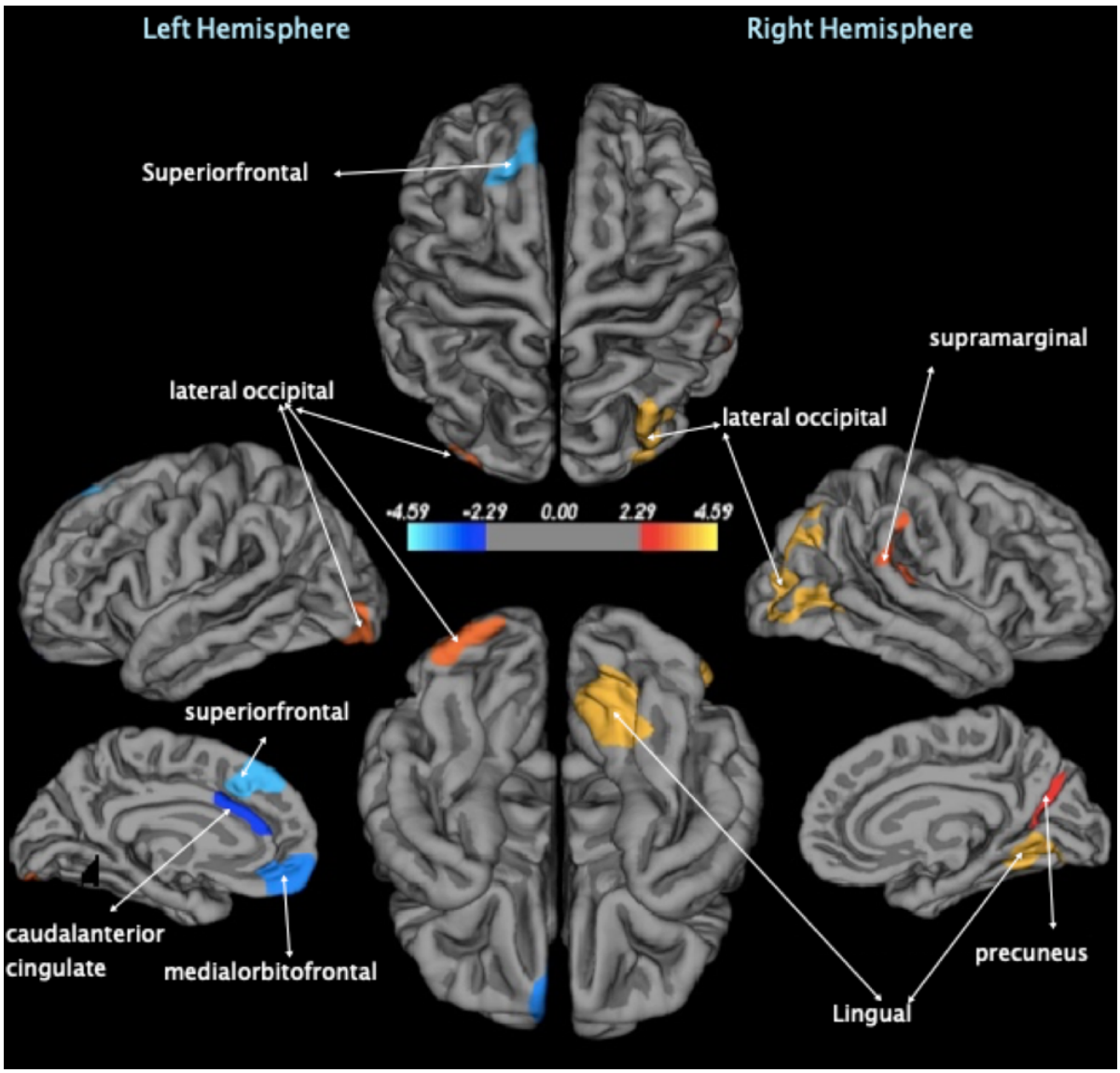


Figure 5.6 Areas of differences in Cortical Thickness between Early Circadian Types versus Late Circadian Types not accounting for Time of Day. Monte Carlo Simulation: vertex-wise threshold p^a <0.01 The value of the scale bar represents a logarithmic scale, $-\log_{10}(p) = 2.3$, with $p = 0.005$. Negative values (blue colour scale) denote areas where ECT's differ from LCT's by having lower cortical thickness measurements in relation to the ROI, whilst positive values (red colour scale) show areas where ECT's have thicker cortical thickness measurements in the regions indicated.

(5.3.2) IS THERE A TIME OF DAY - CHRONOTYPE – THICKNESS INTERACTION? ARE DIFFERENCES BASED ON “CLOCK TIME” OR “INTERNAL TIME”?

An independent-samples t-test was conducted to compare the change in total grey matter volume (tGMV) between circadian chronotypes throughout the day. Using the means of the tGMV for each time point (Afternoon, Evening, Morning) the average change between time points for each group was calculated. An independent sample t test was then carried out using the grand means of change in total Grey Matter Volume between time points.

There was a significant difference in tGMV change between chronotypes ($p=0.03^{*}$).

Early chronotypes displayed a change of total grey matter volume of +0.05% (325.48 mm^3) per 6 hours during the daytime (14:00-20:00), +0.1% (559.82 mm^3) per 12 hours overnight (20:00-08:00) and -0.17% (792.25 $mm^{3)}$ between Morning (08:00) and Afternoon (14:00) measures.

Late chronotypes were observed to have a tGMV change of +0.9% (4345.95 mm^3) per 6 hours during the daytime (14:00-20:00), +0.6% (2822.62 mm^3) per 12 hours overnight (20:00-08:00) and -1.5% (7168.57 mm^3) between Morning (08:00) and Afternoon (14:00) measures.

The cortical regions identified as significantly different between ECT and LCT were investigated as regions of interest (ROI’s) in an analysis of variance (ANOVA) but no main effect between ToD and ROI, nor an interactive effect between circadian type and ToD and ROI was found.

Average cortical thickness changes in the investigated ROI's were observed to be between -0.003 – 0.04mm per 6hours during the daytime (14:00 – 20:00hours) and -0.007 – 0.03mm per 12hours overnight (20:00 – 08:00hours). The largest difference observed between average thickness was in the left medial orbitofrontal gyrus between afternoon and evening measurements, during which cortical thickness increased by 1.69%, per 6 hours, for early circadian types and by 1.1% for late circadian types. These changes were not significant (p=0.2), however.

(5.3.4) DIFFERENCES AT CLOCK TIME

Comparisons between circadian types at the same time points (Afternoon, 14:00, Evening, 20:00, Morning, 8:00) at '***Clock Time'*** were carried out in relation to cortical thickness and task performance.

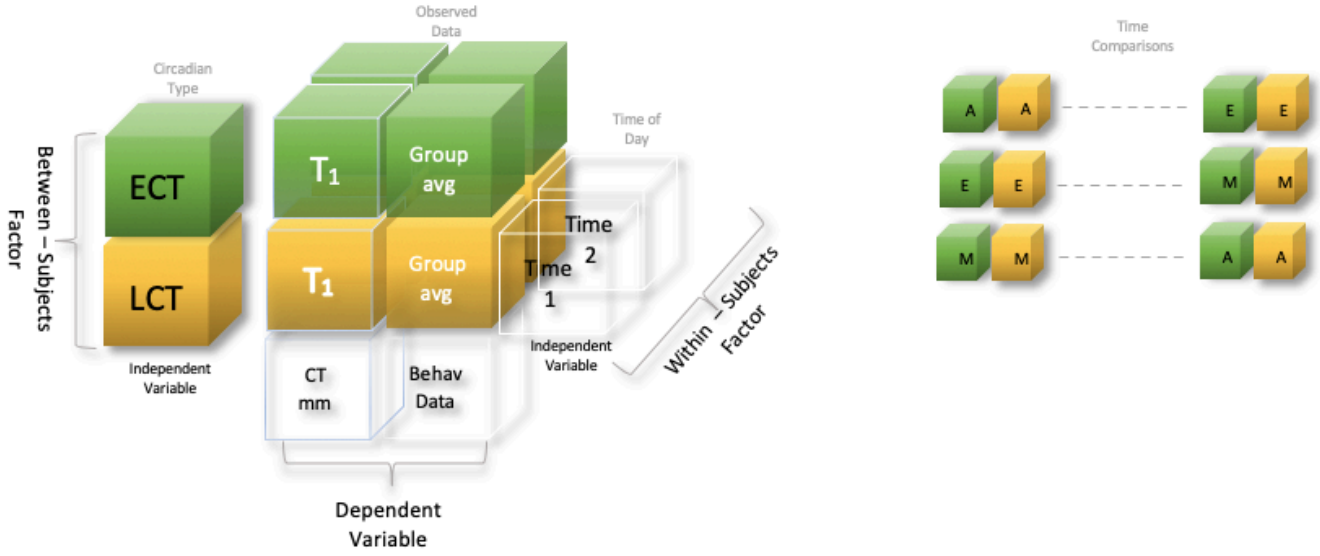


Figure 5.7 Clock time comparison model at two time points. ECTs (ECT_tp1_tp2) are compared against LCTs (LCT_tp1_tp2).

14:00/20:00HRS (ECT_14:00_20:00 VS. LCT_14:00_20:00)

There was no main interaction between chronotype and time (14:00/20:00hrs), nor did thickness differ between times, when chronotype was accounted for. There were no main effects in the thickness – cognitive performance correlations when time of day was considered.

COGNITIVE PERFORMANCE AT 14:00/20:00 HRS

The cortical thickness – memory performance correlation differed significantly at MC_s p^a=0.01 between circadian types, when time of day (14:00/20:00hrs) was accounted for, in the right postcentral gyrus (x 56.9, y -4.6, z 14.9, CWP p=0.004*).

Whilst afternoon and evening performance was not significantly different in the full model, removing the effect of time, thus effectively treating the effect of time as an extraneous variable, showed a significant effect.

Suprathreshold regions after MC_S **p^a=0.01** were found in the right isthmus cingulate cortex (x 13.5, y -47.3, z 6.2, CWP p=0.02*), supramarginal (x 47.3, y -19.7, z 17.7, CWP p=0.03*), inferior temporal (x 54.6, y -25.0, z -17.2, CWP p=0.03*), supramarginal (x 38.2, y -25.9, z 38.5, CWP p=0.03*) with ECT's showing a positive correlation and LCT's showing a negative thickness- executive function correlation , and in the superior temporal gyrus (x 51.6, y -27.3, z 1.8, CWP p=0.03*) where ECT's showed a neutral correlation whilst LCTs showed a negative correlation.

There were no main or interaction effects between cortical thickness, circadian type, time of day and PVT (14:00/20:00) at p^a. Figure 5.9 illustrates the findings of the 14:00/20:00h analysis. Part a) shows how early circadian chronotypes had significantly higher average thickness in the right lingual gyrus, supramarginal gyrus

and precuneus. Bar chart to the right demonstrates differences in ECT – LCT for the right precuneus where average thickness for early types is 2.24mm in the afternoon, and 2.25mm in the evening, and 2.20mm in the afternoon and 2.19mm in the evening in late chronotypes. Bar chart to the left demonstrates average cortical thickness differences in chronotypes in the caudal anterior cingulate gyrus where values for early types in the afternoon are 2.54mm and in the evening are 2.55mm, whereas late types had an average thickness of 2.68mm in the afternoon and 2.69mm in the evening.

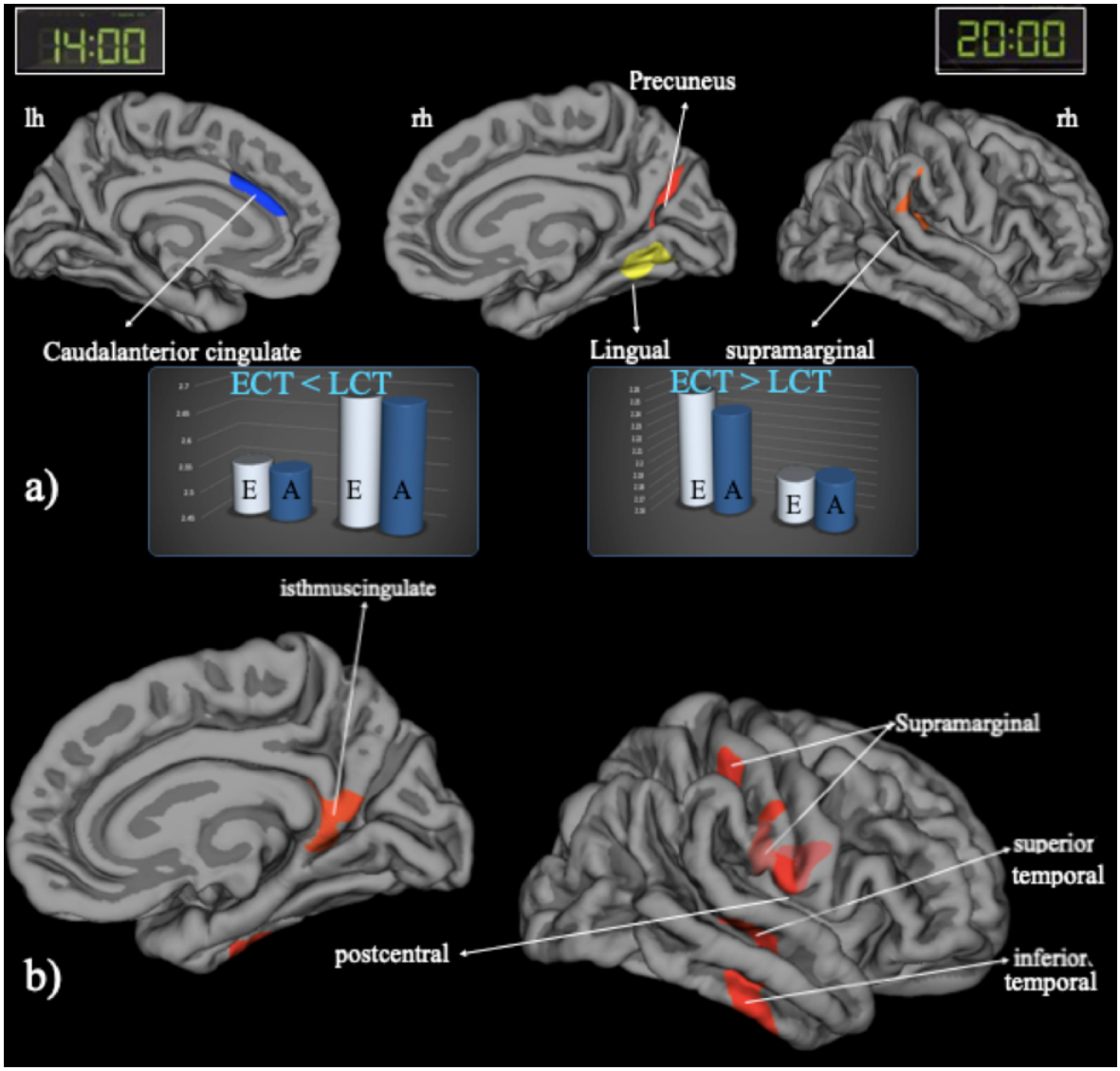


Figure 5.8 a) Average thickness differences in suprathreshold regions, when time was accounted for. b) shows areas where thickness -task performance correlation between chronotypes was significantly different, when time of day was accounted for. For visualisation purposes a -log10(p)=2.3 (p=0.005) threshold was applied.

Part b) shows areas where the thickness - task performance correlation between chronotypes was significantly different, when time of day was accounted for. Right postcentral was significantly different for the memory-cortical thickness correlation between chronotypes, with early circadian types showing a positive correlation whilst late circadian types showed a negative correlation. Right isthmus cingulate cortex, supramarginal gyrus, superior temporal gyrus and inferior temporal gyrus all related to differences in thickness – executive function correlation between chronotypes.

20:00/08:00HRS (ECT_20:00_08:00 VS. LCT_20:00_08:00)

There was no ToD – Ctype interaction in average thickness when comparing groups at 20:00/08:00hrs.

COGNITIVE PERFORMANCE AT 20:00/08:00

The thickness – executive function correlation, differed significantly at MC_S p^a=0.01 between chronotypes when ToD was accounted for. Whilst evening and morning performance was not significantly different in the full model, removing the effect of time, thus effectively treating it as an extraneous variable, showed a significant effect.

Suprathreshold regions in the left hemisphere were the lateral occipital cortex (x -29.2, y -84.5, z 16.1, CWP p=0.004*) and inferior parietal cortex (x -40.5, y -54.3, z 27.0, CWP p=0.004*). ECTs showed a positive thickness functioning correlation in both suprathreshold regions, whilst LCTs showed a negative correlation. Suprathreshold regions to the right were located in the inferior temporal gyrus (x 54.2, y -26.8, z -17.4, CWP p=0.0001*), right middle temporal gyrus (x 58.1, y -31.6, z -6.7, CWP p=0.0001*), right postcentral gyrus (x 56.4, y -13.9, z 31.2, CWP p= 0.002*) and right supramarginal

gyrus (x 38.6, y -25.6, z 38.6, CWP p=0.010*). There were no main or interaction effects between cortical thickness, circadian type, time of day and Memory or PVT (20:00/08:00) at p^a (MC_S p<0.01) or p^b (FDR p<0.05).

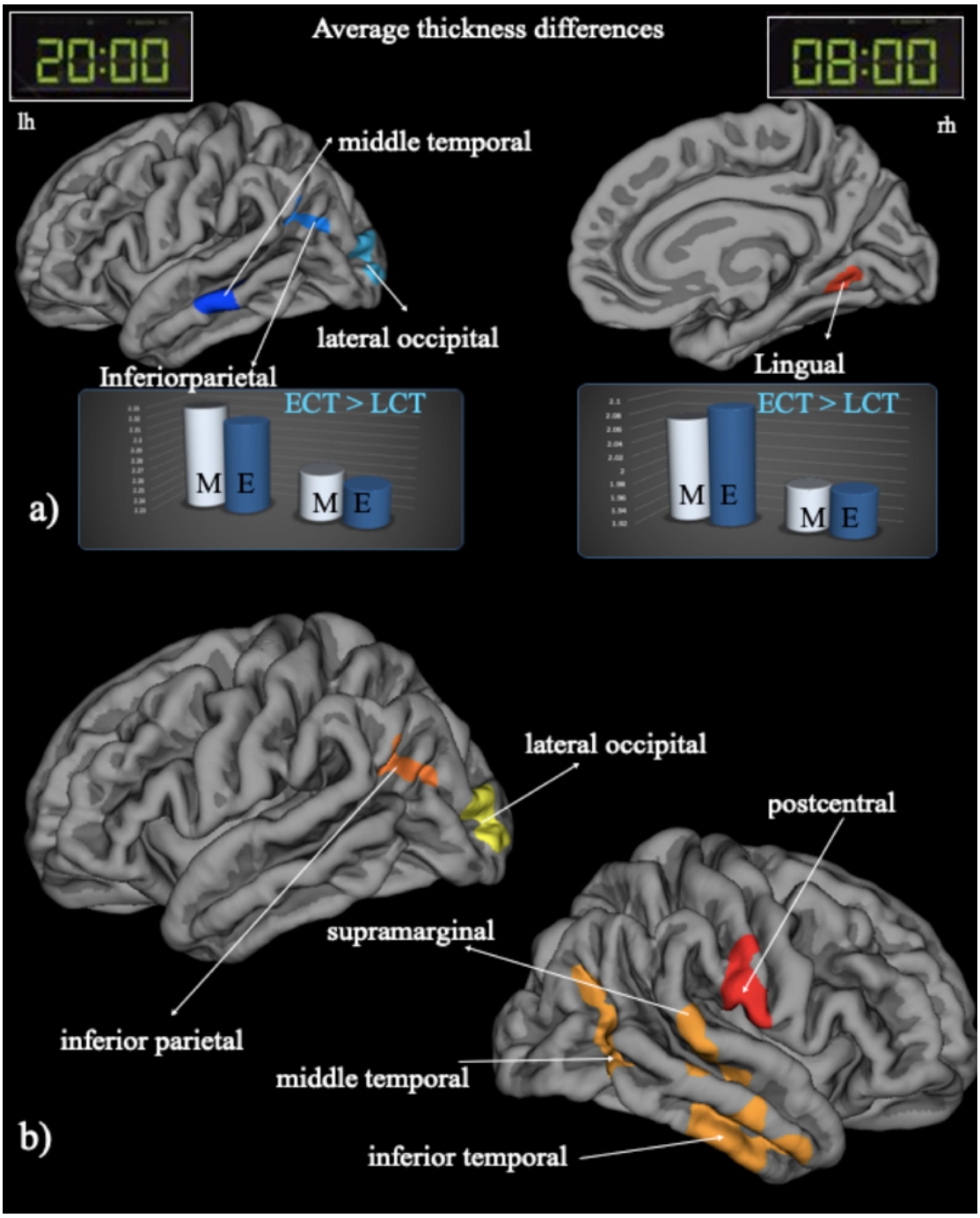


Figure 5.9. a) Average thickness differences in suprathreshold regions when time was accounted for. Early circadian chronotypes had significantly higher average thickness in the left middle temporal gyrus, left lateral occipital cortex and left inferior parietal lobe. ECT's also measured larger on average in the right lingual gyrus. Bar chart to the right demonstrates differences in average thickness for the right lingual gyrus. Early types measured an average of 2.09mm in the evening and 2.07 in the morning, whilst late chronotypes measured

1.983mm in the evening and 1.984mm in the morning. The bar chart to the left demonstrates average thickness in the left inferior parietal lobe with early types measuring an average of 2.32mm in the evening and 2.32mm in the morning. Late types measured an average of 2.26mm in the evening and 2.27mm in the mornings. b) shows areas where thickness – executive task performance correlation between chronotypes was significantly different, when time of day was accounted for. For visualisation purposes a -log10(p)=2.3 (p=0.005) threshold was applied.

08:00/14:00HRS (ECT_08:00_14:00 VS. LCT_08:00_14:00)

There was no ToD – Ctype interaction in average thickness when comparing groups at 08:00/14:00hrs.

COGNITIVE PERFORMANCE AT 08:00/14:00HRS

The thickness- executive functioning correlation differed significantly between chronotypes when time was accounted for. Whilst morning and afternoon performance was not significantly different in the full model, removing the effect of time, thus effectively treating it as an extraneous variable, showed a significant effect.

Suprathreshold regions could be found in the left lateral occipital gyrus (x -29.2, y -84.5, z 16.1, CWP p=0.0005), left inferior parietal lobe (x -41.1, y -53.8, z 26.4, CWP p=0.003) and right lateral occipital gyrus (x 26.5, y -88.3, z 18.8, CWP p=0.02). LCTs showed a negative correlation between functioning and thickness, whilst ECTs showed a positive relationship between thickness and task performance.

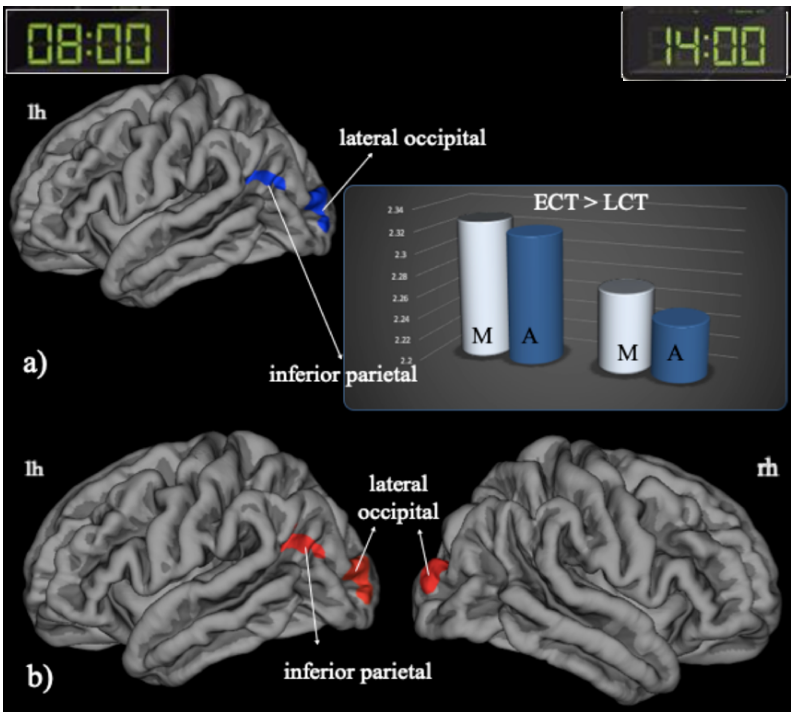


Figure 5.10 a) Average thickness differences in suprathreshold regions, when time was accounted for. Early circadian chronotypes had significantly higher average thickness in the left lateral occipital cortex and left inferior parietal lobe. Bar chart to the right demonstrates differences in average thickness for the left inferior parietal lobe with early types measuring an average of 2.32mm in the morning and 2.31mm in the afternoon. Late types measured an average of 2.27mm in the mornings and 2.25mm in the afternoons. b) shows areas where thickness – executive task performance correlation between chronotypes was significantly different, when time of day was accounted for. For visualisation purposes a -log10(p)=2.3 (p=0.005) threshold was applied to a) and -log10(p)=1.3 (p=0.05) to b).

CLOCK-TIME COMPARISON AT THE SAME TIME

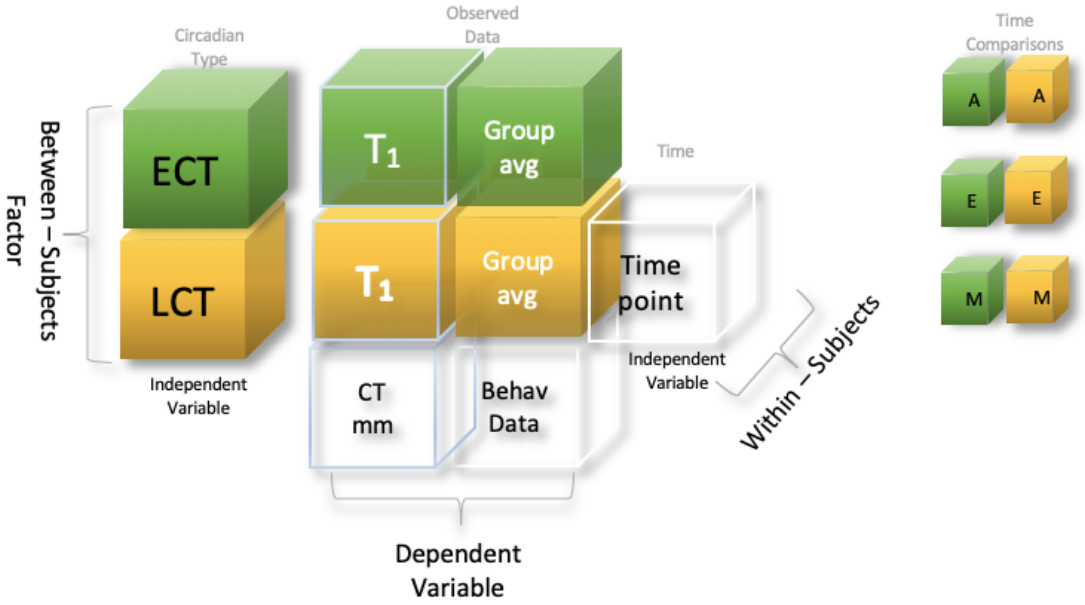


Figure 5.11 Clock time comparison, at the same time of day. ECT's are compared at time point 1 (e.g., Morning) against LCT's at the same time point 1 (e.g., Morning).

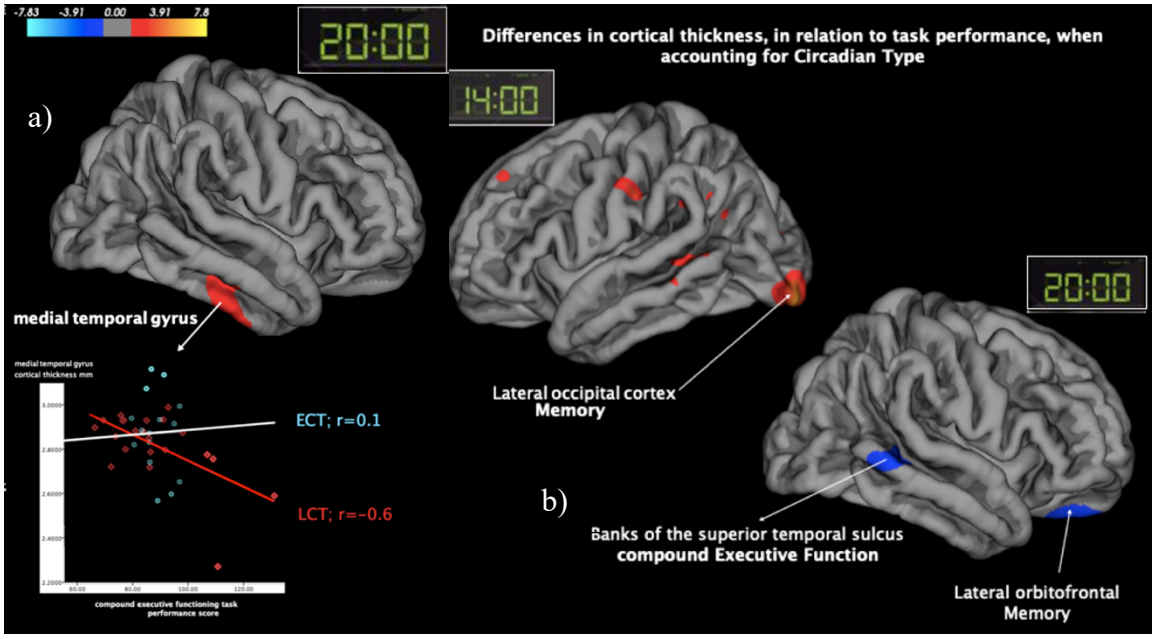


Figure 5.12 Differences in relation to task performance at p^a=0.01. Accounting for circadian type.

The cortical thickness - executive function correlation differed significantly after MCs at a cluster forming threshold (CFT) of $p^a < 0.01$, between circadian types in the evening, in the right inferior temporal gyrus (x 54.3, y -26.2, z -17.4) and middle temporal gyrus (x 55.9, y -21, z -21.9). Late circadian types showed a moderately strong negative relationship (r=-0.592) in the right middle temporal gyrus and a

moderate negative relationship in the inferior temporal gyrus (r= -0.479), whereas early types showed a weak positive correlation. In late circadian types, in addition to the negative correlation between cortical thickness and executive function, the two implied regions had a strong positive correlation with one another (r = 0.787

(5.3.5) DIFFERENCES AT INTERNAL TIME

On the assumption that a different degree of sleepiness due to time since waking was involved for the different circadian types, groups were compared on the Karolynska Sleepiness Scale.

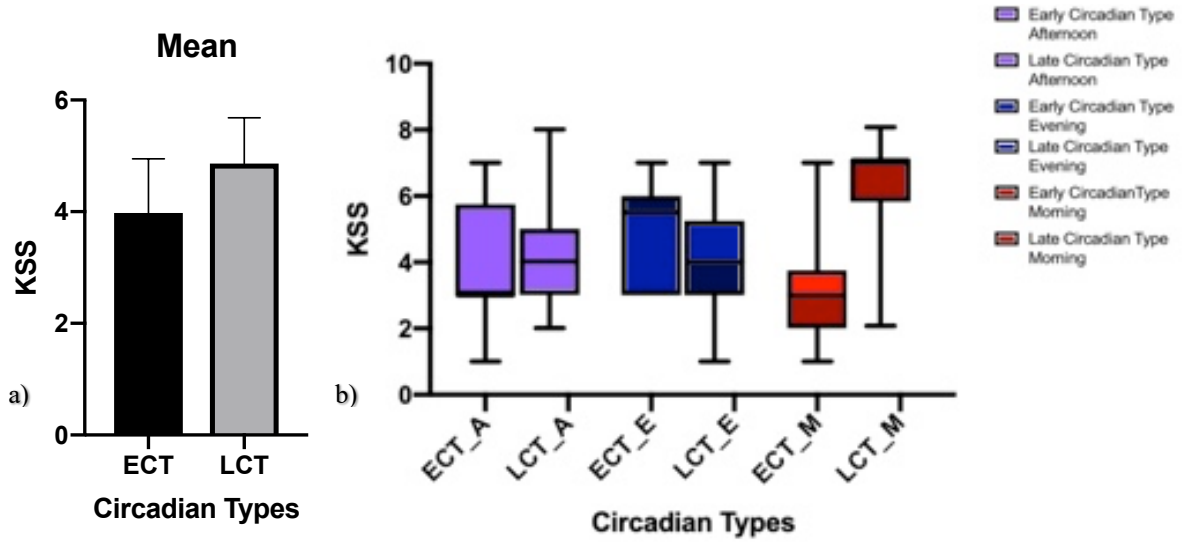


Figure 5.13 Differences in sleepiness rating between chronotypes and at different times of day. A higher score indicates a higher degree of sleepiness. a) Average sleepiness rating was higher in late circadian types, compared to early circadian types. Sleepiness rating particularly high in Late Types (LCT) during the Morning (LCT_M – coloured red), as opposed to particularly low in Early Types (ECT) in the Morning (ECT_M-coloured red).

This was verified with a repeated measures ANOVA, analysing the interaction effect of sleepiness at different types of day and on circadian types. A significant main interaction was found $F(6,140) = 18.142$, $p^c = 0.000^*$, suggesting that self-reported sleepiness ratings were significantly different between chronotypes, as well as a significant interaction effect between ECT's and LCT's at different times of day (Afternoon, Evening, Morning).

Due to the significant interaction of self – reported sleepiness scores between circadian chronotypes at different times of day, further comparisons were carried out to compare groups at different time points, most closely matched by KSS score, i.e., presumed internal time (Figure 5.14). Groups were compared for differences in cortical

thickness alone and correlations between task performance and differences in cortical thickness. Groups were compared for task performance in psychomotor vigilance task (PVT), memory task (STM) and compound executive functioning.

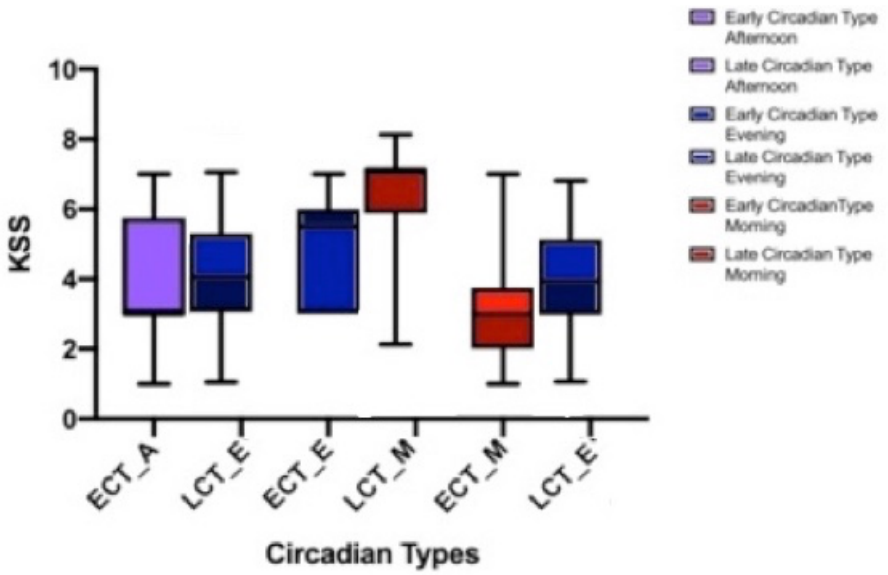


Figure 5.14 Chronotypes matched by 'internal time', as interpreted by the KSS

COMPARISONS AT INTERNAL TIME, BASED ON KSS

Groups (ECT/LCT) were compared based on internal time. Internal time was determined through self-reported KSS scores. Results did not survive the stringent MC_S Cluster forming threshold of p^a=0.01, so further comparisons at a lower threshold were carried out.

Whilst MC_S is a very conservative test and used to ensure the reliability of the results overall, **FDR 2 = p^b 0.05** is also a very well corrected, robust, and commonly used threshold and thus reported for completeness. Differences in cortical thickness between groups ECT_14:00hrs – LCT_20:00hrs, ECT_20:00hrs – LCT_08:00hrs and ECT_08:00hrs – LCT_20:00hrs, in relation to compound executive functioning were found at p^b.

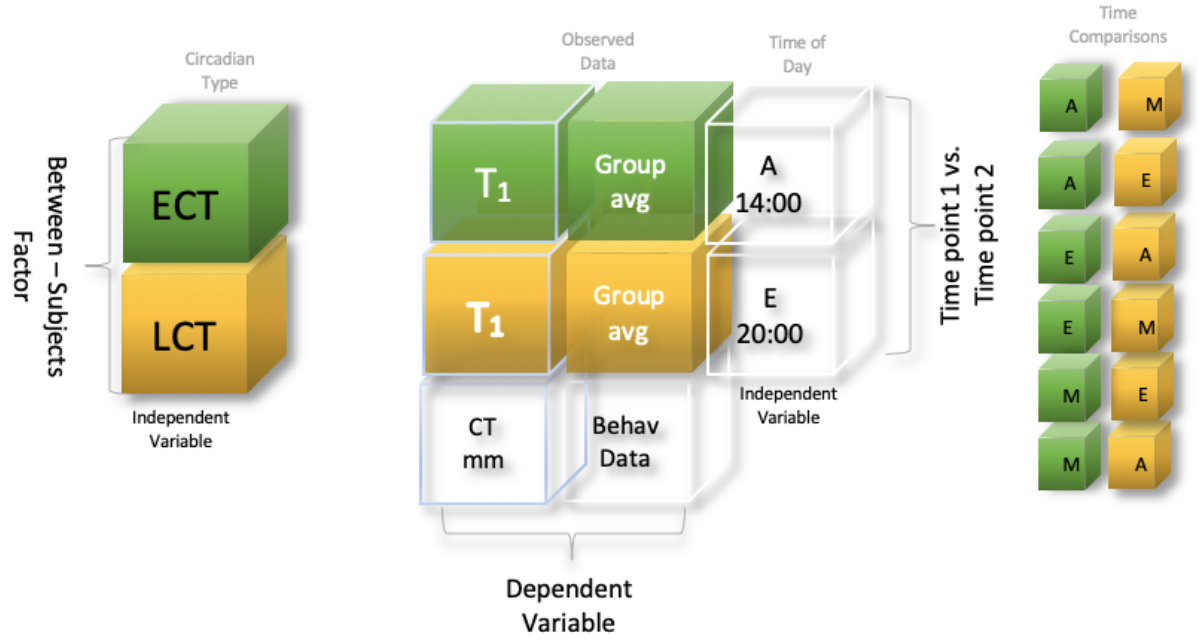


Figure 5.15 Statistical Model - Internal time comparison based on KSS scores. ECT's are compared at time point 1 (e.g., A = Afternoon, 14:00) against LCT's at time point 2 (e.g., E = Evening, 20:00).

Average cortical thickness between ECT's in the afternoon (mean=2.49mm, SD=0.09) and LCT's in the evening (mean=2.47mm, SD=0.15), in relation to compound executive functioning, differed most in the right supramarginal gyrus (x 38.8, y -28.6, z 39.9, p^b0.05, cluster size 39.36mm^2, max. -log10(p)= -5.6933). ECT's (mean=86.41, SD=24.76) performed better than LCT's (mean=87.54, SD=15.76) on the executive functioning test, with a faster accurate completion time and demonstrated a thicker cortex in this region. Thickness differed in the right lingual gyrus (x 6.2, y -77.2, z -1.5, cluster size 126.32 mm^2, max. -log10(p)=7.5419) at p^b when early types were compared in the evening (mean= 2.089 mm, SD= 0.087) against late types in the morning (mean=1.984, SD=0.091). ECT showed a higher mean thickness, as well as better task performance (mean=82.17, SD=22.932) whilst LCT's showed a thinner mean thickness, as well as slower task performance (mean=90.04, SD=15.711).

When comparing task performance and morphometric measurements in ECT's in the morning and LCT's in the evening, two regions met p^b. The supramarginal gyrus (x 39.2, y -28.4, z 39.9, cluster size = 86.34mm^2, max. -log10(p)=6.3134) was notably different between groups, as was the middle temporal gyrus (x 58.7, y -33.4, z -9.1, cluster size = 13.61mm^2, max -log10(p)=4.3277).

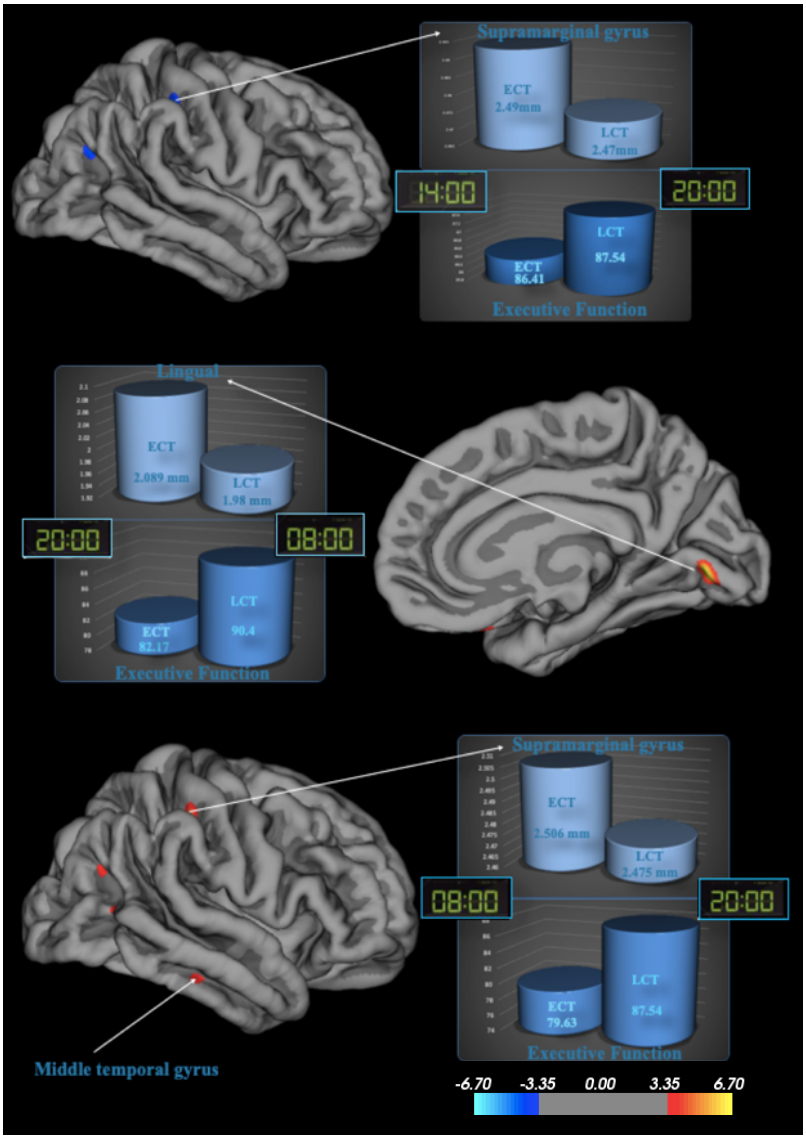


Figure 5.16 Regions of significance at pb for comparisons between chronotypes at different times of day. The value of the scale bar represents a logarithmic scale, which for visualisation purposes was set as the minimum threshold log10 (p) = 3.3, with p = 0.0005. Early circadian types were observed to have higher cortical thickness at the specified times, as well as better (lower) executive functioning performance, when compared against late circadian types. A higher cortical thickness value indicates a thicker cortex in the indicated area, whereas a higher compound executive performance, indicates a poorer task outcome. Successful task performance is measured by speed and accuracy

(5.3.6) COMPARISONS TAKING INTO ACCOUNT THE DEPRESSION, ANXIETY, STRESS SCALE (DASS)

Since the effects of sleep deprivation and sleep debt on mental health are well documented, mental health variables, which could affect performance were taken into consideration. This was done due to an underlying assumption being that sleep deprivation induced cognitive deficiencies aren't caused due to anatomical differences alone. DASS produced significant differences between circadian types (DASS= ECT mean 9.07±1.82SD, ECT mean 17.24± 2.51SD, p^c=0.02), with stress accounting for approximately half of the responses in a scale that measures Depression, Anxiety and Stress (ECT mean 4.9 ± 4.1SD, LCT mean 8.6 ± 7.2SD). When DASS and KSS scores, and thus the effects of mental health variables and sleepiness were taken into account in the statistical models, some of the results changed.

In the Morning (08:00) – Afternoon (14:00) comparison between Chronotypes when including DASS scores in the model, resulted in removing the clusters from the left hemisphere and changing the clusters from the right to the precuneus (x 4.9, y -55.4, z 17.2, CWP p= 0.01*) and postcentral gyrus (x 60, y -16.2, z 22.7, CWP p=0.04*).

In the Evening (20:00hrs) Morning (08:00) comparison, accounting for DASS scores, removed all clusters from the left and changes the significant cluster at MC_S(p=0.01) to the postcentral (x -9.3, y -32.7, z 69.6, CWP p=0.03), and added the lingual gyrus the right hemisphere as an additional cluster to previously existing ones, whilst the factoring out of KSS removed the middle temporal cluster to the right.

The Afternoon (14:00) Evening (20:00) comparison changed when the DASS scores were factored out, with clusters to the left changing to the rostral middle frontal gyrus (x -37.23, y 30.4, z 9.3, CWP p=0.006) and insula (x -32.5, y -20.6, z 6.2, CWP p=0.01)

and removing the supramarginal gyrus (KSS &DASS) and inferior temporal (DASS) to the right.

*MCs $p^a<0.01$	Early Circadian Type						Late Circadian Type					
Anatomical	Lh Lateral occipital		Rh Lateral occipital Supramarginal Precuneus Lingual				Lh Superior frontal Medial orbitofrontal Caudal anterior cingulate					
	A/E		E/M		M/A		A/E		E/M		M/A	
	Rh	Lingual Supramarginal Precuneus	Lh lateral occipital Inferior parietal Middle temporal	Rh lingual	Lh	Lateral occipital Inferior parietal	Lh	Caudal anterior cingulate	Lh Lateral occipital, Inferior parietal , Middle temporal	Rh lingual	Lh	Lateral occipital Inferior parietal
Executive Function – Thickness	Rh isthmus cingulate Rh Supramarginal Rh Inferior parietal		Lh lateral occipital Inferior parietal	Rh Inferior temporal, Middle temporal, Postcentral, Supramarginal	Lh Lateral occipital Inferior parietal	Rh Lateral occipital	Rh Isthmus cingulate Rh Supramarginal Rh Inferior parietal		Lh Lateral occipital, Inferior parietal	Rh Inferior temporal, Middle temporal, Postcentral, Supramarginal	Lh Lateral occipital Inferior parietal	Rh Lateral occipital
Memory – Thickness	Rh Superior temporal Rh Postcentral						Rh Superior temporal Rh Postcentral					
	A		E		M		A		E		M	
Executive Function – Thickness correlation			Rh Lateral orbitofrontal, Bankssts	Rh Inferior temporal Middle temporal					Rh Lateral orbitofrontal, Bankssts	Rh Inferior temporal Middle temporal		
Memory – Thickness correlation	Lh Lateral occipital	Rh Lateral orbitofrontal, Bankssts					Lh Lateral occipital	Rh Lateral orbitofrontal, Bankssts				
** $p^b<0.05$	Early Type 14:00		Late Type 20:00		Early Type_20:00		Late Type 08:00		Early Type _ 08:00		Late Type 20:00	
Executive Function – Thickness correlation	Rh Supramarginal		Rh Supramarginal		Rh Lingual		Rh Lingual		Rh Supramarginal Rh Middle temporal		Rh Supramarginal Rh Middle temporal	

Table 5.3. Overview over anatomy results

- Larger average thickness, when compared to the other group
- Positive correlation
- Smaller average thickness, when compared to the other group
- Negative correlation
- Neutral correlation
- Accounting for Circadian Type

(5.4) DISCUSSION

OVERVIEW

Late Chronotypes, not disordered in their sleeping, exhibit diurnal sleep preferences, which are, at times, largely incompatible with societal norms and expectations. Social jetlag, through a constant cycle of accumulative sleep debt, with negative effects on cognition, followed by sleep recovery on free days, may therefore lead to chronic sleep loss, which, over time, structurally affects certain brain regions.

Though chronotype appears to regulate the neural basis of executive processes during the daytime, it is still unclear exactly how brain activity is influenced (Song et al. 2018) and how the homeostatic sleep drive can be distinguished from chronotype specific effects. Dai et al. (2018) identified several regions found in this study, such as the right precuneus, right inferior parietal lobe and superior temporal cortex (amongst others, such as the right cerebellum, right caudate body, left and right insula, left and right paracentral and precuneus and left superior parietal lobule) in a VBM sleep deprivation study and surmised that differences in grey matter volume (GMV), may provide the neurobiological basis for impairments in memory and attention. They further concluded that acute sleep deprivation is associated with the inhibition of sensory informational processing streams, in particular, in the superior temporal cortex (Dai et al. 201). Reduced GMV in certain regions may therefore explain decreased cognitive capabilities. On the contrary, insomniacs were distinguished by increased GMV in this area, which supports theories of hyperarousal in insomnia (Vargas et al. 2020) and may be one of the core features in the failure to initiate and maintain sleep appropriately in sleep disorders.

Anatomical differences between Early and Late Circadian Types

Although average whole brain measurements of cortical thickness and intracranial volumes are comparable between early and late circadian chronotypes, a closer look into morphometric differences, revealed regions of significant anatomical variances, both at purely anatomical level, but also when correlated with cognitive performance. Accounting for time of day, chronotypes differed in several suprathreshold clusters, found at the very conservative threshold of $p^a<0.01$, after Monte Carlo null simulation. Previous studies (e.g., Rosenberg et al. 2014, 2018, Takeuchi et al. 2015, Song et al. 2018, Dai et al. 2018) began to identify anatomical markers which differentiate circadian types from one another. These regions were largely verified and supported through the results of this study, alongside further information gained in relation to cognitive functioning and mood states in chronotypes.

Early chronotypes were observed to have larger average cortical thickness when compared against late chronotype in the left and right lateral occipital cortex/inferior parietal lobe, right supramarginal gyrus, right precuneus and right lingual gyrus, whilst late chronotypes displayed a larger average thickness in the left superior frontal gyrus, left medial orbitofrontal cortex and left anterior cingulate cortex (Figure 5.6). These regions also correlated highly with task performance when comparisons were carried out at various time points.

Time of Day Effect

Whilst regions of interest were found in both hemispheres at anatomical level, correlations with cognitive data revealed that results weighted heavily towards the right hemisphere. Although a time-of-day effect was found for both cortical thickness and total grey matter volume, with changes in the latter being significant between

chronotypes, ToD did not appear to be a major factor in modulating the results of this study. Cortical thickness changed as much as 1.69% (0.04mm) per 6 hours at regional level, and tGMV as much as 1.5% (7168.6 mm^3) per 12 hours.

Differences in Task Performance

Psychomotor vigilance performance was significantly different between participants and relative to the time of day the test had been taken, these effects were no longer seen, however, when a correlated neural substrate was sought. Compound executive functioning was shown to be most different, when correlated against average thickness and compared between groups, which may indicate that chronotypes rely on different neural profiles for certain executive functioning processes. Furthermore, one emerging major modulating factor of cognitive performance, taking account of previous literature and findings, appears to be affective status in chronotypes. Late chronotypes in this study cohort reported a higher level of tiredness, stress, and anxiety, and this appeared to affect results significantly.

Discussion

Late Chronotypes displayed lower average thickness in most areas of this study, aside from lh superior frontal gyrus, lh medial orbitofrontal gyrus and lh caudal anterior cingulate cortex. Previous studies (Rosenberg et al. 2014) identified a similar profile of differentiated areas of cortical thickness when comparing chronotypes, which supports the notion that these regions may be involved in chronotype specific regulatory processes. In a diffusion tensor imaging study, late chronotypes significantly differed in the white matter underlying the left cingulate and anterior cingulate gyrus, as well as left frontal lobe from both early, and intermittent

chronotypes (Rosenberg et al. 2014). The Superior (banks of the superior temporal sulcus) and middle temporal areas, previously linked to executive functioning (Takeuchi et al. 2010, 2011, 2013), were also shown to be important in relation to executive functioning in this study. When circadian type was accounted for, both regions were significant when correlated with executive functioning and memory in the evening (20:00). Comparing chronotypes on their cognitive performance in the evening to the morning (ECT_20:00/08:00 compared to LCT_20:00/08:00) and when taking account of internal time with early types being compared in their morning (08:00) performance, against late types in their evening performance, showed these regions to be of relevance. Takeuchi et al. (2013) assessed everyday executive functioning, as well as dysexecutive functioning symptoms (measured with the DEX, part of the behavioural assessment of the dysexecutive syndrome, Wilson et al. 1996, www.pearsonclinical.co.uk) and linked the superior and middle temporal areas to executive function and dysfunction. A positive association between rGMV and DEX scores, as well as a negative association between rGMV and executive functioning was observed which is in line with the findings of this study, where LCT's, in particular, were observed to have a negative correlation between executive functioning performance and regional cortical thickness in the superior temporal gyrus (14:00/20:00hrs). This indicates that in this area lower cortical thickness equals higher functioning.

As previously discussed in this thesis, cortical thickness measurements cannot always be assessed under the assumption that "more equals better". Rather, this is circumstantial, and partly dependent on the developmental trajectory of the region, partly on whether the subject cohort was sampled from a clinical, or non-clinical

environment. (Takeuchi et al. 2013). In certain clinical populations (e.g., Alzheimers) cortical thinning may be associated with atrophy, rather than enhanced cognition. The superior temporal gyrus, for instance, follows a quadratic developmental trajectory (Ch1, Table 1., Ch2, Table2), so is not associated with a linear rGMV decrease with age, with overall trajectory depending on age of peak. The orbitofrontal gyrus, one of the few regions in which LCT's displayed a larger average cortical thickness, when compared to ECT's, is also associated with a quadratic developmental trajectory, which associates an earlier peak with more rigorous pruning in adolescence with better executive functioning abilities. It is prudent to point out, however, that the positive association between lower cortical thickness and superior cognitive capabilities is complex and still controversial in literature (Takeuchi et al. 2013). Areas of thinning in this study were not associated with better functioning. However, given that LCT's did not perform significantly worse than ECT's it may be an indicator of compensation within the cortex.

However, the general morphometric profile of late circadian types also differed significantly from early types in the medial orbitofrontal, and caudal anterior cingulate area. Changes in this area, previously detected in relation to chronotypes (Rosenberg et al. 2014), may form part of the anatomical profile that distinguishes those late types, cognitively affected by the chronic loss of sleep, from early types. The attentional network includes executive functions, amongst others (alerting and orienting), which are defined by distinct neural networks (Fan et al. 2002). The executive functioning component of attention involves the anterior cingulate cortex, as well as the prefrontal cortex (Fan et al. 2003, 2005). The orbitofrontal cortex is further connected by the inferior fronto-occipital fasciculus to the lateral temporal and occipital lobe (Martino et

al. 2010, Fernaʹndez-Miranda et al. 2008) and is thought to be involved in certain executive functions (Martino et al. 2010). This could explain in part, why the orbitofrontal cortex is part of the main anatomical markers, that separates LCT's from ECT's and could be an indication that chronotypes utilise different pathways or networks, during executive function processes. Given that attention and vigilance are amongst the most fundamental processes affected by sleep loss (Lin & Dinges 2008) it seems reasonable that structures of the attentional network are most affected by chronic sleep loss. If part of the attentional network structure is disrupted at all, all connecting structures, will be equally impacted, in some way or another, in this case, perhaps measurably, through slower reaction or response times. It is important to point out that cognitive functions tested within the laboratory environment seldom reflect everyday functioning, however, due to the specific nature of tasks and the in-depth nature of measurement of a single skill (e.g., Stroop task, or matching pairs task). So, whilst late circadian types perform marginally, but measurably worse than early circadian type in specific cognitive tests, daily functioning is unlikely to be affected.

The alerting response of the attentional network is associated with the frontal and parietal regions of the right hemisphere (Posner & Peterson 1990, Peterson & Posner 2012), which supports the right hemisphere heavy results of this, and other studies. However, the executive pathway in the alerting network, is also associated strongly with the anterior cingulate cortex (ACC), a region this study attributes positively to the late circadian phenotype. The ACC, a relatively old phylogenetically area of the brain, has long been associated with executive control (Posner & Peterson 1990, Peterson & Posner 2012) and now features in two prominent theories. Associations of the ACC with top-down executive functioning control mainly differ in the specific aspects of task performance it is involved in, and which other regions it communicates to (Dosenbach

et al. 2006, 2007, Botvinick et al. 2001). The ACC is one of the few places where Von Economo neurons (VEN) are found, which likely play an important role in the maintenance of homeostasis (Allman et al. 2005, Stimpson et al. 2011, Cauda et al. 2013). Areas containing VEN's are also thought to be involved in several important networks, such as the saliency detection attentional network which includes the ACC, superior frontal cortex, inferior parietal lobe and anterior insula (Cauda et al. 2013). VEN's are large bipolar neurons located in layer III and V of the cortex and it is likely that larger clusters of these cells could affect cortical thickness measurements, as these are influenced by size and packing density of neurons. As late circadian types were observed to show larger changes in tGMV and are thought to be more affected by accumulated sleep debt, an increase in thickness in areas with these cells, may point towards a greater need for self-regulation to restore the brains homeostatic environment.

Song et al. 2018 identified the right supramarginal gyrus, right inferior parietal lobe, right middle temporal gyrus alongside the, right frontal regions, and thalamus, as well as left cingulate cortex regions in an fMRI study examining response inhibition between chronotypes. Their results also showed a bias towards the right hemisphere, as observed in this study. Functional imaging studies have been clear in how loss of sleep leads to a measurable impact on neural functioning and reduced parietal lobe activity, which was associated with reduced memory capacity (Chee & Chuah, 2007). In this study the rh supramarginal gyrus was profoundly featured in the results, as part of the general volumetric profile distinguishing chronotypes, and also in relation to executive functioning at different times of testing.

Exactly what causes chronotype specific responses remains unclear. Differences may relate to the circadian rhythm and prolonged wakefulness which modulate the overall attentional performance (Dai et al. 2018). However, when this was accounted for by comparing Chronotypes based on their 'internal time', by taking into account their self-rated sleepiness, performance was not 'corrected' and still differed between groups.

Affective Mood States

When KSS (Sleepiness scale) or DASS (Depression, Anxiety, Stress Scale) were applied to the data as covariate factors to be regressed out, results changed, at times, quite significantly. Though it is well known that social jetlag can result in serious health consequences (Fallone et al. 2001, Van Dongen et al. 2003, Wittman et al. 2006) and that stress, poorer mood and a higher risk of developing depression, can be a part of the late chronotype profile (Jannson-Frojmark & Lindblom 2008, Levandovski et al. 2011), this effect is interesting. Chronic social jetlag, because of diurnal sleep preferences is likely to induce high stress levels through prolonged high cortisol exposure (Rosenberg et al. 2014) which has recently become associated with worse memory and visual perception performance, as well as lower occipital and frontal lobe volumes (Echouffo-Tcheugui et al. 2018). It is prolonged exposure over several years that is thought to induce permanent structural and volumetric changes (Cho 2001), as short-term sleep deprivation and any resulting associated atrophy is reversible through recovery (Dai et al. 2018). The experience of stress as a results of incompatible sleep patterns and the prolonged exposure to cortisol may therefore be a key factor in chronotype specific differences.

On this note, at first glance, the findings of Rosenberg et al. (2018) seem to contradict the results of this study. Early circadian types showed significantly lower cortical

thickness in the left inferior parietal lobe, as well as precuneus. However, the late types in Rosenberg et al's. (2018) cohort were neither significantly more stressed than their early counterparts, nor did their mood state assessments differ. Rosenberg et al. (2018) themselves point out that it is LCT's whom usually exhibit a form a functional jet lag (Wittmann et al. 2006) and that their findings are somewhat at odds with this. Takeuchi et al. (2015) also reported a lower GMV in the precuneus, but do not record mood states at all. One may therefore argue that diurnal sleep propensity can create a vulnerability to adverse affective mood states and the resulting stress induced over-exposure to cortisol, eventually cause volumetric differences in chronotypes.

If stress was indeed a major modulating factor in the analysis of chronotype specific findings, the fact that temporary acute sleep deprivation and chronic sleep loss through social jetlag seem to share similar neurobiological presentation in brain morphometry (Dai et al. 2018) makes sense. Those areas of SD induced atrophy, which are able to recover in the short term, are adversely affected in the long term, because insufficient recovery occurs due to long-term incompatibility between sleep preference and societal expectation.

It could be suggested that sleep, aside from being a restorative process, is also "the price for plasticity ". Whilst the glymphatic system takes care of waste products created as a by-product of cognitive functioning, previous studies have shown how cognitive training attenuates changes in cortical thickness, by use (Trefler et al. 2016). Other studies, e.g. Hubert et al 2006 , demonstrated how Arm immobilisation resulted in reduced EEG noise from the corresponding area, which suggests that some of the diurnal changes in brain morphometry may be due to ordinary daily fluctuations.

It is clear, however, that the relationship between chronotypes, sleep, cognition and its underlying neural substrate is complicated. This is even more so, when one considers that diurnal sleep preferences are, in fact, less 'preference' and more related to the individual's genetic material. Between 2-10% of all genes in peripheral cells are expressed in a rhythmic manner, controlled by the circadian rhythm (Brukamp 2009, 38-39).

Genetic studies have revealed that different alleles of the 'clock gene' PERIOD3 (PER3) are significantly associated with circadian chronotypes. Early circadian types are associated with a longer allele ($PER3^{5/5}$), whilst late circadian types are associated with the shorter allele ($PER3^{4/4}$) (Archer et al. 2003). This difference in genetics results in a certain vulnerability to sleep loss, due to its effect on sleep homeostasis (Viola et al. 2007). Individuals therefore show different sensitivities to sleep pressure build up and engage in compensatory mechanisms at different times. In addition, compensatory mechanisms may differ, depending on gene dominance and other innate vulnerabilities and resiliencies, and thus affect brain responses even further.

CONCLUSION

Chronotype specific time of day fluctuations may regulate cerebral activity depending on their response to the homeostatic cycle (Maclaren et al. 2014). Comprising of almost 75% of water, the brain presents an environment which constantly strives to maintain optimal water homeostasis. Hydration effects, for example, can be seen after overnight thirsting, with volumetric changes as large as 0.7% (for further discussion on hydration status on brain volume see Duning et al., 2005, Nakamura et al., 2014, Nakamura et al.2015). With an annual loss in cortical thickness of 0.1-0.3mm in normal healthy ageing (Sowell et al.2004), it is almost obvious that volumetric fluctuations

occur as a part of normal diurnal body function, similar to body temperature, or body weight, as a daily loss at this rate is not sustainable, over time.

Chronotype specificity is complex and not yet fully understood in its entire neural and genetic depth, with genetic, as well as environmental factors, serving as possible variables to affect neural substrates and cortical thickness (Rosenberg et al. 2014).

Furthermore, if the key to morphometric differences between circadian chronotypes lies in stress exposure, through accumulated sleep debt, over time, more effort should be made to record past social jetlag and periods of particular incompatibility, in addition to circadian chronotype (Haraszti et al. 2014), as well as, a more thorough history on depression, anxiety and stress, given their apparent links to anatomical findings.

If permanent neurological changes are accrued over a prolonged period, could they be counteracted by observing a prescribed number of days of ‘restorative sleep’? (Marquie et al. 2015). Since research has shown that sleep deprivation induced atrophy can be repaired after a night sleep recovery (Dai et al. 2018) an important question is, how much does one need to sleep to avoid adverse cognitive effects through chronic social jetlag? Further research should focus on whether there are more factors that distinguish chronotypes from one another, and whether the modulator of cognitive performance is rooted more in how diurnal sleep preference affects personal well-being, rather than whether sleep preference is the driver for capability instead. It is clear there needs to be more integration between chronobiology and neuroscience for theoretical and practical reasons (Matchock and Mordkoff, 2009).

CHAPTER SIX

OVERALL DISCUSSION

""ANY MAN COULD, IF HE WERE SO INCLINED, BE THE SCULPTOR OF HIS OWN BRAIN."

SANTIAGO RAMON Y CAJAL

FATHER OF MODERN NEUROSCIENCE

(1852-1934)

From early musings, in Ancient Greece, about how behaviour might relate to brain functioning, the field of neuroscience has come a long way, whilst simultaneously still being in its infancy. Where early neuropsychology relied on the intense study and observation of traumatic brain injury and brain lesions (Coltheart 2001, p.3, Lassonde et al. 2006, Houston et al. 2013), modern neuroscience has made huge leaps in understanding the brain-behaviour relationship, following the advent of neuroimaging methods (Passingham 2016, p.3).

In an era where 'artificial intelligence' is on the rise, machines are 'learning' to emulate human behaviour and cognitive responses, and the goal posts of what constitutes 'intelligence' continue to change (Dick 2019), understanding the cornerstones of human intelligence and the building blocks of cognition remains relevant.

In an ageing society, where medical advancements ensure increasing longevity the quest to understand cognition continues, to ensure that, as humanity grows older, it can do so in good cognitive and mental health.

(6.1) Neuropsychological methods/ measuring Cognition

The two main constructs of intelligence, gF (overall reasoning) and gC (overall verbal ability) differ in their neural origin and developmental trajectory. However, it is now clear that neural networks, rather than individual regions facilitate cognitive and behavioural processes (Colom et al. 2010), which is why individual processing capacity (IPC) is such an important construct of cognitive capabilities. Whilst the concept of g, as a marker for general intelligence, might be commonly accepted as the most general factor of mental abilities, it is not always the best concept to explain higher order cognition, nor is the intelligence quotient (IQ) a measure of all cognitive abilities and skills. Colom et al. (2002) qualify that, whilst g may be 'general intelligence' and IQ 'intelligence in general', Information Processing Capacity would be defined as:

g + *specific cognitive abilities* + *specific cognitive skills*

Whilst attention appears unrelated to gC, gF, working memory, processing speed and spatial intelligence, working memory is related to all other cognitive factors, and processing speed to gC and spatial intelligence, but not gF (Colom et al. 2013). Because 'g' is contaminated by battery specific factors, it is not a true measure of 'general intelligence' or cognitive capacity, but a measure extracted from whichever neuropsychological assay was used and relative to the abilities and skills measured.

Does it actually make sense to administer an entire neuropsychological battery to then only use a single composite score (e.g., FSIQ), or calculate an unrelated though correlated construct (g)? Would it make more sense to do a select few tests depending on testing objective? If information on verbal fluency is sought, for example, the overall

IQ or g score doesn't yield any more information, than the precise subtests which tap into the specific functioning of verbal testing (E.g VIQ, DKEFS verbal fluency).
From a data collection point of view, it might be easier to just do a few selective tests and analyse the existing material with different analyses /utilities.
Whilst from a clinical point of view, face to face examination of a lengthy battery, is enormously helpful, because it helps establishing a relationship between examiner and examinee which helps interpret /explain the data. Answers on how the patient presents, visual observations on task performance to spot malingering or just information which inform the general discussion, are impossible to gain from CAT testing. So, whilst for larger research studies CAT designs are helpful because all that is really required are scores which will be averaged across the entire groups, individual analysis, requires more information than can be gained from the test battery alone.

Entire test batteries yield a vast amount of information which can make analysis complicated and overwhelming.
Whilst the concept of g, as a common factor to all cognitive tests, may be helpful in generalising results across different batteries and assays, administering highly specific tests in a time-consuming manner, to then strip it back to a generalised score, feels a little counterproductive and not very intuitive.

(6.2) Selecting a neuropsychological Battery

Having administered and analysed a variety of tests during this thesis, it is clear to see benefits and drawbacks to each of them. The Wechsler scales are highly robust with

lots of information on functional distribution and lots of readily available neuropsychological information, which clearly has its advantages.

CANTAB is easier and quicker to administer from an examination point of view and offers readily available results, although programs now calculate Wechsler data and allow administration of tests via the use of an electronic tablet device, with ease, also. CANTAB, like the Wechsler scales is a well validated and robust measure which offers plenty of normative data to compare results to. Since large samples can be acquired much quicker in CAT, a traditional but automated neuropsychological battery may be the method of choice to build normative data sets connecting cortical thickness and Neuropsychology, for example. The value of normative data when attempting to utilise analysis in a clinical context is enormous.

There is a pressing need, not only for more normative data in the field of neuroscience, but also to acquire direct evidence of the processes that underlie the observed changes in grey and white matter volume and cortical thickness (Paus, et.al.2008).

Ecological validity, i.e., the knowledge that what we think we're measuring, is, in fact, what we are measuring, remains an important aspect to consider.

Are we measuring what we think we're measuring especially with MRI based methods, considering a lot of information is based on the water content of different tissues?

Are most results tainted with reaction time?

What does reaction time actually tell about an individual's capacity, given that we are often talking about very small margins, irrespective of statistical significance?

Paus et al (2008) caution that as tempting as it may be to interpret descriptive findings obtained from structural MRI during mechanistic biological processes, such as synaptic pruning or myelination, the evidence that supports these claims Is limited.

Going forward, better MRI methods are required, and careful selection of statistical parameters when processing this data. In subsequent studies it may be advantageous to select a smaller FWHM overall, so as to pinpoint areas of significance more closely, as excessive smoothing may result in regions of interest overlapping.

(6.3) Limitations combining MRI and Neuropsychology

Neuropsychological assays often yield a vast amount of information and it's unclear whether all this information can be used in a group analysis, as opposed to individual cognitive profiling, which is what they were originally intended to do.

A skilled clinician can extract a lot of information from the WAIS/WMS / clinical battery, for example, but a move to more CAT tests, which yield readily interpretable results and don't require such a high degree of expertise and are relatively robust to examiner error / procedural errors/ scorer errors, may be the way forward to make neuropsychological testing more accessible in clinical practise (Helmstaedter & Witt 2017). Since the neurobiological origin of cognition and intelligence is not yet fully understand, the information that a combined approach of MRI and Neuropsychology can offer is limited.

The exact mechanisms that underlie age related trajectories in cognition or changes induced through accumulated sleep debt cannot yet be derived from structural MRI. This is in part due to the lack of normative data. Centile values across the lifespan, from large study cohorts such as Frangou et al. (2020) could be used to study the factors that may cause deviation from intended developmental trajectories. These factors may include innate diurnal sleep preferences, genetic, epigenetic or socioeconomic factors (Frangou et al. 2020).

However, especially where developmental trajectories are concerned, longitudinal data is invaluable to fully understand long term effects of sleep preference, for

example, and how this impacts developmentally on healthy ageing. Whilst cross sectional neuroimaging studies can attempt to correct for missing baseline data, or data from earlier in life, through estimating intracranial volume changes (Royle et al. 2013), studies are rarely able to retrospectively predict corresponding cognitive information (Cox et al. 2018). The combination of well validated cognitive assays with structural, or functional MRI in longitudinal studies, tracking sleep schedules and other health related or socio-economic data, is therefore warranted to understand the underlying mechanisms.

(6.3) Extraneous factors and Sleep in Neuroscience

Sleep, and by extension chronotype, age, and developmental stage matter greatly in neuroscientific research, and should be modulating factors in every experiment, although that isn't always practicable. Historic sleep debt information and position in the menstrual cycle for females may need to be considered and factored into statistical models.

Statistical models incorporating gender, need to do more to account for genetic, hormonal and economic factors that may affect health. Research into circadian chronotypes and individual circadian rhythms has a bright future, as a new medical field, with chrono – medicine being projected to be one of the most important aspects (Roenneberg &Merrow 2016). With the circadian clock implicated as an emerging factor in many aspects of human health and the importance of sleep becoming more and more obvious, further research is needed to optimise health and disease outcomes. Circadian disruption, in particular in shift workers experiencing social jetlag (Lockley & Foster 2012, p.130), may be considered a major risk factor in human

carcinoma (Lewis et al. 2018, Erren & Lewis 2018, Shafi & Knudsen 2019), so sleep must be prioritised.

But will a consumerist society with a high need for human resources actually do so? Circadian Chronotyping could become a protected characteristic if more can be done to show that developmental trajectories and cognitive health are negatively impacted by having to conform to non-optimal sleep routines.

Although increased working-from-home rates during the Covid-19 Pandemic have sparked a large amount of research on its impact on productivity and implementation going forward, research prior to the pandemic already suggested that working from home may increase employee productivity (Beauregard & Henry 2009, Bloom 2014). Allowing employees to choose their own working hours for optimal productivity and offering temporal and geographic flexibility through "Work-from-anywhere" opportunities has been shown to increase productivity significantly (Choudhury et al. 2020). Though data in this area is still sparse, productivity has been shown to increase by around 13%, whilst also improving employee mental health and leading to fewer absence through sickness (Dockery & Bawa 2020). Work-life-balance and choosing personal working hours, may be related to better sleep quality, through being able to align diurnal rhythmicity closer to innate preferences, instead of prescribed working hours. Arntz et al. (2020) discussed positive, as well as negative implications of working-from-home during the Covid-19 Pandemic. Increased availability, through additional time gained, by cutting out daily commuting time was cited as a positive factor. Many of the detrimental factors and results cited, relating to working remotely and being able to choose one's personal working hours, were more related to additional pressures imposed by the global pandemic, such as increased childcare

demands, home-schooling responsibilities, economic instability, and reported health anxiety, rather than employees' abilities to structure their own working day (Arntz et al. 2020).

Taking individual differences in peak productivity through diurnal rhythmicity into account, may improve overall mental health and reduce work related stress, or burnout-syndrome, issue closely related to human resource management.

The development of this field requires novel approaches that can assist with the accuracy and speed of enabling individual Chronotyping, to allow further insight into its many applications, such as Chrono-Medicine (Dijk & Duffy 2020). Chrono-medicine has lots of potential applications in many established medical fields such as Cardiology (Thosar et al. 2018), Immunology (Pick et al. 2019), Poggiogalle et al. 2018) and Oncology (Shuboni-Mulligan et al. 2019, Shafi & Knudson 2019).

Further insight into the circadian rhythm could answer questions such as how molecular processes relate to the circadian cycle (Pick et al. 2019) or how the timing of anti-hypertensives could affect the blood pressure (Thosar et al. 2018).

Light therapy has already been shown to be effective in certain types of cancer, and the rhythmicity of tumours appears particularly sensitive to the effective timing of chemo- or radiotherapy (Shafi & Knudson, 2019). Whilst anti-cancer regimes are already personalised through cellular and genetic analysis, being able to administer highly toxic chemotherapy drugs at the point where they are least toxic, but most effective, could vastly improve the outcome of patients.

Cortical thickness analysis, however, is only on tool, amongst many to understand the relationship between sleep and cognition, and potentially just an 'outcome factor', because of prolonged exposure to a certain sleep schedule.

(6.4) Cortical thickness

Having examined a wealth of information on the development of the cortex and its underlying cytoarchitecture is is clear that whole brain volume, overall thickness, as well as average or global cortical thickness measurements are at best crude estimates of structural and morphometric brain changes (Oschwald et al. 2019), especially when specific functions are considered.

CT measurements are a snapshot of volumetric measurements at a particular stage in life. The cortex does not remain static thanks to, in part, neural plasticity, hydration changes and the ageing process. Measurements of cortical thickness at age 18 in the individual person will not be the same to age 50 in the same person, and how values are to be interpreted depends vastly on age and other environmental factors, such as circadian chronotype, education, time of day hydration, etc.

When comparing cortical thickness papers/ studies, methodological differences in qualification and statistical analysis of cortical thickness make direct comparisons difficult (Menary, 2013), as there still is no universally accepted approach.

Cortical thickness and changes thereof are proof of plasticity and how sleep, at least in part, has a restorative function. Atrophied areas caused by artificial acute sleep deprivation, are restored after one-night recovery (Dai 2018), which is yet again evidence of how complex the interpretation of cortical thickness measurement really is. The link between morphometric changes and intellectual capacity throughout the lifetime, as well as both the short-term and long-term effects of sleep, and lack thereof, as well as circadian chronotype, is significant. Understanding the regional integrity of the cortex and how it relates to functioning , could supply new information in the clinical context, but also inform preventive or rehabilitative measures.

Cortical thickness is a sensible measurement and has great potential in both research and clinical application. Future research into chronotypes and sleep behaviours, risk markers identifying early changes leading to dementia or Alzheimer's Disease, as well as applications of tailored drug treatment for optimal outcomes are on the Horizon.

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