

Brain health in ageing and Parkinson's disease



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Abstract

Age-related decline in brain health appears to be inevitable to some extent. In some people, ageing is also associated with additional burden of neurodegenerative diseases, such as Parkinson's disease (PD). However, distinguishing between normal and pathological ageing trajectories is complicated, as neither are well characterised. This thesis quantifies effects of normal and pathological ageing on mood, motivation, and brain structure, with a focus on PD.

In the first part of the thesis, I estimate general effects of healthy ageing on mood and brain structure. I address whether mood generally improves or whether age-related changes to the brain increase risk for mood disorders. I calculate trajectories of grey matter atrophy, and present norm values for one of the most vulnerable brain areas in ageing, the hippocampus. In the second part of the thesis, I investigate how PD affects mood, motivation, and brain structure differently from healthy ageing. Debilitating mood symptoms like apathy and depression are often reported in PD, but it is unclear whether they might be secondary to the disability that patients live with, or a direct result of PD-related pathology. This is tested formally by analysing prevalence of these symptoms and taking into account levels of disability, as well as by investigating effects of serotonergic modulation on affective processing and decision-making. Finally, I evaluate whether these potential differences in PD can be linked to brain structure.

The results demonstrate that normal ageing is on average more likely to be associated with improvements in mood. In contrast, PD was linked to higher rates of neuropsychiatric symptoms, even when accounting for levels of disability. This supports the hypothesis that neuropsychiatric symptoms in PD are primarily the result of PD-related brain pathology, rather than due to secondary effects. Serotonergic modulation during behavioural testing further revealed a role for serotonin in apathy that may depend on levels of baseline intrinsic motivation. Finally, while healthy ageing is associated with strong declines in volume in almost all areas of the brain, no robust specific effects of PD on brain structure were found. Together, this work contributes to the search for MRI-based biomarkers of neurodegeneration, as well as the understanding of mood disorders in Parkinson's disease.

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Acronyms

ACE Addenbrooke's Cognitive Examination.

AD Alzheimer's Disease.

ADNI Alzheimer's Disease Neuroimaging Initiative database.

AIC Akaike Information Criterion.

AMI Apathy Motivation Index.

ANOVA Analysis of Variance.

APOE Apolipoprotein E.

ATD acute tryptophan depletion.

BA Behavioural Activation.

BDI Beck Depression Inventory.

BIC Bayesian Information Criterion.

BOLD blood-oxygen-level-dependent.

CI confidence interval.

DAT dopamine active transporter.

DRN dorsal raphe nucleus.

DRT dopamine replacement therapies.

DSM Diagnostic and Statistical Manual of Mental Disorders.

ES Emotional Sensitivity.

FA Fractional Anisotropy.

FAST FMRIB's Automated Segmentation Tool.

FERT Facial Emotion Recognition Task.

FIRST FMRIB's Integrated Registration and Segmentation Tool.

FNIRT FMRIB's Nonlinear Image Registration Tool.

FSL FMRIB Software Library.

GAMLSS Generalised Additive model for Location, Scale and Shape.

GDS Geriatric Depression Scale.

GLME Generalized Linear Mixed Effects.

HADS Hamilton Depression and Anxiety Scale.

ICC Intra-class correlation.

IDP Image-Derived Phenotypes.

LADS Leeds Anxiety and Depression scale.

MANOVA Multivariate Analysis of Variance.

MCI Mild Cognitive Impairment.

MDD Major Depressive Disorder.

MDMA 3,4-Methylenedioxyamphetamine.

MDS-UPDRS Movement Disorder Society - Unified Parkinson's Disease Rating Scale.

MMSE Mini Mental State Examination.

MoCA Montreal Cognitive Assessment.

MP-RAGE Magnetization Prepared-Rapid Acquisition Gradient Echo.

MRI Magnetic Resonance Imaging.

MVC Maximum voluntary contraction.

NHS National Health System.

OA osteoarthritis.

OPDC Oxford Parkinson's Disease Centre.

PD Parkinson's Disease.

PET Positron Emission Tomography.

QCAE Questionnaire of Cognitive and Affective Empathy.

RBD Rapid Eye Movement Sleep Behaviour Disorder.

RMSEA Root Mean Square Error of Approximation.

SERT Serotonin transporter.

SHAPS Snaith-Hamilton Pleasure Scale.

SM Social Motivation.

SPECT Single Photon Emission Computed Tomography.

SSRI Selective Serotonin Reuptake Inhibitor.

STAI Spielberger State Trait Anxiety Inventory.

TAS Toronto Alexithymia Scale.

TBSS Tract-based spatial statistics.

TFCE Threshold Free Cluster Enhancement.

TLI Tucker-Lewis Index.

VBM Voxel-based Morphometry.

VGT Vancouver Gambling Task.

WHO World Health Organisation.

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List of Publications

Thesis material

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Nobis, L., Manohar, S. G., & Husain, M. (2019). *HippoFit - Brain volume by age percentile calculator*. https://lnobis.github.io/HippoFit_Tool/index.html

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Other material

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Veldsman, M., Nobis, L., Alfaró-Almagro, F., Manohar, S. G., & Husain, M. (2021). The human hippocampus and its subfield volumes across age, sex and APOE e4 status. *Brain Communications*, 3. <https://doi.org/10.1093/braincomms/fcaa219>

Chapter 1

Introduction and Objectives

The inevitable decline in brain health – and potential added progression to neurodegenerative disease – is one of the largest concerns in our ageing population. The global number of adults aged 80 years or older is estimated to triple by 2050, growing from 137 million to 425 million people (United Nations et al., 2017). Major advances in health and social care, better nutrition, improvements in housing, hygiene, and sanitation, and other public health measures are driving this increase in longevity. However, as people live longer, the risk of developing neurodegenerative diseases like Alzheimer’s Disease (AD) and Parkinson’s Disease (PD) increases substantially. For example, while AD is prevalent in less than 5% of people aged 65 years or older, this reaches 10-15% by age 85 years and older (Hou et al., 2019; Qiu et al., 2009, **Figure 1.1 A**). Similarly, the global prevalence of PD escalates from less than 1% of the population aged 60 years or older, to 2-5% of the population aged 80 years and older (de Lau et al., 2006; Hou et al., 2019; Nussbaum et al., 2003; Wood-Kaczmar et al., 2006, **Figure 1.1 B**). Thus, not all adults who live long, age successfully and live well.

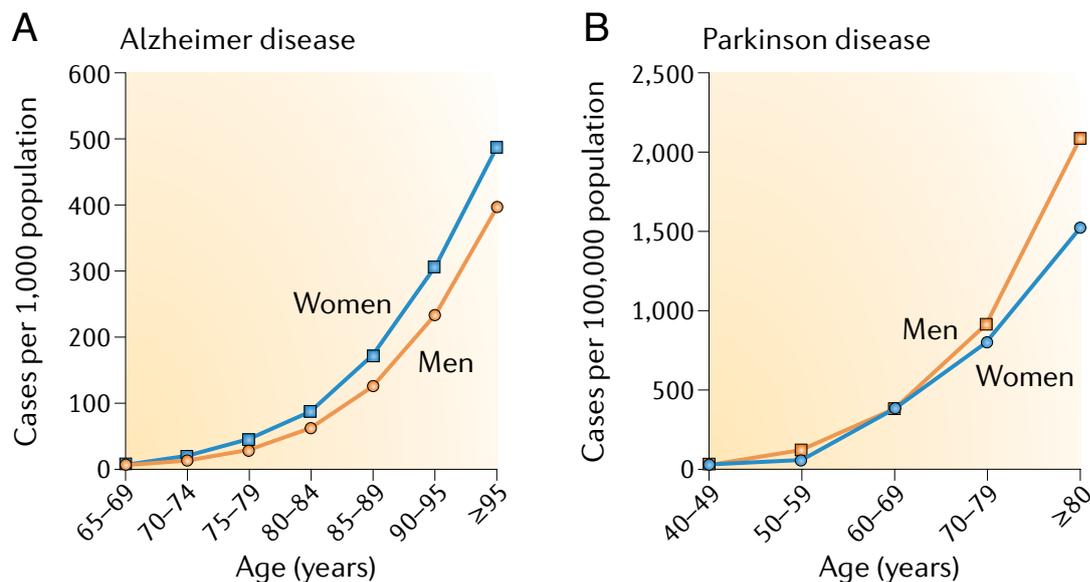


Figure 1.1 – Prevalence of Alzheimer’s disease and Parkinson’s disease by age groups. A. Prevalence (in the US) of AD per 1,000 people. B. Prevalence of PD per 100,000 worldwide. In both disorders, prevalence appears to increase exponentially. Adapted from Hou et al. (2019).

The World Health Organisation (WHO) defines successful ageing as the “process of developing and maintaining the functional ability that enables well-being in older age” (World Health Organization, 2015). When older adults were asked how they themselves would define successful ageing, Stephens et al. (2015) noted that descriptions of comfort, social integration, contribution to society, feelings of security and autonomy, and enjoyment of life were among those mentioned most frequently. These definitions highlight that successful ageing is not just the absence of disease, but the maintenance of well-being. Yet, even as this level of functioning may be preserved, some age-related decline in cognitive function is normal and appears to be inevitable. Decreases in processing speed, memory performance, executive function, and flexible thinking are well-known and occur in almost all older adults even in the absence of disease (Cabeza et al., 2018; Ohayon et al., 2004; Paxton et al., 2008; van Hooren et al., 2007). Evidence from both cross-sectional and longitudinal studies suggests deterioration in all these cognitive domains after age 55 years, though slowing of processing speed may occur even sooner (Hedden et al., 2004). In contrast, autobiographical, implicit, and semantic memory tends to be preserved until late life (Hedden et al., 2004). Although some small levels of decline in these functions may not prevent older adults from living an independent and fulfilling life, accelerated loss of function triggered by neurodegenerative disease often does.

1.1 Trajectories of mood and neuropsychiatric symptoms in late life

While deterioration in cognitive function in the ageing population is fairly well researched, it is less clear how mood and motivation may be impacted by healthy and pathological age-related processes. Yet, there is evidence that brain ageing mechanisms result in systematic changes not just in cognition, but also mood and mental health.

Late-life depression

There are currently two main hypotheses about mood in healthy ageing: one that suggests increased susceptibility to mood disorders in late-life (Charlton et al., 2014; Sheline et al., 2010; Tadayonnejad et al., 2014); and another that proposes a late-life positivity effect (Cotter et al., 2020; Kennedy et al., 2004; Reed et al., 2012). Evidence for the former comes primarily from

research into late-onset depression, which refers to major depressive disorder presenting for the first time in adults older than 65 years (Naismith et al., 2012). This type of late-onset or late-life depression is thought to be associated specifically with an increasing amount of cerebrovascular damage in older age (Alexopoulos et al., 1997; Herrmann et al., 2007; Krishnan et al., 1997; Sexton et al., 2013). For example, older adults with late-onset depression were shown to have more frequent and more severe white matter damage than older adults with early-onset depression (Herrmann et al., 2007). It is thought that this is due to small vessel dysfunction having an impact on the white matter, which in turn disrupts mood regulation by affecting the integrity of fronto-subcortical circuits (Valkanova et al., 2013).

In line with this, it has been demonstrated that patients with late-life depression tend to respond less well to antidepressant treatment (Alexopoulos, 2005), suggesting that the cause or maintenance of depression in these cases may be due to other, serotonin-unrelated processes. This theory might also explain the association between depression and other cardio- and cerebro-vascular disorders. For example, depression is more likely to develop following stroke (Whyte et al., 2002), but can also predict the development of stroke, coronary artery disease or diabetes (der Kooy et al., 2007; Knol et al., 2006). While these associations may be due to common causes like lifestyle factors or stress responses, it could also be argued that they point to shared vascular risks and mechanisms, such as inflammation or reduced synaptic plasticity.

On the other hand, although a meta-analysis confirmed a significant association of vascular disease and late-life depression, this relationship was considerably weakened when controlling for the presence of chronic illness and disability (Valkanova et al., 2013). Thus, it seems that at least some part of the association between vascular disease and depression might be secondary to their disabling effects. In addition, the meta-analysis identified different ways the study participants were classified as being depressed, including Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnoses and depression questionnaire cut-off scores. This likely resulted in generalisability problems for several reasons. Mood disorders like depression, anxiety, and apathy are often treated as monolithic entities, while they might better be considered syndromes with overlapping constituent symptoms (Fried, 2015; Husain

et al., 2018). For example, the Beck Depression Inventory (BDI) includes 21 items that assess a wide range of symptoms, some of which would be considered core depressive symptoms (e.g., sadness, suicidal thoughts), and some of which are less specific (e.g., low energy or sleep problems) (Fried, 2016). However, all items in this questionnaire are equally weighted in the resulting sum-score, such that individuals may reach a cut-off score without showing any core depression symptoms.

This is not only an issue with questionnaires used in research, but also with official clinical diagnosis guidelines. There are up to 16,400 possible unique symptom profiles that could lead to a diagnosis of depression (Fried et al., 2015) in the DSM-5 (American Psychiatric Association, 2013). In a sample of over 3500 depressed patients (Fava et al., 2003), Fried and Nesse (2015) indeed found 1,030 different symptom profiles, with almost half of them only present in a single individual. Thus, groups of participants categorised as ‘depressed’ and ‘not depressed’ might not be as homogeneous as is often assumed. The analysis of effects corresponding to individual symptoms may therefore uncover new insights (Fried et al., 2015).

Late-life positivity

In contrast to the concept that mood worsens with age, the hypothesis of an age-related “positivity effect” is based on findings of a relative preference for positive over negative stimuli in older adults (Kennedy et al., 2004; Reed et al., 2012). This preference has been documented in different domains, such as autobiographical memory (Kennedy et al., 2004), working memory (Gerhardsson et al., 2019), visual attention (Isaacowitz et al., 2006), and facial emotion processing (Czerwon et al., 2011). For example, older adults were shown to have a memory advantage over younger adults for positive, but not negative or neutral stimuli (Kensinger et al., 2007).

A number of potential mechanisms behind this positivity effect have been proposed, the most popular one being the socio-emotional selectivity theory (Carstensen et al., 2011). According to this hypothesis, older adults are increasingly motivated by emotionally meaningful goals, and more invested in emotion regulation to maintain a positive mood because of a shorter future time perspective. As a result, positive stimuli may be preferentially processed

over negative stimuli in daily life, leading to preserved or even improving mood with advancing age. Indeed, several reports have noted that older adults had enhanced attention for emotional information when compared to younger adults (Mather et al., 2005; Wadlinger et al., 2006).

Observational studies on the effect of healthy ageing on mood and motivation are scarce, but some evidence so far, too, seems to favour a general improvement of emotional well-being with age. For instance, the results of one previous report have suggested that there is an increase in happiness and mood up until the seventh decade (Carstensen et al., 2011). This hypothesis was supported by a recent longitudinal investigation, which observed that symptoms related to depression generally declined as adults got older (in a sample of 716 people). This effect was present until around age 70 years, when the improvement levelled off (Cotter et al., 2020). Interestingly, the authors also demonstrated a relationship between emotional well-being and white matter integrity: those older adults who continued to experience improvements in mood until late life were those who also maintained white matter integrity. In contrast, those who showed declines in well-being also tended to have more white matter damage.

Thus, it seems that on average, ageing may improve emotional well-being through the positivity effect, but some people may also develop a "vascular type" of mood disorder through gradual emergence of white matter pathology. In addition to white matter changes, loss of neurotransmitter function with older age - especially within dopaminergic (Raz et al., 2006) and serotonergic (Karrer et al., 2019) systems - paired with potentially smaller social support networks (Cacioppo et al., 2014), and lower levels of physical activity (McPhee et al., 2016), may further increase risk for neuropsychiatric disorders with advancing age.

These individual differences in the population highlight the importance of large datasets to reach adequate statistical power, as they may result in only small effects when averaging within a study sample. Recent efforts for large, long-term databases of openly available population information like the UK Biobank will allow for this kind of research. The UK Biobank cohort includes about 500,000 participants enrolled at ages 40 to 69, with over 14,000 variables each (<https://www.ukbiobank.ac.uk/>). Collected information include environmen-

tal, lifestyle, and genetic data, biological samples, and activity monitor signals. A subset of 100,000 volunteers will undergo full body MR imaging, including brain scans. Thus, a rich dataset like this has the potential and statistical power to reveal small, otherwise undetectable population effects.

1.2 Effects of age on brain structure and function

The changes in cognition and mood coincide with structural and functional transformations that the brain undergoes with advancing age (Crivello et al., 2014; Deary et al., 2009; Gunning-Dixon et al., 2009; Karrer et al., 2017; Volkow et al., 1994; Zarnani et al., 2020). For example, total grey matter volume has been estimated to decline by around 0.8% per year in healthy older adults (Crivello et al., 2014), starting from around age 20 (Hedden et al., 2004) with a relatively stable rate of atrophy across the lifespan. In contrast to linear grey matter declines, the rate of atrophy of the hippocampus seems to accelerate after reaching 50-55 years (Crivello et al., 2014), suggesting that this region of the brain might have a specific vulnerability to age-related pathology. There is some controversy around what causes the decline in grey matter volume, with some arguing for loss of neurons through cell death (Esiri, 2007) and others arguing for a reduction in neuron size (Esiri, 2007; Haug, 1985) and synaptic densities (Hedden et al., 2004; Terry, 2000). The decline of synaptic density has been demonstrated to occur gradually from age 20, with no slowing down until at least 100 years. Because of its steady deterioration, synaptic density has been suggested to be a potential mechanism for the greater risk of developing AD with increasing age (Hedden et al., 2004).

The literature on white matter volume changes is less clear. Most reports suggest no significant decline with age (Gunning-Dixon et al., 2009; Raz et al., 2006), but the severity of white matter hyperintensities on T2-weighted MRI images – thought to reflect white matter damage – is strongly related to advancing age (de Leeuw et al., 2001). The mechanism behind this seems to involve cerebral hypoperfusion and (subclinical) ischemia, resulting in degradation of the myelin sheath around the axons, and in turn producing a hyperintense T2-weighted MRI signal (Sudre et al., 2018). Cerebral hypoperfusion is known to occur in normal ageing (Aanerud et al., 2012), and is also associated with cardiovascular risk factors such as diabetes

mellitus or high blood pressure (Boehme et al., 2017).

Previous reviews and meta-analyses further revealed a strong effect of age on dopamine function that can be visualised with Single Photon Emission Computed Tomography (SPECT) scans in vivo. These have led to estimates of a dopaminergic decline of 3.7-14% per decade even in healthy ageing (Kaasinen et al., 2002; Karrer et al., 2017). Functional Magnetic Resonance Imaging (MRI) studies have provided evidence for possible compensatory mechanisms in brain function, potentially related to changes in blood flow and neurotransmitter availability. The blood-oxygen-level-dependent (BOLD) signal is thought to reflect the time course of blood flow, blood volume, and blood oxygenation level changes during neural activity, thereby indicating levels of involvement of various brain areas (Logothetis et al., 2004). Several investigations have observed greater activation of frontal brain areas in older adults, such as prefrontal cortex, when compared to younger adults during memory tasks (Cabeza, 2002; Hedden et al., 2004). Importantly, this increased recruitment of frontal areas has been linked to preservation of high-level performance in older adults, which has inspired the theory for a compensatory mechanism (Cabeza et al., 2002).

On the other hand, older adults have also been found to engage less specialised brain areas for cognitively demanding tasks. For example, when performing memory encoding tasks, younger adults primarily show activation in the left hemisphere, but high-performing adults show bilateral activation – a common finding also referred to as reduced hemispheric asymmetry (Cabeza, 2002). The extent to which these changes occur and can be compensated for in each individual may provide some explanation for the large variability of functional preservation in ageing.

1.3 Neurodegenerative disease as a diverging path from normal ageing

Given the large variability in the extent of age-related structural and functional decline in brain health, it is conceivable that there are several possible trajectories of ageing (Figure 1.2). Even in healthy ageing, risk of cognitive or behavioural impairments and neurodegenerative disorders increases slowly. In fact, it is estimated (Terry et al., 2001) that for any individual who lives long enough, the risk of developing AD reaches 100% by around age 130!

This trajectory of decline may be accelerated by other factors, e.g., traumatic injury affecting the brain, or decelerated by improvements in lifestyle, such as better diet and exercise (Deary et al., 2009; Licher et al., 2019; McPhee et al., 2016). However, it is not yet clear how to distinguish normal age effects on brain structure and function from emerging neurodegeneration, or how to identify the ideal timepoint for interventions.

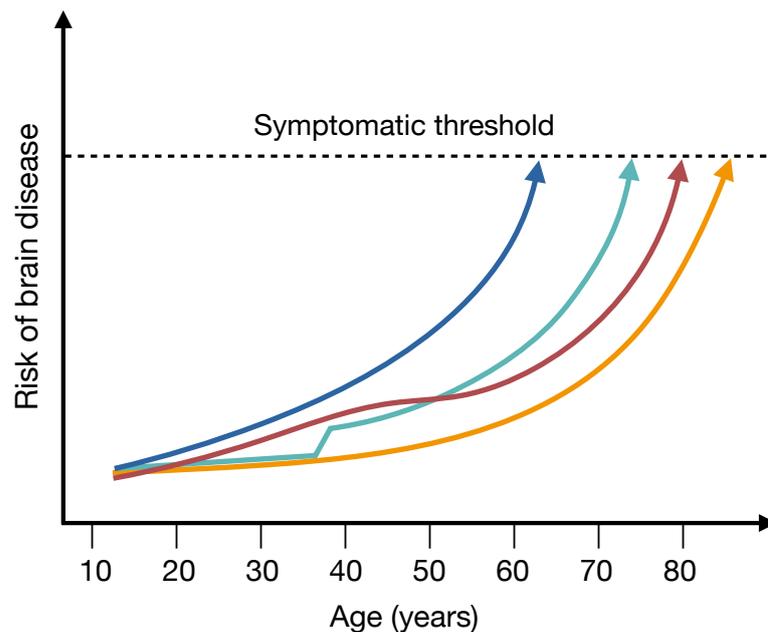


Figure 1.2 – Different trajectories of brain ageing. With increasing age, all individuals will accumulate increasing risk for brain diseases, eventually reaching a symptomatic threshold if they live long enough (yellow). However, the rate of decline differs between people because of genetic or environmental factors. It may also accelerate because of traumatic injury (teal) or slow down with lifestyle improvements (red). Neurodegeneration may have a particularly steep decline (blue), though it remains unclear where to draw the distinction to healthy ageing. Adapted from Cole et al. (2019).

A number of investigations have attempted this, for example by estimating cut-off scores of cognitive function to aid diagnosis of dementia. Cognitive tests like the Mini Mental State Examination (MMSE) or Addenbrooke's Cognitive Examination (ACE) are used widely to measure severity of cognitive impairment after adjusting for age (Kopecek et al., 2017; Mioshi et al., 2006; Roalf et al., 2017). In addition, many studies have set out to quantify grey matter volume loss in healthy and pathological ageing, reporting accelerated rates of total grey

matter or hippocampal atrophy in adults with AD or Mild Cognitive Impairment (MCI) when compared to healthy controls (Barnes et al., 2009).

A meta-analysis of nine studies found a 3.33% difference in hippocampal atrophy rate between AD and controls (Barnes et al., 2009). In fact, hippocampal volume is one of the most commonly used brain imaging markers to study severity and progression of AD (Ahmed et al., 2014; Frisoni et al., 2010). Increased atrophy of the hippocampus has also been associated with neurofibrillary tangle and amyloid plaque deposition, which are considered to be the hallmark features of AD (Krill et al., 2002; Schuff et al., 2009). Similarly, using the rate of hippocampal atrophy, researchers have been able to distinguish between those with MCI who progressed to AD, and those who did not (Frankó et al., 2013). As a result, hippocampal volume estimations are a promising biomarker for the diagnosis and study of AD in clinical practice.

However, challenges with the processing, analysis, and interpretation of structural MRI scans outside of a research setting have so far prevented this method from being used in standard clinical practice. For instance, in order to calculate brain volumes from a structural MRI scan, the image has to be processed with software requiring expert knowledge. This can now be facilitated by automated brain segmentation tools, e.g. the FIRST tool in FMRIB Software Library (FSL) (Jenkinson et al., 2002; Jenkinson et al., 2001), or FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>), with openly available standardised processing pipelines (Alfaro-Almagro et al., 2018). In addition, the acquisition of large MRI datasets is costly, time consuming, and involves highly specialised hardware and staff. As a result previously published studies on hippocampal volume in the general population are often limited by small sample sizes, low statistical power, and cohort effects (Button et al., 2013; Fraser et al., 2015; Ioannidis, 2011; Nord et al., 2017). These challenges, too, may be solved with the large, openly available, brain imaging dataset of the UK Biobank.

Similar to the vulnerability of the hippocampus to age-related pathology and AD, extreme loss of dopaminergic function can indicate the presence (Suwijn et al., 2015) and severity (Ravina et al., 2012) of PD. However, more research is needed for the improvement of PD diagnosis, as outlined below.

1.4 Parkinson's disease

PD is a neurodegenerative disorder that is associated with a gradual loss of dopaminergic neurons in the substantia nigra, causing motor symptoms such as tremor, rigidity, bradykinesia, or postural instability. Diagnosis is made based on the presence of motor symptoms, and in some cases may be supported by measurements of dopamine levels in the basal ganglia by SPECT (Suwijn et al., 2015). However, it is estimated that up to 80% of dopaminergic neurons have already been lost by the time a diagnosis can be made (Fearnley et al., 1991; Mehta et al., 2016, **Figure 1.3**).

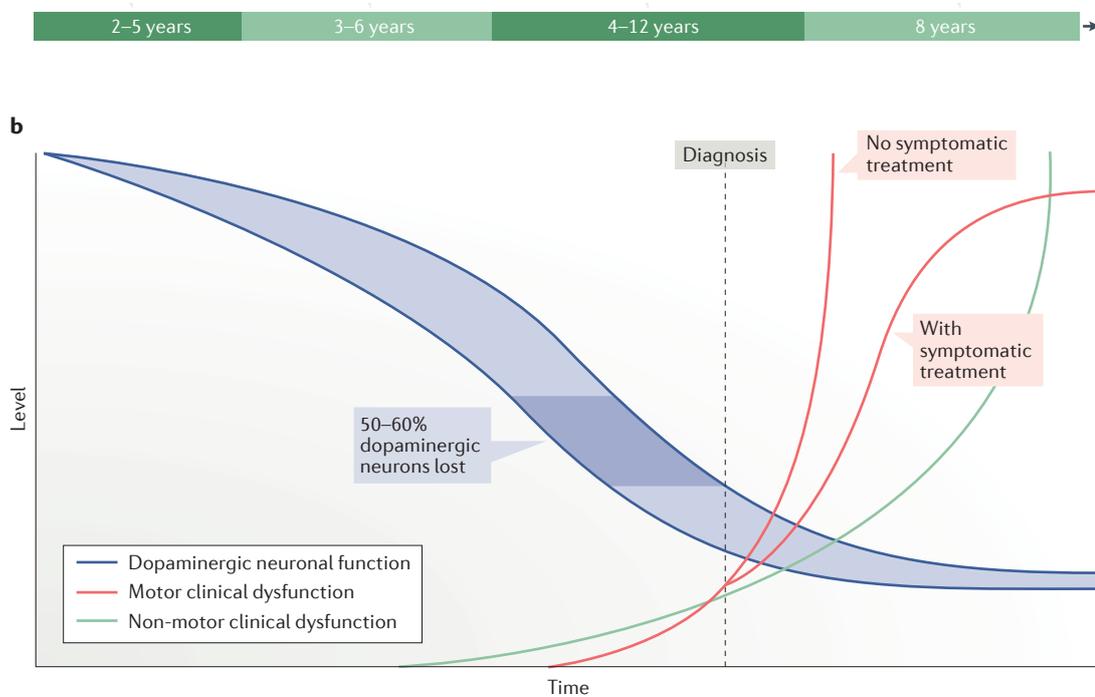


Figure 1.3 – Time course of dopaminergic pathology and symptom onset in Parkinson's disease. Dopaminergic function begins to decline years before symptom onset, caused by death of dopaminergic neurons, so that 50-60% are lost by the time of diagnosis. The rate of decline seems highly variable, reflected by the shaded area. Diagnosis may follow subtle motor and non-motor symptoms, with non-motor symptoms starting to appear 3-6 years before diagnosis. While dopaminergic treatment may slow down the continuation of functional decline, progression of non-motor symptoms is currently less well managed. Reprint from Schapira et al. (2017).

Researchers have attempted to utilise neuroimaging tools to improve clinical diagnosis and evaluation of PD for 30 years, but these efforts have not yet resulted in its routine use (Politis,

2014). SPECT and Positron Emission Tomography (PET) imaging are effective at differentiating PD and atypical parkinsonism, as well as progression of motor and non-motor symptoms, but are expensive and need sophisticated analysis. In contrast, MRI studies have produced highly variable results (Tuite, 2016), potentially due to small effects that are further impacted by insufficient sample sizes. As a result, a definitive diagnosis of PD can currently only be made based on post-mortem neuropathological findings (Adler et al., 2014). The main neuropathological features of PD are degeneration of the substantia nigra, as well as presence of Lewy bodies and Lewy neurites, although Lewy pathology is neither necessary nor sufficient for a diagnosis of PD (Geut et al., 2020; Horvath et al., 2013; Hughes et al., 2001).

Non-motor symptoms in Parkinson's disease

Although PD is traditionally considered a movement disorder, it is now widely recognised that the disease is also associated with a large variety of non-motor symptoms (Figure 1.4). Well-established non-motor symptoms are for example visual hallucinations, sleep disturbances, fatigue, gastrointestinal complaints or dementia (Schapira et al., 2017). However, the presence and severity of these symptoms is highly variable, with potential subtypes of symptom clusters, such as for those who will develop Parkinson's dementia (Oxtoby et al., 2021). In addition, neuropsychiatric manifestations – including depression and apathy (i.e. loss of motivation) – are now known to be some of the most prevalent non-motor symptoms and appear to have the largest impact on quality of life, for both the patient and caregiver (Balestrino et al., 2016).

Although common, prevalence estimations of neuropsychiatric symptoms vary widely, with 7-70% in the case of apathy (Sinha et al., 2013; van Reekum et al., 2005) and 26% to 65% in the case of depression (Farrer, 2006; Pontone et al., 2009). This can be attributed in part to different assessment tools being used, but also to the fact that neuropsychiatric symptoms in PD are not specific and can be difficult to diagnose. For instance, some of the less indicative symptoms of depression, such as fatigue, insomnia, or motor retardation, may also occur in PD in absence of any mood disorder. Thus, whether or not a diagnosis of depression is made relies heavily on the patient's and on their doctor's interpretation of their symptoms.

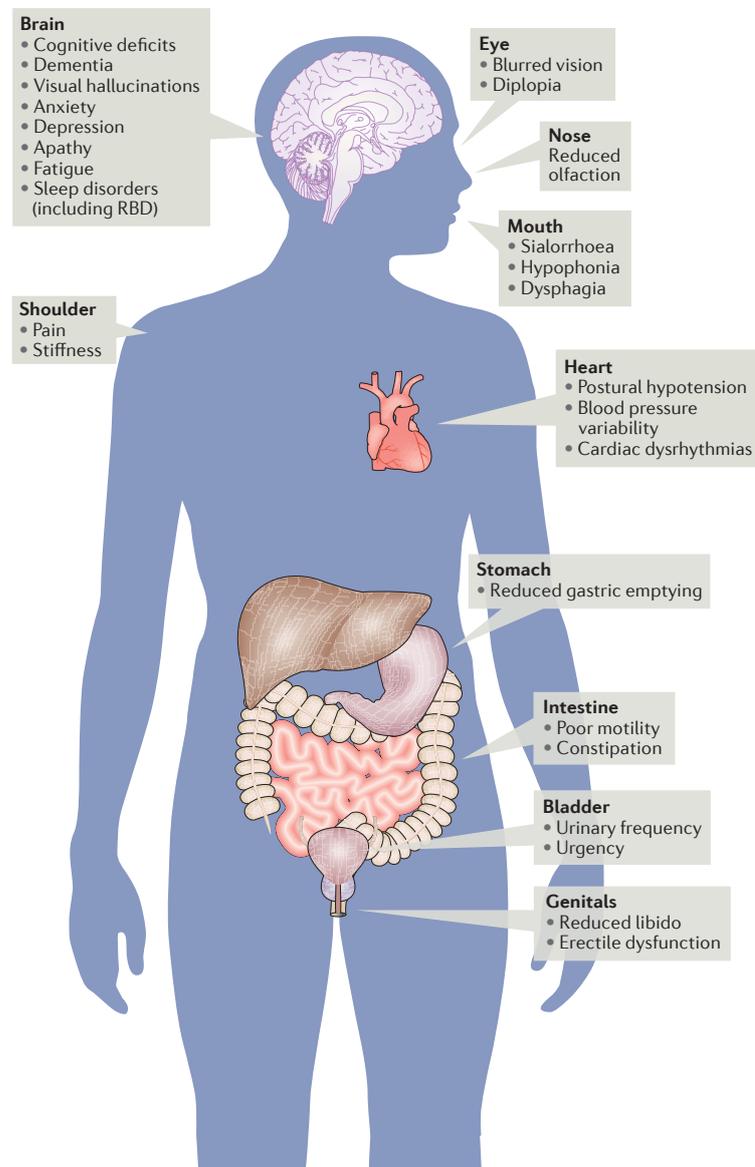


Figure 1.4 – Non-motor symptoms of Parkinson's disease. Parkinson's disease is associated with a large variety of impairments in non-motor domains of the central nervous system and autonomic nervous system. While some symptoms such as gastrointestinal issues, loss of smell and mood changes often precede motor symptoms, cognitive dysfunction including dementia and visual hallucinations usually appear later in the course of the disease. Reprint from [Schapira et al. \(2017\)](#).

Traditionally, neuropsychiatric symptoms were measured using structured interviews or questionnaires. However, more recently, behavioural tasks have been developed that probe the

specific underlying cognitive processes of these symptoms (Bonnelle et al., 2015; Le Heron et al., 2017; Rizvi et al., 2016). For example, apathy has been conceptualised as a multidimensional disorder, including distinct deficits in goal-directed behaviour, cognitive activity, emotion sensitivity, and social motivation (Ang et al., 2017; Nobis et al., 2018). Clinically, caregivers often observe that patients require prompting to do things, but left to their own devices they do not self-initiate behavioural activities. These types of observations have led to considerations of the underlying mechanisms that might be dysfunctional: ranging from a failure to generate options for behaviour, selecting between options depending upon valuation of their potential costs and benefits, action initiation and learning from outcomes (Figure 1.5).

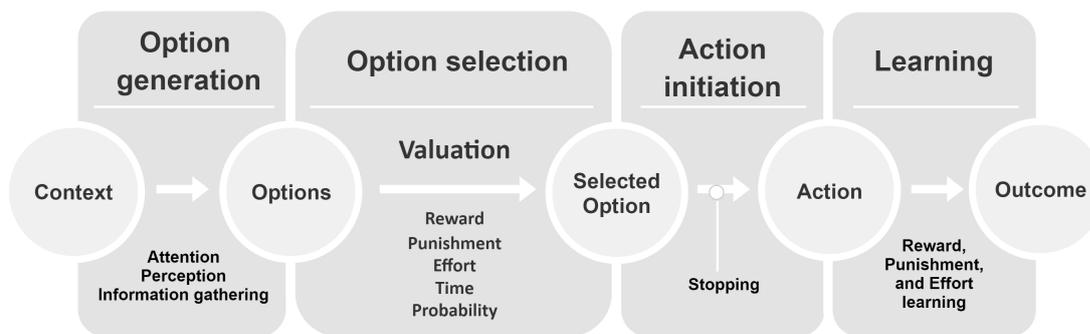


Figure 1.5 – Schema of potential mechanisms involved in motivated behaviour and apathy. Schema of potential mechanisms involved in motivated behaviour and apathy. One scheme to dissect different behavioural components of apathy. Generation of behaviour might depend upon a number of components. First, people must be able to generate options for behaviour, with attentional and perceptual processes being important to produce possible behavioural options in a given context. Out of the options generated, one needs to be selected for action, based on values such as predicted reward, punishment, effort required, time involved, and probability of outcome associated with the option. Next that action needs to be initiated or, just as importantly, ongoing actions might need to be stopped, if they are less appropriate due to changes in the environment or context. They might also interfere with the initiation of action. Finally, if the action has been completed, the outcome of that behaviour needs to be compared with predictions made during valuation to modulate future choices. Reprint from Nobis et al. (2018), adapted from Sinha et al. (2013).

In the case of apathy, potential dysfunction within the option selection step – and especially reduced reward sensitivity – seems to play an important role (Muhammed, Manohar, et al., 2016). Reward sensitivity can be measured using decision-making or gambling tasks, but also using eye-tracking paradigms that measure eye movements and pupillary responses. In

one such study, [Muhammed, Manohar, et al. \(2016\)](#) tested the pupillary responses to reward in thirty PD patients, once while they were ON, and once OFF their dopaminergic medication. The authors could demonstrate that apathetic PD patients showed blunted pupillary responses to reward compared to patients without apathy. Importantly, this reduction in reward sensitivity was restored when ON dopaminergic medication. Thus, reduced sensitivity to rewards may contribute to lower levels of motivation, an effect that may be dopamine dependent. However, an investigation into apathy in PD using an effort-based decision-making task found an effect of apathy that was distinct to that caused by dopamine depletion ([Le Heron, Plant, et al., 2018](#)). In this task, patients with PD and age-matched controls were asked to accept or reject offers of different amounts of monetary reward in return for exerting physical effort on a handheld dynamometer at various difficulty levels. Using this design, it was possible to manipulate effort and reward levels independently, thus measuring behaviour across all possible effort and reward level combinations. The results indicated that apathy indeed reduced motivation to accept offers in this task, especially for those with low associated reward. However, dopaminergic medication in PD increased motivation to accept offers associated with high efforts and high rewards. Thus, although PD-related dopamine depletion within mesocorticolimbic pathways may play some role in the development of apathy, other neurotransmitter systems may too be involved.

While it has been suggested that neuropsychiatric symptoms develop because of pathology associated with the disease itself, it is also conceivable that patients with PD develop them as a reaction to living with a neurodegenerative condition and its associated disability. Generally, higher rates of depression are associated with higher levels of disability, for example in people with AD ([Gómez-Gallego et al., 2017](#)), multiple sclerosis ([Merkt et al., 2017](#)), coronary heart disease ([Palacios et al., 2018](#)), chronic back pain ([Campbell et al., 2017](#)) and rheumatoid arthritis ([Matcham et al., 2013](#)). In PD, too, some studies reported depression levels that were dependent on disease severity ([Sagna et al., 2014](#)). One approach to solving this question would be to compare neuropsychiatric symptoms in PD to a group of people suffering from a similarly chronic, progressive condition, that does not have a neurological component, such as osteoarthritis.

In addition, neuropsychiatric symptoms may also precede the motor symptoms – on which a diagnosis is currently based – by years or even decades (Schapira et al., 2017). Because of the difficulty associated with diagnosing neuropsychiatric symptoms in PD, this type of symptom onset is often noticed only retrospectively (Gaenslen et al., 2011). This is problematic as the potentially prodromal, decade-long loss of dopamine neurons likely impacts the efficacy of dopamine replacement therapies (DRT) that are commenced when a diagnosis can be made. In fact, while DRT can successfully reduce motor symptoms such as bradykinesia or rigidity in most patients, it does not seem to be as effective in treating tremor or non-motor symptoms (Chaudhuri et al., 2009; Lee et al., 2015). The development of rigidity and bradykinesia has been primarily linked to loss of function within the striatum that is caused by reduced dopaminergic innervation (Politis, 2014), offering an explanation for the efficacy of DRT. However, evidence from research into tremor and non-motor symptoms indicates involvement of other neurotransmitter systems. In the case of non-motor symptoms, the serotonergic system in particular has become of interest in PD research in recent years because of its influence on cognitive and affective functions (Chaudhuri et al., 2006; Loane et al., 2013).

Serotonin in Parkinson's Disease

The serotonergic system involves a Serotonin transporter (SERT) and 14 receptor sub-types, with the 5-HT_{1A} and 5-HT_{2A} receptors having been studied most thoroughly. Serotonergic neurons in the brain are located in the raphe nuclei of the brainstem (Jacobs et al., 1992) and have major projections to the caudal brainstem and spinal cord, as well as the forebrain, including the basal ganglia, amygdala, hippocampus, and cingulum (Politis et al., 2015). Thus, the serotonergic system supports widespread areas of the brain, and its dysfunction may contribute to altered function in many domains.

Traditionally, serotonergic function has been primarily linked to the inhibition of behaviour (Faulkner et al., 2014), for example in the presence of aversive stimuli (Crockett et al., 2009) or for delayed gratification (Denk et al., 2005; Miyazaki et al., 2018). Another prominent theory is that serotonin opposes the reward prediction error subserved by dopamine (Schultz et al., 1997), in that it signals a punishment prediction error (Daw et al., 2002). As a result, dopamine

and serotonin have been hypothesised to balance levels of excitation and inhibition in the context of reward and punishment. However, it has become clear that serotonergic function and its interplay with dopamine is much more complex than that (see [Fischer et al., 2017](#) for review). For example, while some reports have demonstrated a role for serotonin in reward processing ([Luo et al., 2015](#)), others have provided contrasting evidence for the dopamine opponency theory of serotonergic function ([Cools et al., 2008](#); [Dayan et al., 2009](#)). These differences become even more difficult to tease apart in the presence of PD.

According to Braak's stages of PD pathology across the brain, serotonergic neurons in the median raphe nuclei are affected early in the progression of PD-related Lewy body pathology and Lewy neurite deposition, potentially even before dopaminergic cells in the midbrain are affected ([Braak et al., 2004](#); [Politis et al., 2010](#)). Indeed, a 30% decline in SERT availability has been documented in patients with both early and established PD ([Politis et al., 2010](#), **Figure 1.6**). While the global severity of SERT depletion did not correlate with disease duration or level of disability, some differences were found in the pattern of SERT loss between early and established PD patients. In those patients with up to 5 years disease duration, reduced SERT availability was found mainly in the caudate, thalamus, hypothalamus and anterior cingulate cortex. In addition to those areas, patients with 5-10 years disease duration also displayed SERT loss in the putamen, insula, posterior cingulate cortex, and prefrontal cortex. Finally, patients who lived with PD for more than 10 years showed additional decline in SERT levels in the amygdala, ventral striatum, and raphe nuclei. Although the sample size in this report was relatively small, with 10 patients in each disease duration group, the results highlight a potentially non-linear progression of serotonergic dysfunction across the brain.

Since SERT is the target of Selective Serotonin Reuptake Inhibitors (SSRIs), its function has been linked to mood, but also to tremor and dyskinesias in PD ([Huot et al., 2013](#)). Loss of 5-HT_{1A} receptors has been observed to correlate significantly with tremor severity ([Doder et al., 2003](#)), depression ([Ballanger et al., 2012](#)) and dyskinesia ([Huot et al., 2013](#)). In addition, reductions in 5-HT_{2A} receptors have been demonstrated, which seem to be more closely related to visual hallucinations ([Huot et al., 2013](#); [Weil et al., 2020](#)). Importantly, a small investigation using PET imaging with dopaminergic and serotonergic presynaptic transporter

radioligands revealed a specific role for serotonergic degeneration in the basal ganglia in PD patients with apathy, as compared to PD patients without apathy (Maillet et al., 2016). In contrast, both patient groups showed dopaminergic degeneration, which was not correlated with apathy. Levels of serotonin metabolites or 5-HT_{1a} receptor availability were also lower in people with PD who were depressed than in those who had PD without depression (Politis et al., 2015). This seems in agreement with increased limbic SERT binding in depressed PD patients (Boileau et al., 2008), suggesting that depression in PD might develop because of increased clearance of serotonin through SERT, and simultaneous loss of serotonergic neurons in the raphe nuclei.

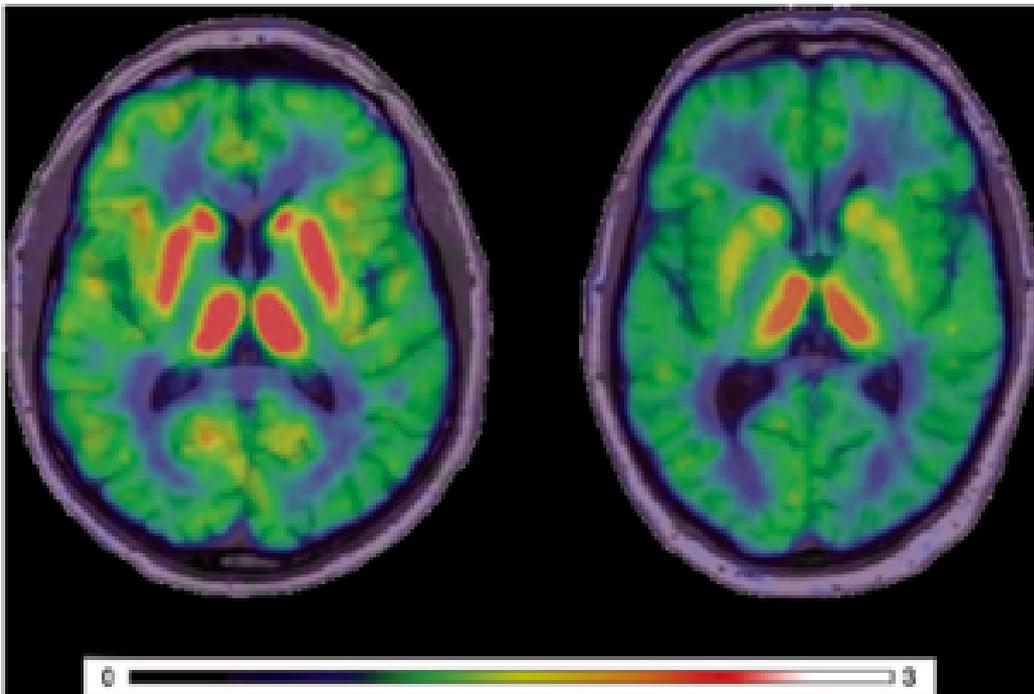


Figure 1.6 – Reduced serotonergic innervation in Parkinson’s disease. Signals from 11C-DASB PET imaging co-registered with 1.5T MRI images show normal serotonergic innervation in the basal ganglia in a healthy subject (left) but markedly reduced in a PD patient at 16 years post-diagnosis (right). Reprint from [Politis et al. \(2015\)](#).

A connection between serotonergic function and depression has been made long ago with the discovery that depleting monoamine neurotransmitters can induce feelings of depression (Bunney et al., 1965; Coppen, 1967). This finding led to the development of new drug

treatments for depression. First in the form of monoamine oxidase inhibitors (Stein et al., 1960) and tricyclic antidepressants (Schuckit et al., 1971), and later – from the 1970s – SSRIs (Hillhouse et al., 2015; Westwick, 1990; Wong et al., 2005). However, after more than 50 years of research into the association between serotonin and depression, the precise mechanism behind SSRI treatment remains elusive (Cowen et al., 2015; Hillhouse et al., 2015). Simply reducing levels of serotonin in healthy volunteers through acute depletion of tryptophan (serotonin's precursor amino acid) does not induce depressed mood (Roiser et al., 2008). Yet, it can result in relapse of clinically significant depressive symptoms in recovered patients (Booij et al., 2002).

More recent studies have provided a potential explanation for the lack of subjective mood change in healthy participants in response to altered serotonin levels. Harmer et al. (2004) demonstrated a shift in affective processing favouring positive over negative stimuli after one week of SSRI administration. This effect was found in absence of any subjective mood changes, so that the authors hypothesised that SSRIs may improve mood secondary to a positive bias in emotion processing. Thus, if serotonergic function is decreased in PD, it may over time cause mood symptoms like depression.

Taken together, these investigations suggest that researching serotonergic function in PD in more detail might be especially useful for the understanding of non-motor symptoms. However, research so far has mainly focused on establishing links between serotonergic function and questionnaire scores for – or diagnoses of – neuropsychiatric symptoms in PD. It has not yet been investigated how the modulation of serotonin in PD might affect operationalised, behavioural decision-making and emotion processing measures. Doing so might allow the dissection of complex concepts like mood or motivation into their underlying neurocognitive components, each of which may be differentially related to serotonergic function. For example, apathy – a loss of motivation – has been operationalised as reduced goal-directed behaviour that may be caused by reduced sensitivity to the reward that an action may be associated with, and/or by increased sensitivity to the effort that needs to be exerted in order to obtain a reward (Le Heron, Plant, et al., 2018). Thus, behavioural tasks that can separate these cognitive processes can add important information to traditional questionnaire measures.

It is probable that the relatively arbitrary definitions of mood disorders, the overlap of their symptoms with PD-related motor symptoms, and the lack of understanding what role age plays in the development of mood disorders, have hampered advances in PD research. The characterisation in terms of component cognitive, behavioural and neuroimaging domains in the ageing population with and without PD might help to improve understanding neuropsychiatric symptoms. In addition, estimating the average trajectory of brain atrophy in successful ageing will be useful to understand how the development of pathology might otherwise indicate neurodegeneration, especially in the case of Parkinson's disease. Eventually, findings from these efforts may advance development of appropriately targeted treatments in PD.

1.5 Objectives of thesis

This thesis aims to contribute to our understanding of how changes in mood, motivation, and brain structure in healthy ageing differs from those in PD, and whether these potential differences can be related to PD-specific brain pathology. This work is divided into two parts:

- I. In the first part, I will establish what may be considered "normal" age-related changes in neuropsychiatric health and brain structure
- II. In the second part, I will discuss these aspects in the special case of PD as a neurodegenerative disorder.

These objectives will be achieved by answering the following questions:

PART I

Chapter 2 | Mood and neuropsychiatric symptoms in healthy ageing

While many studies have investigated "normal" age effects on areas of cognition, little attention has been paid to the impact of healthy ageing on mood. Yet, it is likely that brain ageing mechanisms like atrophy or neurotransmitter dysfunction in limbic and frontostriatal circuits result in systematic changes in mood and neuropsychiatric health – much like hip-

pocampal volume loss may cause memory problems in advancing age. Since neuropsychiatric symptoms are common in neurodegenerative disorders like PD or AD, studying mood changes in healthy ageing will be useful for the distinction between healthy and pathological ageing trajectories. The aim of this chapter is to establish the distribution of symptoms of depression, anxiety, and apathy in the healthy ageing population.

For this I analyse the large UK Biobank cohort of 500 000 generally healthy older adults with regard to symptoms of depression, anxiety, and apathy by using a factor analysis on carefully selected variables available. I further investigate whether there is any relationship between these neuropsychiatric symptoms with age, in terms of prevalence and severity of symptoms experienced. While questionnaire items in the UK Biobank cannot be entirely matched to other commonly used questionnaires, results from this large generally healthy cohort will serve as a reference in following analyses within this thesis.

Chapter 3 | Effects of healthy ageing on brain structure

Next, I explore changes in neuroimaging-derived phenotypes with age. Previous research has shown a strong age effect for brain structures related to memory performance, for example for the hippocampus. In addition, overall brain volume shows a strong decline with age. Both of these phenomena can be observed in healthy ageing adults, in the absence of any unusual memory loss. The aim of this chapter is to quantify these healthy brain ageing effects, and to provide norm values – or nomograms – for the distribution of the extent of these age-related volume losses. Later analyses based on smaller (patient) samples can then be plotted over these nomograms to establish whether results can be considered to fall outside the norm.

PART II

Chapter 4 | Effects of Parkinson's disease on mood

In the first part of Chapter 4 I delve into how neuropsychiatric symptoms are distributed in PD. For this I analyse data from the Oxford Parkinson's Disease Centre (OPDC) Discovery cohort (<http://www.opdc.ox.ac.uk/theme-1-clinical-cohorts>), which consists of almost 1000 PD patients, 320 healthy controls, and 250 patients with Rapid Eye Movement Sleep Be-

haviour Disorder (RBD). Patients with RBD are disproportionately likely to develop PD, and are thus studied as a prodromal stage of the disease. Overlap of these symptoms with PD-specific motor symptoms (e.g. bradykinesia) is discussed.

In the second part of Chapter 4, I briefly present frequency and severity of neuropsychiatric symptoms in a sample of people with a diagnosis of PD, contrasted against people with a diagnosis of osteoarthritis, in the UK Biobank. Osteoarthritis can be considered to cause patients a similar amount of disability as PD, in the absence of neurological changes. Thus, the extent to which people with PD develop neuropsychiatric symptoms as a reaction to their diagnosis, rather than as a symptom of the disease itself, can be established by comparing rates of neuropsychiatric symptoms in these two disease groups.

The third and last part of Chapter 4 explores the theory that a facial emotion recognition impairment in PD occurs in the absence of depression, and is related to apathy instead. In the general population with Major Depressive Disorder, the development and maintenance of depression has been related to a negative attention bias, that is demonstrated with impairments in facial emotion recognition tasks. This negative attention bias may be treated with SSRIs, thereby alleviating depressive symptoms. In PD without depression, it is hypothesised that the same dysfunctional neural circuits that may underlie development of apathy, are also involved in a potential facial emotion recognition impairment. Thus, results from this chapter may provide motivation to test the effect of serotonin on symptoms of apathy in PD.

Chapter 5 | The role of serotonin in decision-making in Parkinson's disease

The fifth chapter of this thesis aims to assess whether the altered motivation and emotion processing often observed in PD is related to serotonergic function. It has mostly been argued that degeneration of dopaminergic neurons in the substantia nigra, and resulting dysfunction of the dopaminergic pathways, affect processing of emotional and rewarding information, which leads to symptoms of depression or apathy. However, a meta-analysis failed to find any systematic effects of dopaminergic medication on emotion processing (Gray et al., 2010), and dopamine alone does not seem to sufficiently explain amotivated behaviour (Le

Heron, Plant, et al., 2018). It is thus likely that another neurotransmitter system is involved. For example, the dorsal raphe nucleus (DRN), considered to be the origin of serotonin, is thought to be affected early in PD (Braak et al., 2004; Politis et al., 2010). In line with this, studies have shown widespread alterations in serotonergic functioning (Politis et al., 2010).

The objective of this experimental medicine study was therefore to investigate how serotonergic modulation through administration of citalopram (20mg) for seven days affects emotion and motivation processing in patients with PD. If degeneration of serotonergic cells is responsible for the difficulty in emotion recognition in PD, modulation of serotonin should affect performance on emotion processing tasks. In addition, I discuss whether citalopram alters PD patients' performance on computerised tests assessing levels of motivation and apathy.

Chapter 6 | How consistent are PD effects on brain structure assessed with MRI?

In the last chapter, I aimed to understand the inconsistencies often found between studies on structural brain effects of PD. As neuroimaging markers have great potential for the improvement of diagnosis and treatment of PD, it is critical to continue efforts to establish these markers. However, it is equally important to focus on new avenues when previous efforts have repeatedly led to null results. Currently, measures derived from PET imaging seem to be most useful for PD biomarkers, but these methods are expensive and not commonly available to researchers.

The aim of this chapter is to replicate earlier MRI findings with two separate, large, cohorts of patients with PD and age-matched healthy controls. I discuss differences in structural neuroimaging phenotypes, such as brain volume, and white matter integrity, between the groups. The implication of these differences and their usefulness as biomarkers - compared to more established, but more expensive methods - are explained. This analysis is performed on data from the OPDC Discovery cohort and on a subset of data from the UK Biobank cohort.

General Discussion

In the final section of this thesis, I will summarise the results from Chapters 2 to 6, and review their implications. I discuss general conclusions and point out potential future directions

within brain health research in healthy ageing and PD.

PART I

Ageing in the general population

Chapter 2

Mood and neuropsychiatric symptoms in healthy ageing

2.1 Introduction

While many studies have investigated “normal” age effects on areas of cognition, little attention has been paid to the impact of healthy ageing on mood (Cotter et al., 2020; Hedden et al., 2004). Yet, it is likely that brain ageing-associated atrophy or neurotransmitter dysfunction in limbic and frontostriatal circuits might result in systematic changes in mood and neuropsychiatric health – similar to how hippocampal volume loss is linked to memory decline in advancing age (Raz et al., 2006). Since neuropsychiatric symptoms are common in neurodegenerative disorders like PD or AD, studying mood changes in healthy ageing might be useful for the distinction of healthy from pathological ageing trajectories. In addition, symptoms like apathy and depression were even shown to precede the diagnosis of PD and AD by many years (Lee et al., 2015), so their onset might, in some individuals, indicate early warning signs for a future diagnosis of neurodegeneration. For example, a longitudinal investigation following a Swedish cohort of over half a million participants found increased risk of developing PD in those individuals with a history of depression as far back as 20 years (Gustafsson et al., 2015). Although mood disorders presenting years ahead of motor or cognitive symptoms of neurodegeneration might just reflect shared risk factors for both diseases, it is currently estimated that the pathological processes of neurodegenerative disorders start about ten to twenty years prior to the time point of diagnosis (Katsuno et al., 2018). Early mood symptoms may therefore also reveal an early phase in the neurodegenerative disease, at least in some individuals. However, next to the low specificity of mood symptoms, a lack of knowledge about what might be considered “normal” age-related effects on mood complicates the early diagnosis of neurodegeneration based on neuropsychiatric symptoms in these cases.

Some evidence for how age might affect mood comes from reports investigating late-life depression, which refers to a depressive episode presenting for the first time past the age of around 55 years (Beekman et al., 1995). Many studies have highlighted an involvement of dysfunction in limbic and frontostriatal networks, as well as deteriorating neurotransmitter levels, in the development and maintenance of late-life depression (Tadayonnejad et al., 2014). It has also been reported that cardio- and cerebrovascular dysfunction and white matter hyperintensities, factors that are strongly related to age, may contribute to the development of a

vascular type of depression in late-life (Sheline et al., 2010; Valkanova et al., 2013). In addition, a longitudinal investigation reported an increase in apathy over a five-year period, especially in men (Brodaty et al., 2010), although this change was not related to baseline measures of white matter integrity. However, no neuroimaging was performed at the 5-year follow-up, so that it is unclear whether those who became more apathetic also developed more white matter damage. Thus, normal ageing processes in the brain may increase the risk for neuropsychiatric symptoms like depression or apathy in older adults.

In contrast, others have suggested that age-related changes in the brain may have a beneficial impact on mood, as demonstrated by the widely replicated *positivity effect* of ageing. A number of studies have revealed a relative improvement in processing positive over negative stimuli in older adults (Reed et al., 2012). For example, compared to younger adults, older adults have been shown to bias their attention towards happy faces, and away from sad faces (Mather et al., 2003; Noh et al., 2015). Similarly, reports using different experimental tasks could demonstrate improved short- and long-term memory for positive over negative stimuli with older age (Kennedy et al., 2004; Piguet et al., 2008). It has been argued that this effect reflects changes in emotion regulation and motivation that direct behaviour towards positive information in older adults (Zebrowitz et al., 2017). On the other hand, a different theory proposes that the positivity bias is based on negative information being more cognitively demanding (Taylor, 1991). However, this would suggest a stronger positivity effect with cognitive decline, when it is usually associated with worse mood symptoms (Chodosh et al., 2007; Gualtieri et al., 2008). Studies have also shown that increasing cognitive demand actually attenuates the positivity effect (Gerhardsson et al., 2019). Thus, while the mechanisms underlying the positivity effect remain unclear, it is unlikely to be explained entirely by cognitive demand. As a result, in absence of cognitive deterioration and other age-associated declines in cardio- and cerebrovascular health, a positive bias in information processing may lead to an improvement of mood in older age for those adults who stay healthy and age successfully.

However, neuropsychiatric symptoms in older adults may also develop based on environmental stressors that are unrelated to ageing or neurodegeneration (Kendler et al., 1999). In fact, one of the strongest predictors for a diagnosis of depression is the experience of adverse

life events (Kim, 2020; Pine et al., 2002; Rousson et al., 2020), such as loss of a spouse (Djernes, 2006). While it will be challenging to distinguish neuropsychiatric symptoms in healthy ageing, neurodegeneration, and psychiatric disorders, focusing on the individual symptoms experienced by patients will help to explore the underlying mechanism. For example, feelings of hopelessness or pessimism may be more common in people who developed a mood disorder as a reaction to an adverse life event, while in neurodegeneration, loss of neurotransmitter function may be more likely to cause loss of interest and pleasure (Le Heron, Holroyd, et al., 2018; Treadway et al., 2011). In contrast, generally healthy ageing with additional environmental stressors may be most strongly associated with experiences such as insomnia, as has recently been noted in light of the COVID-19 pandemic and lockdowns (Cénat et al., 2021).

Therefore, in addition to establishing whether mood and neuropsychiatric health are generally more likely to improve or decline in ageing, it is also important to consider how the profiles and severity of neuropsychiatric symptoms might differ between healthy and psychiatric populations. The aim here was to establish the prevalence of neuropsychiatric symptoms, and their relationship with age, in a large sample of generally healthy older adults in the UK Biobank. In addition, I investigated whether distinct clusters of sub-clinical neuropsychiatric symptoms can be found in the healthy ageing population, how these compare to clinical symptoms in a group of older adults with psychiatric diagnoses, and how they may be affected by age. These results will later be contrasted with the symptom distribution in patients with PD in **Chapter 4.2**. Given the impact of daily stressors on cross-sectional measures of mood (Eckenrode, 1984), any systematic effects of age on these measures will likely be small and difficult to detect. However, data collection efforts like the UK Biobank allow for the study of small effects by providing a large enough sample. The availability of information on health status in the UK Biobank further allows for the selection of healthy older adults through exclusion of confounding factors, such as cerebrovascular disease. Findings will contribute to the understanding of what may be considered normal age-related changes in mood, in turn supporting efforts to allow earlier diagnoses of pathological ageing processes.

2.2 Method

2.2.1 Data selection

Questionnaire data on mood symptoms were collected at an online follow-up session, usually 3-4 years after participants were first recruited for the UK Biobank. Categories for question items included depression, anxiety, and general well-being (**Table 2.1**). While there was no dedicated question set for the assessment of apathy or motivation in the UK Biobank, a question within the depression category was dedicated to loss of interest or pleasure.

2.2.2 Participants

Out of a total of 502,505 participants from the UK Biobank, data of interest were available for 157,378 people. Of these, 134,148 older adults did not have any neurological or psychiatric diagnoses (76,954 women and 57,194 men, *mean age* = 64.05 ± 7.77 years) and were included in the analysis as healthy controls. In addition, I selected a second group of 2654 patients with a psychiatric diagnosis, but without any form of neurological or neurodegenerative disorder (1715 women, 939 men, *mean age* = 61.51 ± 7.39 years). Psychiatric diagnoses available in UK Biobank and included here are depression, anxiety or panic attacks, schizophrenia, self-harm, and bipolar disorder. Information on disease duration or severity were unavailable.

2.2.3 Analysis

Analyses were performed using *R* version 3.6.1 within *RStudio* version 1.3.959 ([R Core Team, 2013](#)) and *MATLAB* version R2020b ([MATLAB, 2020](#)). All analyses were done once for the group of healthy older adults, and once for the group of psychiatric patients.

To visualise the distribution of scores across the individual items on the questionnaires, I created a heatmap for the percentage of agreement by item and Likert scale response. Exploratory factor analysis was performed on the individual question data from the anxiety and depression categories with the *'fa()*' function within the *'psych'* package ([Revelle, 2020](#)) in *R*.

| Category | Question | Response | |
|--------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| | Over the last 2 weeks, how often have you been bothered by any of the following problems? | 4-point Likert scale | |
| | Data field | Question continued | |
| Depression | 20510 | ...Feeling down, depressed, or hopeless | |
| | 20513 | ...Thoughts that you would be better off dead or of hurting yourself in some way | |
| | 20507 | ...Feeling bad about yourself or that you are a failure or have let yourself or your family down | |
| | 20511 | ...Poor appetite or overeating | |
| | 20518 | ...Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual | |
| | 20519 | ...Feeling tired or having little energy | |
| | 20508 | ...Trouble concentrating on things, such as reading the newspaper or watching television | |
| | 20514 | ...Little interest or pleasure in doing things | |
| Anxiety | 20505 | ...Becoming easily annoyed or irritable | |
| | 20512 | ...Feeling afraid as if something awful might happen | |
| | 20506 | ...Feeling nervous, anxious or on edge | |
| | 20509 | ...Not being able to stop or control worrying | |
| | 20516 | ...Being so restless that it is hard to sit still | |
| | 20515 | ...Trouble relaxing | |
| | 20520 | ...Worrying too much about different things | |
| Category | Data field | Question | Response |
| Happiness and subjective well-being | 20458 | "In general, how happy are you?" | 6-point Likert scale |
| | 20459 | "In general, how happy are you with your health?" | 6-point Likert scale |

Table 2.1 – Items in UKB mood questionnaire from online follow-up. These include all questions on recent feelings of depression and anxiety, as well as two questions on general happiness

A parallel analysis using ordinary least squared factoring provided a range for the ideal number of factors to be selected in the following factor analysis, based on eigenvalues larger than zero. Factor analysis was then run using different numbers of factors within the suggested range, with best results being obtained using five factors. As the factors were likely to be correlated, oblique rotation with ordinary least squared factoring was used. Questionnaire items with a loading of larger than .3 were attributed to the corresponding factor.

Individual factor scores were found by regression with the 'fa()' function, where each individual's location on the factor is estimated. This resulted in factor scores with a mean of zero, with positive numbers reflecting higher scorings on the individual items. These scores, as well as scores on questions from the Happiness and well-being category were standardized and plotted against age by using model-free sliding window curves (code available here: <https://osf.io/vmabg/>; *conditionalPlot.m*). In this approach, a fixed width age-quantile window is moved along the age distribution, resulting in data-driven curves. Here, each window contained 10% of datapoints, overlapping with the previous and/or following window. The mean values in each window were then smoothed with gaussian kernel of width 20%. This method is explained in more detail in a recent publication (Nobis et al., 2019). To test for an age effect in a formal way, I also assigned participants to an older and a younger group, based on a mean split of age. I then performed ANOVAs with the two age groups as fixed factors and scores on the different factors as separate dependent variables, in each of the two datasets.

2.3 Results

2.3.1 Tiredness and anxiety are most common in both groups

Out of all items, in both study samples, tiredness and feelings of anxiety were the most commonly reported symptoms (**Figure 2.1 A**, left panel). About 51% of healthy older adults reported feeling tired or having little energy on at least several days in the last two weeks, with 6% feeling this way nearly every day. Other symptoms that more than 20% of healthy participants reported to experience at least on several days included worrying too much, having trouble relaxing, feeling anxious, and feeling irritable. In contrast, only 4% of people reported to have suicidal thoughts. This is also reflected in healthy adult's responses to the two questions assessing overall happiness (**Figure 2.1 B**, left panel). Around 95% reported to be at least moderately happy, with about 10% reporting to be "Extremely happy". Only a minority of the healthy group reported to be at least moderately unhappy in general (5%) and with their health (13%). Similarly, tiredness was also the most common symptom in the smaller group of patients with a psychiatric diagnosis, present in about 66%, though with larger percentages for more severe tiredness than in healthy older adults (**Figure 2.1 A**, right panel).

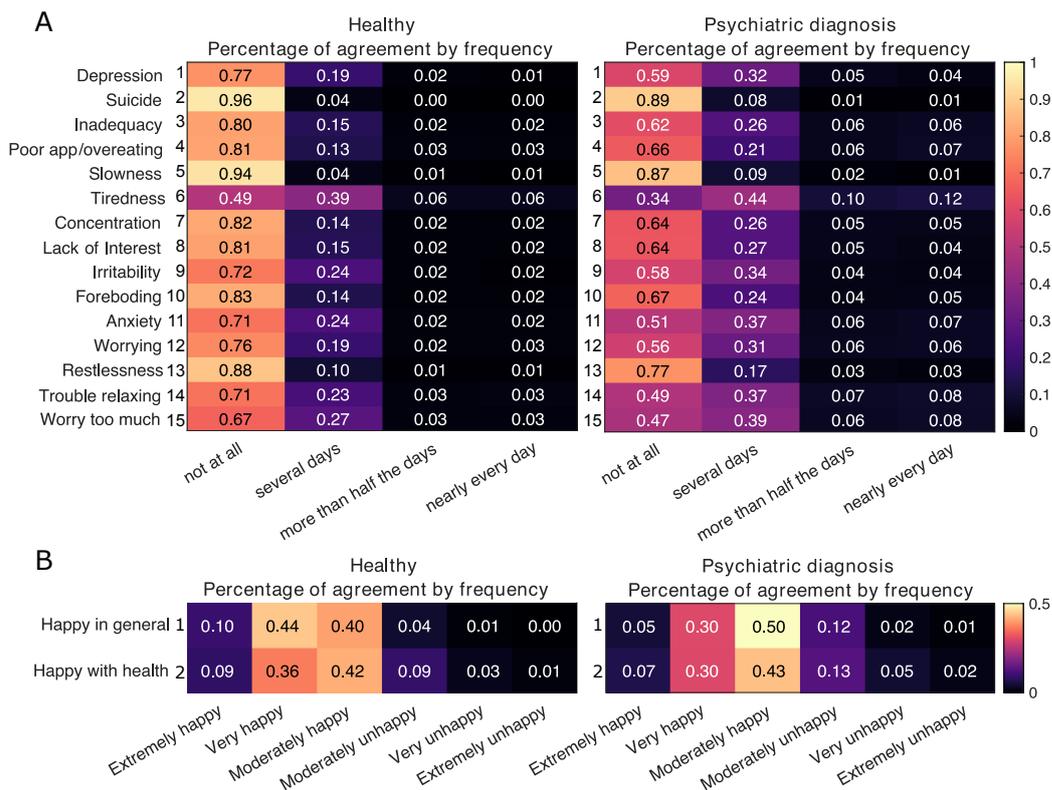


Figure 2.1 – Prevalence of mood symptoms in healthy people (left) and patients with a psychiatric diagnosis (right). A. Tiredness and worry were the most commonly reported symptoms, while suicidal thoughts and psychomotor changes were least common across both groups. **B.** Participants rarely reported unhappiness, but levels of happiness with one's own health were slightly lower than happiness in general. Patients reported lower happiness levels than healthy older adults.

In addition, several symptoms of anxiety were common, with about 40-50% of people experiencing worry, anxiety, or trouble relaxing. Least frequent were suicidal thoughts, feeling slowed down, and feeling restless, again with higher rates than in the healthy study population. Despite this being a psychiatric patient group, happiness levels remained high, with 85% of patients reporting to be at least moderately happy in general, and 80% reporting to be at least moderately happy with their health (**Figure 2.1 B**, right panel).

2.3.2 Different clusters of symptoms between healthy and psychiatric participants

The initial parallel analysis that was performed to explore the ideal number of components in the large healthy participant group suggested five factors. This number was identified based on a Scree plot, where both large drops in the actual data, as well as the point where the

simulated data and actual data converge, are considered. Using different numbers of factors, a model with five factors indeed yielded the best fit indices: The Root Mean Square Error of Approximation (RMSEA) was .03, which indicated a good model fit as the value should be close to zero. In addition, the Tucker-Lewis Index (TLI) was .98, above the ideal value of at least .9.

The five resulting factors were named “Worry”, “Depression/Apathy”, “Physical”, “Agitation”, and “Suicide/Inadequacy”, based on their item loadings. These factors accounted for 20%, 9%, 8%, 6%, and 4% of the variance, respectively, accumulating to 47% in total. Correlations with responses on one of the questions in the depression category, asking for any psychomotor changes (Data field 20518), did not reach the cut-off of .3 to be considered part of any of the five factors. In addition, scorings on having trouble relaxing loaded on two factors, namely “Worry” and “Agitation”. **Figure 2.2 A** shows the item loadings for each factor, colour coded based on loadings larger than .3.

The same approach was taken for the smaller group of people with a psychiatric diagnosis, resulting in four factors ($RMSEA = .05$, $TLI = .97$). Again, based on their associated factor loadings of at least .3, the items were named “Anxiety/Apathy”, “Inadequacy”, “Worry/Appetite”, and “Depression”. In this analysis, “Worrying too much” did not load onto any of these factors, while thoughts of “Suicide” loaded onto both the “Suicide/Inadequacy”, and the “Depression” factor (**Figure 2.2 B**).

2.3.3 Changes of factors with age

Scores for all five factors decreased across age in the healthy study sample, reflecting lower frequencies of the corresponding symptoms (**Figure 2.3 A**). The steepest slope was found for the relationship between age and scores on the “physical” factor, which included symptoms of lack of energy and concentration problems (decrease of almost .5 standard deviations). Similar trajectories were found for the four different factors in the psychiatric group, although larger standard errors caused by the much smaller sample size complicate the distinction between separate factor curves (**Figure 2.3 B**). Yet, the “Worry/Appetite” and “Anxiety/Apathy” symptoms seem to show a slight increase in severity after the age of 65 years, while the other

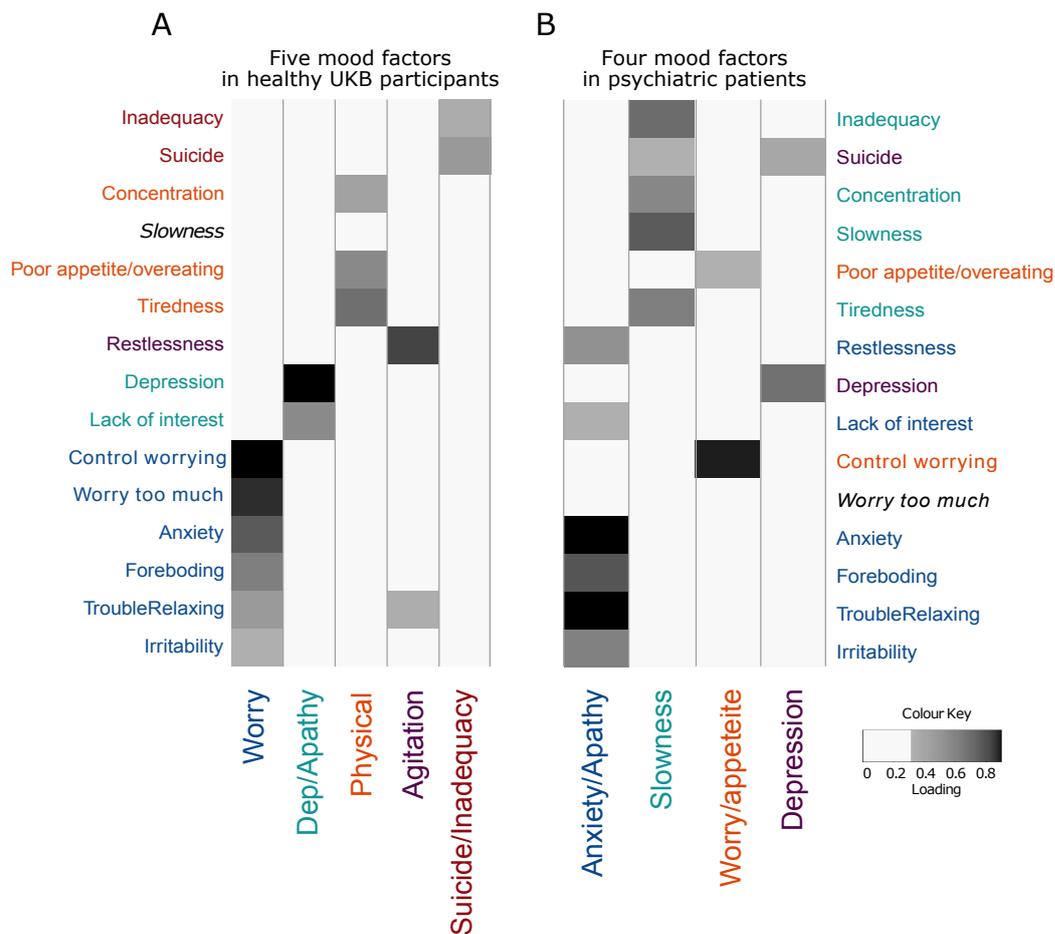


Figure 2.2 – Factors within UKB mood questionnaire, grouped by colour. Factor loadings are colour-coded in greyscale, with a minimum loading of .3 for factor association. **A.** Five factors in the healthy participant group, with most variance explained by Worry. **B.** Four factors in psychiatric patients, most variance explained with symptoms of anxiety.

two factor scores continue to decline.

Formal hypothesis testing for the difference in factor scores between relatively younger and older adults revealed significant effects for all factors in both study cohorts (all $p < .001$, **Table 2.2 & 2.3**). The younger and older adults were selected based on a mean split, with healthy participants of up to 64 years, and for the psychiatric group up to 62 years assigned to each of the younger groups. Effect sizes were small, with $\eta_p^2 = .01$ for all factors, except the “Physical” factor score difference in healthy older adults and the “Suicide/Inadequacy” difference in patients, which had effect sizes $\eta_p^2 = .02$ and $\eta_p^2 = .03$, respectively.

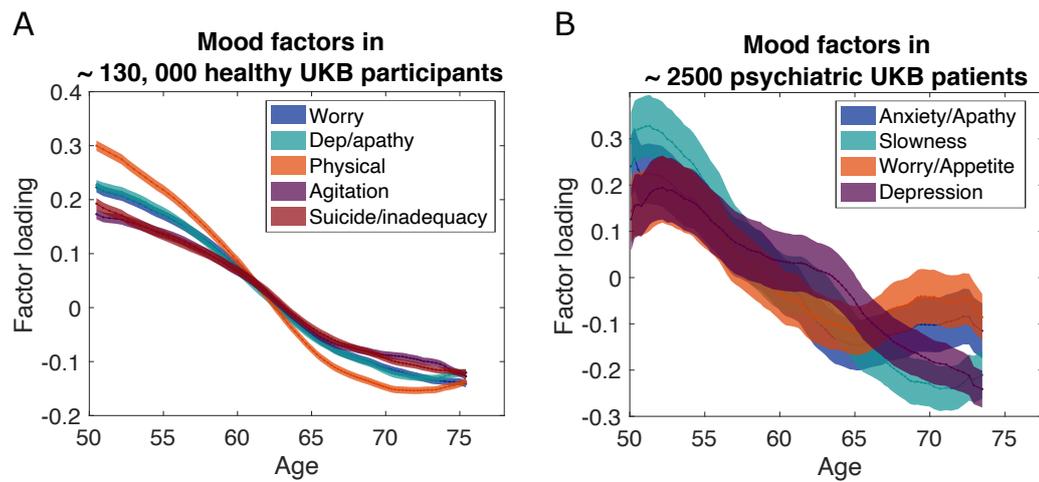


Figure 2.3 – Trajectories of mood factor loadings with age. A. Mood symptoms decline from 50 years and start levelling off around 65 years in healthy older adults. B. Similar trajectory in the patient group, but potentially increase of worry and anxiety after 65 years.

| | Younger (mean \pm std) | Older (mean \pm std) | F-test, p-value | Effect size (n2p) |
|------------|--------------------------|------------------------|----------------------------|-------------------|
| Worry | 0.09 \pm 1.02 | -0.12 \pm 0.84 | F(1,130279)=1625, p < .001 | 0.01 |
| Dep/Apathy | 0.09 \pm 1.04 | -0.12 \pm 0.82 | F(1,130279)=1590, p < .001 | 0.01 |
| Physical | 0.10 \pm 0.96 | -0.14 \pm 0.73 | F(1,130279)=2494, p < .001 | 0.02 |
| Agitation | 0.07 \pm 0.96 | -0.09 \pm 0.76 | F(1,130279)=1064, p < .001 | 0.01 |
| Suicide | 0.06 \pm 0.87 | -0.08 \pm 0.61 | F(1,130279)=1139, p < .001 | 0.01 |

Table 2.2 – Hypothesis tests for age differences on mood factors in healthy adults.

| | Younger (mean \pm std) | Older (mean \pm std) | F-test, p-value | Effect size (n2p) |
|--------------------|--------------------------|------------------------|--------------------------|-------------------|
| Anxiety/Apathy | 0.08 \pm 0.10 | -0.14 \pm 0.89 | F(1,2543)=36.3, p < .001 | 0.01 |
| Suicide/Inadequacy | 0.12 \pm 0.98 | -0.18 \pm 0.79 | F(1,2501)=70.7, p < .001 | 0.03 |
| Worry/appetite | 0.05 \pm 0.98 | -0.09 \pm 0.82 | F(1,2526)=16.3, p < .001 | 0.02 |
| Depression | 0.07 \pm 0.90 | -0.11 \pm 0.72 | F(1,2499)=32.3, p < .001 | 0.01 |

Table 2.3 – Hypothesis tests for age differences on mood factors in patients.

Happiness generally increases with age in over 50-year-olds

Plotting responses on the two questions assessing levels of happiness against age revealed a general improvement with increasing age. Self-reported levels of happiness in general increased by .3 standard deviations between healthy 50- and 70-year-olds (**Figure 2.4 A**). Healthy

participant's reports of happiness with their own health were largely stable across age bins, with only a very slight increase around age 60 years that levelled off again from around 70 years. In contrast, reports of both happiness in general and happiness with health increased linearly with age in the group of psychiatric patients, by about .6 standard deviations in total (Figure 2.4 B).

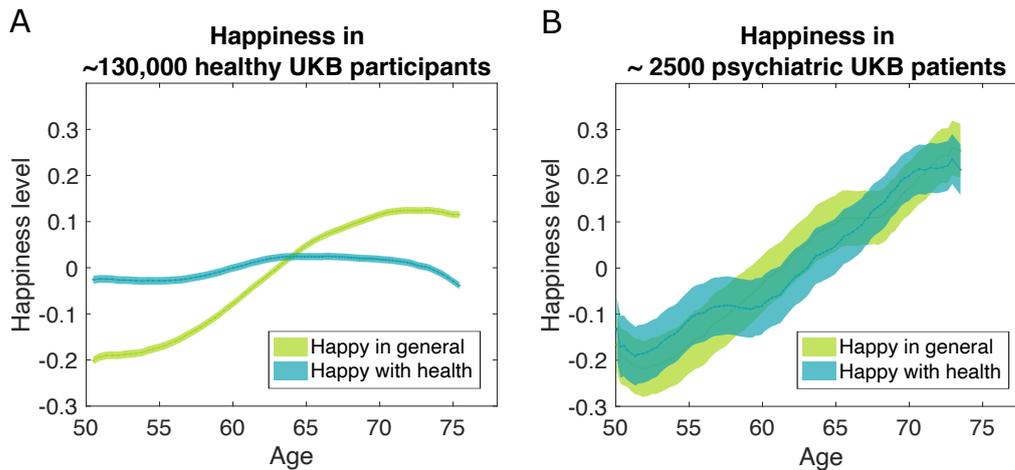


Figure 2.4 – Happiness generally improves with older age. **A.** General happiness increases from around 50 years, while happiness about health increases very slightly around age 60, and decreases again by age 70 years in healthy participants. **B.** Linear increase in happiness levels in the patient group, equally strong for happiness in general and happiness about health. However, the smaller sample size increases standard error margins.

2.4 Discussion

Analysis of the mental health questionnaire data from over 130,000 participants in the UK Biobank demonstrated that mood generally improved with ageing. In addition, while there were distinct clusters of mood symptoms in healthy older adults and psychiatric patients, the types of symptoms that were most common – tiredness and anxiety – were similar between the two groups.

The finding of a small, but systematic age-related improvement of mood in both healthy older adults and those with a psychiatric disorder (Figure 2.3) is in line with other reports of an

age-related increase in happiness, as well as with the positivity effect (Reed et al., 2012). General happiness increased from around 50 years, while healthy participant's happiness about their health increased only very slightly around age 60, before it decreased again by 70 years (Figure 2.4 A). In contrast, levels of happiness with health increased steadily in the patient group. Mood, as indicated by the scores on all five factors, also showed an improvement across age from around 50 years or earlier (Figure 2.4 B).

Previous investigations showed similar trajectories, with mood improving until levelling off around age 70 and older in one report (Carstensen et al., 2011), and until around 71 years in another (Cotter et al., 2020). Importantly, Cotter et al., (2020) showed that in comparison to people whose mood worsened over time, those with improvements in mood over the longitudinal study period had less age-related white matter damage. This further supports a role for vascular damage in late-life mood symptoms such as in late-life depression. As I have excluded participants with any kind of medical diagnosis, including those that are related to cerebrovascular health like diabetes, my results are in line with this finding. In addition, these conclusions further imply that underlying, un-diagnosed neurodegeneration should be considered when addressing late-onset neuropsychiatric symptoms, especially in the presence of additional vascular risk factors.

In contrast to the improvement of psychiatric symptoms with age reported here, Brodaty et al. (2010) found an increase in apathy over a 5-year period in 58- to 85-year-olds that was unrelated to white matter damage. Apathy was measured with the Apathy Evaluation Scale (AES), and analysis of AES subscales showed the largest effect in cognitive apathy. However, the effect of age on apathy scores was related to overall cognitive decline, and white matter integrity was measured only at baseline. A recent pathological study also documented that cognitive decline in later life was mostly associated with pathological postmortem markers like Lewy bodies, rather than normal ageing processes in the brain (Wilson et al., 2020). Thus, it is possible that the results in Brodaty et al. (2010) are confounded by cognitive decline and undetected development of white matter damage in some participants. On the other hand, since the UK Biobank dataset is cross-sectional and people with cognitive decline are less likely to complete research studies (Matthews et al., 2004), results in my analysis may have

underestimated effects that would have been evident in a less biased, longitudinal sample. As the UK Biobank cohort continues to be followed up with online questionnaires and assessment centre visits in the coming years, this can be formally tested.

Since symptoms like tiredness and concentration problems, alongside worry and anxiety, were most common in both samples and also showed the strongest age effect, the improvement in symptoms shown here may also be due to reductions of stress after retirement. However, while data on retirement status or age at retirement weren't directly accessible for this study, the decline in symptoms is evident from as early as 50 years, while retirement age in the UK is around 66 years. Thus, it is unlikely that retirement is responsible for the effect shown here.

The vast majority of healthy older adults who did not have any kind of medical diagnosis reported to be generally happy and only rarely experienced sub-clinical neuropsychiatric symptoms (**Figure 2.1**). However, while less than 5% reported suicidal thoughts, this percentage is surprisingly high given that people with any kind of health condition – psychiatric or other – were excluded from this group. This might be due to missed diagnoses of major depressive disorder and self-harming tendencies in this population and emphasizes the importance for easier access to psychiatric services. Yet, the most common mood symptoms were of less serious nature, such as tiredness, worry, and anxiety, which likely reflect responses to day-to-day stressors and busy lifestyles.

Interestingly, while the frequency of symptoms was overall higher in older adults with a psychiatric diagnosis, the distribution of symptoms was largely consistent across both groups. Similar to the pattern in healthy participants, tiredness, worry, and other symptoms of anxiety were still the most frequent symptoms in patients. In addition, suicidal thoughts, feelings of being slowed down, and restlessness were the least frequent symptoms in both the healthy and patient samples. Thus, in absence of neurodegeneration, it seems that the types of neuropsychiatric symptoms do not differ between sub-clinical and psychiatric populations, but rather the severity of them. It remains to be tested whether the same is true when comparing healthy older adults or psychiatric patients to those with a diagnosis of PD, or whether neurodegeneration may cause specific symptoms as has been suggested in the case of apathy.

This analysis can be found in **Chapter 4.2**, with the caveat that apathy is only covered by one questionnaire item in the UK Biobank.

Interpretation of results in the group of psychiatric patients is limited by the lack of information on disease duration and severity. In fact, the rather high rate of moderate happiness among those patients (**Figure 2.1 B**) could suggest that they are not currently unwell, and have reported a historic diagnosis. This may also be reflected in the relatively low frequency of severe mood symptoms (**Figure 2.1 A**). Future analyses may clarify this by applying methods of estimating current disease status in UK Biobank, such as previously done for depression ([Smith et al., 2013](#)).

Factor analysis further revealed five clusters of mood symptoms present in the healthy group of older adults: (1) Worry, (2) depression/apathy, (3) physical symptoms, (4) agitation, and (5) thoughts of suicide and inadequacy (**Figure 2.2**). While tiredness, part of the physical factor, was the most common symptom overall, the factor including worry and other anxiety-related symptoms explained the most variance in the sample. Thus, worry seems to be the driving factor for sub-clinical anxiety in the generally healthy population, while many older adults may experience tiredness as a symptom independent from neuropsychiatric health. The presence of a factor for agitation and restlessness that was separate from general anxiety and worry may also suggest sub-clinical hyperactive or manic traits among healthy adults, though this needs to be further investigated with more detailed questionnaires. In addition, it is important to consider that the five factors accounted for less than 50% of the overall variance in the data, highlighting the significance of other, potentially environmental factors not analysed here.

An unexpected finding was that in the healthy group, symptoms of depressed mood loaded onto the same factor as loss of interest or pleasure, but not suicidality and feelings of inadequacy. It seems possible that the suicide/inadequacy factor captured individuals in the supposedly healthy adults who suffered from clinically significant depression, but had not been diagnosed. In contrast, the depression/apathy factor may reflect the variance shared between participants who experienced sub-clinical symptoms of depression or apathy that would not usually be accompanied by suicidal thoughts. It is worth mentioning that the de-

pression/apathy factor may also include aspects of anhedonia, which is generally defined as a loss of pleasure in doing things that were previously enjoyed (Treadway et al., 2011). As the corresponding questionnaire item assesses a loss of interest or pleasure (Table 2.1), relating to both apathy and anhedonia, it is not possible to distinguish between the two in this dataset.

In the patient group, a four-factor solution provided the best fit for the mental health data. These four factors corresponded to symptoms of (1) anxiety and apathy, (2) feelings of slowness, (3) worry and loss of appetite, and (4) depression. In contrast to what was found in the healthy sample, depression and suicidal thoughts loaded onto the same factor that did not include apathy/anhedonia. Responses on the item covering apathy and anhedonia were instead paired with symptoms of anxiety and irritability in the first factor. This further supports the hypothesis that depressed mood in the healthy sample reflects sub-clinical symptoms, while clinical depression is more closely related to feelings of inadequacy, slowness, and potentially suicidality. However, it is surprising that apathy/anhedonia was associated with symptoms of anxiety in the patient sample, as they are more commonly reported to be comorbid with, or part of, depression. Since the factor loading for the apathy item associated with the factor for anxiety was weak, this might reflect the fairly low frequency and severity of apathy within the sample. The depression factor in contrast likely captures clinically significant depressive symptoms, thus not correlating strongly with the weak symptoms of apathy in this group. Future research may clarify these relationships with more detailed apathy questionnaires that include a caregiver report.

In conclusion, the practical implications of the current results are that newly presenting, severe mood symptoms in older adults should not be dismissed as normal age effects, but should be clinically assessed in the context of potential neurodegenerative disease. However, these findings are currently limited by the cross-sectional nature of the UK Biobank dataset, and more longitudinal studies are needed to establish the difference between healthy and pathological age effects on mood. For example, the results shown here may reflect a generational effect, such that participants of the older generation were generally less likely to experience mood symptoms, unrelated to their age. Alternatively, there may be an especially

strong selection bias among younger participants, based on the circumstances around their availability to take part in UK Biobank, for example unemployment or extended sick leave. One may also argue that the data selection procedures I applied resulted in an unrealistically healthy sample of older adults, which may not reflect “normal” age effects. However, as I only excluded participants with an explicit diagnosis of a health condition, those adults that may have some – but not severe – age-related symptoms will still be included. In addition, in upcoming **Chapter 4.2**, I discuss how the frequency of symptoms in this healthy sample compares to groups of patients with PD and patients with physical disability comparable to PD, namely those with diagnosed osteoarthritis.

Chapter 3

Effects of healthy ageing on brain structure

3.1 Introduction¹

Previous research has shown an age-related decline in grey matter volume in the brain that can be observed even in healthy ageing. Severe atrophy however can point to neurodegenerative disease like AD, with some brain areas seeming to be more useful to track pathological decline than others. For example, both longitudinal and cross-sectional studies have described reduced volume of the hippocampus in patients with AD or MCI compared to healthy controls (Frankó et al., 2013; Henneman et al., 2009; Shi et al., 2009). Similarly, using the rate of hippocampal atrophy, researchers have been able to distinguish between those with MCI who progressed to AD and those who did not (Frankó et al., 2013). Precise estimations of hippocampal volume may also facilitate earlier diagnosis, with some researchers reporting that the rate of hippocampal atrophy deviated from a healthy trajectory about 5.5 years before the stage of clinical AD was reached (Chételat et al., 2005). Hence, hippocampal volume is considered to be a useful – and widely available – proxy to measure disease burden and progression in AD, including in clinical trials (Choe et al., 2016; Frankó et al., 2013; Kishi et al., 2015; Mielke et al., 2012).

It is now appreciated that estimation of hippocampal volume may also be useful for measuring disease burden or progression in other disorders. For example, hippocampal atrophy has been related to impaired episodic memory in patients with multiple sclerosis (Koenig et al., 2014) and temporal lobe epilepsy (Reyes et al., 2018), and can predict cognitive impairment in patients with PD (Kandiah et al., 2014). Similarly, a cross-sectional study in patients with autoimmune encephalitis (Chakos et al., 2005) found that the severity of the disease course is associated with lower hippocampal volume, which also predicted worse cognitive outcome (Finke et al., 2017).

In psychiatric disorders too, hippocampal volume has been implicated as an important imaging correlate. For example, reduced hippocampal volume has been repeatedly linked to depression (Campbell et al., 2004; Videbech et al., 2004), and a meta-analysis has concluded

¹Parts of this chapter have been published as Nobis et al. (2019)

that smaller hippocampi in depressed patients predict lower response rates to antidepressant drugs (Colle et al., 2016). Similarly, in schizophrenia, hippocampal volume is reduced in chronic cases compared to healthy controls (Adriano et al., 2012). In addition, in a recent investigation on the effects of cognitive remediation therapy for cognitive impairment in schizophrenia, improvement was correlated with increased hippocampal volume post-treatment (Morimoto et al., 2018).

These findings demonstrate that hippocampal volume estimations have the potential to provide important information to assist diagnosis, risk stratification and possibly even monitor the effects of intervention in several conditions. However, three key challenges in the processing, analysis, and interpretation of structural MRI scans outside of a research setting have so far prevented this method from being used in standard clinical practice.

First, in order to calculate brain volumes from a structural MRI scan, the image has to be processed with software requiring expert knowledge. Automated brain segmentation tools, e.g. the model-based FIRST tool in FSL (Jenkinson et al., 2002; Jenkinson et al., 2001), or FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>), and openly available standardised processing pipelines (Alfaro-Almagro et al., 2018), may therefore improve the accessibility of this method in clinical practice.

Second, brain atrophy has not only been described in pathological, but also in healthy ageing. A meta-analysis estimated the average yearly rate of hippocampal atrophy at 1.4% in healthy ageing, and 4.7% in AD (Barnes et al., 2009). Thus, in order to reliably categorise a patient's hippocampal volume, clinicians and researchers require access to age-related normative percentiles to distinguish between healthy and pathological ageing. Few studies have attempted to provide such normative values – or nomograms – not least because of methodological obstacles. The acquisition of large MRI datasets is costly, time consuming, and involves highly specialised hardware and staff. Previously published studies on hippocampal volume in the general population are therefore often limited by small sample sizes, low statistical power, and cohort effects (Button et al., 2013; Fraser et al., 2015; Ioannidis, 2011; Nord et al., 2017).

Third, use of neuroimaging correlates in disorders other than AD, such as psychiatric popula-

tions, poses additional difficulties, as results so far vary considerably. This may be partly due to small sample sizes, but also because of common practices to classify participants with diverse symptoms profiles into one group, such as depressed patients. In addition, many investigations only present effects on questionnaire sum-scores, which may conceal differences between individual symptoms (Fried et al., 2015). It has been argued that psychiatric disorders like depression should be considered heterogeneous symptoms clusters that may overlap with each other, rather than distinct diagnoses. As a result, investigating individual symptoms rather than diagnostic groups with regards to neural correlates may produce more congruous findings.

Here I report a first attempt to provide detailed normative information on the hippocampus in relation to age, sex, symmetry, and mood in 19,793 generally healthy older adults in the UK Biobank resource (<http://www.ukbiobank.ac.uk>). As a comparison, I also show age effects for other temporal, frontal, parietal, occipital, and subcortical volumes. While efforts to harmonize analysis across MRI datasets have not yet been successful, the large dataset analysed here allows an attempt to provide robust normative data when these are used with estimates obtained using the same, or similar, acquisition protocols, hardware and pre-processing pipelines. Associations between volumes of different grey matter areas and mood are documented on the symptom level.

I also supply a web-tool, where a patient's estimated brain volume may be entered to calculate their hippocampal volume status as compared to age-matched norm values (https://lnobis.github.io/HippoFit_Tool/index.html). These norms will become especially useful with the acquisition of longitudinal health outcomes of participants in UK Biobank. The UK Biobank cohort includes over 500,000 participants aged 40-69 years, of which a subset of 100,000 participants will undergo brain imaging. Within this subset, 6000 participants are likely to have developed AD by 2027 (Miller et al., 2016). UK Biobank has been granted access to the UK National Health Service records and can thus follow up on future health outcomes of participants, making it a powerful resource to examine disease progression. In addition, both the acquisition and analysis of MRI are standardised across the scanning sites according to publicly available protocols designed by the UK Biobank Imaging Working Group (www.ukbiobank.ac.uk).

ukbiobank.ac.uk/expert-working-groups). This increases generalisability of results and resolves some of the issues of previous studies using different scanners and protocols.

3.2 Method

3.2.1 Participants

At the time of analysis, the most recent release of brain imaging data of the UK Biobank included scans of 20,542 participants aged 45-80 years. Participants with self-reported neurological and psychiatric disorders, substance abuse disorders or a history of head trauma were excluded from these analyses, leaving a sample of 19,793 generally healthy participants scanned in 2014-2018.

3.2.2 MRI acquisition and analysis

Image acquisition and pre-processing of MRI scans have been performed by UK Biobank. Brain images were acquired on a Siemens Skyra 3.0 T scanner (Siemens Medical Solutions, Germany) with a 32-channel head coil. T1-weighted images with 1 mm³ isotropic resolution were previously analysed with FSL (<http://fsl.fmrib.ox.ac.uk/fsl>), with image-derived phenotypes (IDPs – imaging summary statistics such as brain volume and hippocampal volume) made available for general access. More detailed information on MRI acquisition and analysis have been described elsewhere (Alfaro-Almagro et al., 2018; Miller et al., 2016). UK Biobank also published a standardised MRI analysis pipeline (FMRIB's Biobank Pipeline version 1.0) that is freely available to the public, including the source code (https://git.fmrib.ox.ac.uk/falmagro/UK_biobank_pipeline_v_1) (Alfaro-Almagro et al., 2018).

3.2.3 Analysis

All calculations were performed in *MATLAB 2017b* with the exception of Joinpoint regression, which was computed with the *Joinpoint Regression Program* (Version 4.6.0.0; Surveillance Research Program, National Cancer Institute) (Kim et al., 2000).

Data preparation

Outliers in brain volume estimations were identified and excluded based on a Median Absolute Deviation of > 5 from the median, as this method is more robust to non-Gaussian distributions. The cut-off of 5 was chosen by visual inspection of data histograms. Brain volumes were always corrected for scanning date, and when indicated, for head size and age. This was done with a General Linear Model, 'regressing out' variance accounted for by the confounds. Brain volumes were corrected for scanning date to adjust for gradual changes in the scanner hardware, an effect called scanner drift. These changes lead to variation of the signal distribution in scans over time, resulting in over- or underestimations of volumes (Takao et al., 2012). Head size was corrected for using a head scaling variable obtained from the MRI scan, which is the volumetric scaling for the transformation of the native head image to standard space, with final scaling being driven by outer-skull surface (Smith et al., 2004; Smith et al., 2002). A number of studies have shown that global and regional brain volumes correlate positively with head size (Barnes et al., 2010). Thus, when investigating sex differences in brain volume, head size should be corrected for. This was done by regression rather than using a ratio measure (e.g. brain volume/head size), as not all brain volumes scale proportionately with head size (Barnes et al., 2010). However, measures of head size related variables vary widely in the literature (e.g. total intracranial volume, total brain volume, MRI head scaling, or body height), leading to heterogenous results. I therefore report both head size corrected and un-corrected results.

Statistics

For comparison I also present analyses for volumes of some structures near the hippocampus within the temporal lobe, and all remaining cortical grey matter volumes. Available volume IDPs (originally in mm³, z-scored here) within the UK Biobank dataset were previously calculated using FSL-FAST in conjunction with cortical atlas regions-of-interest (Miller et al., 2016; Alfaro-Almagro et al., 2018).

T-tests (with Bonferroni-correction for resulting p-values) were calculated for differences in hippocampal volume estimations by method (FSL-FIRST, vs. FSL-FAST within Atlas-based

regions of interest; paired t-test). While FSL-FIRST is a segmentation/registration tool that estimates subcortical volumes based on shape and appearance models (Patenaude et al., 2011), FSL-FAST is a brain tissue segmentation tool (Zhang et al., 2001), with which subcortical volumes were estimated from grey matter within Atlas-based regions of interest.

Normative Percentiles

The 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97.5th percentiles for hippocampal volume (left and right) and total grey matter were calculated separately for males and females. This was done using residuals from a corresponding sliding-window analysis (see below), that were added back onto the mean of the brain volume estimations. These values were then used as the age-adjusted input to calculate the percentiles. Percentiles are provided for volumes corrected for head size and scanning date. Percentiles corrected for scanning date, but uncorrected for head size, as well as percentiles for hippocampus-to-total grey matter ratio can be found in **Appendix A, Figures A.1-A.12**.

Sliding-window curves for relationship of volume and age

To analyse trajectories and quantiles of measured volumes as a function of age, I applied a sliding-window, model-free analysis, in which an age-window of observations of fixed age-quantile width was moved along the age distribution (based on function '*conditionalPlot*' in <https://osf.io/vmabg/>; Manohar, 2019). The windows overlapped, so that each window contained 10% of the participants. The analysis of interest was performed for each window, providing in this case the mean volume of brain structure, such as hippocampal volume. The volume estimations were then smoothed using the moving average method with a gaussian kernel of 20. Results from using varying smoothing kernels and quantile widths can be found in **Appendix A, Figures A.13-A.16**. Each mean z-scored brain volume of interest was plotted against the mean bin centre of age, along with standard errors of the mean. This provided an estimate of mean brain volume that varied smoothly as a function of age. This method enables representative contours to be calculated for each quantile as a function of age, in a non-parametric, data-driven manner. Volumes were corrected for head size and scanning date. The trajectory for hippocampal volume across age, uncorrected for head size, is in-

cluded in **Appendix A, Figure A.17**.

I tested for differences in age at which the hippocampal ratio curves peaked between men and women. This was performed using a permuted t-statistic, correcting p-values for false discovery rate. Specifically, I permuted matched age bins of the two groups, i.e. shuffling men and women within age-windows. I then calculated the p-value as the proportion of permuted datasets ($n = 5000$), which produced a mean difference between the peaks of the curves at least as extreme as the one observed from the actual data.

This data-driven analysis is particularly useful for large samples. As opposed to traditional curve fitting methods, it makes few assumptions, has only one free parameter (number of samples per bin), and improves visualisation and interpretation of results and corresponding errors. Note that as there are fewer participants at the minimum and maximum age limits compared to around the mean age, this method leads to wider age ranges for the lowest and highest percentile bins. As shown in **Appendix A, Figure A.18** similar effects to the main analysis were observed when using windows of fixed age bins (5 years width), rather than bins of fixed numbers of observations. Again, the mean brain volume was computed within each age bin, and plotted against the mean bin centre of that bin, along with standard errors.

As a parametric alternative to using sliding-window analysis for the estimation of normative percentiles, I present results from a Generalised Additive model for Location, Scale and Shape (GAMLSS) in **Appendix A, Figure A.19**. This method has previously been used for growth chart percentiles (Cole, 2021), and has some advantages over a non-parametric method as it produces smooth percentile curves, and allows extrapolation to the youngest and oldest age groups. However, the sliding-window analysis was chosen here as it generates a true representation of the raw data, makes no assumptions about the shape of the distribution, and has no risk of overfitting.

Joinpoint regression

To determine if there were points at which the rate of hippocampal atrophy changed across age, I used joinpoint regression. This is a regression analysis recommended by the National Cancer Institute (<https://surveillance.cancer.gov/joinpoint/>, Kim et al., 2000) to estimate

time points of change in trend data, often used for changes in cancer incidence rates. The analysis fits separate line segments to trend data, which are connected at positions called joinpoints. No joinpoints would suggest no changes in slope, and thus no changes in, for example, cancer incidence. Here I applied joinpoint regression to test for the presence of one or more joinpoints (i.e. inflection points) along the brain volume trajectories across age. Thus, instead of cancer incidence rate, here the dependent variable was mean volume per 1-year, non-overlapping age window. Bins of 1-year width were chosen to retain adequate accuracy with a feasible number of datapoints. Similarly, instead of diagnosis year, the independent variable used here was age group.

The Joinpoint Regression Program fits between zero and a chosen maximum number of joinpoints to the data. Starting from zero joinpoints, I tested whether more joinpoints are statistically significant ($p < .05$) using a Monte Carlo Permutation method, assuming uncorrelated errors. The maximum was chosen at 4 joinpoints, as recommended for the number of data points in this dataset using grid search (Kim et al., 2000). This recommendation is based on allowing at least seven data points to find one joinpoint, and at least two data points between consecutive joinpoints. A joinpoint may also not occur within two data points from the beginning or end of a series.

This analysis was done with hippocampal volume, rest of total grey matter volume (total grey matter minus hippocampal volume), superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, fusiform gyrus, parahippocampal gyrus, and temporal pole volume, for men and women separately. All volumes were corrected for scanning date and head size. More detailed information on methods used within the Joinpoint Regression Program can be found at <https://surveillance.cancer.gov/help/joinpoint/>.

Associations with mood

While detailed mood questionnaires are included in the UK Biobank, only a reduced binary choice (yes/no) questionnaire on current mood symptoms was filled out on the day of MRI scanning. Items addressed 'mood swings', 'feeling miserable', 'irritability', 'sensitivity', 'feeling fed-up', 'nervousness', 'being a worrier', 'tenseness', 'worrying for too long', 'suffering

from nerves', 'loneliness', 'guilt', and 'risk taking'. Both imaging and mental health data were available for between 21,012 and 21,620 participants depending on the mental health questionnaire item. T-tests with Bonferroni correction were run for a general analysis of volume differences between groups with and without each symptom, before and after volumes were corrected for age.

3.3 Results

3.3.1 Demographics

Demographics as well as means and standard deviations for uncorrected hippocampal volume with respect to head size are summarised in **Table 3.1**. Number of observations exclude outliers (e.g. 137 outliers removed for left hippocampal volume, 134 outliers removed for right hippocampal volume).

| | Age Mean \pm Std | Total grey matter Mean \pm Std | Average hippocampus p-value | N |
|--------|------------------------|--------------------------------------|--------------------------------------|-------|
| Female | 62.31 \pm 7.34 years | 594,250 \pm 48,028 mm ³ | 3765.18 \pm 366.75 mm ³ | 10463 |
| Male | 63.67 \pm 7.58 years | 641,307 \pm 51,379 mm ³ | 3972.97 \pm 431.03 mm ³ | 9330 |
| Total | 62.95 \pm 7.48 years | 616,484 \pm 54,917 mm ³ | 3863.94 \pm 411.56 mm ³ | 19793 |

Table 3.1 – Demographics of sample. Mean age, total grey matter, hippocampal volume, and sample size by sex.

Mean age was 62.95 years (*std* = 7.48 years), with males slightly older than females ($p < .001$, *Hedges' g* = .18). Mean total grey matter volume (uncorrected for head size) was significantly larger in males than females ($p < .001$, *Hedges' g* = .95), as was the case for uncorrected average hippocampal volume ($p < .001$, *Hedges' g* = .52).

3.3.2 Method of segmentation affects hippocampal volume estimates

Mean hippocampal volumes differed between methods. On average estimates calculated with FSL-FAST with atlas were larger (*mean* = 4285.08 mm³, *std* = 309.32 mm³) than estimates calculated with FSL-FIRST (*mean* = 3863.40 mm³, *std* = 353.61 mm³, $p < .001$, *Hedges' g* =

1.27). This overestimation of hippocampal volume with FSL-FAST compared to FSL-FIRST is further demonstrated in **Figure 3.1**, which shows a Bland-Altman plot of average hippocampal volume. Estimates were corrected for head size, scanning date, and age. However, there were no differences in the overall results from the joinpoint and sliding-window analyses between the two hippocampal volume estimates (see sections below). As FSL-FIRST is the recommended and most widely used method for subcortical segmentation, I present analyses throughout using the IDPs that were generated using FSL-FIRST.

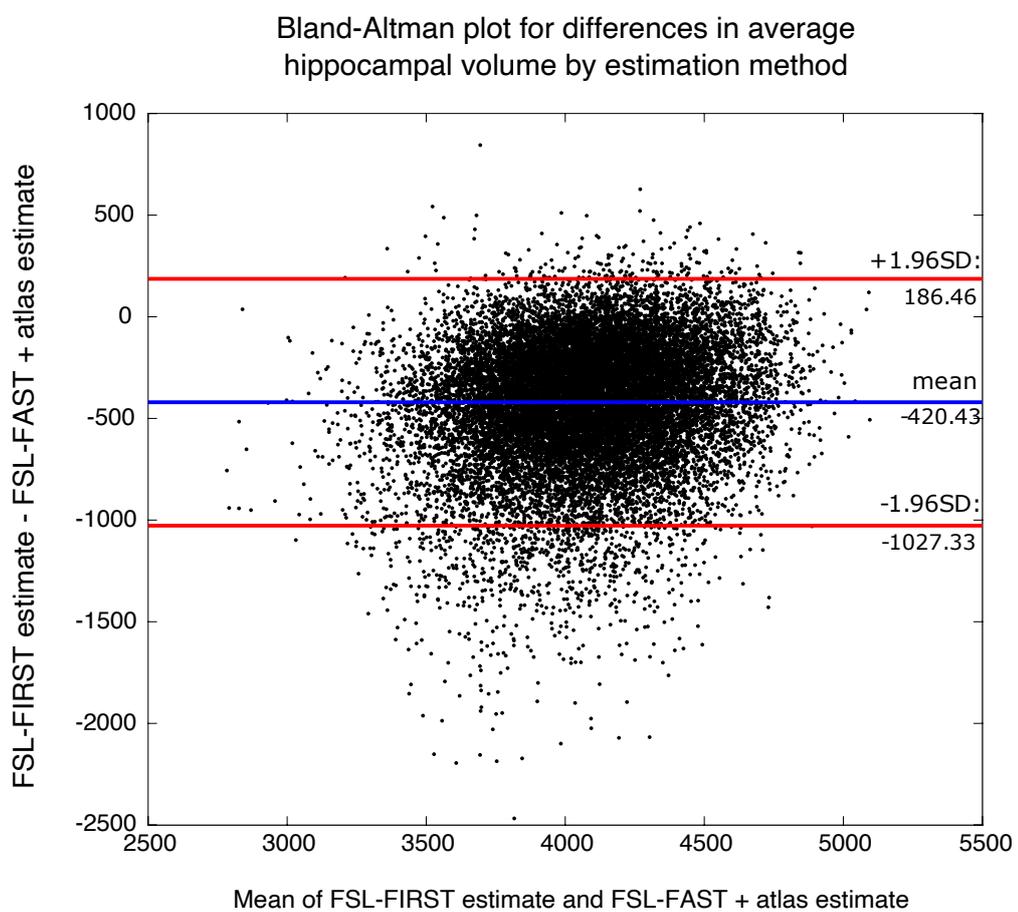


Figure 3.1 – Bland-Altman plot for differences in average hippocampal volume by estimation methods. Mean average hippocampal volume of FSL-FIRST and FSL-FAST + atlas estimates on the x-axis is plotted against the difference between the two methods on the y-axis. The blue line represents the mean of the difference, red lines represent 1.96SD above and below the mean. Perfect agreement between the methods would be reflected by a mean of zero with little spread across the y-axis.

3.3.3 Normative percentiles

Example nomograms for the 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97.5th percentiles for left and right hippocampal volume in women and men, corrected for head size, are shown in **Figures 3.2 & 3.3**. Overlapping, age-adjusted windows of 10% of observations are plotted, with age on the x-axis corresponding to the median age of participants within the overlapping quantile windows. Because there are fewer observations within particularly young (starting at 45 years) and particularly old (up to 80 years) participants, quantile bins for the youngest and oldest participants are wider, and thus have a median age around 50 and 75 years, respectively. Additional moving average smoothing with a gaussian kernel of 20 reduced the age-span further and resulted in percentiles plotted across ages 51 years to 72 years (52 years to 73 years for males).

The nomograms are provided separately for women and men as the previous analyses have shown differential sex-by-age trajectories.

Head-size corrected percentiles can be used by applying the following formula to the corresponding uncorrected brain volume, using the 'Head Scaling' variable calculated from the automated pipeline, and the given slopes for either left hippocampus, right hippocampus, or total grey matter. The formula is based on a general linear model and calculates head-size corrected volumes of left, right, or grey matter volume by subtracting the product of demeaned head scaling and the corresponding slope from the uncorrected volume (**Table 3.2**).

| | Left Hippocampus | Right Hippocampus | Total grey matter |
|---|------------------|-------------------|-------------------|
| b | -1340.89 | -1532.24 | -354,545.84 |

$$\text{Volume corrected} = \text{Volume uncorrected} - [(\text{Head Scaling} - 1.29874) * b]$$

Table 3.2 – Head size correction parameters and formula

The provided nomogram webtool (https://lnobis.github.io/HippoFit_Tool/index.html) enables clinicians to quickly calculate a patient's percentile by entering the volume estimation

from the automated analysis pipeline. The tool then automatically applies head size correction, if the option is selected. For example, a female aged 64 years with a left hippocampal volume of 3150 mm³ (corrected for head size) would score within the 5th percentile. This means that 95% of the women closest to her age in the current sample had a larger volume, highlighting potentially pathological atrophy and providing additional information for the diagnosing clinician.

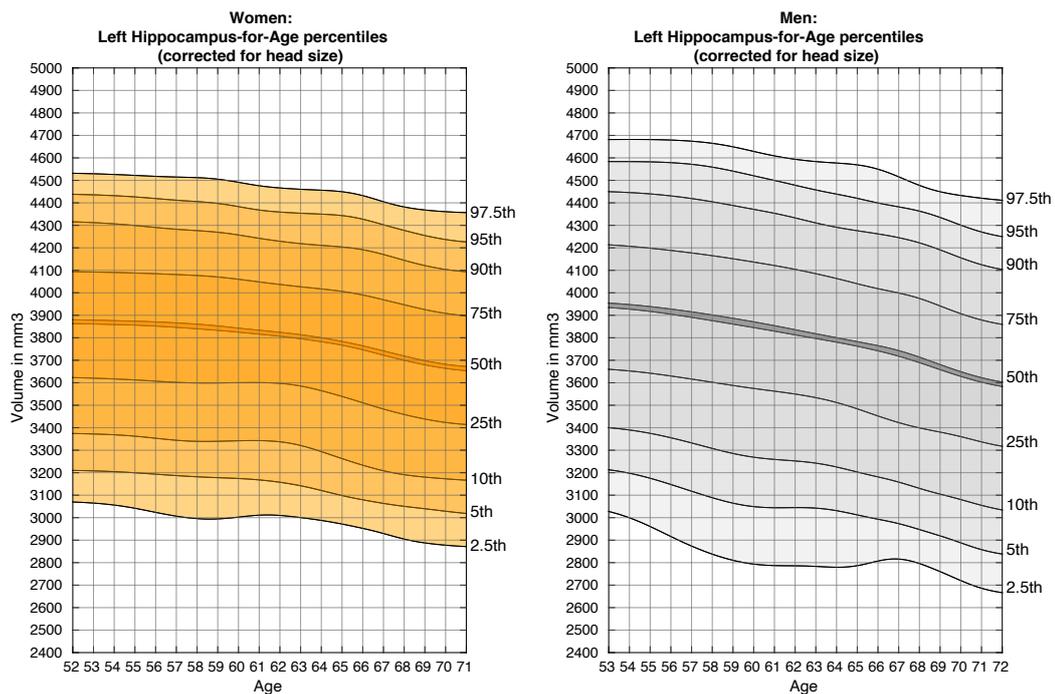


Figure 3.2 – Nomogram of left hippocampal volume for women and men, corrected for head size. Figures show the quantiles of hippocampal volume for the group of individuals in each age window. The x-axis indicates the median age of the window. The midline indicates the median. For someone with a given age and volume, a percentile can be read off the chart, indicating the proportion of the Biobank cohort who have a hippocampal volume below that of the person.

3.3.4 Brain volume characteristics

Hippocampal volumes differed between hemispheres, but not between men and women

A paired t-test resulted in a significant difference between right and left hippocampal volume (uncorrected for head size) with *right larger than left* volume asymmetry ($p < .001$, Hedges' $g = .24$). Head size was not corrected for as left/right differences are within-subject, and will be

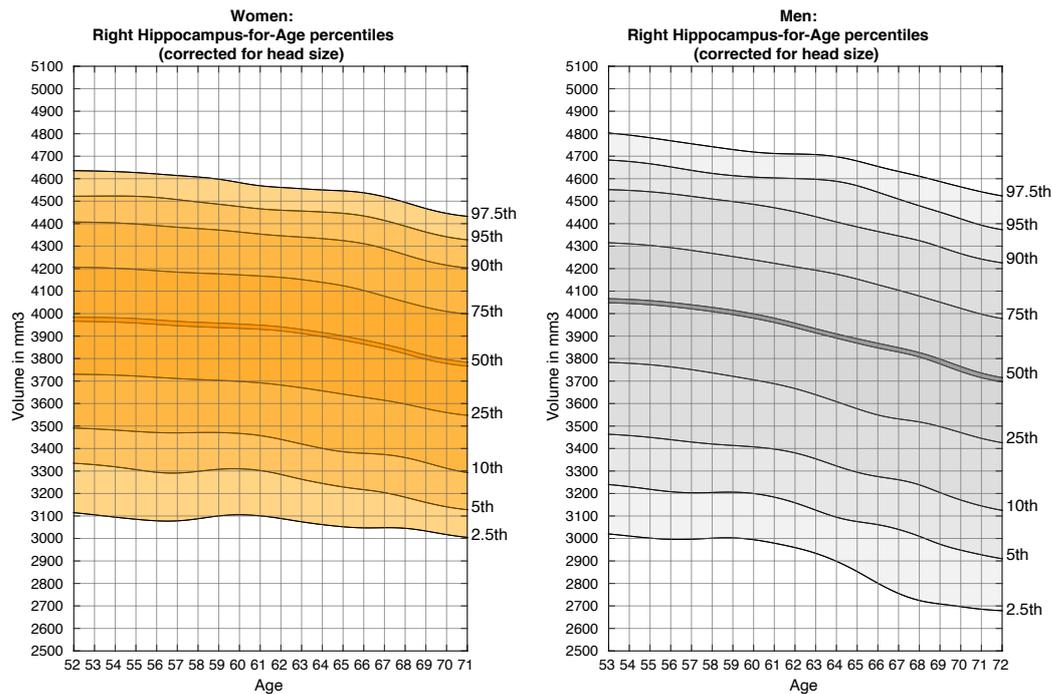


Figure 3.3 – Nomogram of right hippocampal volume for women (orange) and men (grey), corrected for head size. Figures show the quantiles of hippocampal volume for the group of individuals in each age window. The x-axis indicates the median age of the window. The midline indicates the median. For someone with a given age and volume, a percentile can be read off the chart, indicating the proportion of the Biobank cohort who have a hippocampal volume below that of the person.

largely unaffected by head size. There was no correlation between handedness and asymmetry for any of the tested volumes (calculated by asymmetry = left volume - right volume; all $p > \alpha/7 = .007$).

There was no significant difference of mean (average) hippocampal volume between men and women ($p > .05$) after correction for head size. Total grey matter volumes after head size correction showed a small sex effect, with women having larger volumes than men ($p < .001$, *Hedges' g* = .15).

Trajectory of mean hippocampal volume with age demonstrates an inflection

Mean hippocampal volume, total grey matter volume (both corrected for head size), and hippocampal volume are plotted as a percentage of grey matter volume as a function of age. To plot this, I used a sliding-window method, using windows of 10% of the population (**Figure 3.4**). The x-axis displays the median age of participants within the overlapping quantile win-

dows.

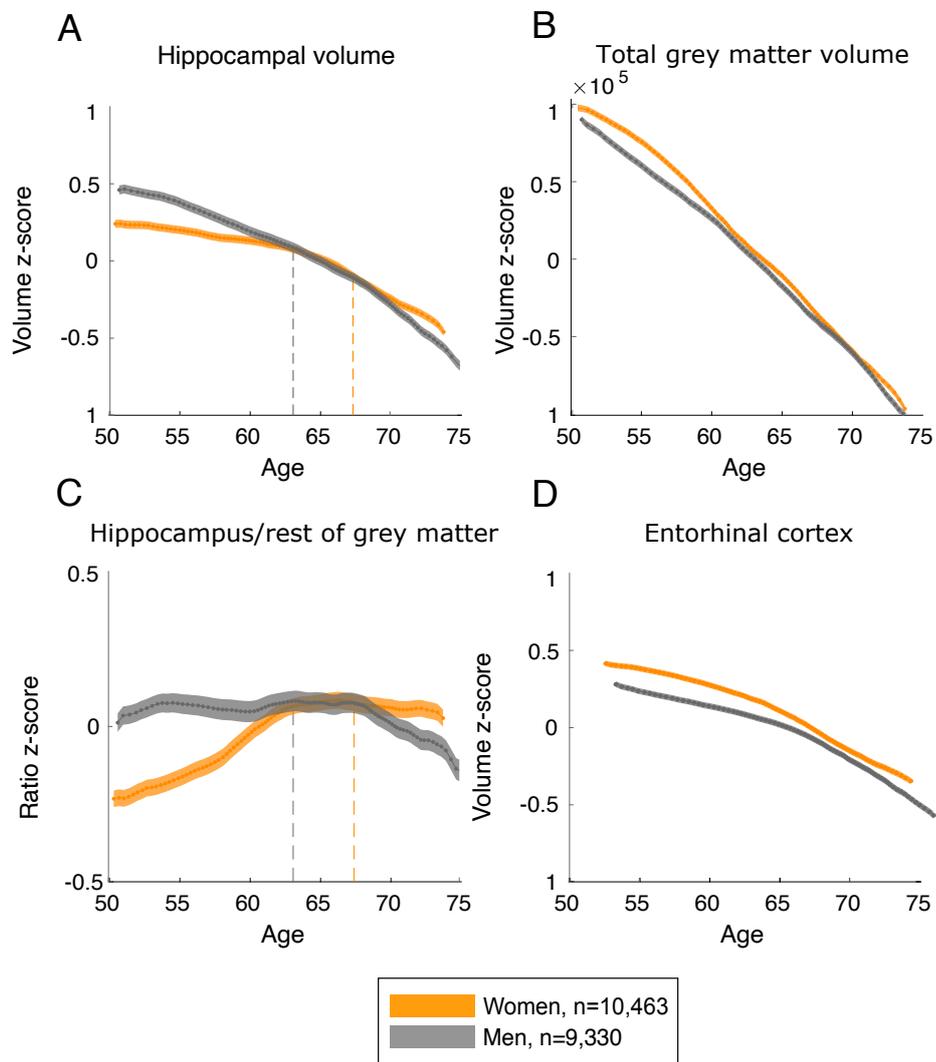


Figure 3.4 – Trajectory of hippocampal volume with age. Dashed lines indicate points of maximum ratio. A. Mean bilateral hippocampal volume including standard errors as a function of age, corrected for head size. **B.** Mean total grey matter volume including standard errors as a function of age, corrected for head size. **C.** Mean hippocampal volume to rest of grey matter ratio including standard errors as a function of age. **D.** Mean entorhinal cortex volume including standard errors as a function of age.

Because there are fewer observations within particularly young and particularly old participants, the median ages of the quantile bins for the youngest and oldest participants are around 50 and 75 years, respectively. Plots for bilateral hippocampal volume uncorrected for head size, plots for fixed 5-year age-bins rather than fixed quantiles for bilateral hippocampal

volume, as well as left and right hippocampal volumes are provided in **Appendix A, Figures A.17-A.18, A.20**.

Whereas whole brain volume appears to decline linearly as a function of age for both men and women (**Figure 3.4 B**), in women the rate of hippocampal volume loss increases at around 60 years (**Figure 3.4 A**). This inflection point (i.e. maximum slope) can be calculated by numerical differentiation, as shown in **Appendix A, Figure A.21** (women: $bin(max\ slope) = 58.67 - 61.28$ years, $max\ slope = -0.27$; men: $bin(max\ slope) = 44.56 - 52.73$ years, $max\ slope = -2.52$).

To compare hippocampal volume more directly to the rest of the grey matter, the ratio between these two volumes was calculated. In women, the ratio of hippocampal volume to the rest of grey matter peaks around age 67 years ($bin(max\ ratio) = 66.33$ years - 68.44 years), suggesting that the rate of volume loss in the hippocampus is smaller relative to the rest of grey matter (**Figure 3.4 C**). As age increases further, this pattern is then reversed. In men, the ratio of hippocampal volume relative to the rest of grey matter peaks around age 63 years ($bin(max\ ratio) = 61.69$ years - 64.32 years), before declining thereafter. These sex differences in the age of transition (maximum ratio) were significant. Men reached peak hippocampal ratio at a significantly younger age than women, calculated by permuting matched age bins of the two groups to compute the null distribution of the difference in the peak ($n(permutations) = 5000$, $p < .001$). This p-value represents the proportion of permuted datasets that produced a mean difference between the peaks of the curves at least as extreme as the one observed from the actual data. These results were replicated using no smoothing (**Appendix A, Figure A.13**), a smoothing kernel of 10 rather than 20 (**Appendix A, Figure A.14**), as well as quantile bins with 20% (**Appendix A, Figure A.15-A.16**) instead of 10% of participants (range of median age at ratio maxima for women: $67.37 - 68.21$ years; for men: $62.48 - 63.32$ years).

In order to confirm the position of a change in slope for the trajectory of hippocampal volume, joinpoint regression (Kim et al., 2000) was applied. This method tests statistically for the presence of zero, or up to four inflection points (joinpoints) in the slope of mean hippocampal volume across age. The maximum number of joinpoints tested for is selected based on the number of observations. There was one inflection point for both men and women (**Figure 3.5 A & B**). In women, there was a significant change in slope at age-group 64-65 years (change of

slope $\Delta m = -32.44\text{mm}^3$; age 95% *confidence interval* (CI) [61-62 years, 67-68 years], $p < .0001$). In men, the change in slope was significant at age-group 63-64 years (change of slope $\Delta m = -26.45\text{mm}^3$ 95% CI [58-59 years, 66-67 years], $p < .0001$; see **Table 3.3** for Model estimates).

| | Women | Men |
|--------------------------------------|------------------------|------------------------|
| Degrees of Freedom | 21 | 21 |
| Joinpoint | 64-65 years | 63-64 years |
| Joinpoint 95% Lower Confidence Level | 61-62 years | 58-59 years |
| Joinpoint 95% Upper Confidence Level | 67-68 years | 66-67 years |
| Slope Change Estimate | -32.44 mm ³ | -26.45 mm ³ |
| Slope Change Std Error | 4.04 mm ³ | 4.94 mm ³ |
| Slope Change Test Statistic* | -8.03 | -5.35 |
| Slope Change p-value | <.0001 | <.0001 |

Table 3.3 – Model Estimates from joinpoint regression of hippocampal volume. * the slope change test statistic is the parameter estimate divided by the standard error that follows a t-distribution with 21 degrees of freedom.

For the rest of the grey matter, there was one joinpoint in the slope (total grey matter – bilateral hippocampus) across age for women (**Figure 3.5 C**), with a significant change in slope of $\Delta m = -1273.98\text{mm}^3$ at age-group 56-57 years ($t(21) = -2.98$, 95% CI [53-54 years, 58-59 years], $p = .007$). By contrast, there was also a small, but significant change in slope for the rest of grey matter across age in men at age-group 62-63 years ($\Delta m = -754.14\text{mm}^3$, $t(21) = -4.87$, 95% CI [57-58 years, 66-67 years], $p < .0001$) (**Figure 3.5 D**).

Trajectories of temporal lobe volumes with age

Next, I aimed to demonstrate that these inflections were specific to the hippocampus. Mean volumes (corrected for head size) were plotted for the remaining brain areas within the temporal lobe available from UK Biobank, namely parahippocampal gyrus, fusiform gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, and temporal pole (**Figure 3.6**). The same sliding-window and joinpoint regression methods were used. All

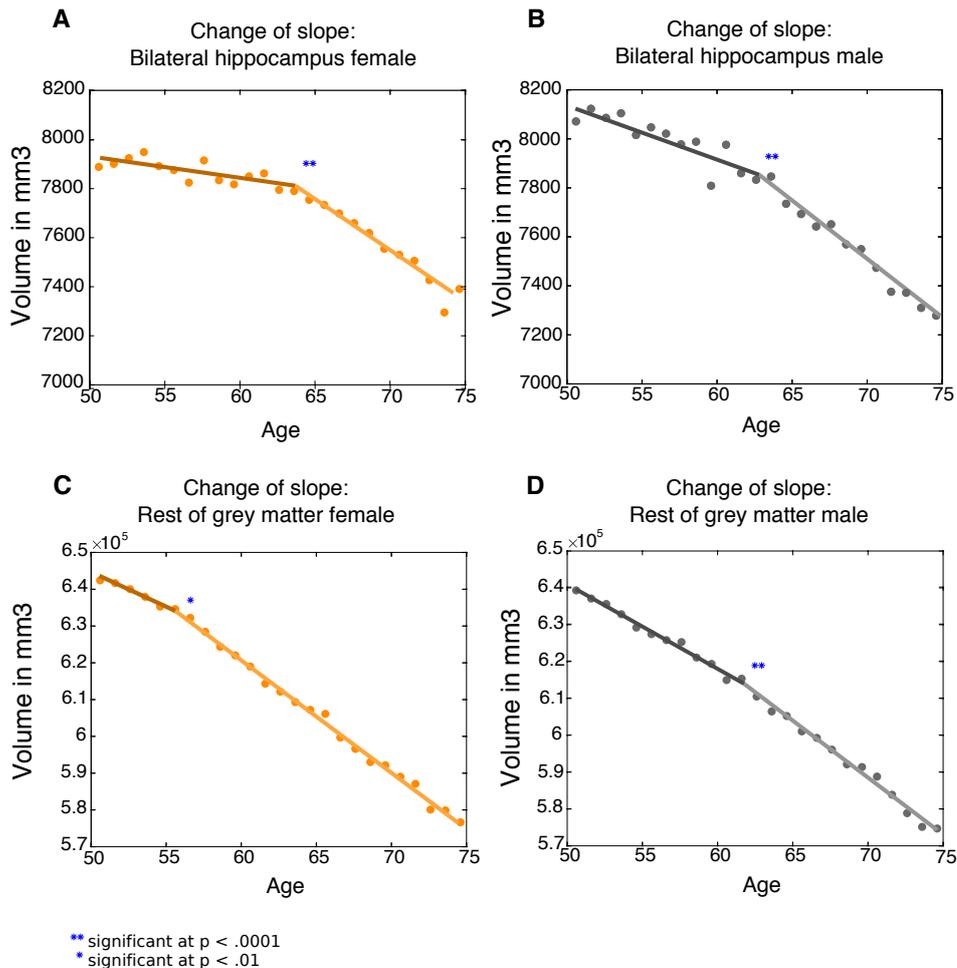


Figure 3.5 – Joinpoint analysis for hippocampal and total grey matter volume. A. Joinpoint (change of slope) in bilateral hippocampal volume over age in females B. Joinpoint bilateral hippocampus in males. C. Joinpoint in rest of grey matter volume (total grey matter – bilateral hippocampus) in females. D. Joinpoint in rest of grey matter for males.

these temporal lobe regions show a largely linear negative relationship with age. In keeping with this, and in contrast to the findings for the hippocampus, there were no significant joinpoints or changes in slope for either men or women in superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus and fusiform gyrus ($p > .05$). However, there was a significant joinpoint for both men and women in parahippocampal gyrus volume, similar to the joinpoints found for the hippocampus (women: $\Delta m = -26.97\text{mm}^3$ at age-group 66-67 years, $t(21) = -5.40$, 95% CI [62-63 years, 70-71 years], $p < .0001$; men: $\Delta m = -30.81\text{mm}^3$ at age-group 59-60 years, $t(21) = -3.77$, 95% CI [56-57 years, 64-65 years], $p = .001$). There was also a significant joinpoint in volume of temporal pole in men, at age-group 55-56 years ($\Delta m = -76.97\text{mm}^3$, $t(21) = -2.57$, 95% CI [53-54 years, 57-58 years], $p = .02$).

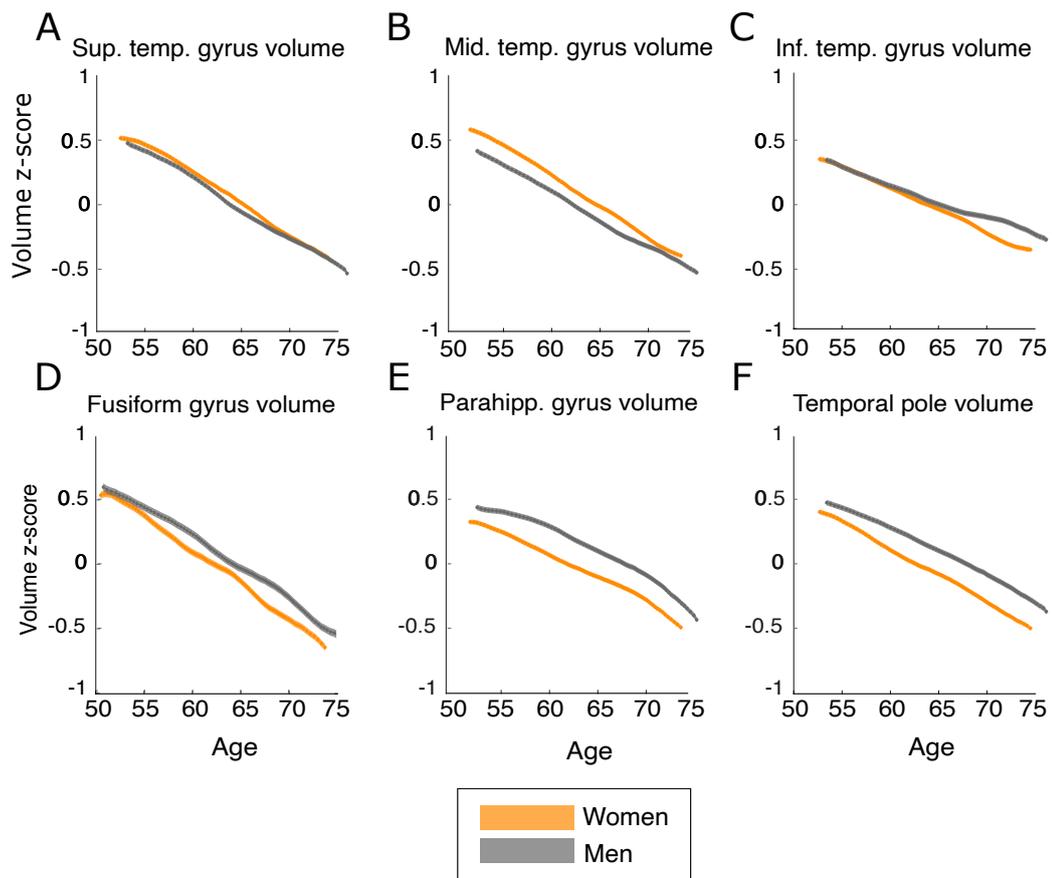


Figure 3.6 – Trajectory of temporal lobe volumes with age, corrected for head-size. All sections of the temporal gyrus (A-C), the fusiform gyrus (D), parahippocampal gyrus (E), and volume of the temporal pole (F) show largely linear decreases with age.

In addition, the ages of the peak ratios with respect to the rest of grey matter differs between regions. For example, the ratios of superior (women: $bin(max\ ratio) = 52.73$ years - 55.85 years; men: $bin(max\ ratio) = 44.45$ years - 52.73 years) and middle temporal gyrus volume (women: $bin(max\ ratio) = 49.30$ years - 53.11 years; men: $bin(max\ ratio) = 48.30$ years - 53.11 years) to rest of grey matter peak in the youngest age groups of the sample. By contrast, ratios for inferior temporal gyrus (women: $bin(max\ ratio) = 71.92$ years - 80.65 years; men: $bin(max\ ratio) = 73.41$ years - 80.27 years), temporal pole (women: $bin(max\ ratio) = 70.22$ years - 73.45 years; men: $bin(max\ ratio) = 72.25$ years - 75.56 years) and parahippocampal volume (women: $bin(max\ ratio) = 71.92$ years - 80.65 years; men: $bin(max\ ratio) = 73.41$ years - 80.27 years) to the rest of the grey matter peak at the oldest age groups. The ratio of fusiform

gyrus volume to the rest of grey matter volume does not show pronounced change over age. There were no significant differences in the age of peak ratio between men and women for any of these temporal lobe regions, calculated by permutation testing ($n(\text{permutations}) = 5000$, all $p > .05$), except for fusiform gyrus ($p = .004$).

Trajectories of other subcortical, frontal, parietal, and occipital volumes with age

To assess whether any other brain areas show previously undetected distinct age effects, remaining IDPs in the UK Biobank are plotted in groups of subcortical (**Figure 3.7**), frontal (**Figure 3.8**), parietal (**Figure 3.9**), and occipital lobe volumes (**Figure 3.10**). With the exception of the globus pallidus, nucleus accumbens, amygdala, and anterior section of the cingulate gyrus, all volumes decline linearly with age. Volumes for the globus pallidus and nucleus accumbens decreased in a similar manner to the hippocampus, with an acceleration of loss around 60-65 years. There was no apparent decline in the volumes of the amygdala and anterior cingulate gyrus.

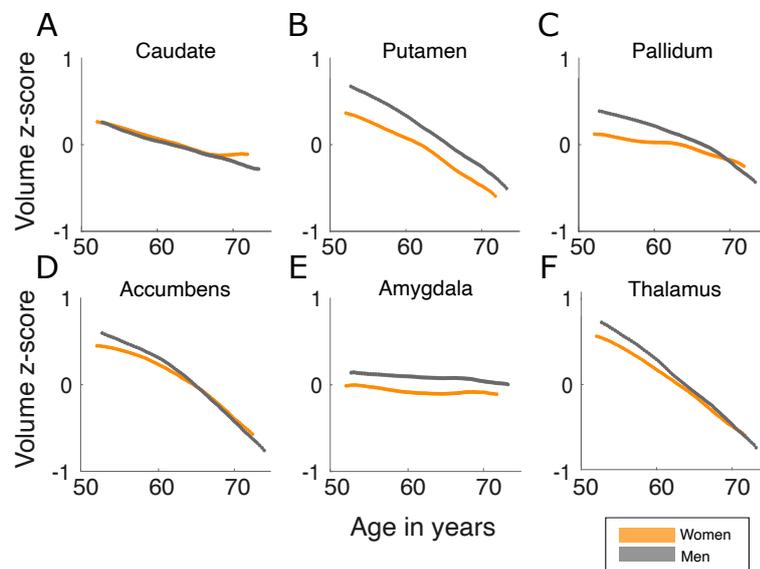


Figure 3.7 – Trajectory of subcortical volumes with age, corrected for head-size. While caudate (A), putamen (B), and thalamus (F) volume decline linearly with age, volume of the globus pallidus (C) and nucleus accumbens (D) have a similar inflection point as reported in the hippocampus. Amygdala (E) volume is largely stable across age groups.

Strong sex differences were present in volumes of the putamen, globus pallidus, amygdala, anterior cingulate gyrus, supramarginal gyrus, postcentral gyrus and lingual gyrus.

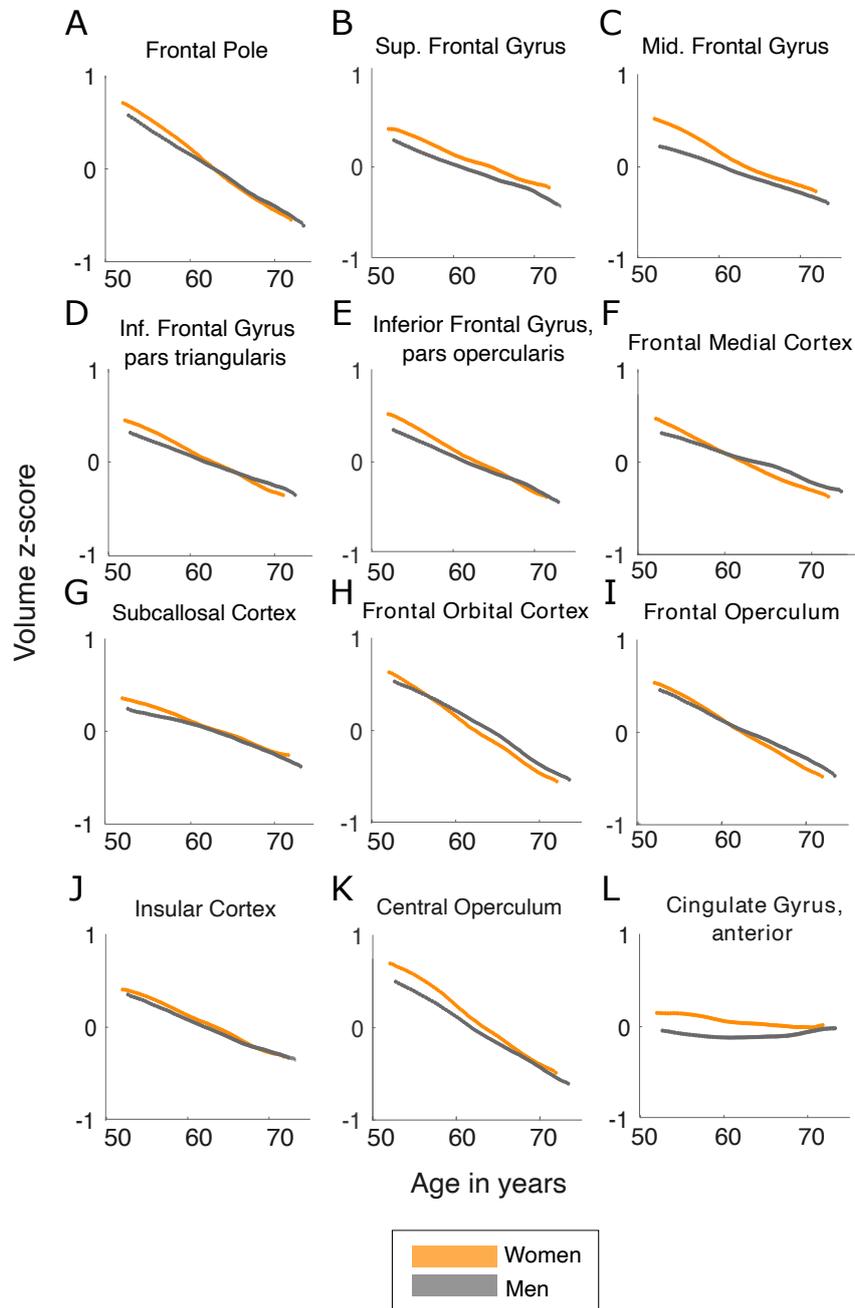


Figure 3.8 – Trajectory of frontal lobe volumes with age, corrected for head-size. All frontal areas here declined linearly with age, with the exception of the anterior section of the cingulate gyrus (L).

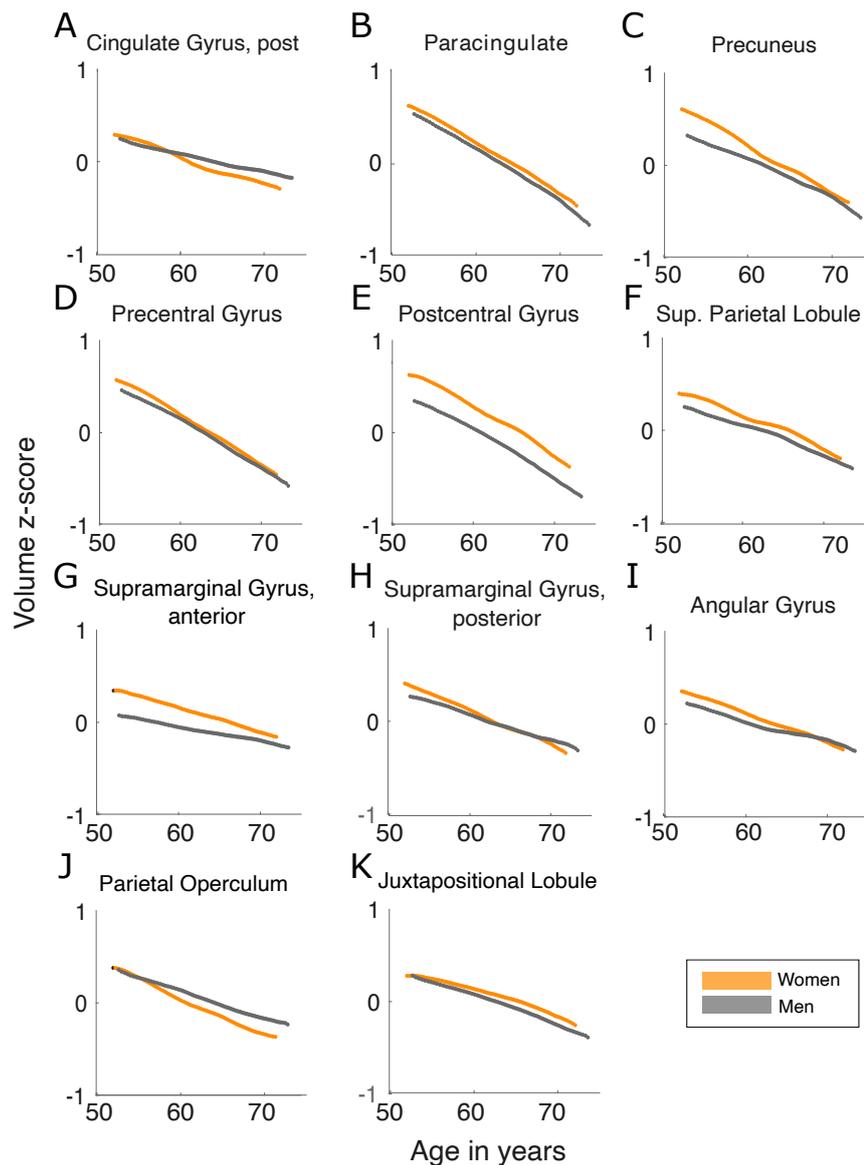


Figure 3.9 – Trajectory of parietal lobe volumes with age, corrected for head-size. All parietal lobe volumes plotted here show a generally linear decline with age. Paracingulate (B) and precentral (D) and postcentral (E) gyrus volume decrease most strongly. Generally, women had slightly larger parietal lobe volumes than men, with the exception of the posterior section of the cingulate gyrus, and the parietal operculum at older ages.

3.3.5 Relationship with mood symptoms

Out of 1573 t-tests (13 questions * 121 brain volume IDPs), 300 associations were significant after Bonferroni correction for multiple testing (Figure 3.11 A), and only seven associations remained significant after correcting the IDPs for age (Figure 3.11 B).

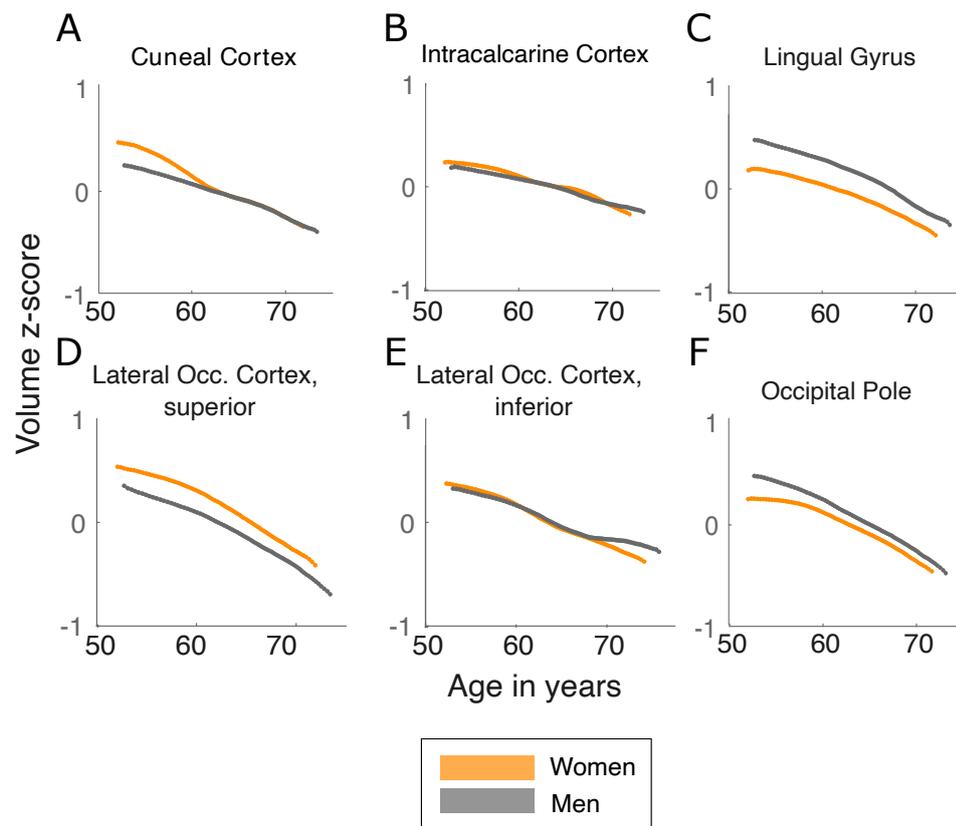


Figure 3.10 – Trajectory of occipital lobe volumes with age, corrected for head-size. Occipital lobe volumes declined mostly linear with age, with similarly steep slopes across volumes.

Before adjusting for age, the most significant differences in volume were found for the two items on feeling miserable, and having mood swings (**Figure 3.11 A**). Those with the largest effect sizes corresponded to total grey matter and total brain volume (grey + white matter), respectively, which were smaller in those participants who did not report the symptom than in participants who did (feeling miserable & total grey matter: $t(19451) = 11.62$, $p = 4.27e-31$, *hedges' g* = .17; having mood swings & total brain volume: $t(19542) = 12.20$, $p = 4.49e-34$, *hedges' g* = .18).

In only one questionnaire item, feeling nervous, were there no significantly different IDPs between groups. Generally, total grey matter, white matter, or brain volume were most strongly associated with individual items from the mental health questionnaire, but significant results were found for each part of the brain, without a clear pattern (**Figure 3.12 A**).

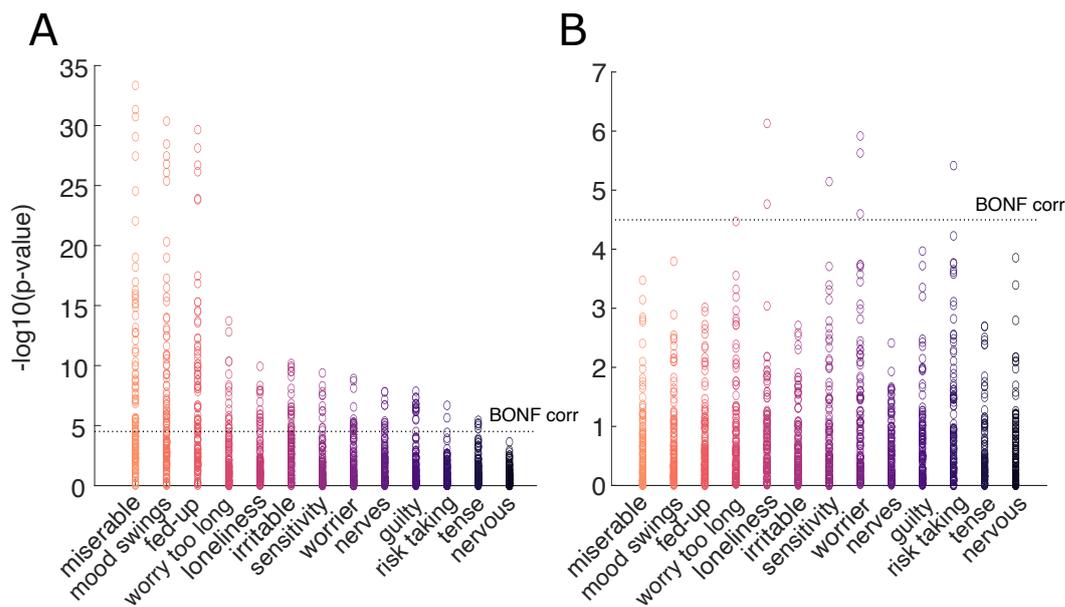


Figure 3.11 – Number of significant IDP differences across different mental health questionnaire items drops after correcting for age. A. Strongly significant differences between IDPs in people who reported mood symptoms were found for items addressing feeling miserable, having mood swings, and feeling fed up. Very little to no associations were found for items on nervousness, tenseness, and risk taking. **B.** Only items corresponding to feeling lonely, being a worrier, being sensitive and taking risks continue to be associated with significantly different IDPs.

Differences in (right) hippocampal volume were significant for questionnaire items 'Feeling miserable' and 'Being fed-up' ($t(19409)=5.32$, $p=1.03\text{e-}07$, $\text{hedges' } g=.08$; $t(19309)=4.48$, $p=7.61\text{e-}06$, $\text{hedges' } g=.07$). In both cases, right hippocampal volumes were smaller in people who did not experience the symptom, than in people who did.

After adjusting for age, the strongest effect sizes corresponded to smaller left and right thalamus volume in people who reported to feel lonely (**Figure 3.11-3.12 B, Table 3.4**). Volumes of the left and right temporal pole and right postcentral gyrus were all smaller in participants who described themselves as worriers. In contrast, volume of the left superior lateral occipital cortex was larger in people who were taking risks. Being sensitive was associated with smaller right precuneus volume.

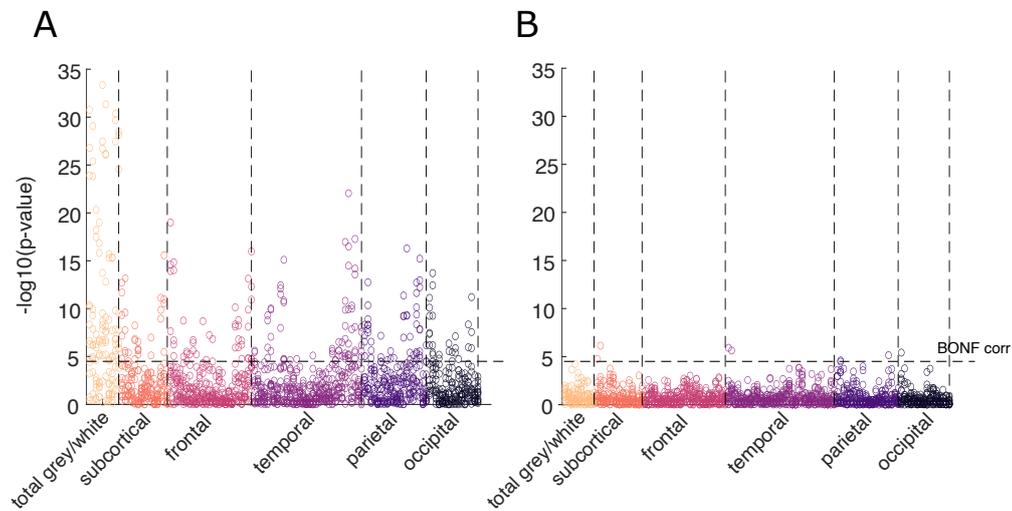


Figure 3.12 – Significant IPD differences across different brain areas before and after age correction. **A.** Strongest effects were found for IDPs measuring total grey and white matter, though significant differences were found for every part of the brain. **B.** Significant differences are largely reduced after correction for multiple testing, without any effects in total grey or white matter and frontal areas.

| Item | IDP | Yes | No | t(df) | p | Hedges' G |
|-----------------|------------------------------------|-----------------------------------------|-----------------------------------------|---------------------|----------|-----------|
| | | Mean \pm Std | Mean \pm Std | | | |
| Feeling lonely | Left thalamus | 7738.6 \pm 511.3 mm ³ | 7784.9 \pm 516.0 mm ³ | t(19502) = -4.3 | 1.72e-05 | 0.09 |
| | Right thalamus | 7540.9 \pm 485.0 mm ³ | 7591.6 \pm 490.4 mm ³ | t(19506) = -4.95 | 7.43e-07 | 0.10 |
| Taking risks | Left sup. lat. occipital cortex | 16378.0 \pm 1888.4 mm ³ | 16235.0 \pm 1877.1 mm ³ | t(19085) = -4.62 | 3.84e-06 | 0.08 |
| Being a worrier | Left temporal pole | 9488.6 \pm 1016.9 mm ³ | 9560.5 \pm 1040.9 mm ³ | t(19269) = -4.86 | 1.21e-06 | 0.07 |
| | Right temporal pole | 9441.9 \pm 980.3 mm ³ | 9510.0 \pm 1020.8 mm ³ | t(19251) = -4.72 | 2.35e-06 | 0.07 |
| | Right postcentral gyrus | 10551.0 \pm 1237.0 mm ³ | 10475.0 \pm 1248.3 mm ³ | t(19263) = 4.21 | 2.52e-05 | 0.06 |
| Being Sensitive | Right precuneus | 10150.0 \pm 1039.6 mm ³ | 10082.0 \pm 1056.6 mm ³ | t(19210) = 4.49 | 7.25e-06 | 0.06 |

Table 3.4 – Significant differences in IDPs for four mood symptoms after correcting for age. Only seven t-tests remained significant after correcting for both multiple testing-associated error and age variance.

3.4 Discussion

Data from the UK Biobank Imaging were analysed to provide normative information on brain volume as a function of age using the largest sample size published to date (N=19,793). I used a model-free sliding window approach to examine absolute and relative hippocampal volume, as well as other brain volumes, as a function of age. This approach was deemed most appropriate as it makes few assumptions, and does not impose a linear relationship between brain volume and age. The analysis resulted in normative reference percentiles – or nomograms – for total grey matter and hippocampal volume along the age distribution, facilitating assessment of an individual's hippocampal volume in relation to their age-group (see online tool at https://lnobis.github.io/HippoFit_Tool/index.html).

For comparison, it is noteworthy that estimated hippocampal volumes from previous studies on patients with MCI or AD fall far below the 50th percentile in the healthy population presented here. For example, mean uncorrected hippocampal volume (bilateral) was 5.55 cm³ in an amnesic MCI group with an average age of 70.7 years (Vos et al., 2013). This would fall below the 2.5th percentile in this sample. In a sample of controls and patients with MCI and AD of similar mean age as in this sample (67 years, 71 years, and 67 years, respectively), controls would score between the 50th and 75th percentiles, while patients score below the 5th percentile (Henneman et al., 2009). Volumes compatible with the current results for healthy controls (3.57 cm³; *mean age* = 75 years), but with far less dramatic reductions for MCI (3.26 cm³; *mean age* = 73 years) and AD (2.97 cm³; *mean age* = 72.6 years), were reported using data from the Alzheimer's Disease Neuroimaging Initiative database (ADNI) (Mulder et al., 2014). These would likely correspond to healthy controls scoring around the 50th percentile, but with patients scoring between the 5th and 25th percentiles.

It is likely that different methods, including sample selection as well as image acquisition, image processing, and hippocampal segmentation tool used, underlie these discrepancies. For example, I found on average smaller estimates of hippocampal volume with FSL-FIRST than with FSL-FAST using atlas-based region of interest selection. Another study also documented significant differences between FSL-FIRST, FreeSurfer, and manual segmentation

(Mulder et al., 2014). However, it is less clear how more severe deviations from acquisition and analysis protocols may affect volume estimations. These issues highlight the importance of large datasets and unified analysis pipelines. Thus, before efforts to harmonise analysis across MRI datasets solve some of these concerns, the nomograms presented here provide a robust comparator, when used with estimates obtained using the same, or similar, acquisition protocols, hardware and pre-processing pipeline.

It can also currently not easily be disambiguated whether a low percentile on the nomogram is due to pathological atrophy or is simply constitutional, e.g., due to an unusually small volume from birth. However, future research with longitudinal data from the UK Biobank may facilitate the resolution of some of these constraints.

The results of two different types of analysis revealed a slight acceleration of hippocampal volume loss around age 60-65 years for women, whereas for men the rate of hippocampal volume loss may increase earlier around 50 years (**Figures 3.4 and 3.5**). In addition, for both women and men, there was an increase in rate of hippocampal volume loss relative to the rest of the grey matter from around ages 67 and 63 years, respectively. While this method does not allow for precise age estimations, I show a robust age-range for the ratio peak with different window bins and smoothing kernels. Thus, hippocampal volume declined slower than the rest of grey matter until around age 67 in women, and age 63 in men, after which hippocampal volume declined faster than the rest of grey matter. This may indicate a particular vulnerability of the hippocampus in ageing, as this effect was mostly specific to the hippocampus and was not found to this extent in neighbouring brain areas such as parahippocampal gyrus or temporal gyrus (**Figure 3.6**). However, similar trajectories were evident in the entorhinal cortex (**Figure 3.4 D**), nucleus accumbens and to some extent in the globus pallidus (**Figure 3.7**).

A previous cross-sectional investigation with results from 1100 participants presented a similar acceleration of rate of hippocampal volume loss (Fjell et al., 2013). Relationships of age and several brain volumes were analysed using a non-parametric smoothing spline approach. The authors reported an acceleration of rate of hippocampal volume loss starting around 50 years of age, with a marked increase in rate of hippocampal volume loss around 60 years. In

agreement with these findings, no such acceleration point was found in grey matter. However, in this study no sex differences in these curves were calculated. In contrast, other cross-sectional studies using linear regression to estimate associations of age with hippocampal volume found an acceleration of volume loss at a slightly later age of 72 years (Zhang et al., 2010), or no acceleration point (Knoops et al., 2012).

Based on the trajectory of hippocampal volume across age presented here however, I argue that a linear fit is not the most appropriate approach to measure this association. Importantly, the trajectories of most other cortical areas across age do not show the same acceleration of volume loss as observed in hippocampal volume. This may underlie the specific vulnerability of hippocampal volume loss in older age. Yet, the findings presented here vary slightly depending on method used (e.g. sliding window or joinpoint), and need to be validated with longitudinal rather than cross-sectional data. For example, results of the joinpoint regression indicate that if there were a change in slope for hippocampal volume across age, then it would occur at 64-65 years, and would be significant. However, joinpoint regression cannot be applied to establish whether a change in slope is present or absent, as the method tends to identify a join point even if there is a continuous transition. In addition, the current data do not allow for conclusions of whether those with the fastest decline, or those with the lowest baseline volume, are at more risk of developing dementia. With the availability of longitudinal health outcomes, future studies may also explore the role of the dementia-associated Apolipoprotein E (APOE) $\epsilon 4$ allele on hippocampal volume across age.

Similar to the hippocampus, the entorhinal cortex, nucleus accumbens, and globus pallidus also showed an acceleration of decline around age 65 years. While hippocampal volume has received most attention in the ageing literature, there is growing evidence that the entorhinal cortex too is particularly vulnerable to age-related pathology. A recent longitudinal analysis documented reduced entorhinal cortex volume in people with mild cognitive impairment 8-11 years prior to diagnosis (Kulason et al., 2020). In addition, according to Braak's staging for pathology in AD, neurofibrillary tangles should start to accumulate in the transentorhinal and entorhinal cortex, before involving also the hippocampus and amygdala (Braak et al., 2006). The similar trajectory of decline between the hippocampus, nucleus accumbens, and globus

pallidus may point to their connectivity through the dopaminergic nigro-striatal pathway. Indeed, nucleus accumbens atrophy is usually associated with PD, and thought to be caused by loss of dopaminergic neurons. However, a recent investigation linked nucleus accumbens atrophy to cognitive impairment in particular, as only PD patients with cognitive impairment, but not those without, were found to have reduced nucleus accumbens volume (Hanganu et al., 2017). It seems possible that additional nucleus accumbens volume loss, caused by dopaminergic pathology in PD, exacerbates atrophy that would otherwise remain at slight, undetected levels, in people without PD. Globus pallidus function, too, is most commonly studied in relation to PD, as it is dependent on dopamine input and has been shown to improve PD-related symptoms when targeted by deep brain stimulation (Magill et al., 2001). In healthy ageing, globus pallidus atrophy has been documented once before, in a cross-sectional study with participants ranging from 18 to 83 years old (Tullo et al., 2019). Tullo et al. (2019) calculated linear regression models for the relationship between brain volume and age, though an acceleration of volume loss around 50-60 years is apparent in their findings that is in line with the current results. However, further work is required to establish the role of the globus pallidus and nucleus accumbens in healthy ageing.

In the absence of differential age-effects on grey matter volume between men and women, I found significantly larger mean total grey matter in women after correcting for head size and age. However, effect sizes were small. The data presented here also indicate hemispheric asymmetry of the hippocampus. The right hippocampus was slightly, but significantly, larger than the left hippocampus for both men and women. The observed asymmetry may be the result of noise in the MRI signals and imperfections of the automated volume segmentation and quality control tools used here, so that it is unclear what these differences entail precisely. However, right-larger-than-left asymmetry of the hippocampus has been noted previously in smaller cohorts of younger and older adults (Pedraza et al., 2018; Wellington et al., 2013; Zhang et al., 2010), as well as in patients with AD and MCI (Shi et al., 2009). A recent study reporting on 400 participants from the ADNI dataset also found increasing right-larger-than-left hippocampus asymmetry going from healthy controls, to patients with MCI, to patients with AD (Alberich-Bayarri et al., 2018). As the left hippocampus is smaller even in healthy ageing, the increasing asymmetry in the course of AD may be explained by greater vulnerability

to pathology of the left compared to the right hippocampus. I therefore provide separate nomograms for left and right hippocampus, as well as for males and females.

A number of brain areas had significantly different volumes between participants with and without mood symptoms, distributed widely across the brain. However, after accounting for age, only very few associations are retained. Before age correction, I found larger grey matter and brain volumes in participants who suffer from mood swings or feel miserable. This is generally in contrast with findings from neuroimaging analyses within groups of patients with symptoms of depression ([Drevets et al., 2008](#)), and likely reflects a confounding relationship with age.

I also document smaller hippocampal volume in people who reported to feel miserable than in those who did not. As this item arguably assesses a core depression symptom, the current findings on hippocampal volume are in line with previous research ([Sexton et al., 2013](#)). For example, smaller hippocampal volume associated with depression was described in an investigation in elderly people with recurrent early onset or late life depression. However, while hippocampal volume was smaller in people with depression compared to controls, there was no difference between patients with early onset and those with late life depression when correcting for age. Rather, hippocampal volume was linked to depressive symptoms regardless of age or duration of disease ([Janssen et al., 2007](#)). In contrast, in the current analysis, hippocampal volume was no longer significantly different between groups after adjusting for age. One simple explanation may be that older participants, who have smaller hippocampal volume, on average also reported feeling miserable more frequently. However, as described in **Chapter 2**, mood symptoms tend to decrease with older age. Thus, the fact that mood symptoms improve but hippocampal volume declines as age increases in UK Biobank participants may have confounded a relationship between hippocampal volume and depressive symptoms.

There were intriguingly strong differences in bilateral thalamic volume associated with loneliness that have not been recorded previously. A recent voxel-based morphometry study in 319 older adults found smaller grey matter volumes in the amygdala, hippocampus, parahippocampus and cerebellum, but not thalamus, in association with loneliness ([Düzel et al.,](#)

2019). In rodents the thalamus has been linked to social behaviour through its influence on the oxytocin system (Kanai, R et al., 2012). While the UK Biobank profits from an unusually large sample size to pick up on potentially small differences, further research with more detailed measurements of loneliness and social isolation is necessary before coming to any definitive conclusions.

Similarly robust associations were significant between bilateral temporal pole volume and worry. Those participants who described themselves as “a worrier” had significantly smaller volumes in left and right temporal pole, and right postcentral gyrus. In line with this, a few investigations have documented changes in functional connectivity between the amygdala and temporal pole in anxiety disorders (Li, Cui, et al., 2016). While the function of the temporal pole is not well studied, some authors have suggested that it modulates emotions (Pehrs et al., 2017) and integrates semantic, visual, and auditory stimuli (Olson et al., 2007).

It is not immediately apparent what a relationship between being sensitive and the right precuneus, as well as between taking risks and the lateral occipital cortex implies. It may be the case that practically insignificant volume differences appeared statistically significant because of the substantial sample size, even after multiple testing correction. This interpretation is supported by the mostly small effect sizes found in the current sample. Yet, it also seems possible that modest downstream effects on various brain areas that are caused by dysfunction in neuronal networks can now be detected with a large sample size.

Conclusion

Analysis of 19,793 generally healthy participants in the UK Biobank revealed effects of age, sex, and hemisphere on hippocampal volumes. The data provide normative values for hippocampal and total grey matter volume as a function of age for reference in research and clinical settings, based on an unprecedented sample size. These norm values may be used together with automated percentile estimation tools such as the one described here to provide a rapid, but objective, evaluation of the patient’s hippocampal volume status. While the current findings are based on cross-sectional data, the longitudinal health outcomes that will become available in UK Biobank over the next years will add invaluable information to the

role of hippocampal atrophy in ageing.

While a few structural markers were associated with mood symptoms in the current report, effect sizes were small, and it seems unlikely that these results will have clinical significance for diagnosis and treatment. Since the UK Biobank provides the largest neuroimaging dataset to date, the absence of strong mood associations is telling. Although the quality and detail of the mental health questionnaire in the UK Biobank are not ideal, the lack of clinically relevant structural differences suggests that other research avenues, such as focusing on network and neurotransmitter function, may provide more useful results.

PART II

Effects of Parkinson's disease

Chapter 4

Effects of Parkinson's disease on mood

4.1 Overview

Though neuropsychiatric symptoms are common in PD, prevalence estimates are highly variable (Pontone et al., 2009; van Reekum et al., 2005), and effective treatment options are still scarce (Aarsland et al., 2009). This may be due to a lack of understanding around the aetiology of these symptoms in PD. It has previously been suggested that neuropsychiatric symptoms in PD may develop as a result of basal ganglia network pathology associated with the disease itself, and that neuropsychiatric symptoms in PD constitute a disease-specific syndrome (Aarsland et al., 2009; Even et al., 2012). If that were the case, this syndrome may present with a distinct symptom profile that may differ from PD-unrelated conditions, such as major depressive disorder, because of different underlying mechanisms. However, studies including newly diagnosed PD patients may also find a higher rate of secondary depressive symptoms as patients may be reacting to the recent news or the disability they have to live with (Sagna et al., 2014). In addition, there is considerable symptomatic overlap between PD and depression, for example in the case of fatigue, insomnia, and motor retardation, which may result in misdiagnoses. Thus, in clinical practice or research trials, neuropsychiatric symptoms may be missed, over-diagnosed, or even wrongly attributed. As a result, it is unclear whether neuropsychiatric symptoms in PD such as depression should be treated as major depressive disorder, or as a PD-specific symptom. This is of particular concern as neuropsychiatric symptoms appear to have the largest impact on quality of life, for both the patient and caregiver (Schiehser et al., 2013).

This chapter aims to improve our understanding of neuropsychiatric symptoms in PD and is divided into three parts. The first section covers the characterisation of neuropsychiatric symptoms in PD, and how their distribution may differ from the distribution in older adults who do not have PD. In the second part, I test the hypothesis that some patients may develop mood disorders as a reaction to their diagnosis and related disabilities. Here I compare the prevalence of neuropsychiatric symptoms in patients with PD to a group of patients with comparable disability and outlook, namely patients with a diagnosis of osteoarthritis. The third part of this chapter explores whether one potential mechanism in the development and maintenance of major depressive disorder – negative affective bias – is also found in PD.

4.2 Characterisation of neuropsychiatric symptoms in PD

4.2.1 Introduction

Prevalence estimates of neuropsychiatric symptoms in PD vary widely, with 7-70% in the case of apathy (Pontone et al., 2009; van Reekum et al., 2005) and 20-55% in the case of depression (Aarsland et al., 2012; Sagna et al., 2014; Yamanishi et al., 2013). One reason for this may be that patients with diverse psychiatric symptoms are often grouped into binary categories, such as 'depressed' and 'not depressed'. This categorisation is often made based on DSM-5 criteria, or cut-off scores in questionnaires like the BDI (Beck et al., 1961). However, this practice results in heterogeneous groups, and potential symptom-specific effects will remain hidden (Fried, 2015; Fried et al., 2015). While categorical diagnoses of neuropsychiatric disorders may be required for treatment decisions or clinical trials, recognising the heterogeneity of these disorders and focussing on individual symptoms in research may uncover new findings.

Here I aimed to describe the frequency, distribution, and associations of different mood symptoms in groups of people with PD, healthy older controls, and people with RBD in the OPDC Discovery Cohort. Patients with RBD lose normal atonia of skeletal muscle during REM sleep, resulting in movement and vocalisations during dreaming (Hoegl et al., 2017). Longitudinal studies found that approximately 80% of patients with RBD will convert to a neurodegenerative disorder, most frequently PD. These patients have therefore been considered a key model of prodromal PD (Hoegl et al., 2017). The large sample size of the OPDC Discovery Cohort allowed me to assess prevalence of neuropsychiatric symptoms, as well as qualitative differences in symptom distribution and relationships across the three groups. The OPDC also provides a dense collection of information on each participant, including detailed clinical information in the patient groups and a large number of questionnaires. A subset of participants in each group has had a brain scan, which are included in **Chapter 6**.

Prevalence of neuropsychiatric symptoms was hypothesised to be higher in the PD and RBD groups than the controls groups. In addition, it was expected that by using individual item scores of the available depression and anxiety questionnaires, other symptom clusters re-

lated to apathy or PD-motor symptoms may emerge. Finally, core depression symptoms were predicted to be less common than symptoms of apathy in the PD group, reflecting common dopaminergic pathology that could lead to both PD-related motor symptoms and apathy.

4.2.2 Method

Participants

A total of 963 PD patients, 319 controls, and 249 RBD patients from the existing OPDC Discovery cohort were included in this study. All patients with PD (*mean age* = 67.19 ± 9.61 years, 36% women) were diagnosed by a neurologist and met the UK Parkinson's Disease Society Brain Bank criteria for idiopathic PD. No patients with atypical parkinsonism or secondary parkinsonism due to e.g. head trauma were included. Out of all PD patients, 512 were taking Levodopa, 272 took a dopamine agonist, 13 were on COMT inhibitors, 8 were taking amantadine, 16 were taking anticholinergic medication, and 219 were prescribed a MAO-B inhibitor. Further information on other medications, such as antidepressants, were not available.

Patients with RBD (*mean age* = 65.15 ± 8.77 years, 12% women) were recruited from OPDC and had previously been identified from sleep disorder clinics at the John Radcliffe Hospital, Oxford, and Papworth Hospital, Cambridge. RBD was diagnosed based on standard International Classification of Sleep Disorders-II criteria (Lapierre et al., 1992) using polysomnographic evidence by a specialised consultant. Specifically, these criteria include increases in tonic or phasic chin Electromyography activity, behavioural manifestations, and/or evidence of motor activity related to dream content during REM sleep. Patients were excluded if the clinical team judged their RBD to be secondary to other neurological conditions or medication use. None of the RBD patients were taking PD-related medications.

Healthy, age-matched control participants (*mean age* = 64.82 ± 10.05 years, 47% women) were included on the basis of being free of any serious medical conditions, as well as not having a first-degree relative with PD.

The assessments were performed with the written consent of each subject, approved by the

local National Health System (NHS) committee and in line with the national legislation and the Declaration of Helsinki.

Assessments

All participants attended research clinics where they were assessed for basic demographic information, as well as for presence and severity of PD or RBD features. Reported here are the MDS-UPDRS (PD symptom severity assessment, [Goetz et al., 2008](#)), Sniffin' sticks (test of sense of smell), and an RBD symptom severity questionnaire. The MDS-UPDRS is divided into four parts: Part I includes six questions asking about presence of cognitive problems, hallucinations, depression, apathy, anxiety, and dopaminergic dysregulation syndrome (excessive gambling, cleaning, sex drive, eating, or other repetitive activities or addictive behaviour); Part II is a daily functioning self-assessment made up of 14 questions; Part III is completed by a trained examiner to rate the severity of motor symptoms. All MDS-UPDRS items were scored between 0 (not present) and 4 (very severe). Note that parts I and II of the MDS-UPDRS were only collected for thirty healthy controls. In addition, trained research nurses performed a comprehensive standardised cognitive assessment, including the Montreal Cognitive Assessment (MoCA, [Nasreddine et al., 2005](#)) and a verbal fluency test. Participants were also asked to fill out a number of self-assessment questionnaires, of which some were selected for the current study: The BDI ([Beck et al., 1961](#)), Hamilton Depression and Anxiety Scale (HADS, [Snaith, 2003](#)) and (for patients) MDS-UPDRS part II. The BDI is a 21-item depression questionnaire and is one of the most often used depression assessment in research. It covers a wide range of symptoms going from core depression symptoms such as sadness and feelings of guilt, to less specific features, such as lack of energy or changes in appetite. The HADS contains 14 items, of which seven are dedicated to depressive symptoms, and the other seven to assessment of anxiety.

Analysis

All analyses were performed using *R* version 3.6.1 within *RStudio* version 1.3.959 ([R Core Team, 2013](#)), with the exception of the Multivariate Analysis of Variance (MANOVA) described below, which was done using *R* version 3.6.1 within *jamovi* version 1.1.9 ([The jamovi project,](#)

2020).

HADS imputation Because initial data collection included the Leeds Anxiety and Depression scale (LADS), which was later changed to the HADS, equipercentile equating (Lawton et al., 2016) was used to convert LADS depression scores to HADS depression scores. A simpler, 1-to-1 matching was possible for the conversion of LADSs anxiety scores to HADS anxiety scores. Concordance between HADS and the LADS equivalent for subjects who had data on both questionnaires was .85 for the anxiety sub-score, and .83 for the depression sub-score. Thus, the conversions were deemed valid and reliable. this part of the analysis was performed by by Dr. Michael Lawton, OPDC.

MANOVA Multivariate Analysis of Variance (MANOVA) was done to test for differences between the three groups in terms of age, cognitive status, mood sum-scores, MDS-UPDRS scores, RBD severity scores, and sense of smell. Significant univariate tests from this analysis were followed up with ANOVA post hoc tests using Bonferroni corrections for multiple testing.

ICC Because both the BDI and HADS categorise severity of depression, the Intra-class correlation (ICC) coefficient was computed to assess agreement between the two scales. For this I selected a two-way mixed effects model to estimate reliability for the average of the two ratings. Because of the model chosen, the results are specific to the questionnaires here, and should not be generalised.

Individual item score heatmaps To visualise the distribution of scores across the individual items on the BDI and HADS questionnaires, I calculated mean scores per item for each group. A heatmap was created using the `"heatmap.2()"` function within package `"gplots"`, which included computation of a dendrogram that has been reordered based on column means. Note that the maximum mean value was one for all groups because individual items could be scored between zero and three, and overall scores were low.

Correlations Exploratory factor analysis was performed on the individual question data from the BDI and HADS for the whole group, with the `"fa()"` function within the `"psych"` package

in *R*. Before running the factor analysis, a parallel analysis using Ordinary least squared factoring provided a range for the ideal number of factors to be selected in the following analysis. Factor analysis was then run using different numbers of factors within the suggested range, with best results being obtained using five factors. As the factors were likely to be correlated, oblique rotation was selected. Again, Ordinary Least Squared factoring was used. Questionnaire items with a loading of larger than .3 were attributed to the corresponding factor.

Pearson's correlation coefficient was computed for the relationships between the resulting factor scores and the remaining clinical and demographic variables, separately for each group. Multiple testing error rate was controlled using Bonferroni correction, so that for each group a *p*-value of $p < .05/\#variables$ was considered significant.

4.2.3 Results

Descriptive information for all variables included in this analysis are shown in (Table 4.1). Significant differences between the three groups based on MANOVA and following univariate post hoc tests are marked with either *, ‡, or †, depending on whether differences were found between all groups (*), between PD and RBD (‡), or between PD and control (†), respectively. There were no differences between RBD and control only.

| Measure | Healthy control Mean ± Std | PD Mean ± Std | RBD Mean ± Std | F-value | p-value |
|----------------|-------------------------------|------------------|-------------------|---------|--------------------|
| Age in y | 64.82 ± 10.05 | 67.19 ± 9.61 | 65.15 ± 8.77 | 4.70 | 0.01 ^{††} |
| Dis. Dur. In y | | 1.42 ± 1.72 | | NA | |
| LEDD | | 283 ± 214 | | NA | |
| MoCA | 26.65 ± 2.66 | 24.97 ± 3.32 | 25.19 ± 2.88 | 0.95 | 0.39 |
| Sniffin Sticks | 12.03 ± 2.32 | 7.11 ± 2.91 | 7.91 ± 3.2 | 26.24 | <.001* |
| UPDRS I | 0.77 ± 0.97 | 1.65 ± 2.01 | 2.15 ± 2.75 | 5.04 | 0.01 ^{††} |
| UPDRS II | 0.78 ± 1.69 | 8.83 ± 6.11 | 3.1 ± 4.7 | 65.93 | <.001* |
| UPDRS III | 1.77 ± 2.68 | 26.64 ± 10.98 | 5.16 ± 5.79 | 298.31 | <.001* |
| RBD Quest | 2.69 ± 2.1 | 4.63 ± 3.14 | 9.98 ± 2.3 | 172.11 | <.001* |

Table 4.1 – Group differences on clinical and demographic features. All groups differed from each other in Sniffin' Sticks, UPDRS II and III, and RBD questionnaire scores. PD were older than controls and RBD, and scored higher on UPDRS I. LEDD = Levodopa equivalence daily dose

The groups differed significantly on all variables except adjusted MoCA score, a measure of cognitive status. While differences on the clinical features were of interest, the significant difference in age was not, and was therefore used as a covariate in the following mood symptom group analyses.

Prevalence of neuropsychiatric symptoms

Distributions of total BDI and HADS anxiety scores, and frequencies of severity categories are shown in **Figure 4.1**. Total BDI scores were significantly higher in PD than controls, as well as in RBD vs controls ($F(2,1440)=54.77, p < .001, \eta = .07$). There was no significant difference between PD and RBD. There was a significant difference in HADS anxiety scores between all groups when adjusted for age ($F(2,1212)=10.80, p < .001, \eta = .02$), with increasing anxiety scores going from controls, to PD, to RBD. However, overall frequencies based on cut-off scores were fairly low. Only 5% of controls, 21% of PD patients, and 31% of RBD patients had at least mild anxiety, with mild to severe depression present in 9% of controls, 22% of PD patients, and 30% of RBD patients. In comparison, 24% of PD patients and 33% of RBD patients scored at least a one on the MDS-UPDRS part I item for depression. For the anxiety item, 33% of PD patients, and 37% of RBD patients were given a rating of at least one. Finally, at least mild apathy was attributed to 20% of PD patients and 26% of RBD patients.

Moderate to good agreement between BDI and HADS depression severity categories

To test the level of agreement between cut-off categories of different mood questionnaires, I computed the correlation coefficient of the BDI and HADS depression sum-scores, as well as the ICC between their cut-off score categories. Pearson correlation was fairly high between the two questionnaires, with $r = .77$, $p < .001$. The ICC for the average between the two fixed rating scales was .75, with a 95% confidence interval between .71 and .77 ($F(1142,1142) = 3.9$, $p < .001$). This suggests moderate to good reliability between the two scales.

Highest scores on mood questionnaires driven by physical symptoms

Summarising mean scores per item of the BDI for each group revealed that in all groups, participants scored highest on physical symptoms, namely lack of energy, fatigue, changes in sleep, and loss of libido. Lowest mean scores were found on core depression items, such as sadness, and suicidal thoughts (**Figure 4.2**). While according to standardised cut-offs, at least mild depression was present in 9% of controls, 22% of PD patients, and 30% of RBD patients (**Figure 4.1**), only 9% of controls, 16% of PD, and 21% of RBD patients reported at

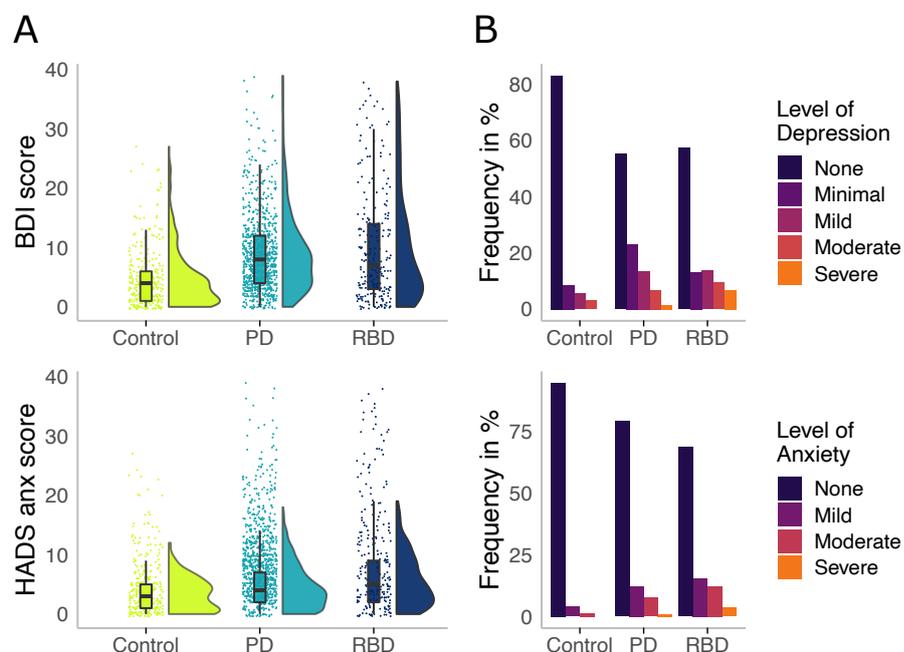


Figure 4.1 – Sum-scores and cut-off categories for BDI and HADS. Most participants scored low on both BDI and HADS, resulting in skewed data with few high scores in few people. Both PD and RBD patients reported higher frequency of symptoms than controls.

least mildly sad mood. In addition, only 1% of RBD patients reported severe sadness. No PD patients or controls reported suffering from moderate or severe sadness. Of the participants who reached cut-off for at least mild depression, 4% of controls, 12% of PD, and 16% of RBD patients did not have sad mood. In contrast, only 2% of controls, 4% of PD, and 5% of RBD patients reached cut-off in absence of loss of pleasure.

In addition, in the PD and RBD groups, patients scored relatively high on items assessing concentration problems, pessimism, and lack of pleasure. For the HADS, higher sum-scores were primarily driven by symptoms of slowness, and present mainly in the RBD group. Other items with higher means in the RBD group indicate core anxiety symptoms, such as "being tense", "worrying", "being restless", and "being fearful". Items assessing depression had overall low scores on the HADS.

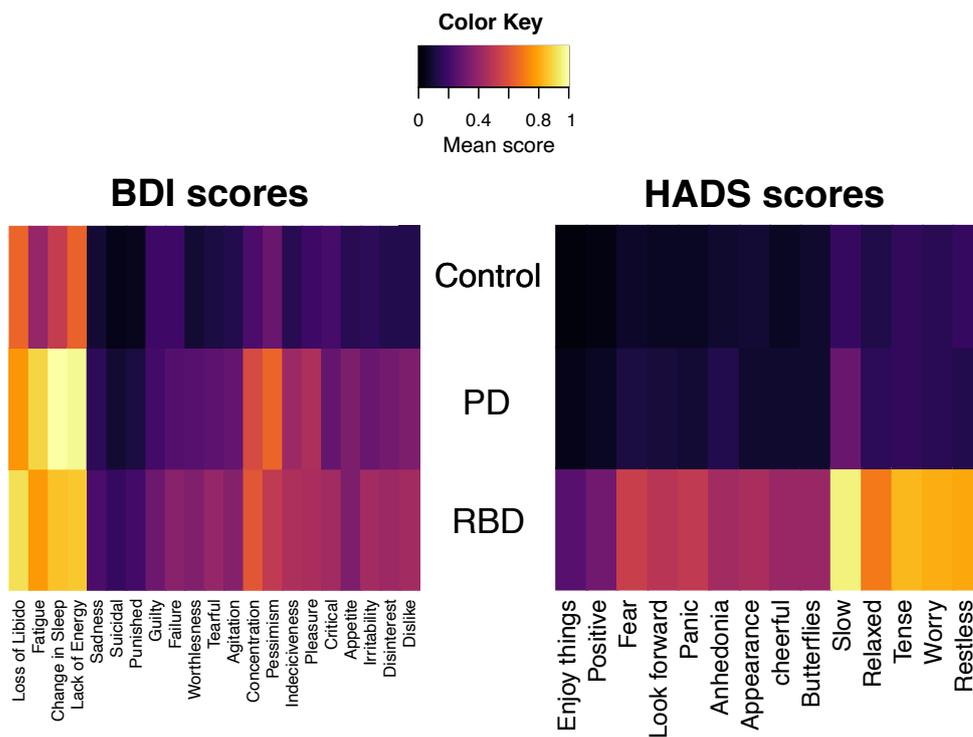


Figure 4.2 – Individual questionnaire item means heatmap for BDI and HADS. All groups report highest frequencies of 'Lack of Energy', 'Change in sleep', 'Loss of Libido' and 'Fatigue', all of which may be symptoms related to general ageing effects. BDI and RBD differ from controls by higher overall levels of symptoms, and additional 'Pessimism', 'Indecisiveness', 'Loss of pleasure', and problems with 'Concentration'. Both controls and PD have generally low levels of anxiety in HADS scores, while RBD score highly especially on items 'Slow', 'Tense', 'Worry', and 'Restless'.

Five separate factors emerge from BDI and HADS item scores

The initial parallel analysis that was performed to explore the ideal number of components suggested a maximum of 10 factors. This number was identified based on the Scree plot in **Figure 4.3 A**, where both large drops in the actual data, as well as the point where the simulated data and actual data converge, are considered. Thus, it was decided that anywhere between 5 and 10 factors would be suitable. Using different numbers of factors, a model with 5 factors yielded the best fit indices: The root mean square of residuals was .03, which indicated a good model fit, as the value should be close to zero. However, the root mean square error of approximation index was slightly above what would be considered ideal (i.e. below .05), with .061. Finally, the Tucker-Lewis Index was .87, again slightly below the ideal value of at least .9.

The five resulting factors were termed "Lack of Pleasure", "Core depression", "Core anxiety", "Lack of energy", and "Agitation", based on their item loadings. These factors accounted for 10%, 8%, 7%, 6%, and 4% of the variance, respectively, accumulating to 34% in total. **Figure 4.3 B** shows the item loadings for each factor, colour coded based on loadings larger than .3.

Small differences in mood correlation profiles between PD, RBD, and controls

To assess and visualise the relationships between the five factors and other clinical and demographic features, correlation matrices were computed separately for each group (**Figure 4.4**).

For controls, PD, and RBD patients, there were strong correlations between age and cognitive status. In addition, in all groups, higher scores on the lack of pleasure and/or core depression factors were significantly associated with older age. Lack of pleasure and to some extent core depression were also strongly associated with cognitive status in RBD and PD, but not in controls. Another similarity between the groups is the negative relationship between sense of smell test scores (the lower the worse) and core anxiety. Perhaps counter-intuitively, higher scores on MDS-UPDRS part I, which is a summary score of six neuropsychiatric symptoms, were associated with being younger, and lower cognitive status in RBD, while lack of pleasure and core depression scores showed the opposite pattern in both the RBD and PD groups.

4.2.4 Interim discussion

This first section set out to characterise the prevalence and severity of individual neuropsychiatric symptoms in patients with PD, teasing out potential differences compared to healthy controls and patients with RBD. The most important clinically relevant finding was that higher sum-scores of the mood questionnaires were driven mainly by somatic symptoms of fatigue, apathy, or restlessness, rather than symptoms of core depression or anxiety. One exception to this is the RBD group, where core anxiety symptoms, such as worry, tension, and feelings of fear and panic, did contribute to some extent to higher sum-scores.

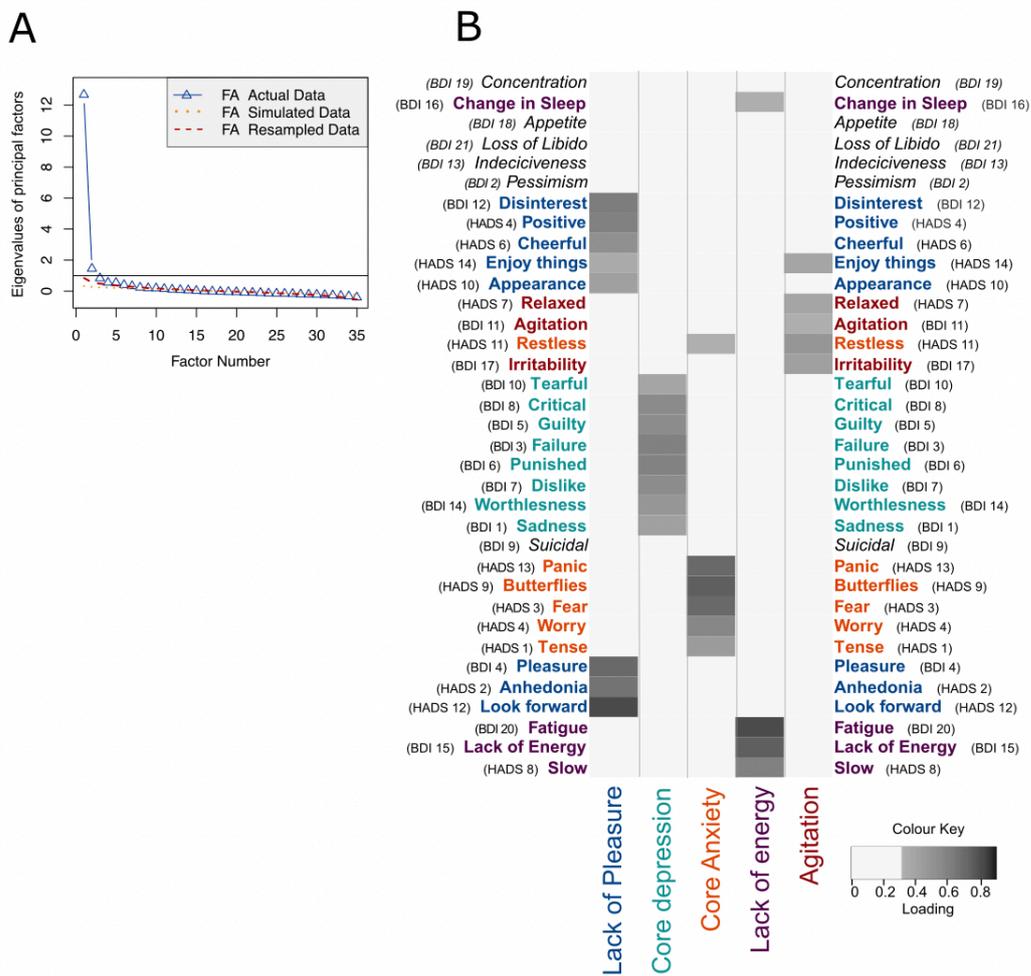


Figure 4.3 – Factor analysis of BDI and HADS items. Factor analysis on data from all three groups combined revealed five factors. Cut-off for factor loadings was at .3. Items that did not reach cut-off on any of the five factors are written in italics.

Overall, prevalence of depression and anxiety according to cut-off scores were similar to what is commonly noted in the literature. For example, while prevalence estimations can vary widely, a meta-analysis documented that based on DSM criteria, major depressive disorder was present in 19%, and clinically significant depressive symptoms without a formal diagnosis were present in 35% of PD patients. Clinical significance was attributed based on cut-off scores for questionnaires such as the BDI (Reijnders et al., 2008). This highlights the importance to explore individual symptoms scores, as in this current sample, many participants who reached cut-off would in fact not be considered to experience ‘clinically significant’ depression. Thus, the higher rate of patients with ‘clinically significant’ depression in the meta-analysis may be due to more severe somatic symptoms, rather than more severe core depression.

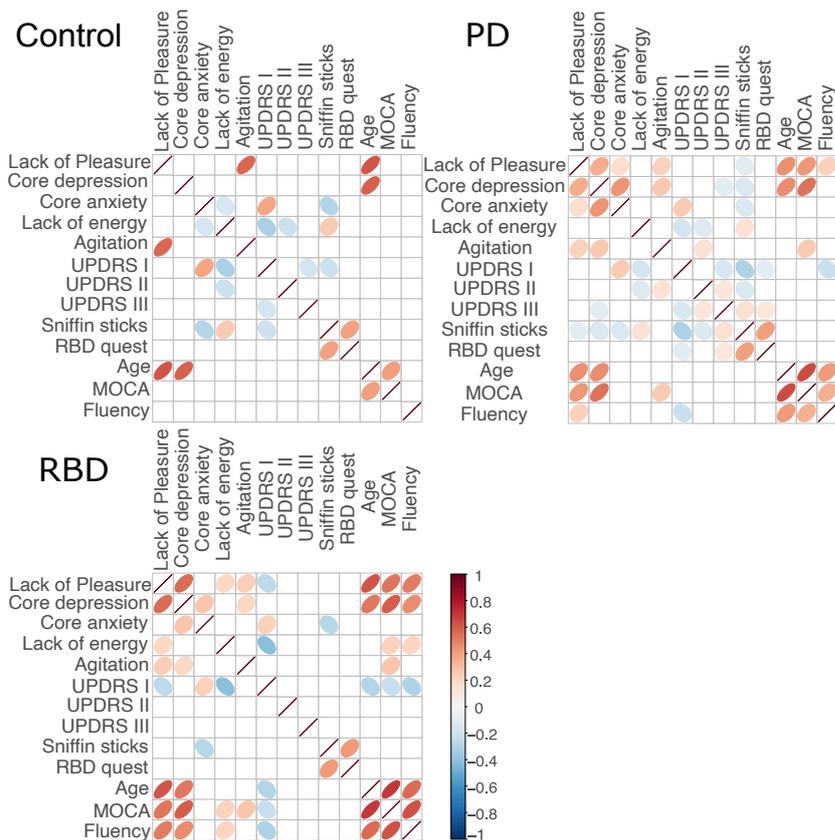


Figure 4.4 – Correlation matrices of mood questionnaires with clinical and demographic features for Controls, PD, and RBD. Generally, correlation patterns were similar across groups, with the strongest correlations involving age, cognitive function, and UPDRS/Sniffin’ sticks scores. However, in PD and RBD, mood symptom scores correlated significantly with each other and with cognitive status, while this was not the case in healthy controls.

In patients with RBD, prevalence of anxiety (31%) and depression (30%) according to cut-offs was higher than in patients with PD. This is a finding that has previously been published based on OPDC data with fewer participants (Lawton et al., 2015), and is in line with other research suggesting that RBD may in fact not simply be a prodromal PD disease stage, but may be a different type of synucleinopathy with a distinct symptom profile involving more severe neuropsychiatric features (Barber et al., 2017). As RBD is relatively rare, there are few other reports with adequate sample size that have assessed prevalence of neuropsychiatric symptoms. For example, one small investigation measured anxiety and depression with the HADS in a sample of 49 RBD patients in an Australian cohort. Based on the cut-off scores for at least mild anxiety or depression, the authors found a prevalence of 14.6% and 17%, respectively. Because of the fairly low number of participants in that study, recruitment bias may have resulted in fewer RBD patients with significant mood disorders.

However, by summarising different symptoms into one depression score as is done in the BDI or HADS, important information on different symptom profiles is lost. In this sample, higher sum-scores in the BDI were mainly driven by somatic symptoms such as loss of energy, fatigue, sleep disturbances, and loss of libido. In the PD and RBD groups, concentration problems and loss of pleasure were often present, too. These symptoms would not necessarily be considered a depressive disorder when assessed in a structured interview, especially in the presence of neurological disease with overlapping symptoms such as PD or RBD. It is important to note however that such structured interviews, for example using DSM-5 criteria, are now also being scrutinised for not being sufficiently backed by research (Fried et al., 2016). Still, a recent network analysis showed that the required DSM-5 symptoms 'sad mood' and 'loss of pleasure' were among the most central symptoms in their depression network. Thus, even though they might have similar sum-scores on the BDI, patients who suffer primarily from loss of pleasure and interest may benefit more from traditional depression treatments than those with loss of energy, but not loss of pleasure.

In line with this, I show that by performing factor analysis on individual item scores of the BDI and HADS, five separate components of neuropsychiatric symptoms can be unmasked: Lack of pleasure, Core depression, Core anxiety, Lack of energy, and Agitation. These findings

provide further support for a more nuanced distribution of neuropsychiatric symptoms as is often assessed in PD, which may have important implications for successful treatment. Antidepressant therapies result in remission in only a small number of patients with depression in the general population, with less than half the trials demonstrating a group effect (Khan et al., 2002; Kirsch et al., 2008; Pigott et al., 2010). In addition, if PD-related motor symptoms get worse during a clinical trial for the treatment of depression – because of time progression or potentially as a side effect of the medication – any improvement in mood would not appear as statistically significant. Similarly, medications may affect some specific symptoms, such as sad mood, but not others. It is therefore important to understand whether a patient suffers from symptoms of apathy, core depression, core anxiety/agitation, low energy, or a combination of these, before enrolment into treatment studies.

The results also support the hypothesis that PD is more often associated with symptoms of apathy rather than sad mood. Symptoms related to apathy are loss of interest, loss of pleasure, and indecisiveness – all of which were more common than sadness or suicidal ideation in this sample. Interestingly, the single MDS-UPDRS part I questions asking about presence of depression (*'Have you felt low, sad, hopeless or unable to enjoy things?'*) and apathy (*'Have you felt indifferent to doing activities or being with people?'*) showed higher ratings for the depression item than the apathy item. Since the MDS-UPDRS part I is expert-rated, but the BDI and HADS are self-assessments, this raises the possibility of bias when it comes to the interpretation of behaviour. On the one hand, there is evidence that patients underestimate their own levels of apathy when compared to caregiver ratings (Muhammed and Husain, 2016; Pfeifer et al., 2017). On the other hand, depression symptoms may be mistaken for apathy and vice versa. A previous investigation estimated the overlap between apathy and depression in a cohort of PD patients, and noted that only 4% of patients showed signs of pure depression. In contrast, 29% of patients qualified for pure apathy. A combination of apathy and depression were present in 22% of patients (Kirsch-Darrow et al., 2017). Given the likely involvement of dopaminergic dysfunction in apathy, future research should test whether any differences in reward and effort sensitivity can be linked to the specific symptoms of pure depression and pure apathy.

Finally, the main limitation of this analysis is that overall variance in mood questionnaire scores was low, and that some data was missing for the individual HADS items. As a result, goodness of fit scores for the factor analysis were slightly below what would be desirable. This may be a general issue in the literature, as the number of distinct factors that are found within questionnaires like the BDI differs substantially between studies (Bech, 2010; Lichtenberg et al., 2010; van Loo et al., 2012). This is likely due to the large amount of different symptom profiles that appear to be present in the population, which small sample sizes will not be able to reflect. However, while there is variability in the ideal number of factors, what these reports agree on is that depression and anxiety are not one-dimensional conditions. Yet, most trials treat questionnaires such as the BDI as a single measurement (Skapinakis et al., 2010; Troeung et al., 2013). Another limitation is that no dedicated apathy measurement was available in this dataset. Recent developments in apathy research have included the distinction between social, behavioural, and emotional apathy, which I was not able to explore here.

4.3 To what extent are neuropsychiatric symptoms in PD secondary to living with the disease?

4.3.1 Introduction

Because neuropsychiatric symptoms have such strong prevalence in PD, it has been suggested that they may develop as a result of monoamine and basal ganglia network pathology associated with the disease itself, constituting a disease-specific syndrome (Aarsland et al., 2012). Indeed, dysfunction in the dopaminergic and serotonergic systems is frequently linked to development of neuropsychiatric symptoms, in both PD (Andersen et al., 2015; Chaudhuri et al., 2009; Maillet et al., 2016) and the general population (Dunlop et al., 2007; Godlewska et al., 2016; Godlewska et al., 2012; Nestler et al., 2006). In addition, damage to the basal ganglia has also been associated with symptoms of depression or apathy, for example after stroke (Adam et al., 2013; Fang et al., 2009).

However, it is also conceivable that patients with PD develop neuropsychiatric symptoms as a reaction to living with a neurodegenerative condition and its associated disability. Generally, higher rates of depression are associated with higher levels of disability, for example in people with AD (Gómez-Gallego et al., 2017), multiple sclerosis (Merkt et al., 2017), coronary heart disease (Palacios et al., 2018), chronic back pain (Campbell et al., 2017) and rheumatoid arthritis (Matcham et al., 2013). In addition, an analysis into the risk of depression in a large population of adults with physical or sensory disabilities found a 3.7-fold higher incidence of depression compared to the general population (Shen et al., 2017). In PD, too, some studies reported depression levels that were dependent on disease severity (Sagna et al., 2014).

One approach to solving this question is to compare levels and severity of neuropsychiatric symptoms in PD to a group of people suffering from a similarly chronic, progressive condition, that does not have a neurological component. An early investigation did just that (Ehmann et al., 1990). The authors assessed levels of depression in 45 patients with PD, and compared them to 24 patients suffering from deteriorative disorders with gradual onset, without curative treatments, and without associated psychiatric symptoms. Most patients in this

group suffered from osteoarthritis (OA), though other disorders were included too. PD patients scored higher on somatic, but also on cognitive-affective items of the BDI, an effect that was not related to motor symptom severity or disease duration. In addition, the two groups did not differ in levels of disability, mean age, or sex (Ehmann et al., 1990).

Thus, it seems that on average, neuropsychiatric symptoms in PD are indeed related to neurodegenerative processes in the brain, potentially involving dopamine and serotonin dysfunction. However, the sample size of Ehmann et al. (1990) was small. Here I aimed to reproduce their findings in a larger sample of participants from the UK Biobank. Patients with PD are compared to patients with OA and healthy controls in terms of frequency of neuropsychiatric symptoms, general happiness, and health satisfaction. OA is a chronic and progressive condition that usually occurs in middle-aged adults. In OA, the cartilage between the bones in a joint breaks down, causing joint pain and stiffness (Felson et al., 2000). Because of the age of onset, the progressive nature of the disease, and the associated disability in absence of a neurological component, OA is an especially useful comparison to PD-related disability (Ehmann et al., 1990).

4.3.2 Method

Data selection

Categories for online follow-up questionnaire items included depression, anxiety, and general well-being. The same items as in previous analyses from **Chapter 2** were chosen, explained in more detail in **Table 2.1** of **Chapter 2**.

During the same online follow-up session, participants also completed a number of cognitive assessments. Here I present data on a numeric memory (digit span) and pairs matching task to test whether there were any cognitive differences between groups.

Participants

The UK Biobank population is described in more detail in **Chapters 2 & 3**. Here, I selected a group of 133,617 healthy controls without any neurological or psychiatric diseases, 2320 patients with diagnosed or self-reported PD, and 2845 patients with diagnosed or self-reported

OA. Of these, mood questionnaire data was available for all healthy controls, around 345 patients with PD, and around 1990 patients with OA. Small discrepancies may exist for individual items because of missing data. Cognitive data was collected for 94,816 healthy controls, 296 patients with PD, and 1361 patients with OA.

Analysis

Analyses were performed using *R* version 3.6.1 within *RStudio* version 1.3.959 ([R Core Team, 2013](#)) and *MATLAB* version R2020b ([MATLAB, 2020](#)).

To visualise the distribution of scores across the individual items on the questionnaires, I created a heatmap for the percentage of agreement by item and Likert scale response for each of the three groups. Significant differences in mood scores and cognitive function between the three groups were tested for using ANOVA with and without age as a covariate.

4.3.3 Results

PD patients (*mean age* ~69 years) were slightly, but significantly than older patients with OA (~65 years) and healthy controls (~64 years, **Table 4.2**). Patients with OA and healthy controls did not significantly differ in mean age. As the UK Biobank recruited participants up to the age of 70 years at the time of enrolment, maximum ages do not differ between the groups.

PD patients report more frequent mood symptoms

While patients with OA and healthy controls rated the frequency with which they were experiencing mood symptoms on similar levels, PD patients displayed higher levels for almost all questionnaire items. As shown in **Figure 4.5** and **Table 4.2**, the largest differences in frequency rating are apparent for tiredness, slowness, trouble relaxing, restlessness, and concentration problems. Because PD patients were significantly older than the other two groups, differences in mood ratings were tested with and without age as a covariate. Without taking age into account, PD patients recorded more frequent mood symptoms compared to both OA and control for all items but 'Irritability'. Similarly, age correction resulted in reduced *p*-values for all tests, with significant differences between PD and OA or control after Bonferroni

correction in all items except 'Irritability'.

Compared to control, OA reported higher frequency of having trouble relaxing, restlessness, lack of interest, concentration problems, tiredness, loss of appetite/overeating, and depression (Table 4.2).

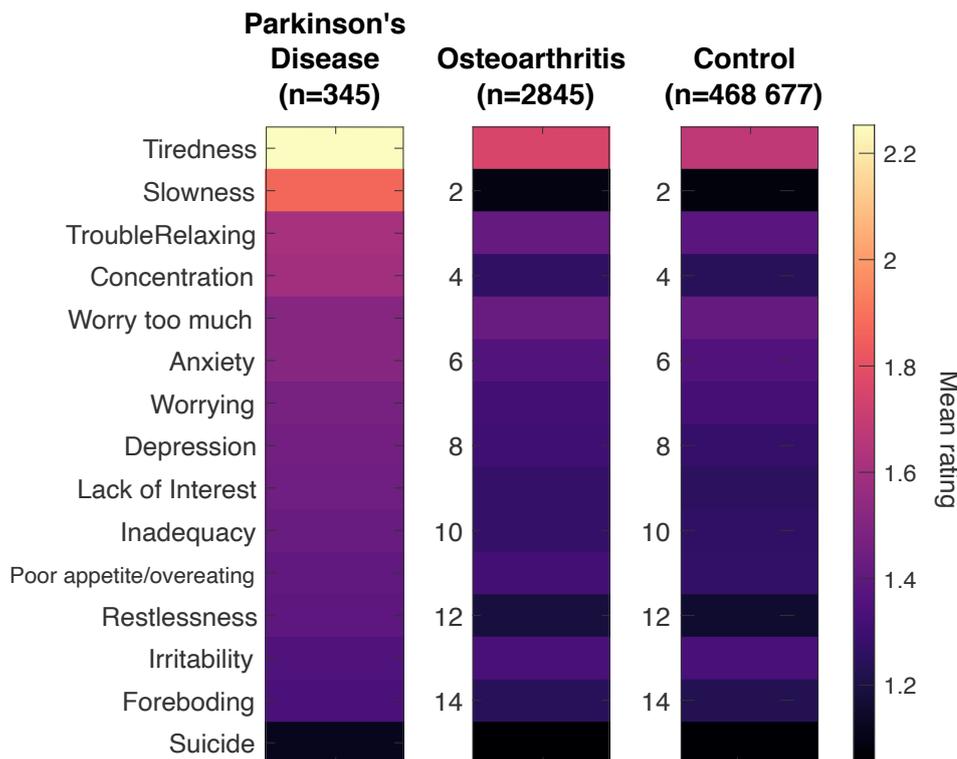


Figure 4.5 – Frequency of mood symptoms by group. Patients with PD reported higher frequency of almost all symptoms, but especially "Tiredness", "Slowness", "Trouble relaxing", and problems with "Concentration". OA patients and controls in contrast noted similar frequencies across all symptoms.

PD and OA are associated with lower levels of health satisfaction

Mean ratings on general happiness and health satisfaction on a 6-point Likert Scale are displayed in **Figure 4.6**. Overall, the majority of people in all groups reported to be at least moderately happy in general. However, 59% of PD patients and 18% of OA patients, compared to 13% of healthy controls described to be at least moderately unhappy with their health. When collating ratings across all answer possibilities, PD patients rated significantly lower levels of happiness (i.e. higher scores) in general and with health than both OA and controls, with or

| | PD Mean ± Std | OA Mean ± Std | HC Mean ± Std | p-value | p corr. |
|----------------------------|------------------|------------------|------------------|---------------|----------------|
| Age (y) | 68.98 ± .04 | 65.33 ± .17 | 64.05 ± .02 | 9.12e-43 ** | n/a |
| Depression | 1.46 ± 0.03 | 1.31 ± 0.01 | 1.28 ± 0.001 | 7.34e-09 ** | 1.61e-13 **† |
| Suicide | 1.12 ± 0.2 | 1.05 ± 0.01 | 1.06 ± 0.001 | 2.86e-04 ** | 1.15e-05 ** |
| Inadequacy | 1.43 ± 0.03 | 1.28 ± 0.01 | 1.27 ± 0.002 | 2.38e-06 ** | 4.86e-11 ** |
| Poor app/overeating | 1.40 ± 0.03 | 1.32 ± 0.01 | 1.27 ± 0.002 | 1.02e-06 *† | 5.08e-12 **† |
| Slowness | 1.88 ± 0.02 | 1.09 ± 0.01 | 1.08 ± 0.001 | <1.00e-308 ** | <1.00e-308 ** |
| Tiredness | 2.25 ± 0.04 | 1.75 ± 0.02 | 1.68 ± 0.002 | 1.21e-40 **† | 1.91e-49 **† |
| Concentration | 1.59 ± 0.03 | 1.26 ± 0.01 | 1.24 ± 0.002 | 1.54e-29 ** | <1.00e-308 **† |
| Lack of interest | 1.45 ± 0.03 | 1.27 ± 0.01 | 1.25 ± 0.002 | 9.85e-10 ** | <1.00e-308 **† |
| Irritability | 1.35 ± 0.03 | 1.34 ± 0.01 | 1.33 ± 0.002 | 0.69 | 0.03 |
| Foreboding | 1.34 ± 0.03 | 1.24 ± 0.01 | 1.23 ± 0.002 | 6.96e-04 ** | 4.36e-06 ** |
| Anxiety | 1.51 ± 0.04 | 1.36 ± 0.02 | 1.36 ± 0.002 | 8.15e-05 ** | <1.00e-308 ** |
| Worrying | 1.47 ± 0.04 | 1.32 ± 0.02 | 1.32 ± 0.002 | 8.78e-05 ** | 5.30e-07 ** |
| Restlessness | 1.40 ± 0.03 | 1.19 ± 0.01 | 1.16 ± 0.002 | 1.07e-20 **† | 7.36e-25 **† |
| Trouble relaxing | 1.61 ± 0.04 | 1.41 ± 0.02 | 1.38 ± 0.002 | 1.86e-09 ** | <1.00e-308 **† |
| Worry too much | 1.51 ± 0.04 | 1.43 ± 0.02 | 1.41 ± 0.002 | 1.92e-02 * | 0.0001 ** |
| Happiness | 2.65 ± 0.04 | 2.46 ± 0.02 | 2.43 ± 0.002 | 4.85e-07 ** | <1.00e-308 **† |
| Health satisfaction | 3.92 ± 0.05 | 2.82 ± 0.02 | 2.64 ± 0.003 | 4.20e-152 **† | <1.00e-308 **† |
| Digit span (num digits) | 6.48 ± 0.09 | 7.01 ± 0.04 | 6.91 ± 0.01 | 1.62e-07 **† | 0.02 |
| Pairs matching (num pairs) | 2.85 ± 0.03 | 2.94 ± 0.01 | 2.92 ± 0.01 | 0.005 ** | 0.32 |

Table 4.2 – Significance tests across groups with and without age correction. P-values are marked with either *, ‡, or †, depending on whether differences were found between PD and control (*), between PD and OA (‡), or between control and OA (†). PD patients reported significantly higher frequency of all mood symptoms compared to controls and/or OA, except 'Irritability'. These differences are unlikely explained by age or cognitive status. Note that 'Happiness' and 'Health satisfaction' are reversely coded. alpha = .05/22 tests = .002

without age correction (**Table 4.2**). Using either ANOVA, or ANCOVA with age, patients with OA differed from controls in health satisfaction and general happiness ratings (**Table 4.2**).

No differences in cognitive function

Without accounting for age as a covariate, PD patients remembered significantly fewer digits than controls, but not patients with OA. PD patients also matched significantly fewer pairs

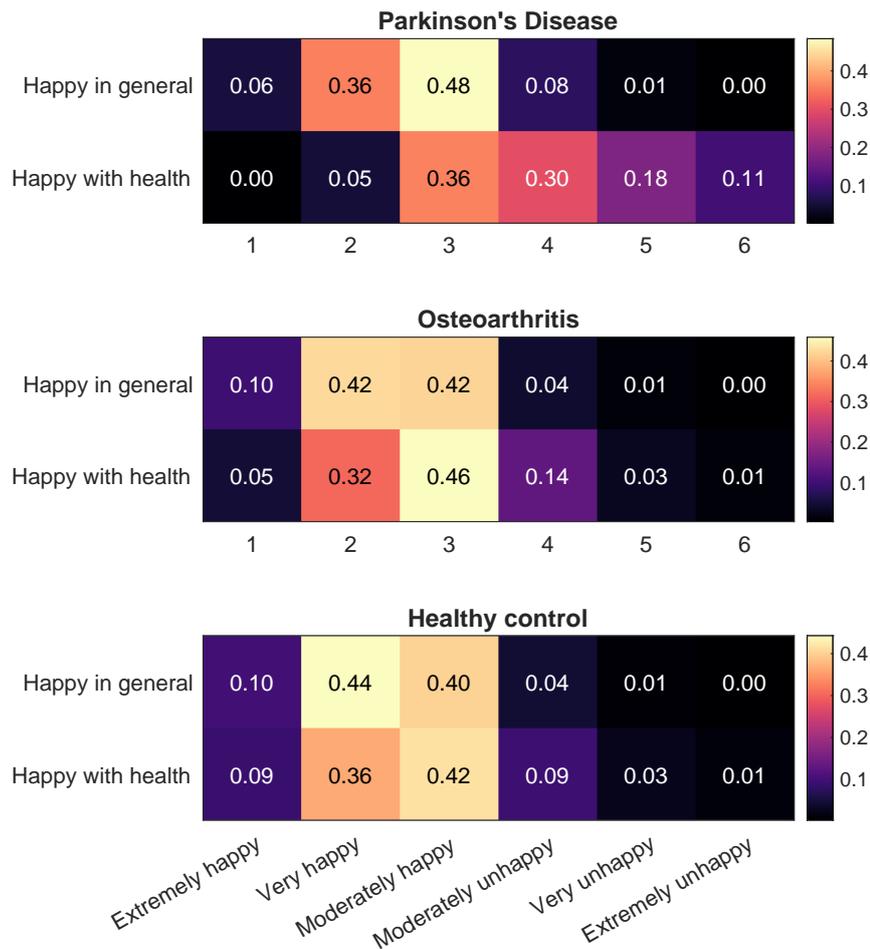


Figure 4.6 – Levels of happiness across groups. The majority of participants in all groups were found to be at least moderately happy in general. Patients with PD and OA both reported to be less satisfied with their health compared to healthy controls. However, PD patients noted dissatisfaction with their health with highest frequency.

than both controls and OA patients (**Table 4.2**). However, these differences are no longer significant at the corrected alpha level (.05/22 tests = .002) when adjusting for age.

4.3.4 Interim discussion

This study set out to establish whether patients with PD suffer from higher rates of mood symptoms than other people with comparable disability and outlook – patients with OA. It was hypothesised that the high rates of mood symptoms in PD are not merely a secondary reaction to the PD diagnosis and associated physical impediments, but develop as a result of PD-associated monoamine and basal ganglia network pathology. PD patients should there-

fore experience more mood symptoms than OA patients.

Indeed, compared to both healthy control and OA, patients with PD reported more frequent symptoms on all mood questionnaire items, except for 'Irritability'. The largest differences were apparent for items on 'Slowness', 'Tiredness', and 'Restlessness', all of which have been directly linked to the motor symptom profile of PD before (Lawton et al., 2015). However, compared to both healthy control and OA, PD patients also noted higher frequency of core mood disorder symptoms, such as 'Anxiety', 'Depression', 'Lack of Interest', or 'Foreboding' (**Figure 4.5, Table 4.2**). In addition, patients with OA indicated to experience 'Depression', 'Lack of Interest', or 'Trouble relaxing' more often than healthy controls, but not more often than patients with PD – suggesting that living with a disabling condition indeed increases likelihood of suffering from mood symptoms. Thus, if we can assume that patients with PD and patients with OA suffered from the same levels of psychological stress because of their diagnosis and disability, it seems that patients with PD may have additional mood symptoms directly related to PD pathology. These results are unlikely to be explained by differences in age or cognitive function. In fact, correcting for age increased effect sizes for mood item differences, likely because as shown in **Chapter 2**, mood generally improved with older age. Since PD patients were on average older than the other two groups, correcting for age removed this confounding effect. Patients with PD performed worst on the two cognitive tests, and it has previously been shown that lower cognitive function may be associated with higher levels of mood symptoms (Gualtieri et al., 2008; Kasahara et al., 2006). However, this effect was no longer significant when correcting for age.

I further examined whether the three groups experienced different levels of overall happiness and health satisfaction. Interestingly, while PD patients reported substantially lower health satisfaction than both OA and healthy control, there were only small differences in general happiness (**Figure 4.6**). It seems that while suffering from a chronic illness like PD may impact health satisfaction considerably – and more so than suffering from OA – it may not necessarily affect overall happiness and mood. Hence, it could conceivably be hypothesised that the higher rates of mood symptoms present in patients with PD in this population are indeed related to primary PD pathology.

A limitation of the current investigation is that a larger percentage of mental health questionnaire responses were missing for the PD group than for the OA or healthy control groups, with the reasons for this unknown. Thus, it may be that some PD patients have progressed to the point where they were unable to take part at the time of the online follow-up. However, drop-out due to the patients being unwell would not change the direction of the reported effect, with PD patients reporting the most severe symptoms. Another limitation is that the UK Biobank dataset did not include a reliable measure of disability or physical functioning, such that I could not confirm whether the patients with PD and OA in this sample actually did experience a comparable level of disability. In fact, OA patients displayed significantly lower levels of health satisfaction than PD, which might suggest that this was not the case. Future research with detailed assessments into levels of physical functioning and the psychological effects of receiving a diagnosis are recommended. However, it is also conceivable that health satisfaction would drop as a result of higher levels of mood symptoms. In addition, regardless of the associated physical disability, OA is a chronic, non-neurological, progressive disorder, and therefore still a useful comparison to PD.

4.4 Is depression in PD associated with negative affective bias?

4.4.1 Introduction

It has previously been hypothesised that in Major Depressive Disorder (MDD), symptoms are reinforced and maintained because of a negative bias in information processing (Harmer, O'Sullivan, et al., 2009; Porter et al., 2010). For example, recent evidence suggests that memory is selectively biased towards negative stimuli in people with depression (Russo et al., 2006). In addition, a number of studies have tested whether depression is associated with a negative bias in the recognition of facial expressions. The ability to perceive emotions from facial expressions is essential for human interaction as they provide non-verbal cues to our emotional state, and influence other people's behaviour toward us in response to those cues (Phillips et al., 2003). Thus, impaired emotion recognition may be involved in the aetiology or maintenance of depressive symptoms such as negative bias, poor interpersonal relationships, and social isolation.

Facial emotion recognition is usually assessed by showing participants photographs or videos of an actor's face while expressing an emotion. The participant is then asked to identify the emotion, either from a given set of labels, or by free choice. In most tasks, the range of expressions includes the six basic emotions as noted in Ekman (1992), namely sadness, anger, surprise, happiness, fear, and disgust. More recently, research has included pictures of facial expressions that are the result of a morphing process with a neutral face, allowing for presentations of more subtle emotions (Bilderbeck et al., 2017; Gray et al., 2010).

Using such a paradigm, a report including 239 patients with MDD and 128 controls found that particularly women with MDD misinterpreted fearful and sad faces more often as angry faces (Wright et al., 2009). In addition, a meta-analysis of 22 investigations documented an effect of impaired emotion recognition in depression. Specifically, this impairment was evident for the recognition of anger, disgust, fear, happiness, and surprise, but not for sadness (Dalili et al., 2019). However, it is noteworthy that the size of the observed meta-effect was small. Thus, the individual studies included in this meta-analysis may suffer from low statistical power, which is associated with an increased likelihood of false positive findings (Button et al., 2013).

While far larger sample sizes are required for the interpretation of emotion recognition bias in depression, recent research examining the mechanisms of antidepressants provided further evidence for an emotion processing bias.

For example, facial emotion recognition improved in a sample of depressed participants after two weeks of treatment with the SSRI citalopram. Notably, improvements in the recognition of happy faces at two weeks of treatment correlated with clinical outcome after six weeks (Tranter et al., 2009). However, as there was no control group, these effects may be due to learning. Yet, this finding was supported by another investigation using neuroimaging. Thirty-five participants with MDD were given an SSRI over six weeks. Before commencing treatment, and after one week, participants completed a facial emotion recognition task while undergoing functional magnetic resonance imaging. The authors found that the extent to which neural responses during the task changed after one week of treatment correlated with later clinical outcome. In more detail, depressed patients showed increased insula and anterior cingulate activation to fearful versus happy faces at baseline. Those participants who could be classified as responders to the SSRI treatment after six weeks had a greater reduction in these activations after seven days of treatment than those who were classified as non-responders. Crucially, a mediation analysis suggested that this change in neural activation was not due to changes in depressive symptoms. Therefore, the authors concluded that antidepressants may induce a correction of the hypothesised negative bias in depression that precedes the alleviation of symptoms (Godlewska et al., 2016).

Given the likely involvement of biased emotion processing in MDD, one remaining question is whether this bias may also underlie the high rates of depression associated with PD. Intriguingly, however, a number of studies have suggested impaired emotion recognition in PD in absence of any depressive symptoms (see Argaud et al. (2018) for a review). One report examined this apparent lack of association in more detail by comparing emotion recognition performance between depressed PD patients and non-depressed PD patients. There was no difference in facial emotion recognition scores between the two groups, and the authors concluded that the observed deficit compared to participants without PD was not secondary to depression (Gray et al., 2010). Thus, impaired emotion recognition in PD might occur due to

PD-specific brain pathology. This impairment might be related to depression only in some groups of patients, such as those at increased risk due to other negative life events. However, the results of reports on facial emotion recognition in patients with PD are far from consistent. Although some authors present no impairment (e.g., [Wabnegger et al., 2015](#)), three reviews and one meta-analysis concluded that the evidence suggests a small facial emotion recognition deficit in PD ([Argaud et al., 2018](#); [Assogna et al., 2008](#); [Gray et al., 2010](#); [Péron et al., 2012](#)). This deficit seems to correlate with a number of factors, including disease severity, visual dysfunction, cognitive impairment, and dopamine replacement therapy ([Argaud et al., 2018](#)).

While there does not seem to be a strong association with depression, [Martínez-Corral et al. \(2010\)](#) noted that patients with PD - who were also apathetic - performed significantly worse on a facial emotion recognition task compared to healthy controls. This effect was not observed in patients with PD who were not apathetic. Importantly, none of the PD patients included in the study suffered from cognitive impairment or depression. Another investigation documented a significant correlation between emotion recognition performance and scores on the Apathy Evaluation Scale in 36 patients with PD. The authors also examined metabolic activity using FDG-PET. By applying conjunction analysis, the authors identified common areas between the two metabolic networks that were found to underlie both apathy and emotion recognition. The areas showing a significant correlation included the premotor cortex, orbitofrontal cortex, middle frontal gyrus, and posterior cingulate gyrus ([Robert et al., 2012](#)). Both the orbitofrontal cortex and cingulate gyrus have been related to apathy and PD as part of the mesocorticolimbic dopaminergic system ([Le Heron et al., 2017](#); [Moretti et al., 2016](#)). In addition, apathy has previously been divided into three domains, namely behavioural activation, social motivation, and emotional sensitivity ([Le Heron, Plant, et al., 2018](#)). The emotional sensitivity subtype mainly involves blunted affect, and might thus be related to emotion recognition impairments and might also relate to emotional aspects of apathy ([Ang et al., 2018](#)).

Here we examined performance on a well-established facial emotion recognition task in a group of patients with PD, a group of healthy age-matched controls, and a group of age-

matched patients with RBD. We hypothesised that a deficit in emotion recognition would occur in a dose-dependent manner increasing from patients with RBD to patients with PD, when compared to healthy controls. We further hypothesised that task performance would correlate with apathy scores, potentially differentiating subtypes of apathy.

4.4.2 Method

Participants

Three groups of participants were included. Patients with PD, control participants, and patients with RBD were recruited from the existing OPDC Discovery Cohort, and were tested as part of an additional follow-up clinic (Szewczyk-Krolkowski et al., 2014). The thirty patients with PD (*mean age* = 65.62 ± 7.16 years, 12 women) were diagnosed by a neurologist within the past 4 years and met the UK Parkinson's Disease Society Brain Bank criteria for idiopathic PD (mean disease duration 3.37 ± 0.77 years). No patients with atypical parkinsonism or secondary parkinsonism due to e.g. head trauma were included. Of the 30 PD patients, 27 were taking Levodopa, 8 were taking a dopamine agonist, 9 were taking MAO-B inhibitors, and one patient was taking only a COMT inhibitor. In addition, five patients took clonazepam, one patient took citalopram, and one patient was on sertraline.

Twenty-nine patients with RBD (*mean age* = 64.69 ± 9.09 years, 4 women) were recruited from OPDC, and had previously been identified from sleep disorder clinics at the John Radcliffe Hospital, Oxford, and Papworth Hospital, Cambridge. RBD was diagnosed as described previously. Of the 29 RBD patients, 8 were taking clonazepam, 4 were on citalopram, one patient each were taking duloxetine, venlafaxine, and sertraline.

Thirty healthy, age-matched control participants (*mean age* = 65.73 ± 9.05 years, 12 women), also recruited from OPDC, were included on the basis of not having any serious clinical condition, nor a first-degree relative with PD. None of the controls took medication that could affect task performance.

The assessments were performed with the written consent of each subject, approved by the local NHS committee and in line with the national legislation and the Declaration of Helsinki.

Assessments

Assessments included the Facial Emotion Recognition Task (FERT), validated questionnaires for apathy, depression, and anhedonia, as well as the MDS-UPDRS as a standardised assessment for PD symptoms.

Facial Emotion Recognition Task In this task, participants were presented with a touchscreen displaying a photograph of a face with an emotional expression that was either neutral, sad, angry, fearful, surprised, happy, or disgusted. Below the photograph, fields containing labels for each of the seven possible facial expressions served as response buttons (**Figure 4.7**). Each photograph was the result of a morphing process between a neutral face and one of the remaining emotional faces taken from the Pictures of Facial Affect series ([Ekman, 1992](#)). Each emotional expression was morphed to an extent of 10%, 20%, 30%, 40%, 50%, 60%, 70%, or 80% ([Young et al., 1997](#)). Pictures from three different actors were chosen for each emotion, with each actor covering all emotion levels, resulting in 144 stimuli (6 emotions x 3 actors x 8 levels). In addition, ten neutral faces were added to the stimulus set, all from different actors, resulting in a total of 154 trials. The photographs were presented randomly for a duration of 500ms. After 500ms, the photograph disappeared, while the response fields stayed on the screen. Participants were asked to respond as quickly and accurately as possible by tapping the label they believed most accurately described the facial expression in the photograph. Accuracy was defined as the number of correctly identified faces divided by the total number of faces showing that emotion that were presented throughout the task. *Presentation Version 18.1* (Neurobehavioural Systems, Albany, CA, USA) was used for stimulus presentation.

Questionnaires Questionnaire assessments were completed by the patients at home in the week prior to their research visit. These self-evaluating questionnaires included the HADS ([Snaith, 2003](#)), BDI ([Beck et al., 1961](#)), Spielberger State Trait Anxiety Inventory (STAI) ([Spielberger et al., 1970](#)), and the Apathy Motivation Index (AMI) ([Ang et al., 2017](#)). The AMI can be further divided into Emotional Sensitivity (ES), Social Motivation (SM), and Behavioural Activation (BA) sub-scores. Items are reversely coded, so that a higher score in the total AMI and its subscales corresponds to more severe apathy.

During the research visit, a trained member of the team also administered the MoCA (Nasreddine et al., 2005), and the MDS-UPDRS parts I and III to every participant, including healthy controls (Goetz et al., 2008).

Analysis

Responses on the FERT were averaged over emotion intensity levels and summarised for accuracy, misclassifications, and reaction time in *MATLAB 2017b*. Signal detection analysis was performed to correct for response tendency and response bias in FERT performance. For example, higher accuracy on neutral faces may be driven by a tendency to classify many of the stimuli as neutral. To account for this, sensitivity (d') per emotion was calculated after Grier (1971):

$$d' = 0.5 + ((y - x)(1 + y - x)/4y(1 - x)) \quad (4.1)$$

where $x = \text{number of false alarms} / \text{number of trials not showing the emotion} =$
probability of misclassifications,

and $y = \text{number of hits} / \text{number of trials showing the emotion} =$ accuracy,

and $0 < d' < 1$

A higher value of d' is therefore associated with higher accuracy for a given emotion.

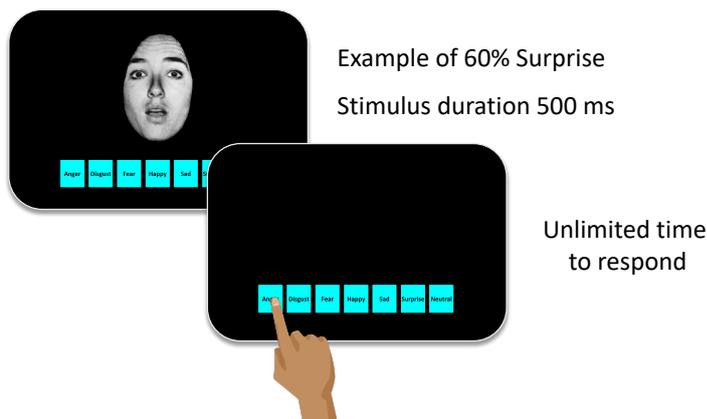


Figure 4.7 – Example of stimulus presentation in FERT. Participants were presented with the stimulus for 500ms. Seven touchscreen buttons with labels for the six emotions, and neutral, stayed on the screen continuously. There was unlimited time to respond. When a response was made, a new stimulus appeared.

Demographic information, group differences, and correlations were calculated in *R* version 3.6.1 within *jamovi* version 1.1.9 ([The jamovi project, 2020](#)). Differences between groups for demographic variables were calculated with a multivariate ANOVA. One participant was excluded from FERT analyses because of reaction times more than two standard deviations above the mean and chance performance.

Group differences in facial emotion recognition accuracy were analysed with repeated measures ANOVA, including group membership as a between-subject factor, and accuracy per emotion (averaged over all intensity levels) as the within-subject factor. The same was done for group differences in reaction times, misclassifications, and sensitivity. As there were no group differences in age or education, no covariates were added to the model.

Sum-scores on the questionnaires were correlated with accuracy, sensitivity and reaction times for overall FERT scores, and per emotion category in each group (averaged over all intensities).

Figures were created using *R* version 3.6.1 within *RStudio* version 1.3.959 ([R Core Team, 2013](#)).

4.4.3 Results

Demographics

Information on age and questionnaire scores are summarised in **Table 4.3**. Questionnaire data was missing for one member of the RBD group. The three groups did not differ significantly in age or cognitive status. Patients with PD scored significantly higher on the MDS-UPDRS-III than controls and patients with RBD. Scores on the BDI, and the HADS depression part were significantly higher in the two groups of PD and RBD, when compared to healthy controls. In addition, RBD, but not PD, was associated with significantly higher anxiety scores on the HADS. There were no significant group differences for STAI and AMI scores.

No group differences in FERT accuracy

Accuracy in the FERT was defined as the number of correctly identified faces divided by the total number of faces showing that emotion presented throughout the task. Inspection of raw

| | PD Mean ± Std | RBD Mean ± Std | Control Mean ± Std | F(2,83) | p-value |
|------------------|-------------------------|--------------------------|------------------------------|----------------|----------------|
| Age in y | 65.62 ± 7.16 | 64.48 ± 9.19 | 65.73 ± 9.05 | 0.08 | 0.930 |
| MoCA adj. | 28.37 ± 1.40 | 28.64 ± 1.94 | 28.97 ± 0.78 | 2.00 | 0.140 |
| UPDRS-III | 22.27 ± 9.74 | 7.23 ± 4.40 | 4.74 ± 3.08 | 62.97 | 0.009 |
| LEDD | 737.70 ± 2183.05 | | | | |
| BDI | 9.37 ± 5.40 | 11.51 ± 9.72 | 4.38 ± 5.38 | 8.51 | 0.010 |
| AMI total | 1.29 ± 0.45 | 1.46 ± 0.45 | 1.22 ± .53 | 1.60 | 0.210 |
| AMI ES | 1.03 ± 0.54 | 0.90 ± 0.60 | 0.92 ± 0.45 | 0.43 | 0.650 |
| AMI SM | 1.57 ± 0.68 | 1.97 ± 0.73 | 1.58 ± 0.88 | 2.35 | 0.100 |
| AMI BA | 1.29 ± 0.78 | 1.51 ± 0.90 | 1.17 ± 0.64 | 1.31 | 0.270 |
| HADS anx | 4.43 ± 3.09 | 5.71 ± 3.77 | 3.30 ± 2.73 | 3.79 | 0.030 |
| HADS dep | 3.67 ± 2.72 | 5.25 ± 3.64 | 1.67 ± 2.17 | 13.10 | 0.010 |
| STAI state | 43.73 ± 9.73 | 44.93 ± 4.47 | 46.64 ± 3.52 | 1.80 | 0.170 |
| STAI trait | 42.47 ± 7.37 | 45.04 ± 4.21 | 44.17 ± 3.21 | 1.96 | 0.150 |
| Valid N | 30 | 27 | 30 | | |

Table 4.3 – Group differences on clinical and demographic features. PD patients scored higher on UPDRS-III than both RBD and controls. Both PD and RBD scored higher than controls on the BDI and HADS depression. However, only RBD patients scored higher than controls on HADS anxiety scores.

accuracy scores and studentised residuals did not reveal any outliers. Q-Q-plots of studentised residuals were further examined, showing no violation of the normality assumption. In addition, Levene's tests of Equality of Error Variances were non-significant, thus supporting homogeneity of variances. The sphericity assumptions were not met according to Mauchly's Test of Sphericity ($p < .001$). Tests of within-subjects effects are therefore reported after applying Greenhouse-Geisser corrections.

Results indicated neither a significant group difference ($F(2,85) = 1.09, p = .34$), nor an interaction effect of emotion and group ($F(9.67,410.75) = 1.14, p = .33$). Mean accuracies are plotted by group and emotion category in **Figure 4.8**.

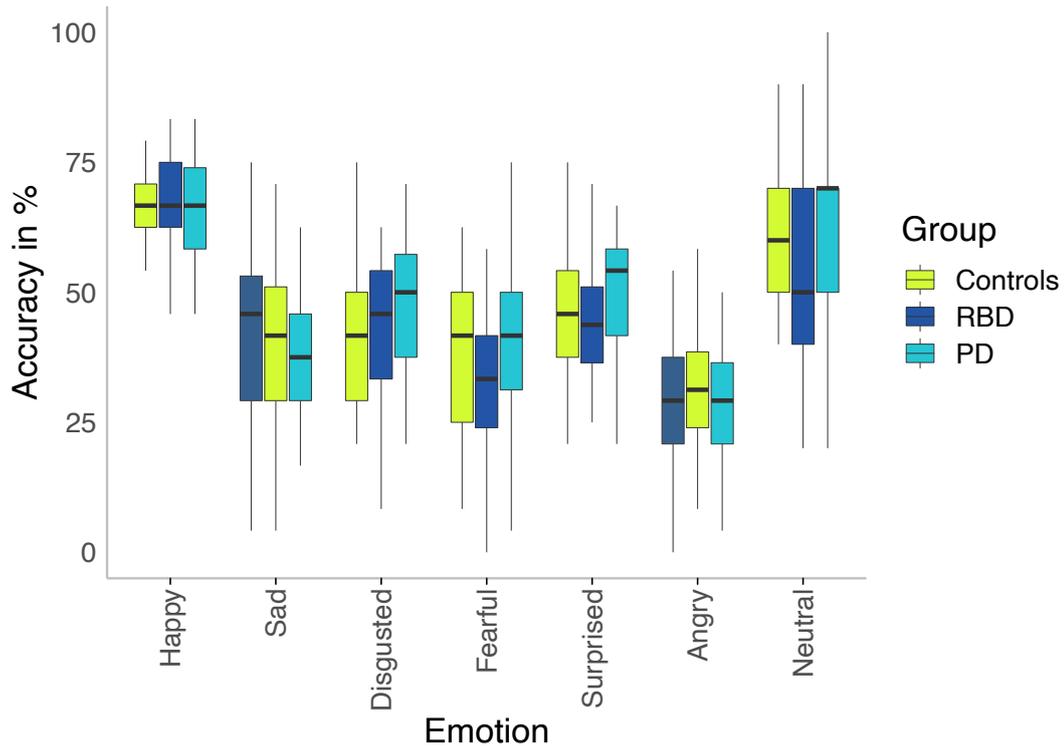


Figure 4.8 – No group differences in accuracy per emotion conditions in FERT. While all participants performed with higher accuracy for some emotions (e.g., happy faces) than others (e.g., angry faces), there were no differences across the three groups.

Significantly better performance for happy faces across all groups

There was a significant within-subject effect of emotion ($F(4.83,410.75) = 73.84, p < .001, \eta_p^2 = .47$). Pairwise comparisons are shown in **Table 4.4**. Accuracy for happy faces was significantly higher than for all other emotional expressions, except neutral expressions. In addition, performance for sad faces was significantly worse compared to surprised, and neutral faces. Participants scored higher for disgusted faces than for angry and sad faces, but lower for neutral faces. Similarly, accuracies for fearful faces were significantly higher compared to angry faces, but significantly lower for surprised and fearful faces. Overall, performance was highest for happy faces with $67 \pm 1\%$, followed by neutral faces ($59 \pm 2\%$), with lowest performance for angry faces ($30 \pm 1\%$) across all groups (**Figure 4.9 A**).

No group differences in proportions of misclassifications

Misclassifications (number of false alarms/number of distractors) were analysed by group and emotion condition. No outliers were observed. The sphericity assumption was violated based on a significant Mauchly's Test ($p < .001$). Tests of within-subjects effects are therefore reported after applying Greenhouse-Geisser corrections.

There were no group differences in the percentage of misclassifications by emotion, and no interaction effect of group by emotion ($p > .05$).

| Emotion (a) | Emotion (b) | Mean Difference ± Std. Error (a-b) | p-value |
|-------------|-------------|---------------------------------------|---------|
| Happy | Sadness* | 26.53 ± 2.11 % | < .001 |
| | Disgust* | 22.82 ± 2.11 % | < .001 |
| | Fear* | 29.30 ± 2.11 % | < .001 |
| | Surprise* | 19.85 ± 2.11 % | < .001 |
| | Anger* | 37.05 ± 2.11 % | < .001 |
| | Neutral* | 7.55 ± 2.11 % | 0.008 |
| Sadness | Disgust | -3.72 ± 2.11 % | 1 |
| | Fear | 2.76 ± 2.11 % | 1 |
| | Surprise | -6.68 ± 2.11 % | 0.03 |
| | Anger* | 10.51 ± 2.11 % | < .001 |
| | Neutral* | -18.99 ± 2.11 % | < .001 |
| Disgust | Fear | 6.48 ± 2.11 % | 0.05 |
| | Surprise | -2.96 ± 2.11 % | 1 |
| | Anger* | 14.23 ± 2.11 % | < .001 |
| | Neutral* | -15.27 ± 2.11 % | < .001 |
| Fear | Surprise* | -9.44 ± 2.11 % | < .001 |
| | Anger* | 7.75 ± 2.11 % | 0.006 |
| | Neutral* | -21.75 ± 2.11 % | < .001 |
| Surprise | Anger* | 17.19 ± 2.11 % | < .001 |
| | Neutral* | -12.31 ± 2.11 % | < .001 |
| Anger | Neutral* | -29.50 ± 2.11 % | < .001 |

Table 4.4 – Pairwise comparisons for accuracy per emotion condition. * significant at $p < .01$

No group differences for sensitivity

Signal detection analysis was performed to identify sensitivities to the emotion conditions that are corrected for tendencies of misclassifications and response bias. This was done because of the large proportion of misclassifications for neutral faces (**Figure 4.9 B**), which might reflect a bias towards classifying the facial stimuli as neutral, thus driving higher accuracy for neutral faces (**Figure 4.8**).

The mean sensitivity index d' is shown by emotion in **Figure 4.9 B**. There was no group effect of sensitivity, and no interaction effect of group and emotion condition ($p > .05$).

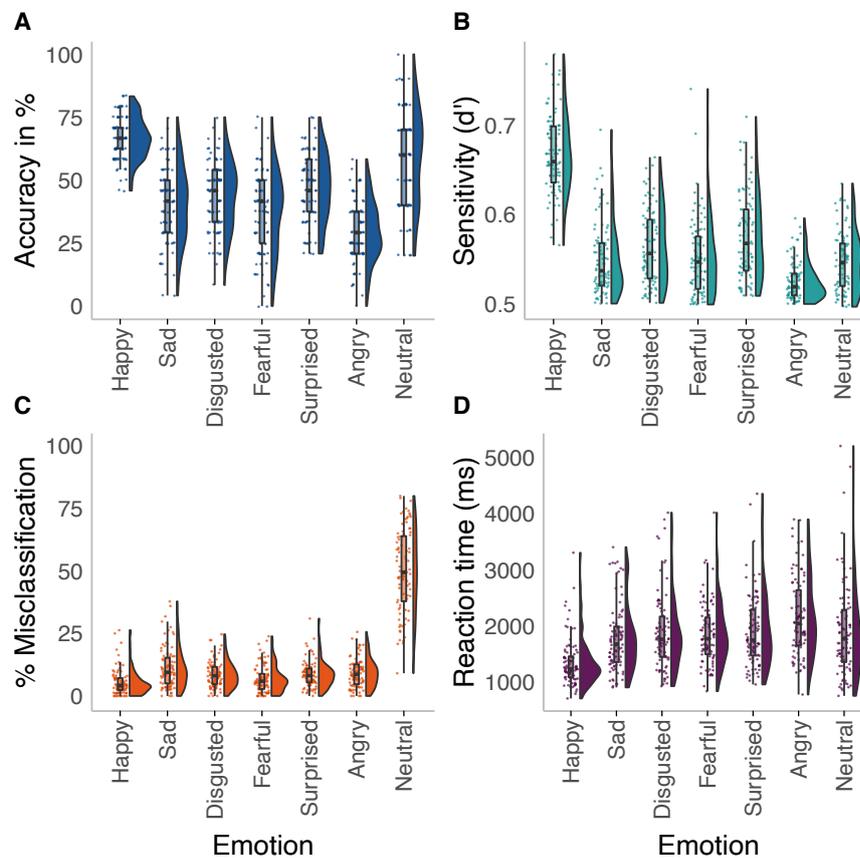


Figure 4.9 – Signal detection theory analysis results for all participants. A. Highest accuracy for happy faces, lowest for angry faces across groups. **B.** Neutral faces were most often misclassified. **C.** Participants were most sensitive for detecting happy faces. **D.** Shortest reaction times for happy faces, large variability for neutral faces

Highest sensitivity to happy faces across all groups

There was a strong within-subject effect of emotion ($F(4.92,393.68) = 124.63, p < .001, \eta_p^2 = .61$). Participants were on average significantly more sensitive to happy faces compared to any of the other emotions (**Figure 4.9 C**). In addition, participants were least sensitive to angry faces. Finally, participants were more sensitive to surprised faces compared to sad, fearful, angry, and neutral faces. Results of post-hoc pairwise comparisons are shown in **Table 4.5**.

| Emotion (a) | Emotion (b) | Mean Difference ± Std. Error (a-b) | p-value |
|-------------|-------------|---------------------------------------|---------|
| Happy | Sadness* | 0.12 ± 0.01 | < .001 |
| | Disgust* | 0.10 ± 0.01 | < .001 |
| | Fear* | 0.12 ± 0.01 | < .001 |
| | Surprise* | 0.10 ± 0.01 | < .001 |
| | Anger* | 0.14 ± 0.01 | < .001 |
| | Neutral* | 0.12 ± 0.01 | < .001 |
| Sadness | Disgust | -0.02 ± 0.01 | 0.21 |
| | Fear | -0.01 ± 0.01 | 1 |
| | Surprise* | -0.02 ± 0.01 | < .001 |
| | Anger* | 0.02 ± 0.01 | < .001 |
| | Neutral | 0.01 ± 0.01 | 1 |
| Disgust | Fear | 0.01 ± 0.01 | 0.42 |
| | Surprise | -0.01 ± 0.01 | 1 |
| | Anger* | 0.04 ± 0.01 | < .001 |
| | Neutral | 0.02 ± 0.01 | 0.07 |
| Fear | Surprise* | -0.02 ± 0.01 | < .001 |
| | Anger* | 0.03 ± 0.01 | < .001 |
| | Neutral | 0.01 ± 0.01 | 1. |
| Surprise | Anger* | 0.05 ± 0.01 | < .001 |
| | Neutral* | 0.03 ± 0.01 | < .001 |
| Anger | Neutral | -0.02 ± 0.01 | 0.002 |

Table 4.5 – Pairwise comparisons for sensitivities per emotion condition. * significant at $p < .01$

Most misclassifications for neutral faces across all groups

There was a strong within-subject effect of emotion ($F(2.07, 165.27) = 252.62, p < .001, \eta_p^2 = .76$). Post hoc tests showed that participants were significantly more likely to misclassify a face as neutral, compared to all other emotion conditions (**Table 4.6**). On average, participants identified a neutral face on 50% of the trials that did not in fact show a neutral face (**Figure 4.9 B**). In addition, participants were significantly more likely to mistake a facial expression for sad (~11% of trials) than for happy (~5% of trials) (**Table 4.6, Figure 4.9 B**).

| Emotion(a) | Emotion(b) | Mean Difference ± Std. Error (a-b) | p-value |
|------------|------------|---------------------------------------|---------|
| Happy | Sadness* | -5.85 ± 1.36 % | < .001 |
| | Disgust | -3.09 ± 1.36 % | 0.51 |
| | Fear | -1.45 ± 1.36 % | 1 |
| | Surprise | -3.10 ± 1.36 % | 0.49 |
| | Anger | -3.84 ± 1.36 % | 0.11 |
| | Neutral* | -44.58 ± 1.36 % | < .001 |
| Sadness | Disgust | 2.76 ± 1.36 % | 0.91 |
| | Fear | 4.40 ± 1.36 % | 0.03 |
| | Surprise | 2.75 ± 1.36 % | 0.94 |
| | Anger | 2.10 ± 1.36 % | 1 |
| | Neutral* | -38.74 ± 1.36 % | < .001 |
| Disgust | Fear | 1.63 ± 1.36 % | 1 |
| | Surprise | -0.01 ± 1.36 % | 1 |
| | Anger | -0.75 ± 1.36 % | 1 |
| | Neutral* | -41.50 ± 1.36 % | < .001 |
| Fear | Surprise | -1.65 ± 1.36 % | 1 |
| | Anger | -2.39 ± 1.36 % | 1 |
| | Neutral* | -43.13 ± 1.36 % | < .001 |
| Surprise | Anger | -0.74 ± 1.36 % | 1 |
| | Neutral* | -41.48 ± 1.36 % | < .001 |
| Anger | Neutral* | -40.75 ± 1.36 % | < .001 |

Table 4.6 – Pairwise comparisons for misclassifications per emotion condition. * significant at $p < .01$

No group differences in reaction times

Data from one participant was removed due to unusually long reaction times (> 2 standard deviations). Despite the characteristic long tail in reaction time data, no assumption violations, except sphericity, were found according to the appropriate tests reported above. As a result of a significant result of Mauchly's Test of Sphericity, Greenhouse-Geisser corrected results of within-subject effects are reported. There were no significant group differences ($F(2,85) = 1.63, p = .20$), and no interaction effect of emotion and group ($F(9.17,366.84) = 1.37, p = .20$).

Significantly shorter reaction times for happy faces across all groups

Reaction times significantly differed by within-subject emotion condition ($F(4.67,397.09) = 43.02, p < .001, \eta_p^2 = .34$, **Figure 4.9 D**). Pairwise comparisons (**Table 4.7**) revealed that reaction times for happy faces were significantly shorter than for any of the other emotional expressions. In addition, participants reacted significantly slower to sad, disgusted, fearful, surprised, and neutral faces, than to angry faces.

Correlations of questionnaire scores with FERT performance

There were no significant correlations between total AMI scores and FERT measures of accuracy, sensitivity and reaction times ($p > .05$). Similarly, there was no relationship between FERT performance and AMI subscales of Behavioural activation and Social Motivation. However, the Emotional Sensitivity subscale correlated negatively with accuracy and sensitivity for disgusted faces (accuracy: $r = -.26, p = .01$; sensitivity: $r = -.23, p = .03$), and accuracy and sensitivity for surprised faces (accuracy: $r = -.26, p = .02$; sensitivity: $r = -.29, p = .007$). There were also significant positive correlations between adjusted MoCA scores and accuracy ($r = .23, p = .03$) as well as sensitivity ($r = .23, p = .04$) for angry faces. Higher HADS anxiety scores were associated with higher accuracy for fearful faces ($r = -.23, p = .03$). Total MDS-UPDRS-III scores correlated positively with accuracy for disgusted faces ($r = .24, p = .03$), sensitivity to both disgusted ($r = .25, p = .02$) and neutral ($r = .33, p = .001$) faces, as well as reaction times for sad faces ($r = .23, p = .03$). Finally, higher BDI scores were associated with longer reaction times for sad ($r = .23, p = .03$), and neutral ($r = .22, p = .04$) faces. However, given the large amount of correlations explored here, all p-values reported are not corrected for multiple

testing, and would not survive such corrections.

4.4.4 Interim discussion

In the current investigation, we found no differences in FERT performance between patients with PD, patients with RBD, and healthy age-matched control participants. However, in line with our hypothesis, participants scoring higher on the Emotional Sensitivity subscale of the AMI (i.e., more emotional apathy), performed worse for disgusted and surprised faces.

While there are no previous accounts of emotional processing bias in patients with RBD, our findings are in contrast to a recent meta-analysis of emotion recognition studies in PD. The

| Emotion (a) | Emotion (b) | Mean Difference ± Std. Error (a-b) | p-value |
|-------------|-------------|---------------------------------------|---------|
| Happy | Sadness* | -430.00 ± 52.40 ms | < .001 |
| | Disgust* | -542.62 ± 52.40 ms | < .001 |
| | Fear* | -501.81 ± 52.40 ms | < .001 |
| | Surprise* | -562.99 ± 52.40 ms | < .001 |
| | Anger* | -801.52 ± 52.40 ms | < .001 |
| | Neutral* | -567.73 ± 52.40 ms | < .001 |
| Sadness | Disgust | -112.63 ± 52.40 ms | 0.33 |
| | Fear | -71.81 ± 52.40 ms | 0.82 |
| | Surprise | -132.99 ± 52.40 ms | 0.15 |
| | Anger* | -371.52 ± 52.40 ms | < .001 |
| | Neutral | -137.73 ± 52.40 ms | 0.12 |
| Disgust | Fear | 40.82 ± 52.40 ms | 0.99 |
| | Surprise | -20.37 ± 52.40 ms | 1 |
| | Anger* | -258.90 ± 52.40 ms | < .001 |
| | Neutral | -25.11 ± 52.40 ms | 1 |
| Fear | Surprise | -61.18 ± 52.40 ms | 0.91 |
| | Anger* | -299.71 ± 52.40 ms | < .001 |
| | Neutral | -65.92 ± 52.40 ms | 0.87 |
| Surprise | Anger* | -238.53 ± 52.40 ms | < .001 |
| | Neutral | -4.74 ± 52.40 ms | 1 |
| Anger | Neutral* | 233.79 ± 52.40 ms | < .001 |

Table 4.7 – Pairwise comparisons for reaction times per emotion condition. * significant at $p < .001$

meta-analysis suggested that there was enough evidence to support a slight emotion recognition impairment in patients with PD (Argaud et al., 2018). However, the authors stress the variability in FERT performance in patients with PD, and provide a number of factors that might explain these discrepancies. Next to differences in study design and analysis approaches, participant's sociodemographic characteristics and clinical features need to be considered. For example, previous research included patients with PD under DRT, patients who were not yet taking medication, or patients who had temporarily withdrawn their medication for their participation. In addition, some analyses excluded patients based on cognitive abilities, or disease severity and duration (Argaud et al., 2018).

In this report, all patients with PD were within four years of diagnosis, with all except one patient receiving DRT. Previous research points to a positive relationship between an emotion recognition impairment and disease severity, suggesting that a potential emotion recognition bias might not have emerged yet in our sample of patients with early PD. However, there have also been accounts of emotion recognition bias in patients with PD within just two years of diagnosis (Dujardin et al., 2004; Hipp et al., 2014). For example, Dujardin et al. (2004) note that unmedicated patients, who received their diagnosis of PD up to two years ago, responded less accurately when recognising angry, sad, and disgusted faces compared to healthy controls. Patients with PD also rated the intensities of the displayed emotions as less intense than their matched controls. Similarly, Hipp et al. (2014) showed that patients with PD within 1.5 years of diagnosis performed worse when recognising sad faces (but not any other emotion) compared to healthy controls. Importantly though, PD patients were also impaired on lower order visual tasks probing for colour and contrast discrimination.

In fact, visual dysfunction is a common symptom in PD, and can involve deficits in colour vision, contrast sensitivity, and visual acuity (Weil, 2020; Weil et al., 2016), potentially already in early pre-motor stages of the disease (Han et al., 2020). It can be argued that facial expressions of negative emotions have less prominent visual discriminatory features than expressions of happy emotions, and are thus more visually challenging to recognise. For instance, a happy face might be easily recognised by the clear upward motion of the mouth and showing of teeth, while a sad face might only show a subtle downward motion of the mouth (Hipp et

al., 2014; Johnston et al., 2003). In addition, the lower recognition performance for negative facial emotions as compared to neutral faces may also be due to the involvement of subcortical pathways in the former, but not the latter (Weil et al., 2016). General identification of faces relies on the fusiform face area and the slow processing of detailed visual information, while recognition of emotional – especially fearful – faces involves fast, but coarse processing through subcortical pathways and the amygdala (Jessen et al., 2017; Vuilleumier et al., 2003). It has been suggested that this subcortical pathway may be subjected to more PD-related dopaminergic pathology than the pathways around the fusiform face area, resulting in stronger impairments in negative emotion recognition (Weil et al., 2016). Thus, considering Hipp et al. (2014) found a visual impairment in the PD group, and a deficit only in the potentially more challenging condition of recognising sad faces, their result might be mainly due to visual factors.

This hypothesis is also supported by strong within-subject effects of emotion condition for accuracy, misclassifications, sensitivity and reaction times found in the current study. Across groups, participants performed with the highest accuracy for happy faces, followed by neutral faces. Angry faces were identified with the lowest accuracy. This is a well-known finding, and again might reflect the different levels of difficulty of recognising a positive or a negative facial emotion, especially at lower intensities. While low intensity expressions of sadness or anger might have similar visual features, expressions of happiness might be more easily recognisable and distinguishable. In addition, participants were more likely to mistake a stimulus for a neutral face than any other emotional expression. The sensitivity score calculated with signal detection analysis also suggests that the fairly high accuracy for neutral faces is driven mostly by a response bias, rather than actual sensitivity to the neutral stimulus. In contrast, participants scored with high accuracy and low misclassification proportions on happy faces, resulting in a high sensitivity score for happy faces. This suggests that happy faces were indeed more easily identified than neutral or sad faces. Thus, in the presence of visuospatial or executive function deficits, patients with PD might be especially prone to making errors with negative faces. This might explain the variability in results, as different stimuli and study designs would require differing levels of visuospatial and executive abilities.

This hypothesis is further consistent with a previous report assessing facial emotion recognition in healthy controls with different levels of stimulus resolution. At normal resolution, participants performed at ceiling across all emotions. However, when the photographs of emotional faces were degraded in resolution, participants were most inaccurate for fearful, angry and sad faces. Performance for neutral and surprised faces declined slightly, while participants did not show any performance decline for happy faces (Johnston et al., 2003).

Next to visual recognition of emotion, previous research also established evidence for an impairment in recognition of prosody (auditory emotional information) in patients with early PD (Buxton et al., 2013). Again, this might be due to impairments in sensory processes in PD, such as auditory acuity. Indeed, a few studies documented slightly lower auditory acuity in PD compared to controls (Folmer et al., 2017; Pisani et al., 2015). However, evidence for a hearing impairment related to PD is limited, and most investigations on prosody perception in PD have only included participants without any hearing impairments (e.g., Buxton et al., 2013; Schröder et al., 2006). As these questions remain unanswered, I refined the FERT in a follow-up study to the current report, which includes rating scales for an intensity and confidence rating per trial, as well as a visual acuity control task, but no neutral stimuli (see **Chapter 5**).

We hypothesised that FERT performance would correlate with severity of apathy, especially with the emotional sensitivity subtype of apathy, due to overlapping neural correlates. In accordance with this, we found that Emotional Sensitivity subscale scores were correlated with FERT performance for disgusted and surprised faces. Specifically, more emotional blunting (i.e., a higher score on the Emotional Sensitivity subscale) was associated with lower accuracy and sensitivity in detecting disgusted and surprised faces. These results must be interpreted with caution as the significance of the correlations does not survive multiple testing correction. However, given the small sample size for such a correlational analysis, the application of multiple testing correction here might yield a Type-II-Error, and conceal a true relationship between emotional sensitivity and FERT performance. Still, not correcting for multiple testing largely increases the probability for Type-I-Errors (Chen et al., 2017). Thus, additional research with larger sample sizes and higher statistical power will be needed to replicate these

relationships.

Keeping in mind the possibility of a Type-I-Error, a relationship between emotional blunting and lower FERT performance would be supported by previous research. Compared to healthy controls, [Martínez-Corral et al. \(2010\)](#) found an impairment in FERT performance in a group of patients with PD with comorbid apathy. This deficit was not present in a group of patients with PD without apathy. Given that the mean severity of apathy was fairly low in our sample, with no group reaching the cut-off for clinical apathy on any of the subscales, the absence of a group difference in FERT performance might be consistent with our hypothesis. In addition, the weak correlation between Emotional Sensitivity subscale scores and FERT performance reported here might reflect a true relationship that is dampened by low variability in apathy. There is also evidence that emotional apathy may be less common than behavioural or social apathy. [Ang et al. \(2018\)](#) did not find significant emotional apathy in a group of over 100 PD patients, but report six cases with pure emotional apathy, without signs of social or behavioural apathy. Thus, a deficit in facial emotion recognition may only be present in those PD patients with emotional apathy.

Emotional blunting is a symptom common to both apathy and depression, and refers to experiences such as reductions in the ability to cry, caring about other's feelings, or ability to feel pleasure ([Berenbaum et al., 1987](#)). A relationship between emotional blunting and impaired facial emotion recognition would therefore be reasonable in both causal directions: emotional blunting might cause a difficulty to identify emotions because of a reduction of perceived valence; and a facial emotion recognition impairment might cause emotional blunting through a decrease in perceived emotional feedback from others. As it was shown previously that SSRI treatment affected bias in FERT performance independently of any reduction in depressive symptoms ([Godlewska et al., 2016](#)), it remains to be seen whether (emotional) apathy scores are involved in this change. This hypothesis was tested in **Chapter 5**.

Further exploratory correlation analyses revealed a potential relationship between MoCA scores and performance for angry faces. As accuracy for angry faces was overall low, a relationship with cognitive status might support the increased difficulty of identifying angry faces. In addition, higher anxiety scores were associated with higher accuracy for fearful faces.

Similarly, higher depression scores were related to longer reaction times for sad and neutral faces. Both of these correlations are in accord with previous accounts, suggesting an attentional bias for fearful stimuli in anxiety (Bradley et al., 1999), as well as psychomotor slowing resulting in longer reaction times in depression (Sabbe et al., 1996). PD motor symptom severity correlated positively with accuracy for disgusted faces. However, this correlational analysis was done on the whole sample, meaning that PD symptom severity reflects group membership. Thus, the correlation likely corresponds to the small, but non-significant, group difference in accuracy for disgusted faces, as shown in **Figure 4.8**.

Finally, we note differences between healthy controls, patients with PD, and patients with RBD, with respect to severity of depression and anxiety scores. Somewhat counterintuitively, patients with RBD reported more severe symptoms of depression and anxiety compared to patients with PD. Given that RBD is seen as a prodromal stage to PD, and anxiety and depression are considered possible symptoms of the disease, one might expect this relationship to be reversed. However, this pattern has previously been described in a sample of 171 patients with RBD, 296 controls, and 119 patients with PD (these numbers include some of the participants in the current study) (Barber et al., 2017). In this larger sample, the authors record more severe depression and anxiety, as well as more severe apathy in the RBD group than in the PD group. This suggests that the non-significant difference in AMI scores observed in our sample might be due to lack of power. In addition, researchers have previously proposed that PD following from RBD might be a subtype of the disease that is characterised by more prominent non-motor features than PD without RBD (Barber et al., 2017). A dose-dependent impairment of facial emotion recognition skills increasing from healthy controls, to RBD, to PD, as hypothesised here, might therefore not reflect the underlying disease processes.

One major limitation to this analysis is that some of the PD and RBD patients were taking antidepressant medication at the time of testing. As mentioned previously, antidepressants have been shown to affect the emotion recognition bias measured in the FERT. In addition, some patients were taking either only dopamine agonists, or a combination of levodopa and dopamine agonists, which may also have affected behaviour on the task in a way that is difficult to predict. Since the patients with RBD were generally more severely affected by mood

symptoms than PD patients, and also took antidepressant medication more frequently, this may have masked some possible differences between the groups. Future investigations may attempt to test this hypothesis in antidepressant-naive patient groups.

4.5 Discussion

In this chapter, I analysed how neuropsychiatric symptoms are distributed in PD, to what extent the frequency and severity of these symptoms might be secondary to the diagnosis of PD, and whether the facial emotion recognition impairment associated with major depressive disorder also occurs in PD.

In Part 1 of this chapter, I describe results supporting the hypothesis that neuropsychiatric symptoms are more common in PD than in healthy older adults, and that distinguishing between core depression, anxiety, apathy, and somatic symptoms can yield more precise prevalence estimations. In addition, these differentiations suggest that symptoms resulting from changes in reward and effort sensitivity - such as low motivation, lack of interest, fatigue (Husain et al., 2018) - are more common in PD than signs of core depression (such as sadness, feelings of guilt, suicidal ideation).

The analysis in Part 2 revealed that patients with PD experience more neuropsychiatric symptoms, both somatic and psychological, than patients with OA and healthy controls. While the majority of PD patients described to be unhappy with their health, this was not the case for their self-assessment of general happiness. This raises the question whether dopaminergic pathology may cause variations of mood symptoms like depression and apathy that do not impact people's overall happiness as much as major depressive disorder developed in response to negative life events. Thus, this potential complicated relationship between mood, health satisfaction, and overall happiness in PD deserves further investigation.

Finally, in Part 3, I found no evidence for differences in FERT performance between groups of PD, RBD, and healthy controls. A weak relationship was documented between the Emotional Sensitivity subscale of the AMI, and FERT performance for disgusted and surprised faces. This is consistent with our hypothesis that apathy, rather than depression, may be as-

sociated with facial emotion recognition abilities. However, on average, participants mistook emotional expressions for neutral on 50% of trials that did in fact show one of the six emotions. Thus, the presence of neutral stimuli and response options may have masked other performance and group differences for the remaining emotions by introducing a response bias. A revised version of this task was therefore used in the study in **Chapter 5**.

Taken together, these results support the hypothesis that neuropsychiatric symptoms in PD are primary, specific features of the disease itself, potentially underlying dopaminergic and serotonergic dysfunction. Moving away from the use of questionnaire sum-scores, and towards investigations of mechanisms and treatments of individual symptoms may advance not only treatment for patients with PD, but also for patients experiencing mood disorders in the general population.

Chapter 5

The role of serotonin in decision-making in Parkinson's disease

5.1 Introduction

Although neuropsychiatric symptoms like depression or apathy are common in Parkinson's Disease (PD), the mechanisms underlying them remain unclear. Several lines of research have recently attempted to investigate some of these conditions within modern neuroscience frameworks of decision-making and emotion processing. For example, one hypothesis for the development and maintenance of depression proposes a negative bias in affective information processing that results in observable changes in mood over time (Harmer, Goodwin, et al., 2009; Matt et al., 1992). This bias may be indicated by enhanced attention or memory for negative stimuli, but also by a tendency to interpret ambiguous facial expressions as negative (Gur et al., 1992). Importantly, there is evidence that this selective bias for negative information responds to serotonergic treatment. For example, patients with depression showed increased activation in the amygdala, ventral striatum, and frontoparietal cortex when viewing sad facial expressions at baseline, but not after an eight-week treatment with the SSRI fluoxetine hydrochloride (Fu et al., 2004). While it is still unclear how and why SSRIs may benefit people with depression, these findings suggest that increasing serotonin may improve mood through its effect on emotion processing.

Similarly, apathy has been described in the framework of goal-directed behaviour, where a loss of motivation may result from alterations in different stages of the decision-making process (Husain et al., 2018). These could include a reduced willingness to exert effort to obtain a reward, lower valuation of rewards, or impaired reinforcement learning from rewarding outcomes. Traditionally, these decision-making concepts have been studied extensively in relation to the mesolimbic dopamine system, since dopamine is well-known for its role in signalling the magnitude and probability of rewards (e.g. Alikaya et al., 2018). However, there is now growing evidence for an equally important role of serotonin in decision-making and disorders of motivation. For instance, while dopaminergic neurons have long been thought of as the main encoders for reward signals, it has become clear that serotonergic neurons, too, are activated by both expected and unexpected rewards, during their anticipatory and consummatory phases (Li, Zhong, et al., 2016). In addition, a role for serotonin in apathy may be especially indicated for the emotional subtype, characterised by a blunting of affect, which

may be more closely related to depression and emotion processing than the behavioural or social subtype of apathy (Lockwood et al., 2017).

While a role for dopamine in the modulation of neuropsychiatric symptoms in PD is implied by the very nature of traditional views regarding PD pathology, there are several arguments for the (additional) involvement of serotonin. First, apathy and depression in PD seem to be responsive to dopaminergic medication only in some, but not all cases (Chung et al., 2016; Muhammed and Husain, 2016; Seppi et al., 2019). In fact, a recent probe into effort and reward-based decision-making in apathetic PD patients highlighted distinct effects of apathy and dopamine on behaviour: While apathy was associated with reduced incentivisation by low rewards, dopaminergic medication increased responding to high reward, high effort options (Le Heron, Plant, et al., 2018). Thus, dopamine could not reverse the behavioural pattern related to apathy, indicating the importance of exploring alternative treatment options.

Second, serotonergic dysfunction is a well-established aspect of PD that may even precede the loss of dopamine function. The DRN, considered to be the main source of serotonin in the brain, is affected early on in the progression of PD (Braak et al., 2004), such that its deterioration may contribute to the development of PD-related symptoms. Finally, an increasing number of investigations have been able to directly link serotonergic function to neuropsychiatric symptoms in PD. Levels of serotonin metabolites or 5-HT_{1a} receptor availability were lower in people with PD who were also depressed than in those who had PD without depression (Politis et al., 2015). This seems in agreement with increased limbic SERT binding in depressed PD patients (Boileau et al., 2008), suggesting that depression in PD might develop because of increased clearance of serotonin through SERT, and simultaneous loss of serotonergic neurons in the raphe nuclei. A meta-analysis of PET studies imaging SERT in patients with PD could confirm striatal SERT dysfunction and its association with motor and non-motor symptoms (Pagano et al., 2017). One report even suggested that serotonergic – not dopaminergic – degeneration, was related to severity of apathy, anxiety, and depression in patients with PD (Maillet et al., 2016).

However, research so far has mainly focused on establishing links between serotonergic function and questionnaire scores for - or diagnoses of - neuropsychiatric symptoms in PD. It has

not yet been investigated how the modulation of serotonin in PD may affect carefully operationalised, behavioural decision-making and emotion processing measures. The aim here was therefore to investigate how serotonergic modulation through administration of citalopram (20mg) affects decision-making and emotion processing in patients with PD. Citalopram is an SSRI that blocks reuptake of serotonin in presynaptic cells through the serotonin transporter, thereby increasing the level of serotonin within the synaptic cleft. It is most commonly used as an antidepressant, but also has anxiolytic effects (Izumi et al., 2006). While clinical trials testing effects of antidepressant drugs usually involve periods of 6 to 24 weeks, previous research has validated the usefulness of short-term administration of citalopram for probing the effects of acute serotonergic modulation in the brain. For example, investigations in healthy participants and patients with PD have demonstrated that short-term citalopram affected emotional or cognitive processing in absence of any antidepressant response (Harmer, O'Sullivan, et al., 2009; Harmer et al., 2004; Scholl et al., 2017; Ye et al., 2014).

As the current study was not investigating the effectiveness of citalopram against depressive symptoms, but intended to probe the serotonergic mechanisms of decision-making and emotion processing in PD, seven days of citalopram were deemed sufficient. If PD patients, while on their regular dopamine medication, presented different patterns of decision-making and emotion processing compared to healthy controls, performance on serotonin might shift towards the healthy level. However, several case reports have also suggested that SSRIs may in fact induce or worsen apathy and emotional blunting in people with and without PD (Barnhart et al., 2004; Muhammed and Husain, 2016; Price et al., 2009; Wongpakaran et al., 2007). Thus, I considered baseline motivation levels in the analyses, and applied generalised linear mixed-effects models where appropriate to account for individual differences in serotonergic responses. To assess motivation and decision-making, patients and age-matched controls were examined on experimental tasks that assess various aspects of decision-making and emotion processing: effort and reward sensitivity, risk aversion, reinforcement and punishment learning, facial emotion recognition, as well as a set of questionnaires that index neuropsychiatric symptoms.

5.2 Method

5.2.1 Participants and study design

This was an experimental medicine study using a double-blind, placebo-controlled within-groups cross-over design. Twenty patients with a diagnosis of idiopathic PD made according to Parkinson's Disease Society Brain Bank criteria were recruited via an outpatient clinic (Hughes et al., 1992). Of the twenty PD patients, 16 were taking dopaminergic medication: 16 were taking Levodopa, three patients took an additional dopamine agonist, and two were taking additional amantadine. In addition, two patients also took clonazepam.

In addition, 20 age-matched healthy controls were recruited from the general population. Due to the COVID-19 outbreak beginning in March 2020, data collection had to be concluded before reaching the planned sample size of 36 participants in each group.

Each PD patient received seven days of citalopram and placebo in a counterbalanced, randomised order. The citalopram and placebo tablets were encapsulated to ensure that the two compounds were visually identical. There was a wash-out period of at least two weeks between the two phases. With an initial screening visit, two first dose visits (one for drug, the other for placebo), and two research visits (following a week of being on drug or on placebo), the study consisted of five visits for each patient (**Figure 5.1**). Controls were tested once without medication.

During the screening visit, patients underwent a medical history review, cognitive assessment, and a physical examination to ensure that they were safe to take the citalopram tablets. In addition, they were asked to fill out a set of questionnaires (described below) at screening and at both research visits. Questionnaire answers at screening were taken as baseline measures for the PD group.

At the first dose visit, patients were pseudo-randomised to receive seven days of citalopram and placebo in a counterbalanced order. As the sample was stratified by gender at a 1:1 ratio, and the randomisation scheme was performed within each stratum, the allocation is 'pseudo-random' as opposed to truly random. This was to ensure that there was a balanced distribu-

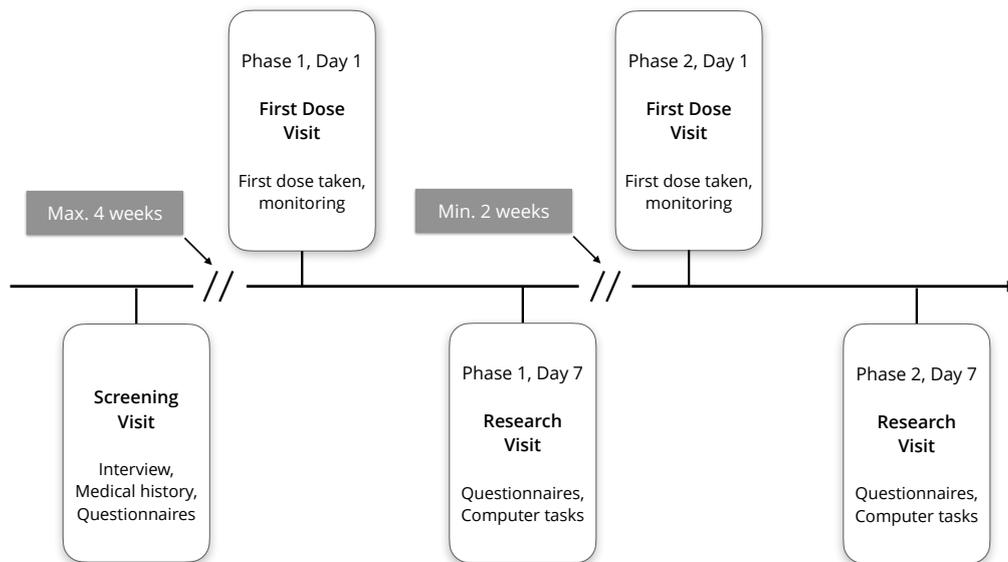


Figure 5.1 – Schematic outline of study design. Patients were invited for a screening visit, and if enrolled, returned for a first dose visit and a research visit for the placebo and citalopram phase each. Placebo and citalopram orders were counterbalanced. Healthy controls were invited for a combined screening and research visit.

tion of gender between the two drug administration orders. Although data collection was cut short, this balanced distribution was still met in the current sample. Patients were given the first dose of their assigned compound, and were monitored for one hour after receiving the first dose. At the end of this visit, they received the remaining drug/placebo tablets to take home, with full instructions of when and how to take them.

Testing was completed at the research visit on the morning of day seven after the first drug/placebo administration. Participants were asked to complete a number of computer-based tasks and fill out the set of questionnaires. Healthy controls completed this research visit once. After a minimum of two weeks without any drug/placebo administration, the procedure was repeated beginning from the first dose visit, where patients started the second phase of the study.

5.2.2 Questionnaires

All questionnaires were self-evaluating questionnaires. These included the HADS, BDI, STAI, AMI, and MDS-UPDRS, explained in more detail in **Chapter 4**. On top of these, the Geri-

atric Depression Scale (GDS), the Snaith-Hamilton Pleasure Scale (SHAPS), the Toronto Alexithymia Scale (TAS), and the Questionnaire of Cognitive and Affective Empathy (QCAE) were added to collect more detailed affect-related information. The Addenbrooke's Cognitive Examination (ACE) was collected as a measure of cognitive function.

5.2.3 Behavioural tasks

Effort based decision-making for rewards This task, henceforth called “Apples”, was designed to estimate reward and effort based decision-making processes, and is explained in detail in [Le Heron, Plant, et al. \(2018\)](#). Participants were presented with a picture of an apple tree and were asked to react to offers of a certain number of apples (indicative of money) in return for a certain amount of physical effort. Effort was indicated by a red bar positioned at different levels of height on the tree trunk (**Figure 5.2**). The main task was to decide whether the effort would be worth the reward. Effort was exerted by squeezing a handle, where the different effort levels were calibrated to a percentage of each participant's Maximum voluntary contraction (MVC) force. There were five levels of reward (1, 4, 7, 10, and 13 apples), and five levels of effort (16%, 32%, 48%, 64% and 80% of MVC), resulting in a decision space of 25 possible combinations of reward and effort (**Figure 5.3**).

The experiment was divided into three parts. First, participants were asked to squeeze the handlebars twice, as hard as possible, to obtain a measure of their MVC force. They were then trained on the different effort levels that were adjusted to their strength. Second, 125 different offers were presented, and for each offer, a *Yes* (accept) or *No* (decline) response had to be made on a keyboard. The positions of the *Yes* and *No* labels on the left and right side of the screen were randomised to prevent biased responses. Before these decision trials, participants were informed that ten of their decisions would be randomly selected, on which they will have to follow through in the end. In reality, the same ten trials were preselected for everyone: 13 apples for 16% MVC, 7 apples for 48% MVC, 4 apples for 64% MVC, 10 apples for 32% MVC, 10 apples for 16% MVC, 4 apples for 16% MVC, 1 apple for 16% MVC, 7 apples for 32% MVC, 4 apples for 64% MVC and 10 apples for 80% MVC. Thus, in the third part, the handle needed to be squeezed if the offer had been accepted, in order to obtain the apples and win money (**Figure 5.2**). While the instructions explained that more apples collected

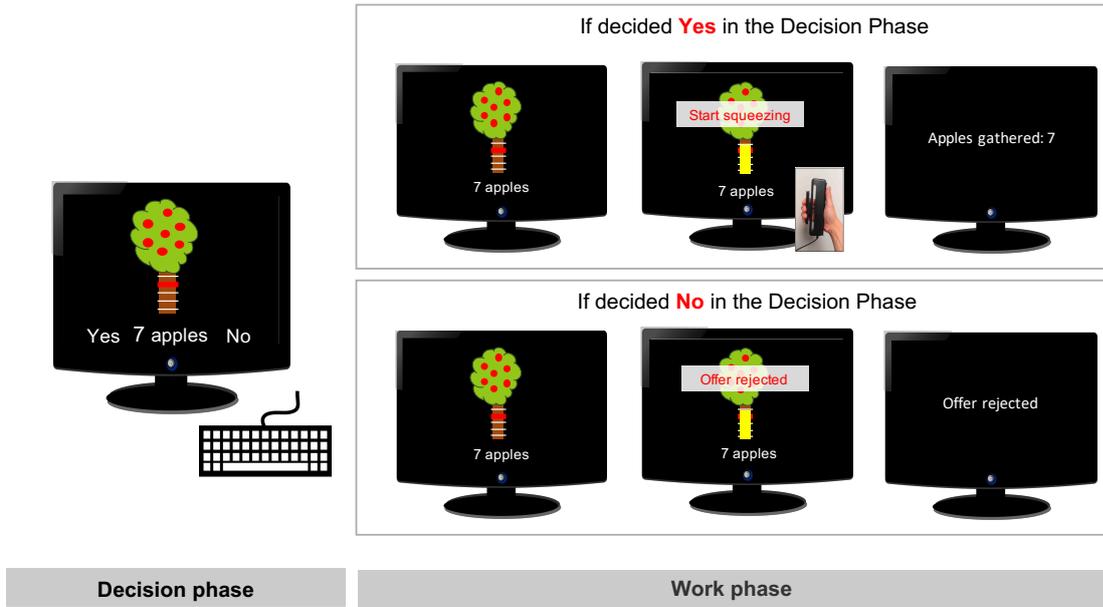


Figure 5.2 – Apples task design. The task was divided into a decision and a work phase. In the decision phase, participants were asked to give yes or no responses to offers with different reward and effort levels on a keyboard. Out of 125 decisions in this phase, 10 decisions had to be acted upon in the following work phase, depending on whether the offer was accepted or rejected. Everyone received the same ten trials to follow through on during the decision phase. If an offer was accepted, squeezing the bar to the associated effort level resulted in a gain of apples, that translated into money. If an offer was rejected, no action was required.

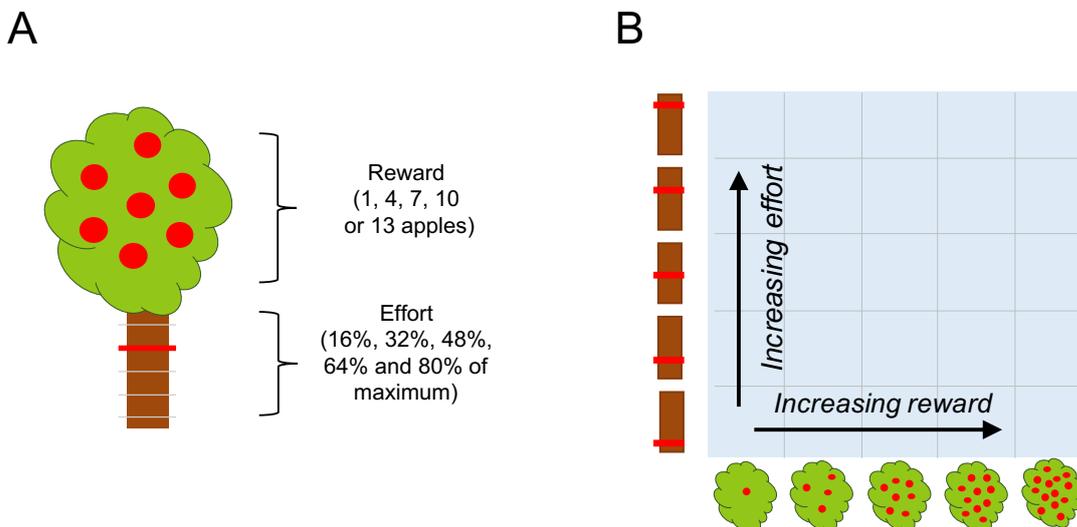


Figure 5.3 – Apples decision space. A. Reward was indicated by the number of apples in a tree, effort was represented by the height of a red bar on its trunk. B. Five different reward and effort levels comprise a decision space of 25 possible combinations and offers.

translated to more money earned, everyone received the same payment and was debriefed on conclusion of their study involvement.

Decision-making under risk In this task, henceforth called “Risk”, participants were presented with two options to choose from. One option represented a 100% chance of winning a certain amount of money (the certain option), while the other option represented a 50/50 gamble of either winning an amount larger than in the certain option, or not winning anything (the risky option, **Figure 5.4 A**). The position of certain and risky options on the screen was randomised. The task was to consider whether the additional money would be worth taking the risk of not winning any money at all on each individual trial. A response was made by tapping on preferred option. After their response, a new offer was presented, without showing the outcome of the previous choice, or collecting any money that was won. Thus, each offer was to be considered independently of previous choices. In half of the 210 trials, the risky gamble was to avoid losing, rather than to win. In this Loss condition, the certain option represented a 100% chance of losing a certain amount of money, while the risky option involved a 50/50 gamble of either not losing anything, or losing more than in the certain option (**Figure 5.4 B**). There was no time limit, and the offers stayed on the screen until a response was given.

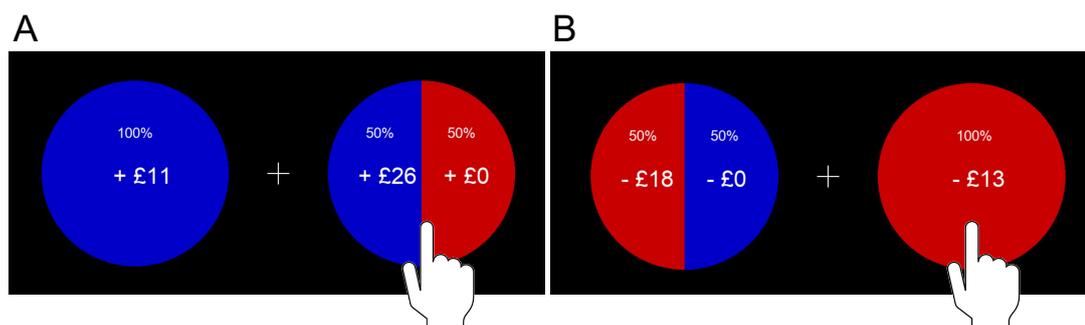


Figure 5.4 – Risk task design. This binary choice task represented a risky gamble to increase a win, or avoid a loss of money. **A.** In the Gain condition, the risky option could result in a larger monetary win than the certain option, or result in no win. **B.** In the Loss condition, the risky option could prevent participants from losing money, or lose them more money than the certain option.

Reversal learning task To measure potential effects of citalopram on learning of reward and punishment associations, a reversal learning task (roughly based on [Swainson et al., 2000](#), henceforth called “Cards”) was included. On a touchscreen, two squares, labelled *A* and *B* were presented (**Figure 5.5**). Instructions were given to think of these squares as decks of cards, with each deck having an associated probability of winning when a card is turned: For example, deck *A* could win 75% of the time, while deck *B* could win 25% of the time. Participants were made aware that they would not be told the actual odds behind the decks, and that they would have to try and learn them by trial and error. The positions of decks *A* and *B* on the left and right side of the screen varied randomly, independent of underlying odds.

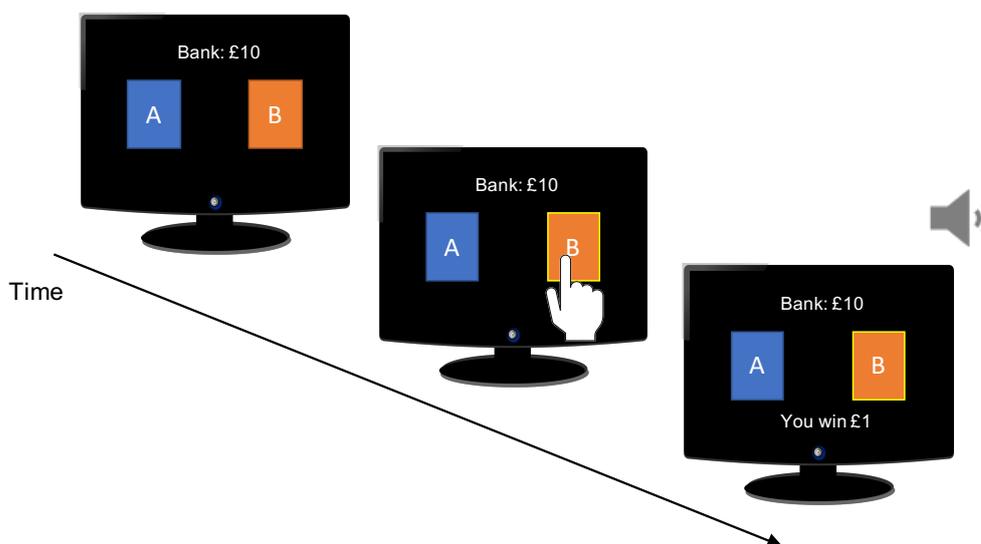


Figure 5.5 – Cards task design. In this reversal learning task, participants had to learn the underlying probabilities behind two decks of cards in order to maximise winnings. These were 75% and 25%, and switched every 16-20 trials, with 12 reversals in total. The two decks of cards were represented by two squares A and B on a touch screen. Everyone started with £10 “in the bank”, and every trial could win or lose £1 by tapping on one of the decks of cards. Visual, as well as auditory feedback was given based on the outcome of each trial.

In addition, they were instructed that these odds were not stable throughout the task, but that they might change a few times. Thus, while deck *A* might be more likely to win at first, these

odds would switch to deck *B* at some points during the task, and again switch back to deck *A*. Everyone started out with £10 in a virtual bank. On each trial, one of the two decks had to be chosen by tapping on the square, without a time limit. After one of the decks was selected, a cash register sound (ka-ching!) was played and “You win £1” appeared on the screen, if the choice resulted in a win. If the choice lost, an error sound was played and “You lost £1” was displayed on the screen. The amount of money in the bank was updated after every trial and stayed visible on the screen throughout the task. Depending on performance, the amount of money in the bank could go negative, or as high as £100 after the task was completed. At the start of the task, participants were told that the amount of money won in this task will be proportionally related to their payment. However, as in *Apples*, all who took part were paid the same.

Facial Emotion Recognition task This facial emotion recognition task was adapted from the previous emotion recognition task used in **Chapter 4.3** and is henceforth called “Faces”. In this version of the task, participants were presented with averaged faces created from overlaid photographs from the Karolinska Directed Emotional Faces (Lundqvist et al., 1998) set. An averaged composite of men and women was available for seven different facial expressions: afraid, angry, disgusted, happy, sad, surprised, and neutral. To increase the difficulty of the task, and to match the previous task version in **Chapter 4.3**, I then created new images showing the six different emotional expressions at different intensities, by morphing them with the corresponding neutral face. This was done in the open-source program “Psychomorph” (Tiddeman et al., 2005, **Figure 5.6**).

Eight different intensity levels (10% - 80%) for each of the six emotions were included. Each level and emotion were shown once with a female and once with a male face, resulting in 96 trials in total. In each trial, the face was presented for 500ms. Afterwards, the stimulus was replaced with labels for the six emotions as possible answers (**Figure 5.7**).

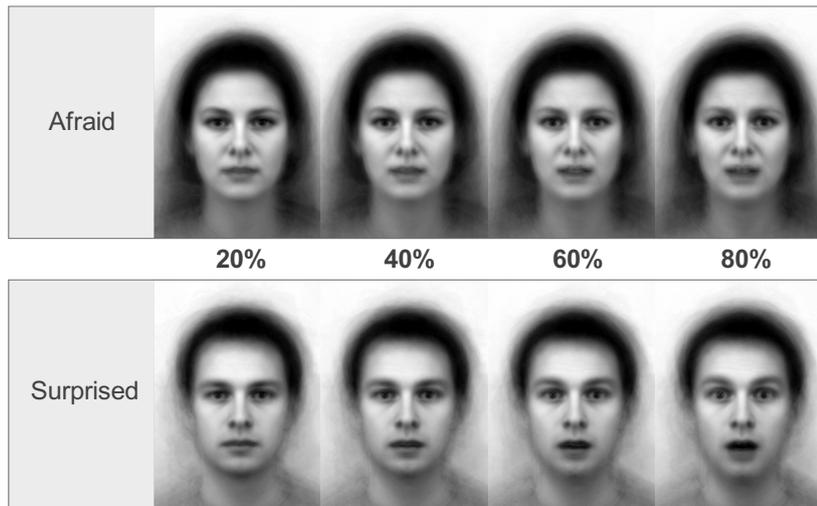


Figure 5.6 – Examples of morphed facial expressions. Averaged pictures of emotional facial expressions were morphed with an averaged neutral expression to different levels, resulting in slight and continuous changes in the extend of facial cues for each emotion.

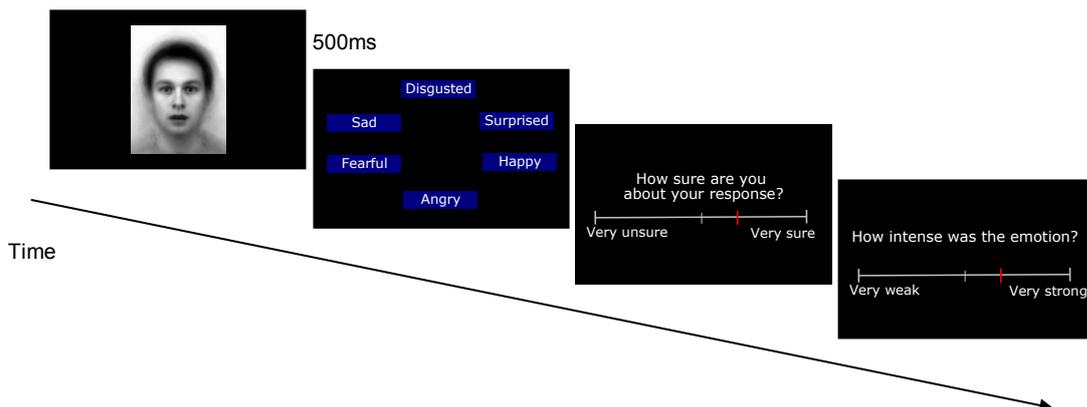


Figure 5.7 – Faces task design. The stimulus was presented for 500ms, after which six response buttons appeared. These were labelled with the six emotions included in the stimulus set. Participants were instructed to click on the label that most accurately describes the stimulus. The mouse cursor was placed at the centre of the button arrangement, so that there was an equal distance to all six button locations. There was no time limit to respond. After a response was logged, a question on confidence in the response, and intensity of the stimulus had to be answered by sliding the mouse cursor along a rating scale, and clicking at the desired location.

Responses were made by mouse-click, with the mouse cursor starting out at the centre of the arrangement of labels. After participants clicked on their preferred answer, two questions appeared on the screen sequentially. First, they were asked: “How sure are you about your response?”, with a rating scale going from “very unsure” to “very sure”. The second question

asked: “How intense was the emotion?”, with a sliding scale going from “very weak” to “very strong”. Responses on the sliding scales were again made by mouse click. After the second question was answered, a new face stimulus was presented. There were no time limits to respond.

Emotion recognition control task In order to measure whether performance on the FERT may be related to overall visual acuity, I designed a visual control task, henceforth called “Twins”. In this task, a neutral face was presented on the left of the screen, with the same face expressing an emotion to some extent on the right side of the screen (**Figure 5.8**). Half of the trials displayed a male face, the other half a female face. The face on the right was chosen at 20%, 40%, 60% and 80% intensity of each of the six emotions. Below the faces, participants could move the mouse cursor along a sliding scale. By doing so, the neutral face on the left slowly changed into the emotion shown on the right, by increments of 5%. The task was to find the position on the sliding scale that resulted in the most accurate match between the left and the right picture. The error around the correct percentage of emotion intensity could be measured by the position on the scale.

5.2.4 Analysis

Tests for differences in demographic variables were done with paired t-tests between PD on placebo and on citalopram, and with unpaired t-tests between PD on placebo and healthy controls. Questionnaire scores, such as the AMI, were taken from baseline questionnaires collected at the screening visit for PD patients and at the research day for healthy control.

Apples | Effort-based decision-making for rewards Data from this task were analysed in *MATLAB R2020b* using custom scripts. Before further analysis, trials with decision times of less than 0.4 seconds were considered accidental squeezes and therefore removed. Given the hierarchical design of the task, I fit a generalised linear mixed effects model with a logistic link function (*fitglm* in *MATLAB*) with accept/reject choices for each trial. The full model, including all interactions between reward, effort, apathy, and medication status, as well as random intercept and slopes, was compared with less complex models using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). The effort term was squared in

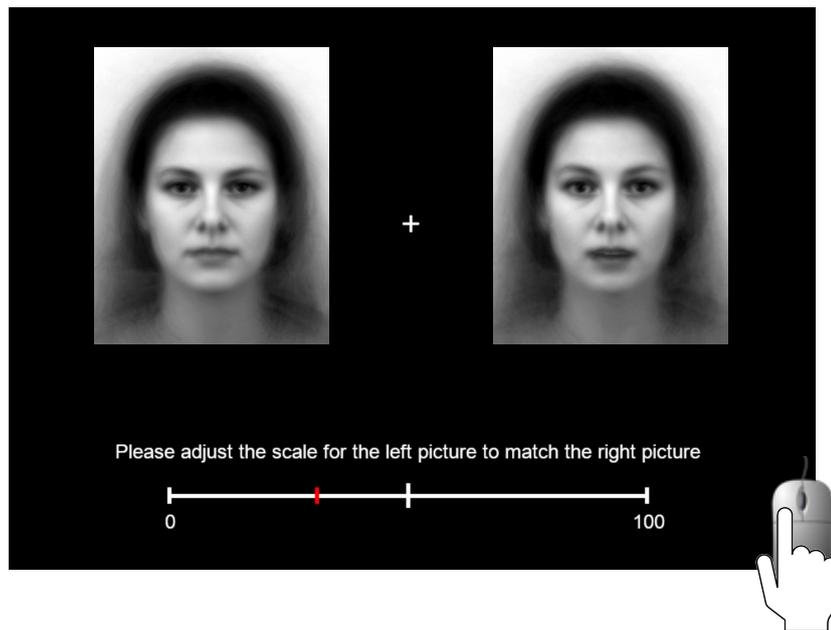


Figure 5.8 – Twins task design. A neutral expression on the left was paired with a face of the same sex with an emotional expression at 20, 40, 60, or 80% intensity. By sliding the mouse cursor along a scale positioned below the two pictures, the neutral face slowly changed into the expression on the right. The task was to find the position on the scale where the left and right pictures matched most closely and log a response by clicking the left mouse button.

line with previous literature on perceived effort costs (Morel et al., 2017). No model improved fit by > 2 *AIC* or *BIC* units (chosen as standard cut-off level, Burnham et al., 2004) over the full model. The winning model included fixed effects for reward, effort, apathy, and medication status, a random intercept, and random slopes for reward and effort. The same approach was taken using a depression or anxiety term instead of apathy, neither of which was significant or improved fit (difference *AIC* and *BIC* > 2). Thus, no effects of depression or anxiety are reported.

To test for potential session order effects (placebo then citalopram vs citalopram then placebo), the same model was evaluated, this time including a session main effect and session x medication interaction term. As the session x medication interaction term was not significant, no other coefficient estimations were affected, and model fit did not improve, session was not included in the final model.

In addition, to further investigate the mechanism of potential medication effects, a reduced model including only reward and effort as fixed effects, a random intercept, and random slopes for reward and effort was run. This produced estimations for each participant's intrinsic motivation (random intercept per person), reward sensitivity (random slope for reward), and effort sensitivity (random slope for effort). I then tested whether these interacted with level of apathy and medication status with a robust regression using medication difference scores for each coefficient as the dependent variable, and AMI scores as independent variable.

Finally, to test for differences in accepted offers between patients on placebo and healthy controls, I ran a one-way ANOVA for the two groups using arcsine transformed choice data. Correlational analyses involving questionnaire (sub-)scores for anxiety, depression, and apathy were done using robust regression because of one outlying score ($> 2x$ standard deviation).

Risk | Decision-making under risk Two PD patients had incomplete data on this task and were excluded. Binary choice data were analysed on a trial-by-trial basis with a generalised linear mixed effects model, using *fitglm* in *MATLAB R2020b* (MATLAB, 2020). This was done separately for the Gain and Loss condition. The same procedure as for *Apples* data was followed here, starting with a full model including fixed effects for the absolute difference in expected value between risky and certain options in each trial, and for medication, apathy, and depression. In addition, the full model included a random intercept, and a random slope for difference in expected value. A term for depression was added here as depression was considered likely to be related to risk taking. The winning model was chosen based on AIC and BIC scores, with AIC favouring the full model over any other combination of terms by at least 30 units, and BIC favouring a model with random effects for subject and difference in expected value, a fixed effect for medication, but no terms for apathy and depression, by at least 14 units. Given the small sample size and the large increase in coefficients when using the whole model preferred by AIC, the more conservative winning model indicated by BIC was chosen. Finally, to test for session effects, the same model was fit including a main effect for session and an interaction term for session x medication.

For both the gain and loss condition, the model including session did not improve fit based on BIC change. Based on AIC change, a model including all main effects and interactions for depression, apathy, and session terms had the best fit for loss data (*AIC difference* = 8.6). However, as this model includes 32 fixed effects coefficients and multiple four-way interactions, I chose to select the model according to the more conservative BIC. The same two models for gains and losses were fit again using only data from PD patients during the placebo phase, and data from healthy controls to test for group effects.

Correlation coefficients were calculated to test for relationships between choice behaviour and measures of apathy, depression, and anxiety, with multiple testing corrections applied.

Cards | Reversal learning task Data on this task was collected for 19 PD patients and 16 healthy controls. Before further analysis, trials with decision times of less than one second were excluded as accidental clicks. Based on histogram inspection of the skewed reaction time data, trials with unusually long decision times of more than six seconds were also excluded.

Accuracy was measured by mean correct choices, based on whether the option with high winning probability was selected. As correct choices and reaction time were likely to differ between the first few trials after reversal and the last few trials within one reversal block, both measures were analysed time-locked to the first trial since reversal. Medication effects on accuracy were analysed with a repeated-measures ANOVA. Unpaired t-tests were used to test for differences between PD on placebo and healthy controls.

Because of non-normality in the reaction time data, medication effects were determined using a generalised linear mixed effects model, again following the same model selection approach as in *Apples* and *Risk*. Raw trial-by-trial data was first summarised into one median reaction time for each reversal block of 16-20 trials, for each participant. This allowed for the inclusion of a predictor measuring changes in reaction time throughout the course of the experiment as learning occurs. A number of possible models that included combinations of the dependent variable reaction time, and predictors for reversal block, medication status, and medication order (i.e. placebo or citalopram first) were then tested using an Inverse

Gaussian distribution with an Identity link function. The winning model included main effects for reversal block, session order, and medication status, as well as a random slope for reversal block, but no interactions.

Finally, relationships between accuracy or reaction time and measures of apathy, depression, and anxiety were tested using correlation analyses, with multiple testing corrections applied.

Faces | Facial Emotion Recognition task One PD patient had incomplete data on this task and was excluded. Responses were averaged over emotion intensity levels and summarised for accuracy, mean rating, and reaction time as reported previously in **Chapter 4**. Trials with extremely low (< 500ms) reaction times were excluded as accidental clicks. The three dependent variables were analysed with separate repeated measures ANOVAs including main effects and interactions for apathy and depression (emotion x medication x apathy and emotion x medication x depression) in *Jamovi version 1.1.9* ([The jamovi project, 2020](#)). Between-subject models were fit for data from healthy controls and patients during the placebo phase.

Session effects were tested for by running additional models including terms for a session main effect and interactions with medication. While there were no significant effects for the accuracy or reaction time model, there were significant effects for session in predicting responses on question one (“How sure are you about your response?”), with people who took placebo first rating higher confidence during their second citalopram session and vice versa. As this suggests learning effects, all ANOVAs were run using session as a covariate term.

Twins | Emotion recognition control task Two PD patients and one healthy control had incomplete data on this task and were excluded. Data were analysed in *MATLAB R2020b* ([MATLAB, 2020](#)). Precision was calculated as absolute error around the target intensity as given by the location on the sliding scale. For example, a target intensity of 60% may have been responded to on the sliding scale in position 55, resulting in an error of 5 units. Differences in precision between medication phases in PD, and between PD on placebo and healthy controls were calculated with repeated measures ANOVAs (emotion x medication, emotion x group).

5.3 Results

5.3.1 Demographics

At baseline, PD patients did not differ from healthy controls in terms of age, gender ratio, or cognitive status (ACE) (**Table 5.1**). However, they scored slightly higher than controls on the AMI, BDI, and TAS, with differences significant at the uncorrected level of $\alpha = 0.05$. Importantly, there was no change in questionnaire scores after administration of citalopram.

5.3.2 Apples | Effort-based decision-making for rewards

Parkinson's disease reduces overall offer acceptance for effortful tasks

A one-way ANOVA for mean differences between patients with PD and healthy controls revealed that patients accepted fewer offers than controls across the experiment (**Figure 5.9**; $F(1,38) = 4.40, p = .04$). Robust regression between offers accepted and AMI scores for healthy controls and PD on placebo (treated as one group) revealed no relationship ($p = .14$). This was also the case for the association between offers accepted and AMI sub-scores for social, emotional, and behavioural apathy (all $p > .05$). Similarly, none of the other questionnaire scores were significantly associated with offers accepted (all $p > .05$).

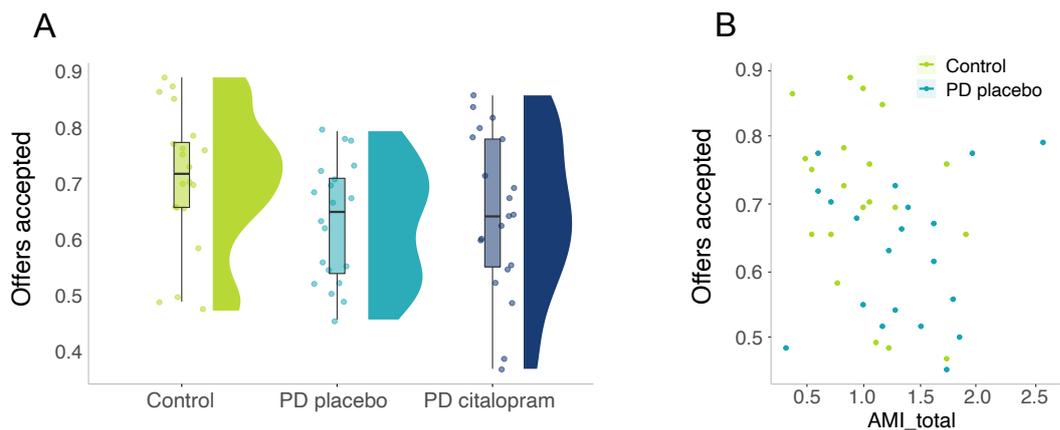


Figure 5.9 – Mean offers accepted by group and apathy scores. **A.** Significant difference in proportion offers accepted between healthy controls and PD on placebo. There were no mean differences between PD on placebo and citalopram. **B.** No significant relationship between proportion offers accepted and AMI scores which index apathy.

| Measure | Healthy control | PD baseline | Control vs PD baseline | PD placebo | PD citalopram | Placebo vs citalopram |
|------------------|---------------------|----------------------|---------------------------|---------------|---------------|--------------------------|
| | Mean ± Std | Mean ± Std | p-value | Mean ± Std | Mean ± Std | p-value |
| N | 20 | 20 | n/a | 20 | 20 | n/a |
| Age | 66.95 ± 8.13 | 68.05 ± 8.40 | 0.68 | See baseline | See baseline | n/a |
| H&Y | n/a | 1.95 ± 0.69 | n/a | See baseline | See baseline | n/a |
| Dis. Dur. in y | n/a | 5.59 ± 3.91 | n/a | See baseline | See baseline | n/a |
| LEDD | n/a | 299 ± 311 | n/a | See baseline | See baseline | n/a |
| Gender (F/M) | 11/09 | 10/10 | 0.75 | See baseline | See baseline | n/a |
| ACE | 97.65 C7± 2.50 | 95.45 ± 4.42 | 0.08 | n/a | n/a | n/a |
| AMI total | 0.98 ± 0.42 | 1.32 ± 0.53 | 0.03* | 1.37 ± 1.36 | 1.36 ± 1.36 | 0.15 |
| AMI behavioural | 0.89 ± 0.56 | 1.21 ± 0.62 | 0.1 | 1.33 ± 0.63 | 1.22 ± 0.64 | 0.2 |
| AMI social | 1.18 ± 0.68 | 1.61 ± 0.76 | 0.07 | 1.53 ± 0.79 | 1.48 ± 0.74 | 0.46 |
| AMI emotional | 0.87 ± 0.46 | 1.15 ± 0.50 | 0.08 | 1.24 ± 0.49 | 1.19 ± 0.51 | 0.45 |
| BDI | 3.80 ± 4.44 | 8.55 ± 4.22 | 0.001** | 8.95 ± 6.00 | 7.85 ± 4.63 | 0.15 |
| GDS | 0.85 ± 2.06 | 1.85 ± 1.35 | 0.08 | 1.74 ± 1.45 | 1.32 ± 1.16 | 0.06 |
| STAI - state | 22.45 ± 13.25 | 28.40 ± 7.14 | 0.09 | 29.05 ± 7.72 | 29.50 ± 9.43 | 0.74 |
| STAI - trait | 23.45 ± 13.50 | 30.70 ± 8.12 | 0.05 | 32.30 ± 6.76 | 31.95 ± 7.74 | 0.77 |
| SHAPS | 0 | 0.15 ± 0.49 | n/a | 0.30 ± 0.73 | 0.25 ± 0.55 | 0.72 |
| TAS | 36.05 ± 5.99 | 42.10 ± 11.30 | 0.04* | 45.70 ± 11.53 | 44.35 ± 12.01 | 0.27 |
| QCAE | 91.40 ± 9.81 | 92.20 ± 11.57 | 0.82 | 95.30 ± 10.97 | 95.70 ± 11.66 | 0.81 |
| UPDRS | n/a | 29.95 ± 2.88 | n/a | 29.95 ± 15.71 | 33.16 ± 9.58 | 0.37 |

Table 5.1 – Demographics and differences between healthy controls and PD at baseline, and between medication phases. H&Y = Hoehn & Yahr stage, ACE = Addenbrooke's Cognitive Examination, AMI = Apathy Motivation Index, BDI = Beck Depression Inventory, GDS = Geriatric Depression Scale, STAI = State Trait Anxiety Inventory, SHAPS = Snaith-Hamilton Pleasure Scale, TAS = Toronto Alexithymia Scale, QCAE = Questionnaire of Cognitive and Affective Empathy, UPDRS = Unified Parkinson's Disease Rating Scale.

Note: * significant at $p < .05$; ** significant at $p < .01$

Citalopram interacts with baseline motivation

The Generalized Linear Mixed Effects (GLME) model included significant two-way interactions for reward x effort, effort x apathy, and medication x apathy, as well as significant three-way interactions for reward x effort x apathy and reward x apathy x medication (see **Table 5.2** for fixed effects coefficients and significance).

The variables with the strongest impact on whether offers were accepted or rejected were the

associated effort and reward. The significant main effects and interaction for effort and reward suggest that participants were more likely to except an offer with larger reward ($p < .001$), and less likely to accept with higher effort ($p < .001$, **Figure 5.10 A**). In addition, higher effort levels affected acceptance of lower reward offers more strongly than acceptance of higher reward offers ($p < .001$), reflecting that both effort and reward processing were involved in the decisions in this task (**Figure 5.10 B**).

Importantly, the effect of citalopram on offer acceptance depended on patient's levels of apathy (apathy x medication interaction, $p = .001$). This can be visualised by plotting the difference in accepted offers between citalopram and placebo phases against AMI scores. As shown in **Figure 5.11 A**, higher apathy scores were associated with a decrease in accepted offers on citalopram, while lower apathy scores were related to increased acceptance on citalopram ($r = -.62$, $p = .003$). There was an even stronger correlation between the change in accepted offers and the social sub-scale of the AMI ($r = -.68$, $p < .001$). The correlation with the behavioural subscale was significant at the uncorrected ($\alpha = .05$), but not the multiple

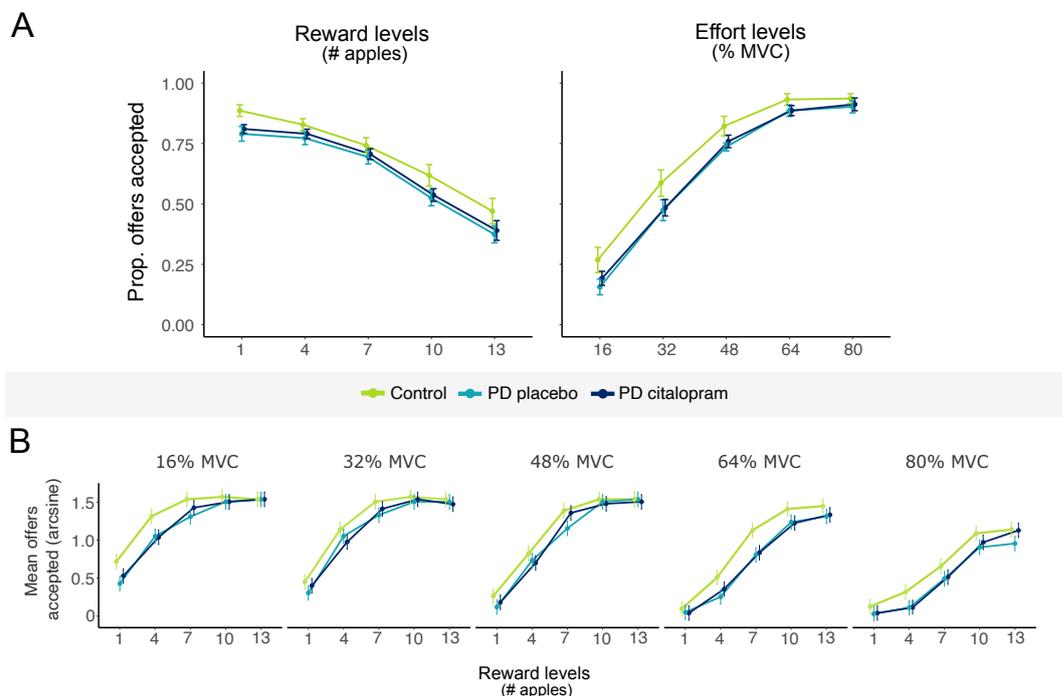


Figure 5.10 – Effort by Reward interactions, split by group. Typical effects of reward sensitivity and effort discounting were reproduced. **A.** Acceptance increased with increasing reward, and decreased with increasing effort. **B.** Effort discounting was strongest for low-to-medium rewards.

| | Coefficient | SE | t | DF | p |
|---------------------------|--------------|-------------|--------------|-------------|------------------|
| Intercept *** | 1.61 | 0.35 | 4.66 | 9968 | < .001 |
| Reward (Rew) *** | 2.80 | 0.22 | 12.56 | 9968 | < .001 |
| Effort (Eff) *** | -1.75 | 0.18 | -9.83 | 9968 | < .001 |
| Apathy (Ap) | 0.08 | 0.35 | 0.23 | 9968 | 0.818 |
| Medication (Med) | 0.04 | 0.04 | 0.86 | 9968 | 0.389 |
| Rew x Eff *** | -0.26 | 0.05 | -5.33 | 9968 | < .001 |
| Rew x Ap | 0.16 | 0.23 | 0.73 | 9968 | 0.468 |
| Eff x Ap * | -0.37 | 0.18 | -2.04 | 9968 | 0.042 |
| Rew x Med | -0.02 | 0.05 | -0.32 | 9968 | 0.746 |
| Eff x Med | 0.01 | 0.04 | 0.24 | 9968 | 0.813 |
| Ap x Med *** | -0.26 | 0.05 | -5.10 | 9968 | < .001 |
| Rew x Eff x Ap *** | -0.29 | 0.06 | -5.09 | 9968 | < .001 |
| Rew x Eff x Med | 0.05 | 0.04 | 1.04 | 9968 | 0.3 |
| Rew x Ap x Med *** | 0.22 | 0.06 | 3.95 | 9968 | < .001 |
| Eff x Ap x Med | 0.08 | 0.05 | 1.64 | 9968 | 0.101 |
| Rew x Eff x Ap x Med | -0.03 | 0.05 | -0.58 | 9968 | 0.559 |

Table 5.2 – Apples GLME model coefficients.

Note: * significant at $p < .05$; *** significant at $p < .001$

testing corrected alpha level ($\alpha = .01$; $r = -.46$, $p = .04$). The emotional subscale was not related to change in accepted offers ($p = .09$), neither were any of the other questionnaires (all $p > .05$). Thus, more motivated patients were more willing to exert effort for reward on citalopram, while more apathetic patients were less willing to do this on the drug.

By classifying patients into no (n patients = 10, n controls = 17) and mild (n patients = 10, n controls = 3) apathy groups based on a mean split, it becomes apparent that apathy was not associated with differences in accepted offers in the placebo phase (**Figure 5.11 B**). The effect of citalopram in relation to apathy can be further disentangled by plotting the change in accepted offers across the different reward (**Figure 5.11 C**) and effort (**Figure 5.11 D**) levels. What stands out is that citalopram increased accepted offers in patients without apathy especially for low reward, or low-to-medium effort levels. In contrast, in patients with apathy, the effect of citalopram is evident for mostly for medium effort levels (**Figure 5.11 C**, **Figure**

5.11 D, Figure 5.12).

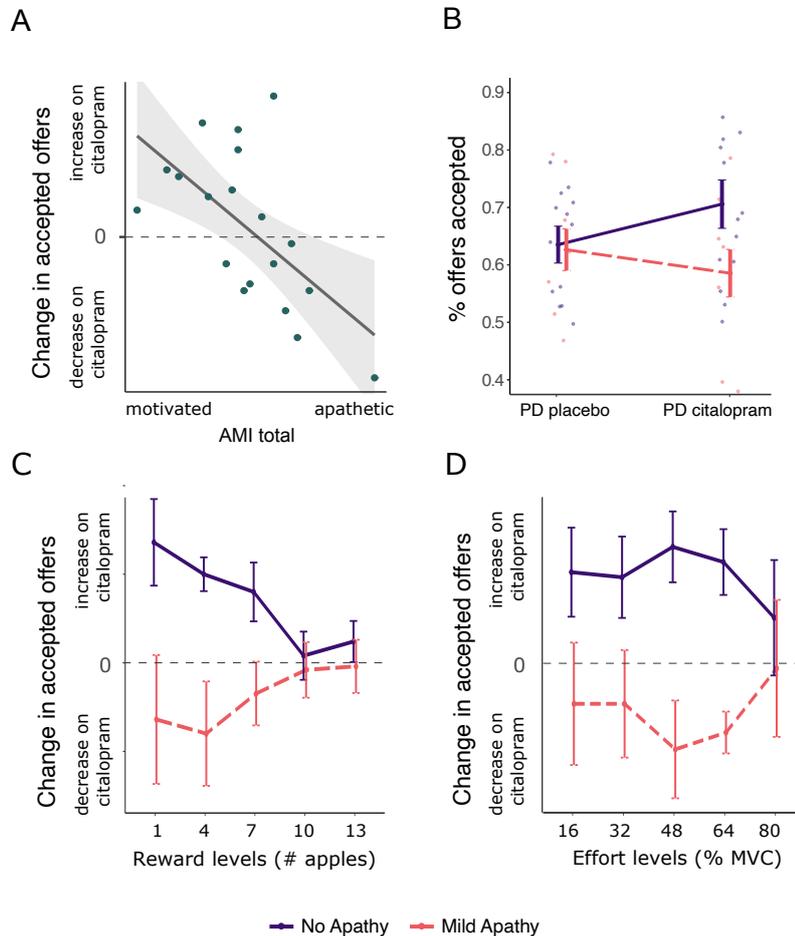


Figure 5.11 – Medication by apathy interaction for accepted offers. **A.** Significant correlation between change in accepted offers (citalopram - placebo) and AMI scores, reflecting interaction. **B.** Visualisation of apathy x medication interaction by binary mean-split of apathy groups. Citalopram increased the proportion of accepted offers for patients who scored low on apathy, but not for patients scoring high on apathy at baseline. **C.** Change in accepted offers (citalopram – placebo) by reward levels, illustrating strongest citalopram x apathy interaction for low rewards. **D.** Change in accepted offers (citalopram – placebo) by effort levels, showing strongest citalopram x apathy interaction for medium effort levels.

Finally, I estimated each patient's intrinsic motivation (random intercept per person in GLME), reward sensitivity and effort sensitivity to examine what aspects of motivated behaviour might be affected by apathy and citalopram. **Figure 5.13** shows significant relationships between change scores (citalopram – placebo) and total AMI scores for intrinsic motivation, calcu-

lated with robust regression because of an outlier (**Figure 5.13 A**; $b = -.27$, $p = .01$) This was not the case for reward (**Figure 5.13 B**; $b = .39$, $p = .05$) or effort sensitivity (**Figure 5.13 C**; $b = .36$, $p = .15$). AMI sub-score analysis revealed a significant association between the social subscale and intrinsic motivation ($b = -.41$, $p = .004$), but not other subscales. Similarly, no sub-scale associations for reward or effort sensitivity reached significance. Thus, in patients with higher apathy scores, citalopram was associated with a decrease in intrinsic motivation, while lower apathy scores were paired with an increase in intrinsic motivation on citalopram.

5.3.3 Risk | Decision-making under risk

The data are visualized best on a heat map depicting likelihood of accepting offers as a function of risk and certainty for gains or losses (**Figure 5.14**).

Citalopram decreases patients' risk aversion for gains

The GLME for data from the gain condition included two significant fixed effects, difference in expected value, and medication. As might be anticipated, participants were more likely to choose the risky option (> 50% of choices), when its expected value was higher than the certain option ($b = 2.22$, $p < .001$; **Figure 5.14** top panel).

In addition, patients were more likely to choose the risky option when on citalopram, compared to placebo ($b = .12$, $p = .01$, **Figure 5.15**). This effect also depended on the difference in expected value between risky and certain offers (interaction $b = .12$, $p = .03$, **Figure 5.16 A**). On citalopram, patients chose the risky option more often, especially for offers where the difference in expected value was between zero and five.

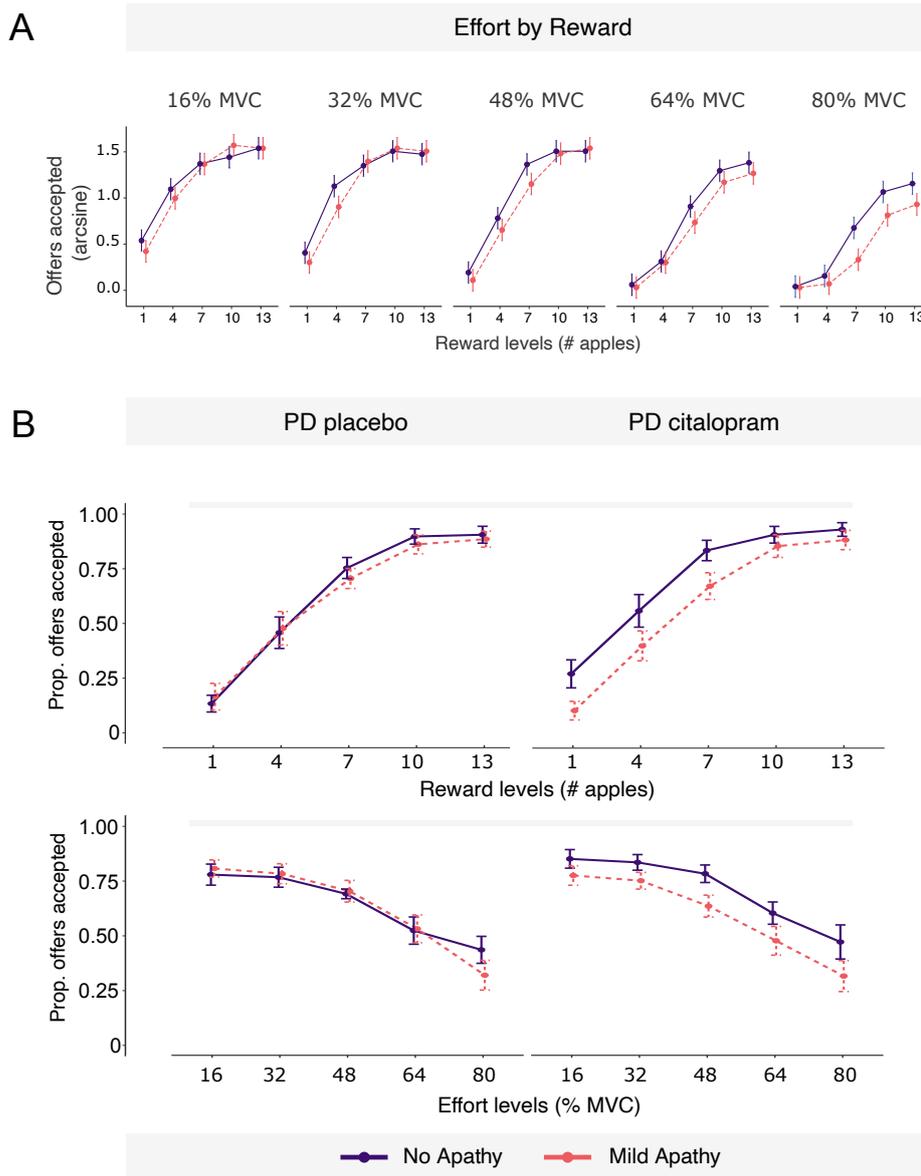


Figure 5.12 – Reward by Effort interaction depends on apathy. **A.** Effort discounting is strongest for patients scoring higher on apathy, mostly for high effort and high reward offers (reward x effort x apathy interaction). **B.** Reward sensitivity depends on apathy only for patients on citalopram (reward x apathy x medication interaction).

Figure 5.16 shows percentages of risky choices meaned across trials with equal expected value differences. Note that expected value differences close to zero (diagonal of heatmap in **Figure 5.14**) are represented in more offers than the extremes (top right and lower left edges of heatmap in **Figure 5.14**), resulting in different weighted means when grouping trials by expected value difference.

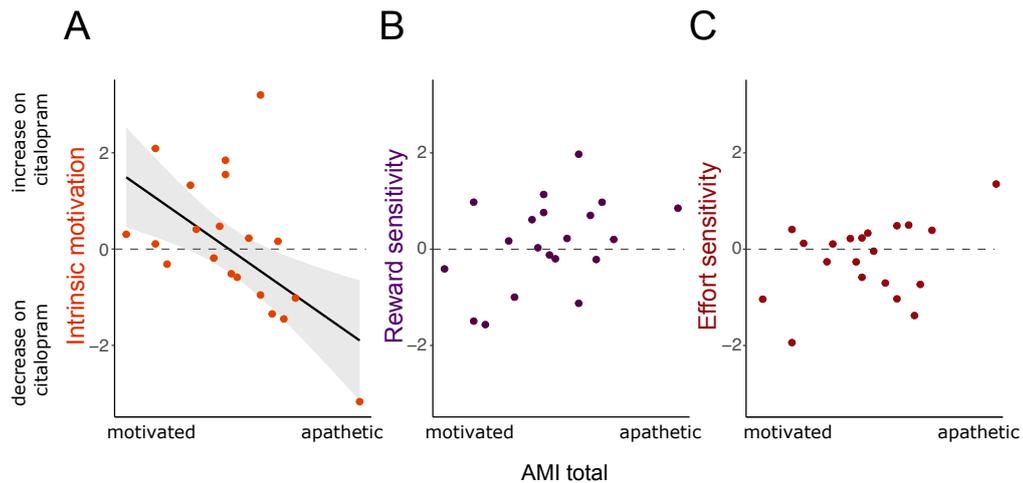


Figure 5.13 – Correlation of medication effect measures. Only change in intrinsic motivation (**A**) calculated with each patient’s random intercept during the citalopram and placebo phases, correlated negatively with level of apathy. Higher levels of apathy were associated with a decrease in intrinsic motivation on citalopram, and vice versa. Correlations with reward (**B**) and effort (**C**) sensitivity were not significant.

While there was no main effect of group when comparing mean choices of patients with PD on placebo and healthy controls (main effect group $b = .006$, $p = .90$), there was a group \times expected value difference interaction ($b = .14$, $p < .001$, **Figure 5.16**). Healthy controls had a steeper slope for the increase in risky choices with increasing expected value differences, with lower percentage of risky choices for low differences, and higher percentage for large differences.

PD associated with risk aversion for losses

In the loss condition, participants were more likely to choose the risky option when the expected value (here: money to lose) was lower than for the certain option (**Figure 5.14** lower panel, main effect difference: $b = -1.65$, $p < .001$). Citalopram did not affect decision-making for loss ($b = .02$, $p = .68$), and there was no interaction between citalopram and difference in expected value to lose ($b = .08$, $p = .18$).

However, in the model including only PD on placebo and healthy controls, a significant main effect of group suggests that PD chose fewer risky options than controls (main effect group, $b = .14$, $p = .005$, **Figure 5.15**). In addition, the difference in risky choices between PD and

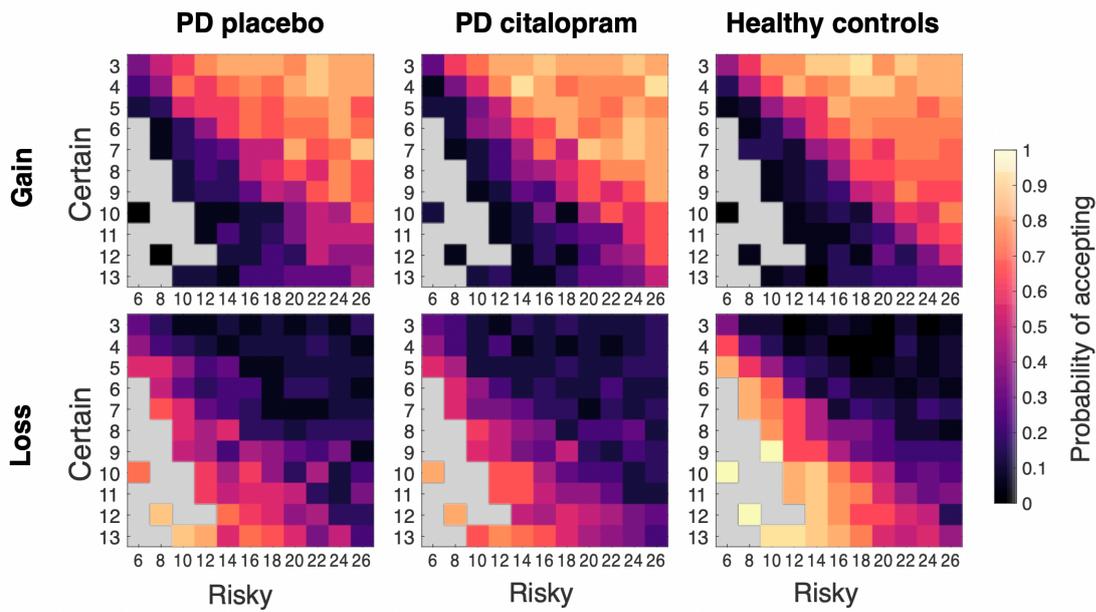


Figure 5.14 – Choice heatmaps for risk decisions. In the gain condition, participants were more likely to choose the risky option when its expected value (= money to win) was larger than the certain offer. In the loss condition, they were more likely to choose the risky option when the expected value (= money to lose) was lower than in the certain offer.

controls depended on the expected values between risky and certain offers (interaction effect group x difference, $b = -.37, p < .001$, **Figure 5.16 B**). PD chose fewer risky options only for

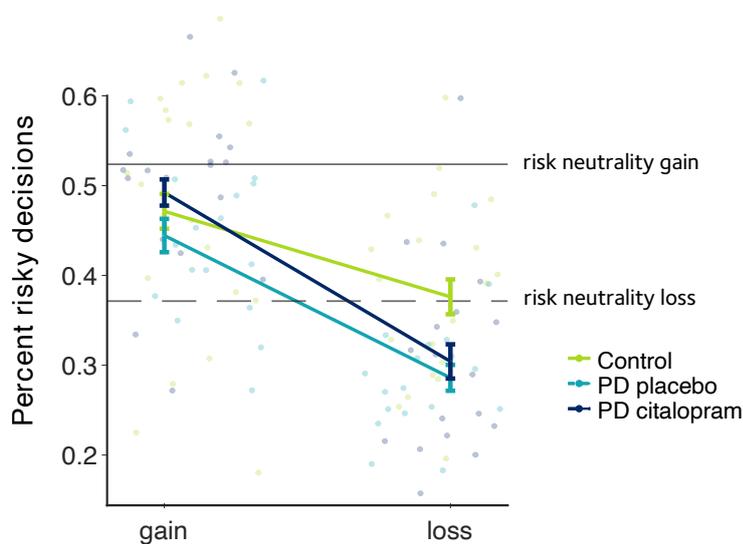


Figure 5.15 – Effect of medication and PD on risky decisions. PD patients on citalopram were less risk averse for gains than during placebo phase. PD patients were generally more risk averse for losses than controls.

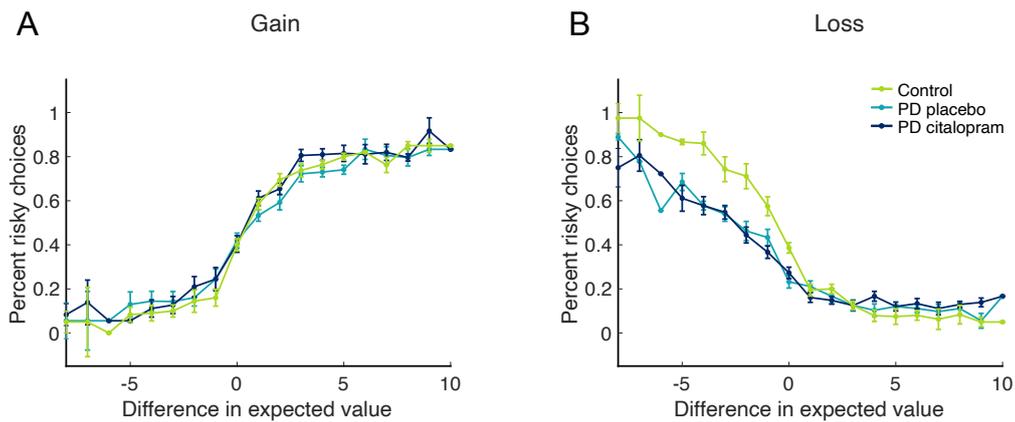


Figure 5.16 – Differences in risky decisions across expected values. **A.** Patients on placebo accepted slightly fewer risky options for offers with expected values between one and five (i.e. difficult decisions) than patients on citalopram. **B.** Healthy controls accepted more risky offers whenever the expected loss was lower than in the certain offer, reflecting more rational decision-making than patients on placebo.

trials in which the risky offer was objectively preferable. In the Loss condition, the lower the expected value difference, the lower the expected loss of money. Thus, a rational decision-maker would always choose the risky option if the expected value difference is lower than zero, meaning that PD patients showed more risk aversion than controls.

Finally, there were no significant correlations between the medication effect on gain or loss choices and any of the questionnaire scores (all $p > .05$).

5.3.4 Cards | Reversal learning

There were no significant differences in accuracy (i.e. percentage of high-probability choices) either between the placebo and citalopram phase (paired t-test, $p > .05$), or between PD on placebo and healthy controls (unpaired t-test, $p > .05$; **Figure 5.17 A**). Accuracy improved equally in all groups as the number of trials since reversal increased.

A two-way, repeated measures ANOVA with mean choices as dependent variable, and choice type (win-stay vs. lose-switch) as well as medication status as within-subject factors, revealed a significant effect of choice type ($F(1,18) = 26.44$, $p < .001$), but not of medication ($p = .80$). As shown in **Figure 5.17 C**, patients were more likely to stick to an option when the previous trial

won, than to switch when the previous trial lost. Similarly, patients on placebo did not differ from healthy controls in their win-stay and lose-switch behaviours, shown by a repeated measures ANOVA with group membership (PD placebo vs. healthy control) as between-subjects factor ($p = .24$).

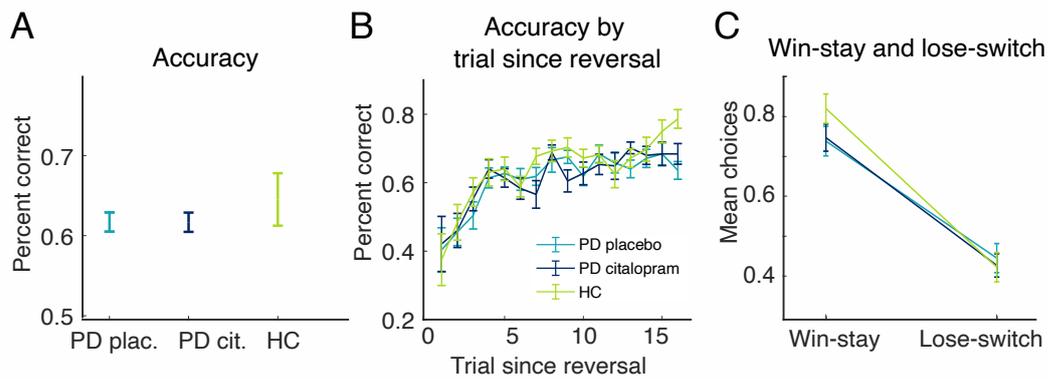


Figure 5.17 – Choice behaviour on Cards task. **A.** No group or medication effects on accuracy, indicated by percent correct (i.e. high-probability) choices. **B.** Accuracy time-locked to trial since reversal, averaged over all blocks, reflecting learning rate. As more trials since reversal are completed, accuracy improves equally for all groups. **C.** All groups were more likely to stay with an option after winning (win-stay), than to switch to another option after losing (lose-switch).

As reaction time data was positively skewed and differed throughout the course of the experiment (**Figure 5.18 A**), medication effects were calculated using a GLME with reaction time as dependent variable, and medication status, reversal block, and session order as predictors. Session order had the strongest impact on reaction time, decreasing reaction time by .07 units ($p < .001$). Patients also responded faster with increasing number of blocks completed ($b = -.06$, $p < .001$). Importantly, citalopram significantly decreased reaction time by .05 units ($p < .001$), but did not interact with reversal block or session order. In other words, citalopram's effect on reaction time was independent of the learning rate, and not confounded by session order.

A separate GLME was run to test for differences between PD on placebo and healthy controls. The winning model for this design included only a fixed main effect for reversal, a random intercept and a random slope for reversal, but no significant group differences.

There were no significant correlations between accuracy or reaction time and questionnaire scores ($p > .05$).

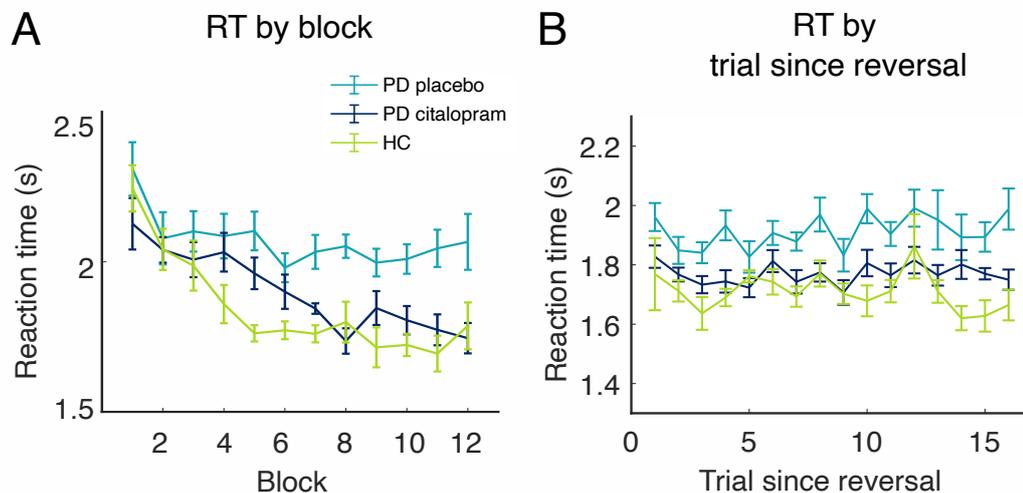


Figure 5.18 – Cards reaction time (RT) data by group. **A.** RT from first to 12th block of reversals, averaged over all trials within each block, thus indicating task difficulty. PD patients on placebo have larger RT throughout the whole experiment. While there seems to be a trend for larger RT differences towards later blocks, this interaction was not significant. **B.** RT from first to 16th trial since reversal, averaged over all blocks, thus indicating average learning rate. PD on placebo were slower to respond independent of learning than PD on citalopram.

5.3.5 Faces | Facial Emotion Recognition task

Neither PD, nor citalopram were associated with changes in facial emotion recognition

There were no significant within-subject effects for citalopram, or between-subject effects for PD, in accuracy, question ratings, or reaction time ($p > .05$). In addition, there were no effects for apathy and depression in accuracy or reaction time ($p > .05$). There was a significant main effect for emotion in both the medication models and the healthy control models, for all four dependent variables (all $p < .001$, **Table 5.3 & 5.4**). Overall, participants were most accurate, most confident, reported highest intensity, and responded fastest for happy faces, with the opposite pattern evident for angry faces (posthoc test results in **Appendix B, Tables B.1-B.8**).

| | F-test | p-value | Effect size (n2p) |
|---------------|---------------|---------|-------------------|
| Accuracy | F(5,80)=29.30 | < .001 | 0.65 |
| Question 1 | F(5,80)=17.61 | < .001 | 0.52 |
| Question 2 | F(5,85)=15.83 | < .001 | 0.48 |
| Reaction time | F(5,80)=4.82 | < .001 | 0.23 |

Table 5.3 – FERT significance tests in patient group.

| | F-test | p-value | Effect size (n2p) |
|---------------|----------------|---------|-------------------|
| Accuracy | F(5,185)=87.40 | < .001 | 0.70 |
| Question 1 | F(5,185)=47.99 | < .001 | 0.57 |
| Question 2 | F(5,185)=42.70 | < .001 | 0.54 |
| Reaction time | F(5,175)=10.85 | < .001 | 0.24 |

Table 5.4 – FERT significance tests in patients and controls.

Apathy may affect confidence in decisions

The main effect for medication was not significant ($p = .08$). There was an interaction between apathy and emotion ($F(5,75) = 3.87, p = .004, \eta_p^2 = .2$) for ratings on question one (“How sure are you about your response?”, **Figure 5.19**). Participants scoring higher on the AMI ($n = 10$) tended to report lower confidence in most expressions, except happy and surprised faces. None of the questionnaire scores correlated significantly with change in accuracy, reaction time, or responses on the two questions (all $p > .05$).

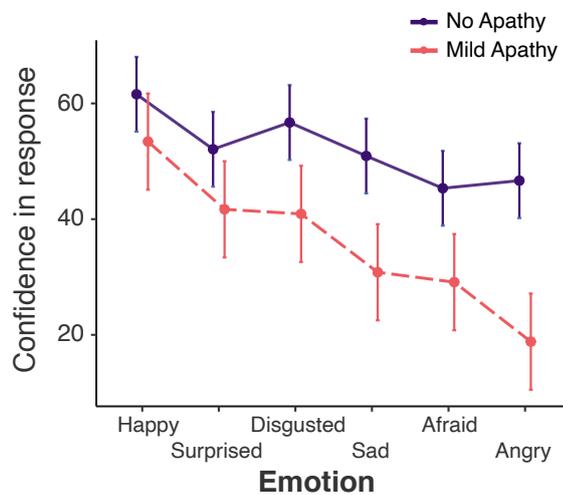


Figure 5.19 – Effects of apathy on confidence ratings. Patients scoring higher on the AMI (red) rated themselves as less confident in their response across all emotion conditions except happy facial expressions.

Twins | Emotion recognition control task

Participants were most precise for happy faces, and least precise for sad and angry faces (main effect emotion, medication model: $F(5,75) = 6.96, p < .001$; healthy control model: $F(5,175) = 17.96, p < .001$). There were no significant differences between placebo and citalopram phases, or between PD and healthy control, on precision in facial emotion expression matching ($p > .05$). There were also no effects for apathy or depression, nor were there significant correlations between precision and questionnaire scores (all $p > .05$).

5.4 Discussion

In this within-subject, placebo-controlled cross-over study, I investigated how a seven-day administration of 20mg citalopram affected mechanisms of decision-making and emotion processing in PD. An age- and sex-matched healthy control group was added to test for general effects of PD. Results indicated that PD patients were overall less motivated (**Figure 5.9**), and more risk averse for potential losses (**Figure 5.15**) than healthy controls, but did not differ in terms of reinforcement learning (**Figure 5.18**) or facial emotion recognition performance. Citalopram increased or decreased willingness to exert effort for reward, depending on whether baseline motivation was high or low, respectively (**Figure 5.11**). This was the case especially for low effort or low reward offers. Citalopram also caused PD patients to make more risk-seeking choices for gains, though it did not restore the change in responses for losses when comparing PD to controls (**Figure 5.15**). In the reversal learning task, citalopram decreased reaction time, which did not seem to be related to a change in cognitive processes like reward or punishment learning (**Figure 5.18**). Finally, while PD did not differ from control on any of the facial emotion recognition measures, apathy decreased patient's confidence in their response, for all stimuli except happy expressions (**Figure 5.19**).

PD reduces baseline motivation

At baseline, PD patients scored higher on the AMI, and thus had lower levels of motivation than healthy controls. Analysis of performance on the *Apples* task, which probes effort-based decision making for rewards, revealed that PD was also associated with fewer accepted offers when compared to healthy controls (**Figure 5.9 A**). Thus, I could reproduce earlier results that apathy and low motivation is more prevalent in PD than in healthy age-matched controls (Le Heron, Plant, et al., 2018). However, I did not find a correlation between AMI scores and offers accepted in this task (**Figure 5.9 B**), and on placebo, patients with mild apathy did not differ in their performance to patients without apathy. This is likely because of the small sample size and overall low levels of apathy in this group. As there was an outlier in the sample and a trend for a correlation between AMI scores and offers accepted, future larger investigations may be able to confirm this link.

Citalopram increases intrinsic motivation only in already motivated patients

A novel finding is that the effect of citalopram on motivated behaviour (accepted offers) depended on baseline levels of motivation as measured by the AMI. Citalopram increased acceptance of offers only in patients who scored low on the apathy measure, thus were already motivated, while this effect was reversed for patients who were more apathetic (**Figure 5.11**). Inspecting how the medication effect related to the different effort and reward levels in each offer, I determined that in an already motivated state citalopram increased, while in an apathetic state it decreased acceptance, especially for low reward and low-to-medium effort offers. In a previous report using this task, [Le Heron, Plant, et al. \(2018\)](#) tested PD patients with and without diagnosed apathy, while ON and OFF their usual dopaminergic medication. They described that apathy was associated with reduced responding to low reward outcomes while OFF dopaminergic medication, concluding that apathy might be associated with reduced incentivisation by reward specifically. Apathetic patients still agreed to high effort offers, but only if the affiliated reward was large.

It has previously been argued that SSRIs might exacerbate apathetic symptoms ([Zahodne et al., 2012](#)), so that citalopram may have intensified the behavioural pattern of apathy reported by [Le Heron et al. \(2018\)](#). As apathy levels were low overall, the already slightly unmotivated patients may have experienced a further citalopram-induced reduction of motivation to a level that could be detected in task performance. However, the interaction between apathy and citalopram was linked to changes in intrinsic motivation and effort sensitivity, not changes to reward sensitivity. This might point to a slightly different process through which serotonin is involved in reward and effort-based decision-making. More work is required to develop a full picture of this pattern, for example by modulating serotonin in the opposing direction, such as with acute tryptophan depletion (ATD).

The interpretation of these findings is complicated by the fact that most of the patients tested in the current study were taking dopaminergic medication, and of these, all were tested while on their usual regimen. This likely resulted in some interaction between the two medications that will need to be further investigated in future cross-over studies. In [Le Heron et al. \(2018\)](#), an effect of dopaminergic medication was primarily observed for acceptance of high effort,

high reward offers. Crucially, the authors did not find an interaction between apathy and dopamine, such that the effect of dopamine on offer acceptance rate did not depend on levels of motivation. This may suggest that while dopamine influences goal-directed behaviour especially in terms of reward valuation, serotonin may be more involved with a baseline 'readiness to act' or overcome effort.

One general theory regarding serotonin is that it regulates how action costs, such as punishments or time delays, influence initiation of behaviour (Cools, Nakamura, et al., 2011; Fischer et al., 2017; Luo et al., 2016; Meyniel et al., 2016). While research is sparse, it is conceivable that this theory could extend to the regulation of effort costs for action initiation. An investigation into the effect of escitalopram in healthy young volunteers reported a specific role for the drug in decreasing effort sensitivity, and not increasing reward sensitivity (Meyniel et al., 2016), thereby resulting in higher motivation. This is in line with the effect of citalopram here in already motivated patients. However, again it is unclear how these mechanisms might be confounded by an interaction with a pathological dopaminergic baseline, which might explain the opposite effect of citalopram in already amotivated patients found here.

Intriguingly, the correlation between the change in motivated behaviour on citalopram and baseline motivation was strongest for the social subscale of the AMI. This subscale measures levels of social engagement, including statements like "*I start conversations without being prompted*". A role for serotonin in social motivation is in accord with reports of increased pro-social behaviour after increasing serotonergic levels in the brain, for example by administration of citalopram or 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy, Crockett et al., 2010; Hysek et al., 2014). One mechanism for this may be through serotonin's ability to promote the release of the neuropeptides oxytocin and vasopressin, both of which are associated with pro-social behaviour (Insel, 2010; Jørgensen et al., 2003). Establishing whether social, emotional, and behavioural forms of apathy may be differentially influenced by neurotransmitter function may help decode the vast individual differences in response to drug treatment for apathy.

Citalopram increases rational risk-seeking for gains depending on expected value

In *Risk*, participants were asked to choose between two offers: A certain win of money, or a risky – larger – win, with a 50% chance of not winning anything. The offers could also involve a certain loss and a 50/50 gamble to lose more, or not lose anything. In the gain condition, a fully risk-neutral decision-maker would choose the risky option whenever its expected value was as high as, or higher than, that of the certain option. For example, if you could be certain to win £5, or take a gamble with 50% probability to win either £10 or nothing, the expected value for each offer would be £5. If you were entirely risk-neutral, you would choose the gamble. However, humans are typically risk-averse, meaning that the potential win of £10 rather than £5 does not seem worth taking the risk of not winning anything. This is a well-established phenomenon from economic prospect theory (Kahneman et al., 1979), and was replicated in the current study.

On citalopram, PD patients were more likely to choose the risky option when playing for rewards, but not when playing to avoid losing (Figure 5.15). Choices of risky options for gains increased towards the risk-neutral boundary in PD patients during the citalopram phase. In addition, the effect of serotonin on risk-seeking in this task was strongest for offers where the difference in expected value was small (Figure 5.16). Thus, patients on citalopram required smaller rewards as incentive to switch their preference to the risky option than on placebo. This difference between medication phases decreased towards the more extreme offers.

One conclusion may be that in the presence of risk, serotonin is involved in the regulation of reward-seeking, but not punishment-avoidant behaviour. This is somewhat surprising, as serotonin is generally thought to be more closely involved in punishment processing than reward processing (Cools, Nakamura, et al., 2011; Tanaka et al., 2009). In addition, the one-week administration of citalopram in this experiment, hypothesised to increase serotonin levels, was associated with increased risk-seeking for gains. This is in contrast to an investigation in primates, that increased risk-seeking after reducing levels of serotonin through ATD (Long et al., 2009). Likewise, people with two short alleles of the serotonin transporter gene have been shown to be more risk averse than others (Kuhnen et al., 2009). The short allele of the transporter gene differs from the long variant by deletion of 44 base pairs, lead-

ing to a lower level of transporter gene expression, lower levels of serotonin uptake, and thus higher baseline levels of serotonin (Manchanda et al., 2016). Following this theory, increasing levels of serotonin in the absence of PD should increase avoidance of potentially aversive choices. Based on findings that ATD resulted in better encoding, prediction, and learning from punishments (see Faulkner et al., 2014), it has been suggested that this bias towards avoidance may be supported by reduced cognitive engagement with aversive stimuli when increasing serotonin. However, this is in contrast to the finding here in PD of an increase in risk-seeking on citalopram.

Patients responded more rationally while on citalopram, which should reflect increased cognitive engagement with risk rather than decreased engagement. In addition, in the loss condition (discussed in more detail below), even though PD patients responded less rationally when compared to controls, citalopram did not affect performance in this condition. Since the loss condition arguably requires more punishment processing than the gain condition, this may be further evidence that citalopram affected reward-seeking instead of punishment-avoidant behaviours.

However, it is unknown how these mechanisms of serotonin differ in a pathological dopaminergic state as in PD. Cools, Nakamura, et al. (2011) argued that serotonin may inhibit behavioural activation when punishment may occur, whereas dopamine may promote this activation. They further hypothesise that a baseline of low dopamine and/or high serotonin levels should promote risk aversion, while high dopamine and/or low serotonin levels should promote risk seeking. In PD, this relationship might be more complicated. Guthrie et al. (2009) built a neurocomputational model for the roles of tonic and phasic dopamine during a sequence learning task, and concluded that while both functions are likely to be involved in cognitive dysfunction in PD, dopaminergic medication only restores the function of tonic dopamine. Thus, future research may investigate how the potential downregulatory effect of serotonin on risk-seeking is affected by its interaction with tonic and/or phasic dopamine activity, and what role dopaminergic medication plays.

PD decreases rational risk-seeking for losses

In contrast to the Gain condition, I did not find a medication effect in the loss condition of *Risk*. Here, healthy controls performed remarkably close to a fully rational decision-maker, choosing the risky option whenever its expected loss value was as small, or smaller, than in the certain option. PD patients were significantly more risk-averse than healthy controls for all offers where rational decision-making was required to overcome risk-aversion for loss, i.e. offers where the certain option was not necessarily preferable. A previous report compared Vancouver Gambling Task (VGT) performance of PD patients ON and OFF dopaminergic medication to controls in both gain and loss conditions. A small effect for PD while OFF medication was documented, with increased risk aversion for large losses (Sharp et al., 2013).

In contrast, Cherkasova et al. (2019) used a version of the VGT with only a gain condition, and reported increased risk aversion in PD when compared to healthy controls after withholding dopamine medication overnight. When patients were tested again on their usual dopamine medication, this difference was no longer observed. It is possible that the presence of a loss condition might impact behaviour in the gain condition by altering the perception of the value of gains, so that results from these tasks may not be directly comparable. However, the overarching finding seems to be that PD patients are more risk-averse than healthy controls, though this was only in unmedicated states in the two previous reports.

In the current study, PD patients on their usual dopaminergic medication were still more risk-averse than controls, and citalopram did not reverse this difference. Thus, PD seems to be associated with changes in decision-making under risk, though neither serotonin, at least as increased by the seven days of citalopram given here, nor the patient's regular dopaminergic medication could restore these changes to normal. If, as often hypothesised, increasing the level of serotonin does increase risk-aversion, while dopaminergic medication is thought to increase risk-seeking, these two effects may have cancelled each other out in the loss condition. While the effect of serotonin was reversed in the gain condition, it is not unlikely that serotonin affects reward and punishment processing differently, as argued above (Cools, Nakamura, et al., 2011; Kranz et al., 2010; Tanaka et al., 2009). Future investigations might profitably test PD patients on citalopram, but without dopaminergic medication.

Neither PD nor citalopram affect emotion processing

There was no difference between healthy controls and PD on facial emotion recognition and its visual acuity control task, measured in Faces and Twins, as already shown in a similar task in **Chapter 4.3**. Both the Faces results here and in **Chapter 4.3** are in contrast to a recent meta-analysis of emotion recognition studies in PD, which concluded that there was enough evidence to support a slight emotion recognition impairment in patients with PD (Argaud et al., 2018). However, these findings have been criticised for being confounded with visual and executive impairments in PD (Argaud et al., 2018; Hipp et al., 2014). For example, it has been argued that facial expressions of negative emotions have less prominent visual discriminatory features than expressions of happy emotions, and are thus more visually challenging to recognise. A happy face might be easily identified by the clear upward motion of the mouth and showing of teeth, while a sad face might only reflect a subtle downward motion of the mouth (Hipp et al., 2014; Johnston et al., 2003). Thus, in the presence of visuospatial or executive function deficits, patients with PD might be especially prone to making errors with negative faces. Since most reports describe a deficit only in these potentially more challenging conditions, the differences may be mainly due to visual factors. This was one reason why *Twins* was included in the current study. As there were also no differences in *Twins* performance, this is further evidence for the absence of a purely affective processing impairment in PD. It has been shown previously that SSRI treatment improved facial emotion recognition performance independently of any reduction in depressive symptoms in otherwise healthy people (Godlewska et al., 2016), and one hypothesis following from **Chapter 4.3** was whether a potential improvement during the citalopram phase in PD could be related to apathy instead. However, as there was no medication effect, this hypothesis could not be tested. As levels of depressive symptoms were very low in this sample, another open question remains whether clinical depression in PD is similar to major depressive disorder in the general population, and whether similar changes in emotion processing after citalopram treatment could be observed in these groups.

Apathy reduces confidence in emotion ratings

In *Faces*, participants who scored high on the AMI tended to report less confidence in their response than those who scored low on the AMI. This is an unexpected result that to my knowledge has not been reported before. One explanation may be based on the theory that apathy involves higher levels uncertainty in decision-making. For example, in the AMI, patients were asked to rate their agreement on statements like “*I make decisions firmly and without hesitation*” or “*After making a decision, I will wonder if I made the wrong choice*”. Higher scores on these questions may reflect general uncertainty. It could also be argued that unmotivated patients exerted less effort into their response, and therefore reported less confidence. However, as there were no differences in accuracy or reaction times between motivated and unmotivated patients, this explanation seems unlikely. If a relationship between apathy and reduced confidence in decisions can be replicated in other tasks, this could have important implications for the development of cognitive-behavioural therapies for apathy.

PD is not associated with impaired reversal learning

I did not find any differences in learning rate, or overall accuracy on the reversal learning task between PD on placebo and age-matched controls. This is in contrast with a number of previous studies, as a general impairment in reversal learning especially for learning from negative rather than positive outcomes is commonly found in PD (Cools and D’Esposito, 2011; Cools, Nakamura, et al., 2011; Graef et al., 2010; Peterson et al., 2009). One possible explanation for the lack of a difference in this sample is that the relatively few number of trials in each reversal block may have created an especially difficult task for both PD patients and healthy controls. However, **Figure 5.17 B** supports the assumption that some learning did take place within each block.

These findings may also have been confounded by dopamine effects. Previous research suggests that PD patients are more impaired on reversal learning tasks only when ON, than when tested OFF their usual dopaminergic medication (Cools and D’Esposito, 2011; Cools, Nakamura, et al., 2011; Graef et al., 2010). Overdose effects of dopaminergic medication on relatively preserved functions like reversal learning were hypothesised to explain this phe-

nomenon. The fairly small sample in the current study, paired with the fact that most, but not all patients were taking medication, may therefore have resulted in a lack of power to detect a difference between PD and controls.

Citalopram reduces decision times during and after reversal learning

During the citalopram phase, patient's reaction times were significantly shorter relative to the placebo phase. This effect was robust against correcting for practice effects. While there was no significant reaction time difference between patients on placebo and controls, **Figure 5.18 B** suggests a trend that may have suffered from a lack of power for between-subject testing given the small sample size. Thus, the most likely interpretation is that citalopram corrected a reaction time slowing in PD relative to healthy levels. Although this particular finding has not been reported in PD before, it is in line with one previous investigation of serotonergic modulation in PD. [Ye et al. \(2014\)](#) documented that citalopram administration in PD reduced reaction times in a stop-signal task, an effect that depended on disease severity. The authors concluded that citalopram may have counteracted the progressive loss of forebrain serotonergic projections in patients with more advanced disease.

Another piece of evidence for the involvement of serotonin in reaction times is an analysis of the effects of ATD in healthy volunteers, thought to decrease serotonin levels, which resulted in slowed responding during a visual discrimination and reversal learning task ([Murphy et al., 2002](#)). Similar to the findings here, the authors did not find impaired performance following ATD, concluding that the decrease in serotonin levels may have affected inhibitory control, which was compensated for by the participants through increased deliberation times. Following this line of reasoning, the PD patients in the current sample may have overcome reduced inhibitory control by slowing reaction times, a process that was no longer necessary with potentially replenished serotonin levels during the citalopram phase.

The lack of a serotonergic effect on learning rate or accuracy in this task is however in contrast with the majority of the literature, albeit based on animal research. For example, chronic SSRI treatment in rodents was reported to improve reversal learning by increasing learning rate and reducing the number of errors ([Brigman et al., 2010](#)), or by higher frequency of win-

stay choices (Bari et al., 2010). In addition, depletion of serotonin in the marmoset brain induced a failure to inhibit responses to the previously rewarded option (Clarke et al., 2004; Clarke et al., 2005). It may simply be the case that differences in reaction time are the most prominent findings in human reversal learning tasks as they reflect higher-order compensation processes that cannot be measured in animals. However, in the case of PD, the interaction between serotonin and dopamine seems especially important to disentangle, and may provide further insight into their involvement in reversal learning performance.

Synopsis

This study provides more evidence that PD is associated with motivational deficits and that the serotonergic system influences these processes. However, in motivated patients (without apathy), citalopram led to increases in willingness to act, rather than decreases, as reports in healthy volunteers often documented. Abnormal baseline serotonergic and dopaminergic function in PD may be the reason for these opposing effects. It is now established that early in the progression of the disease, PD patients have evidence of serotonergic dysfunction, for example measured by PET in the caudate, thalamus, hypothalamus, and anterior cingulate cortex (Politis et al., 2015). In patients with more advanced disease, this extends to the putamen, posterior cingulate cortex, prefrontal cortex, ventral striatum, raphe nuclei, and amygdala (Politis et al., 2015; Politis et al., 2010).

A role for serotonin in developing PD pathology is also supported by a recent investigation into serotonergic and dopaminergic pathology in carriers of a gene mutation called A53T SNCA causing early onset, autosomal PD. Serotonergic uptake was decreased in multiple subcortical areas, including the raphe nuclei, caudate, and putamen in carriers of this gene mutation, even before the onset of motor symptoms (Painous et al., 2019). Thus, temporarily replenishing declining levels of serotonin through administration of citalopram may reverse behavioural effects of underlying serotonergic PD pathology, such as loss of motivation. In contrast, in healthy volunteers, additional serotonin may push performance past an optimal maximum. While inverted-U shaped optimum levels for serotonin have not yet been established, this model has previously been argued to underlie research findings for dopaminergic effects on working memory and cognitive control (Cools and D'Esposito, 2011).

However, already mildly apathetic PD patients showed a further reduction in motivation on citalopram as usually seen in healthy controls, a pattern that does not fit with an inverted-U shaped function of serotonin levels and motivation. Untangling the function of serotonin has been notoriously difficult, partly because of suboptimal in vivo methods of measuring serotonin levels specifically, but also because the serotonergic system likely strongly interacts with other neurotransmitters and neuromodulators, like dopamine, noradrenaline, and glutamate. For example, it has been demonstrated that in the presence of reward some serotonergic neurons in the dorsal raphe nuclei not only released serotonin, but could also control excitation of dopamine neurons via glutamate release (Liu et al., 2014; Qi et al., 2014). While these interactions are highly complex and new technical advances are needed to fully understand them, what stands out is that dopamine and serotonin are interdependent for encoding reward and punishment signals. In the special case of PD, solving these uncertainties will have important implications for the treatment of neuropsychiatric symptoms. For example, precision medicine approaches that carefully balance dopamine and serotonin levels based on each patient's individual symptom and pathology profile may improve outcomes considerably.

Chapter 6

Effects of Parkinson's disease on brain structure

6.1 Introduction

Since the development of neuroimaging tools, there has been considerable interest in identifying structural neuroimaging biomarkers for PD. Biomarkers are characteristic measurements of biological samples or pathological processes using plasma, serum or brain imaging (Biomarkers Definitions Working Group., 2001; Delenclos et al., 2016) that can be used to confirm diagnosis or track disease progression. Ideally, a biomarker is sensitive, non-invasive, and inexpensive (Delenclos et al., 2016).

Neuroimaging markers have been of interest in PD (Politis, 2014), because a definitive diagnosis of PD can currently only be made post-mortem (Braak et al., 2004), and is otherwise based primarily on the presence of characteristic clinical signs. This results in a number of issues around the treatment of the disease. For example, there is some degree of syndromic overlap between PD and other parkinsonian disorders, like supranuclear palsy or corticobasal degeneration (Correia et al., 2020). As a consequence, these conditions can be difficult to differentiate, leading to inaccurate diagnoses and inappropriate therapies. The results of a meta-analysis of post-mortem studies have revealed that the accuracy of clinical diagnosis of idiopathic PD is only 80% even in expert hands (Rizzo et al., 2016).

In addition, it is widely accepted that the degeneration of dopaminergic neurons begins 10-15 years before the onset of motor symptoms (Schapira et al., 2017). Thus, by the time of diagnosis based on motor symptoms, it is estimated that up to 80% of dopaminergic neurons have already been lost (Schapira et al., 2017). While patients may be experiencing non-motor symptoms during this phase, these are not specific and are often identified only retrospectively when a diagnosis of PD has already been made at the motor stage of the disease (Gaenslen et al., 2011; Schapira et al., 2017). This delay between first symptom onset and diagnosis can stretch 10 years, as one retrospective study of 93 PD patients documented (Gaenslen et al., 2011). Treatment that is commenced only at this point in the progression of the disease may then have only limited efficacy. Thus, identifying in vivo neuroimaging markers has great potential to aid diagnosis, track progression, and support the identification of therapeutic targets.

The most commonly used neuroimaging techniques include structural and functional MRI scans, as well as metabolic imaging methods like PET or SPECT (Delenclos et al., 2016; Ravina et al., 2012). Of these, DAT-SPECT is especially promising for the study of PD. Previous reports have demonstrated that DAT-SPECT has extremely high sensitivity (up to 98%) and specificity (up to 100%) for identifying PD patients and controls (Suwijn et al., 2015). DAT-SPECT has also proven useful to study neuropsychiatric symptoms in PD, which may be particularly important for evaluation of PD in early, premotor stages. For example, one report found lower striatal DAT levels in PD patients with more severe depression symptoms (Ravina et al., 2012). However, as PET and SPECT are expensive or involve ionizing radiation exposure, they are not always readily available in clinical practice and not suitable for repeated testing in progression studies (Politis, 2014).

In contrast, conventional MRI scanning is non-invasive and more cost-effective. T1-weighted and diffusion-weighted MRI scans can be acquired and analysed comparatively quickly in order to test for associations between PD and grey or white matter volumes. Two frequently used analyses for this are Voxel-based Morphometry (VBM) and Tract-based spatial statistics (TBSS), which allow for the voxel-wise assessment of group differences in grey matter volume and white matter integrity (Douaud et al., 2007; Smith et al., 2006). Using these methods, previous reports have noted a number of brain regions showing atrophy in PD that involves the basal ganglia, motor and visual networks, involving the striatum, hippocampus, occipital fusiform gyrus, precuneus, and motor cortex (Khan et al., 2018; Martinez-Horta et al., 2017; Xu et al., 2020). White matter changes, especially in Fractional Anisotropy (FA), have been found in the corpus callosum, sagittal stratum, cingulum, and superior longitudinal fasciculus (Duncan et al., 2016; Kandiah et al., 2014; Khan et al., 2018; Taylor et al., 2018; Yang et al., 2018).

However, after over 30 years of research on MRI biomarkers in PD (Politis, 2014), there still remains large variability in results and little translation to clinical practice. This may be due to small sample sizes in individual studies, heterogeneous sample characteristics, and distinct MRI scanning sequences and analysis pipelines between reports. Here I set out to address some of these issues by comparing results from two separate cohorts of PD patients in the UK

Biobank and OPDC that were scanned at different locations, but analysed with the same MRI preprocessing pipeline. I will further evaluate whether previous findings could be replicated, how volume estimations in these cohorts compare to the nomograms created in **Chapter 3**, and whether any associations with mood symptoms emerge.

6.2 Method

T1-weighted and diffusion-weighted images from PD patients and healthy controls in both the UK Biobank and OPDC datasets were analysed to assess structural grey and white matter differences between groups of people with PD and healthy controls.

6.2.1 Data selection

To test for associations with mood in the OPDC cohort, using the factor scores that were created from more general questionnaire scores in **Chapter 4** may result in more informative associations. However, because of missing data in individual HADS questions (Snaith, 2003, see *HADS imputation* in **Chapter 4**), this was not feasible for the imaging subset. In order to still be able to distinguish between core depression, anxiety, and apathy scores in addition to using sum-scores for the BDI, I averaged those items of the BDI that were previously found to load onto either the “Loss of Pleasure/Apathy” factor, or the “Core depression” factor. Anxiety was measured with the total anxiety sub-score of the HADS (**Table 6.1**).

| Measure | Questionnaire | Items |
|-----------------------|---------------|-----------------------------------------------------------------------------------------------------------------|
| Core depression | BDI | 1 (Sadness), 3 (Failure), 5 (Guilty), 6 (Punished), 7 (Dislike), 8 (Critical), 10 (Tearful), 14 (Worthlessness) |
| Core apathy/anhedonia | BDI | 4 (Pleasure), 12 (Disinterest) |
| Core anxiety | HADS | 1 (Tense), 3 (Fear), 5 (Worrying), 7 (Relaxed), 9 (Butterflies), 11 (Restless), 13 (Panic) |

Table 6.1 – Details for neuropsychiatric scores.

In the UK Biobank cohort, the BDI and HADS were not available. Instead, I selected three separate questions on recent feelings of either (1) depression, (2) disinterest/apathy, and (3)

tenseness/anxiety. Answer possibilities were "Not at all", "Several days", "More than half the days", and "Nearly every day". These three items were chosen as opposed to the complete mental health questionnaire dataset described in **Chapter 2**, in order to preserve statistical power while capturing the most important aspects of mood.

In order to have an estimation of cognitive status, I also present MoCA scores for participants in the OPDC cohort, and the maximum number of remembered digits in the Digit Span test for patients and controls in the UK Biobank cohort.

6.2.2 Participants

OPDC cohort

A subset of 113 patients with PD and 62 controls within the OPDC cohort (explained in more detail in **Chapter 4**) had usable T1-weighted MRI scans. BDI data that were collected within 6 months of scanning were available for 79 PD patients and 42 controls, HADS data within 6 months were available for 44 controls and 78 PD patients. Diffusion-weighted imaging was missing for one control and six PD patients. Of all PD patients, 53 were taking Levodopa, 29 a dopamine agonist, 3 patients took amantadine, 4 patients were taking anticholinergic medication, and 29 patients were taking a MAO-B inhibitor.

UK Biobank cohort

Within the large UK Biobank cohort (explained in more detail in **Chapter 2**), I identified 75 PD patients with usable MRI data. Based on age and sex of each of the participants within this group, I then selected 75 matched control participants. As a result, the PD and control groups were matched not only for mean age, but also age distribution, and sex. Of the 75 PD patients, complete mental health questionnaire data were available for 69 patients. Diffusion-weighted images were available for 55 patients with mental health questionnaire data. Information on disease duration, severity, or PD medication were unavailable.

6.2.3 Imaging protocols

OPDC

MR images were previously collected on a 3T Siemens (Erlangen, Germany) Trio MR scanner using a 12-channel head coil. T1-weighted images were acquired with a 3D Magnetization Prepared-Rapid Acquisition Gradient Echo (MP-RAGE) sequence (1x1x1mm voxel size, 192 axial slices, 8 degrees flip angle, 4.7ms TE, 2040ms TR, 900ms TI, 6 min acquisition time). Diffusion-weighted images were recorded using an echo planar imaging sequence (2x2x2 mm voxel size, 65 slices, 60 directions, 1,000 s/mm² b-value, 94ms TE, 9,300ms TR, 13min acquisition time). Four additional images without diffusion weighting were obtained. A field map was measured with a gradient echo imaging sequence (2x2x2 mm voxel size, 65 slices, 5.19ms TE1, 7.65ms TE2, 655ms TR).

UK Biobank

T1-weighted images with 1 mm³ isotropic resolution were acquired on a Siemens Skyra 3.0 T scanner (Siemens Medical Solutions, Germany) with a 32-channel head coil as explained in more detail in **Chapter 2**. Diffusion-weighted images were obtained using a standard Stejskal-Tanner pulse sequence (2x2x2mm voxel size, 3600ms TR, 92.00ms TE, 7 min *acquisition time*). Ten baseline volumes ($b = 0$ s/mm²), as well as 50 volumes with $b = 1000$ s/mm² and 50 volumes with $b = 2000$ s/mm² were collected. A detailed description of both sequences can be found elsewhere ([Alfaro-Almagro et al., 2018](#)).

6.2.4 Imaging analysis

Preprocessing and Imaged Derived Phenotype creation

As detailed in **Chapter 2**, the UK Biobank imaging data has previously been analysed by UK Biobank, with an openly available processing pipeline ([Alfaro-Almagro et al., 2018](#); [Miller et al., 2016](#)). To improve generalisability between the UK Biobank and OPDC cohorts, I used the same analysis pipeline for the OPDC dataset ([Griffanti et al., 2020](#)). In short, T1-weighted images are registered non-linearly to MNI152 space with 1mm resolution using FMRIB's Non-linear Image Registration Tool (FNIRT, [Andersson et al., 2007](#)). The native T1-weighted image

is then brain-extracted by applying the inverse of the previous MNI152 alignment warp (thus generating a native T1 space map). White matter, grey matter, and cerebrospinal fluid are segmented using FMRIB's Automated Segmentation Tool (FAST, [Zhang et al., 2001](#)). This step also estimates the intensity bias, thereby generating a bias-field-corrected, brain-extracted T1-weighted image. Using the FAST grey matter partial volume estimates, a further 164 grey matter regions of interest – or IDPs – were parcellated using a combination of the Harvard-Oxford cortical and subcortical, and Diedrichsen cerebellar atlases ([Desikan et al., 2006](#)). Finally, SIENAX ([Smith et al., 2002](#)), and FMRIB's Integrated Registration and Segmentation Tool (FIRST, [Patenaude et al., 2011](#)) were used to estimate tissue type and whole brain volumes (SIENAX), as well as subcortical volumes (FIRST).

As the diffusion-weighted sequences differed between the OPDC and UK Biobank cohorts (60 vs 100 directions), slightly different preprocessing parameters were used for each set of diffusion images. However, crucial preprocessing steps were aligned, such as adjustment for eddy currents and head motion, and correction of outlier slices using the EDDY tool ([Andersson et al., 2018](#); [Andersson et al., 2016](#)). DTIFIT ([Basser et al., 1994](#)) was then used to create FA IDPs for 47 white matter tracts.

Before further analysis, variance associated with age, head size, and scanning date was removed from the IDPs using a general linear model as described previously in **Chapter 3**.

TBSS

TBSS was run to test for general white matter differences between healthy controls and PD patients, as well as associations with mood questionnaire items, on a voxel-by-voxel basis. Here I used the estimated FA images as the white matter variable of interest. These images were first eroded slightly, and outlier slices were removed. In the next step, all FA images are aligned non-linearly to a 1x1x1mm standard space, using the FMRIB58_FA standard-space image as the target. Once a standard-space version of each subject's FA image was created, they were merged into a 4D image, meaned, skeletonised, and thresholded (at 0.2 for the mean FA skeleton).

Finally, randomise was used to test for differences in FA between controls and PD patients, as

well as for associations with the mood questionnaire items, in separate models. Each model contained FA as dependent variable, covariates for age, sex, and scanning-date, and one of the mood questionnaire items as a continuous independent variable. Contrasts tested for mean differences in FA between the two groups (corrected for all other variables), correlations between FA and mood in each group, and differences in slope of the FA and mood correlations between the two groups. In addition, the same models were run without adding covariates for age and sex. Results were corrected for multiple comparisons with Threshold Free Cluster Enhancement (TFCE) (Smith et al., 2009), and considered significant at $\alpha = .05$.

VBM

VBM was used to test for general volume differences between healthy controls and PD patients, as well as associations with mood questionnaire items, on a voxel-by-voxel basis. Here I used FSL-VBM on raw T1-weighted images from both cohorts separately. VBM first brain-extracts the image, then carries out tissue-type segmentation and aligns the grey matter partial volume images to MNI152 standard space using FLIRT and FNIRT. In the next step, a study-specific grey matter template is created by averaging the aligned images. This template is used to register the native grey matter images non-linearly. When creating the study-specific grey matter template, researchers may choose to do so with only images from controls, an equal number of controls and patients, or all participants, depending on what biological effects on grey matter one might expect. However, an investigation of these different possibilities found no downside of including all participants, even when groups are not balanced (Marchewka et al., 2014). Thus, in order to retain as many participants as possible, the template was created using the complete sample. Each participant's registered partial volume image is then multiplied by the Jacobian of the warp field, which corrects for local expansion or contraction.

Again, differences between healthy controls and PD patients were tested for using the same models as described for TBSS (randomise, Winkler et al., 2014).

6.2.5 IDP analyses

Nomogram plotting

Using the hippocampal volume nomograms created in **Chapter 2**, I plotted hippocampal volume estimations for PD patients and controls from the OPDC cohort, as well as from the UK Biobank cohort against norm values. Because the nomograms can currently only be used for people up to 71 (for women) and 72 (for men) years, some participants that were included in the remaining analyses are not plotted on the nomograms.

IDP differences

As a complementary analysis to VBM, I also tested for differences between the IDPs for all 164 partial grey matter volumes and 47 FA tract means. This was done with an ANOVA for each IDP, testing for differences between PD and control for each cohort separately. Multiple testing error rate was adjusted for using Bonferroni correction.

6.3 Results

6.3.1 Demographics

In both cohorts, PD patients did not differ significantly from controls in terms of mean age. In all groups, men made up the majority of the sample size (**Table 6.2**). In the OPDC cohort, patients had significantly lower scores on the MoCA than controls. Patients also had higher scores on the BDI in total, as well as on the core apathy and core depression sub-scores, but not on the HADS anxiety sub-score. In the UK Biobank cohort, controls and patients did not differ on digit span performance or any of the mood questionnaires.

6.3.2 Nomograms

Hippocampal volumes were plotted for men and women, and controls and PD patients separately for each cohort over the nomograms that were created in **Chapter 3**. All estimations were corrected for head size. Some participants were older than the nomogram boundaries and could not be included.

In the OPDC cohort (**Figures 6.1-6.2**), most participants scored within the 2.5th to 97.5th percentiles. For the left hippocampus, two controls and two PD patients scored lower than the 2.5th percentile, while one control and two PD patients scored unusually high above the 97.5th percentile. For the right hippocampus, one control and two PD patients scored lower, and one control and four PD patients scoring higher than those boundaries.

| Measure | Control OPDC Mean \pm Std | PD OPDC Mean \pm Std | Control OPDC vs PD p-value | Control UKB Mean \pm Std | PD UKB Mean \pm Std | Control UKB vs PD UKB p-value |
|-------------------|------------------------------------|------------------------------------|--------------------------------------|-------------------------------|--------------------------|-------------------------------------|
| Age in y | 65.34 \pm 8.98 | 64.36 \pm 9.91 | t(173) = .65, p = .52 | 68.93 \pm 6.07 | 69.30 \pm 6.02 | t(148) = -.37, p = .72 |
| Dis. Dur. in y | | 0.9 \pm 0.63 | | | | |
| LEDD | | 235 \pm 201 | | | | |
| MoCA | 27.60 \pm 1.92 | 26.45 \pm 2.76 | t(119) = 2.45, p = .02* | n/a | n/a | n/a |
| BDI total | 4.93 \pm 6.05 | 8.43 \pm 5.35 | t(119) = -3.23, p = .002** | n/a | n/a | n/a |
| BDI dep. | .12 \pm .24 | .24 \pm .26 | t(119) = -2.45, p = .02* | n/a | n/a | n/a |
| BDI apathy | .21 \pm .37 | .41 \pm .49 | t(119) = -2.20, p = .03* | n/a | n/a | n/a |
| HADS anx. | 3.47 \pm 3.04 | 4.06 \pm 3.29 | t(119) = -.98, p = .33 | n/a | n/a | n/a |
| UKB dep. | n/a | n/a | n/a | 1.22 \pm .58 | 1.26 \pm .56 | t(148) = -.43, p = .67 |
| UKB apathy | n/a | n/a | n/a | 1.25 \pm .66 | 1.25 \pm .55 | t(148) = -.002, p = .99 |
| UKB anx. | n/a | n/a | n/a | 1.26 \pm .62 | 1.37 \pm .61 | t(148) = -1.12, p = .25 |
| Digit span | n/a | n/a | n/a | 6.40 \pm 2.12 | 6.15 \pm 1.52 | t(102) = -.69, p = .49 |
| n VBM | 62 (22W/40M) | 113 (41W/72M) | n/a | 75 (34W/41M) | 75 (32W/43M) | n/a |
| n VBM dep/ap | 42 (7F/35M) | 79 (32W/47M) | n/a | 75 (34W/41M) | 75 (32W/43M) | n/a |
| n VBM anx | 43 (9W/34M) | 78 (31W/47M) | n/a | 75 (34W/41M) | 75 (32W/43M) | n/a |
| n TBSS | 61 (21W/40M) | 107 (40W/67M) | n/a | 75 (34W/41M) | 75 (32W/43M) | n/a |
| n TBSS dep/ap | 42 (8W/34M) | 74 (31W/43M) | n/a | 75 (34W/41M) | 75 (32W/43M) | n/a |
| n TBSS anx | 43 (9W/34M) | 73 (30W/43M) | n/a | 75 (34W/41M) | 75 (32W/43M) | n/a |

Table 6.2 – Demographic information for participants with brain imaging in the OPDC and UK Biobank cohorts. PD patients and controls did not differ from each other in terms of age within the respective cohorts. Patients in the OPDC cohort differed from controls in cognitive status, as well as levels of depression and apathy. No differences between patients and controls were found in the UK Biobank.

In the UK Biobank dataset (**Figures 6.3-6.4**), only two PD patients and no controls scored lower, and four controls and one PD patient scored higher than the 2.5th and 97.5th percentiles for the left hippocampus.

Note that the axes for left and right hippocampus are slightly different, reflecting on average larger right hippocampal volumes within the population.

6.3.3 No baseline differences in FA using TBSS in either cohort

Performing TBSS for FA values in 107 patients with PD and 61 controls of the OPDC cohort, I found no group differences. Similarly, FA did not differ between the 75 PD patients and 75 controls in the UK Biobank cohorts. In both analyses, these results did not change whether or not covariates for age and sex were added. Scanning date was generally controlled for.

6.3.4 Significant main effect for FA and mood in the OPDC, but not UK Biobank cohort

TBSS was run again using total BDI, core depression, core apathy, and HADS anxiety scores for participants from the OPDC, and using either depression, anxiety, or apathy questionnaire items in the UK Biobank. While there were no significant associations in the UK Biobank dataset, there was a significant main effect for FA and all mood scores within the OPDC groups (**Figure 6.5, Table 6.3**).

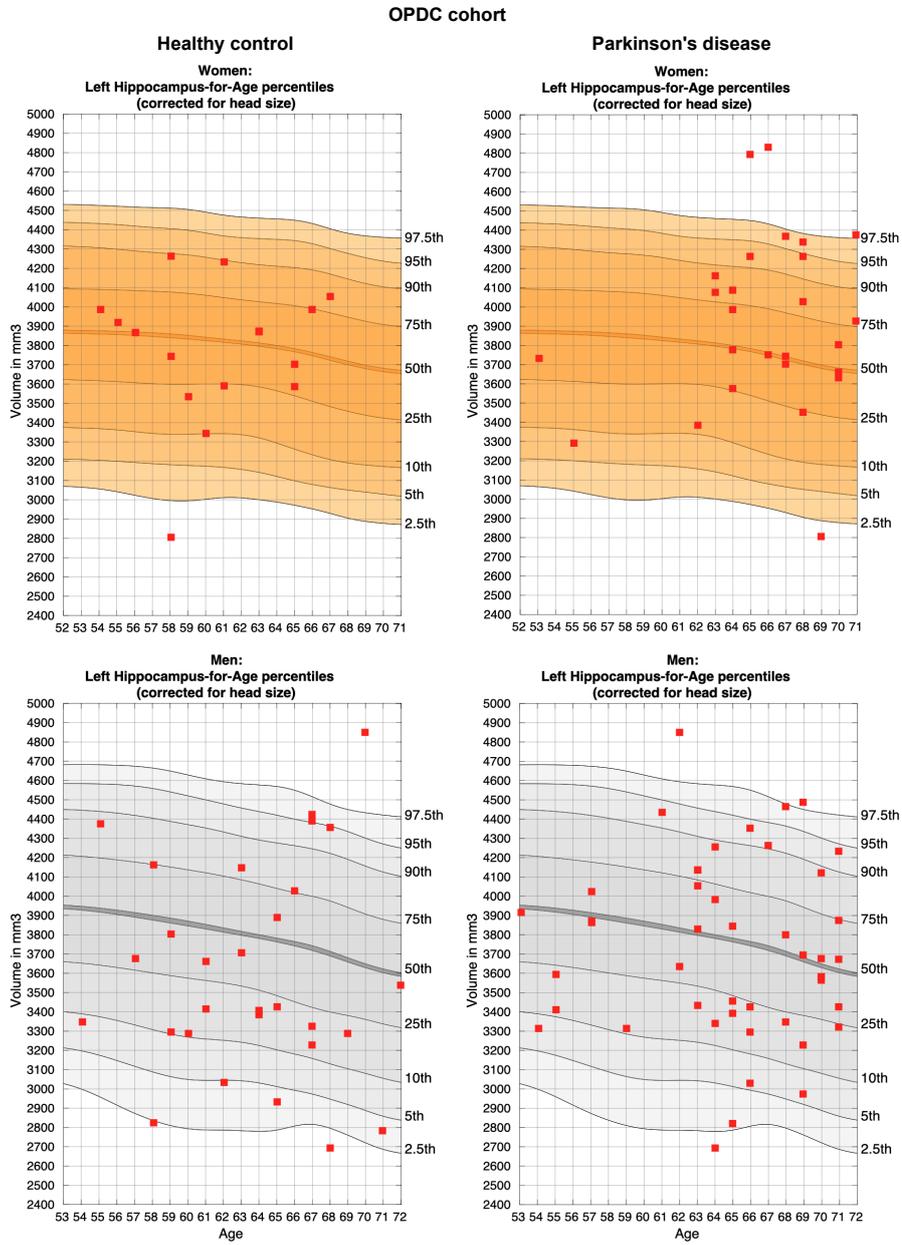


Figure 6.1 – Left hippocampal volume of participants in OPDC cohort plotted over nomograms. Each dot represents one participant. The majority of participants score within the 2.5th and 97.5th percentiles, with only two controls and two PD patients scoring lower, or one control and three PD patients scoring higher than those boundaries. All estimations were corrected for head size.

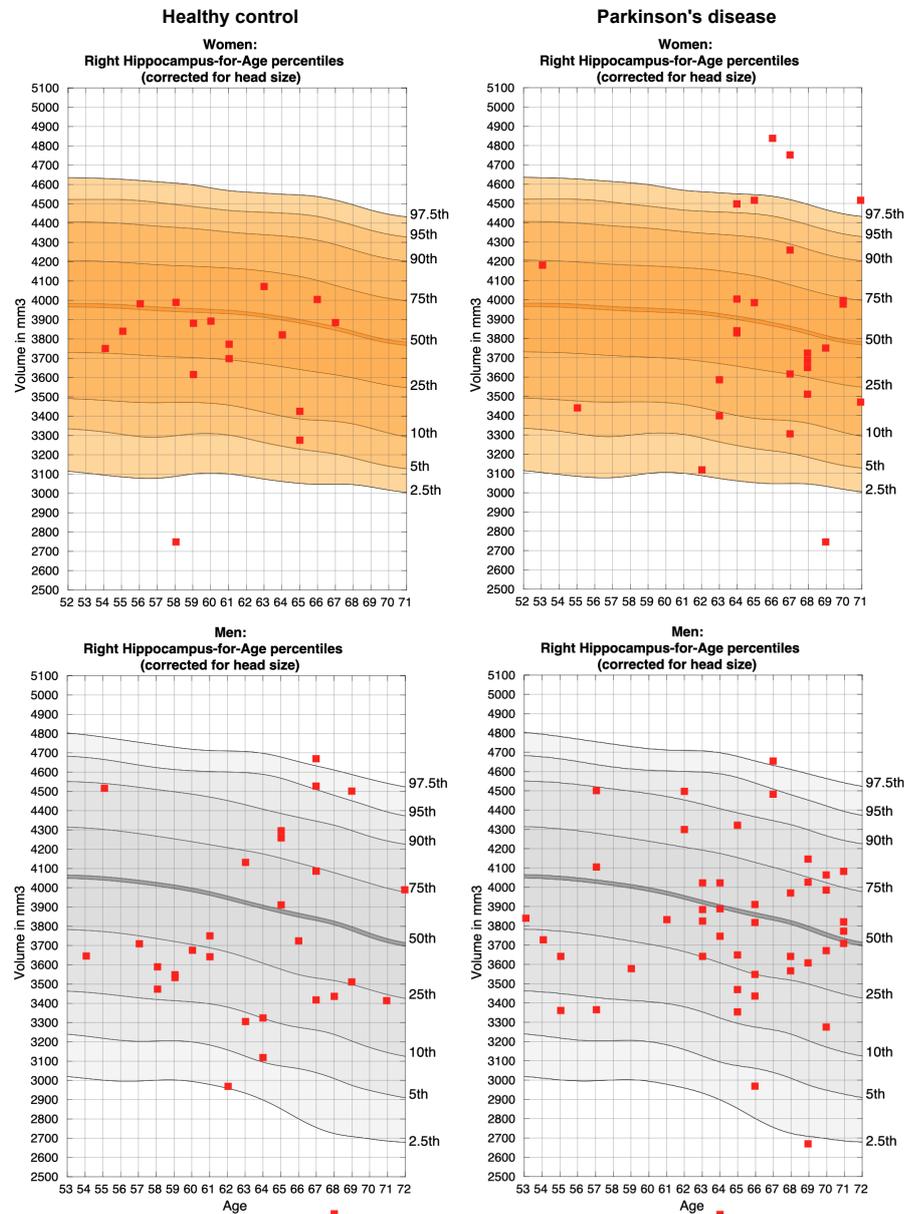


Figure 6.2 – Right hippocampal volume of participants in OPDC cohort plotted over nomograms. Each dot represents one participant. The majority of participants score within the 2.5th and 97.5th percentiles of the nomograms, with only one control and two PD patients scoring lower, or one control and four PD patients scoring higher than those boundaries. All estimations were corrected for head size.

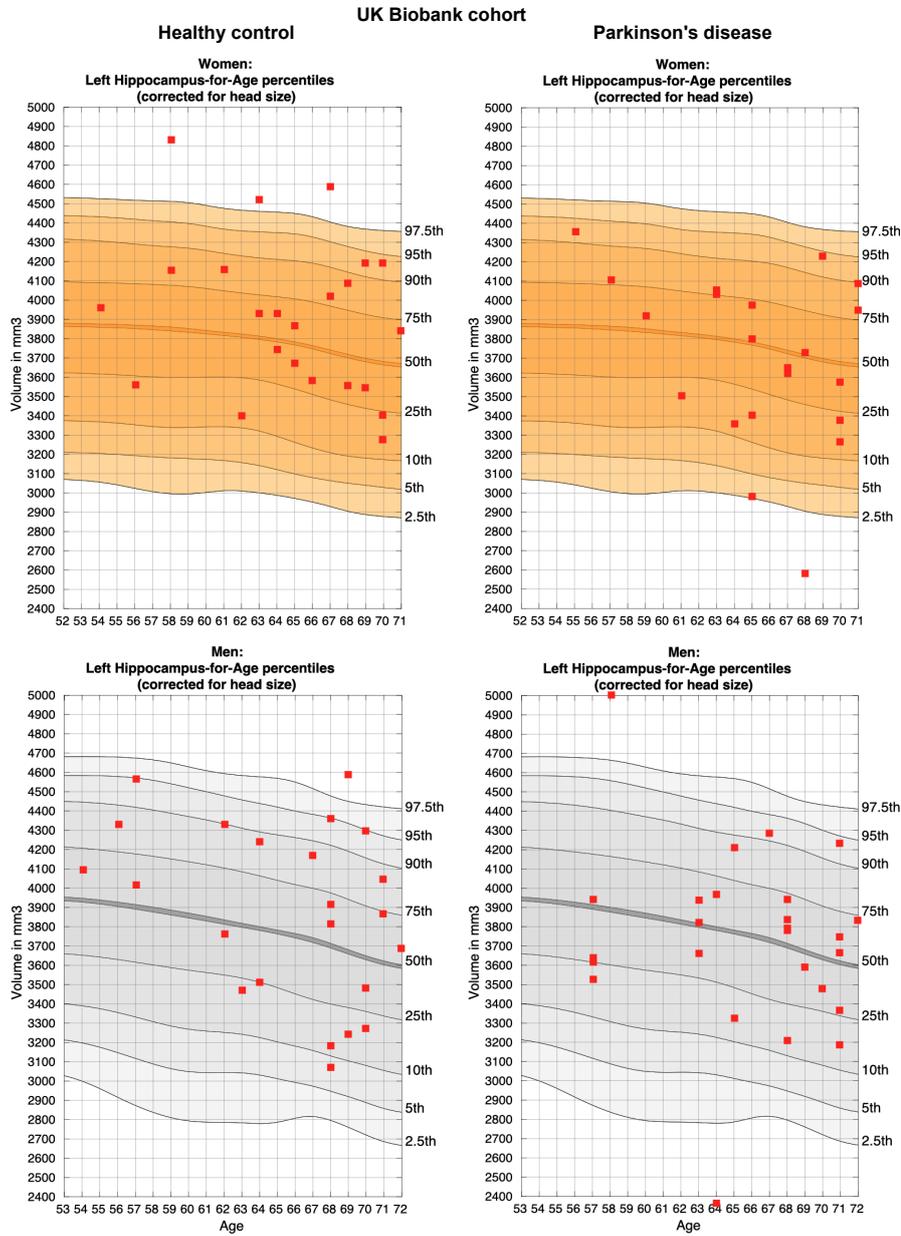


Figure 6.3 – Left hippocampal volume of participants in UK Biobank cohort plotted over nomograms. Each dot represents one participant. The majority of participants score within the 2.5th and 97.5th percentiles of the nomograms, with two PD patients and no controls scoring lower, or four controls and one PD patient scoring.

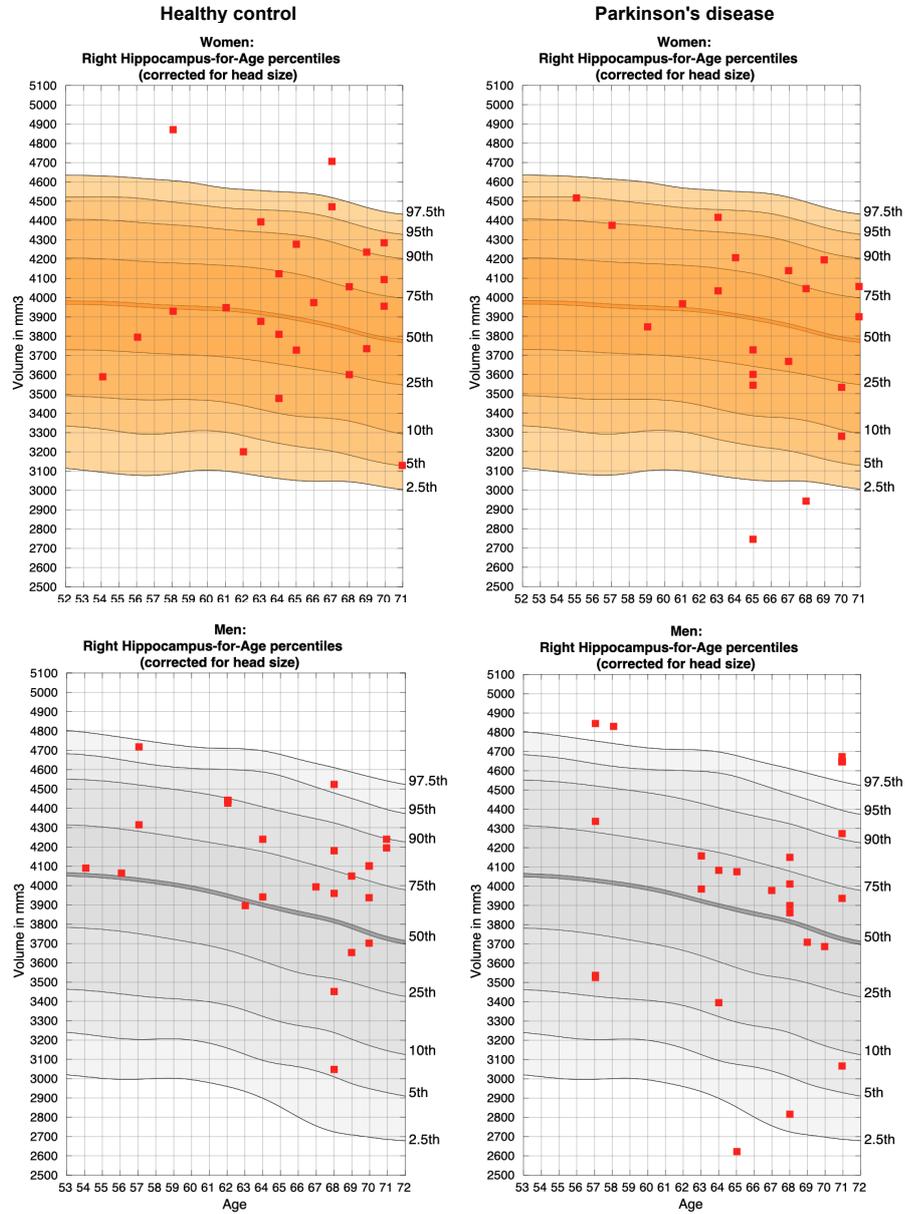


Figure 6.4 – Right hippocampal volume of participants in UK Biobank cohort plotted over nomograms. Each dot represents one participant. The majority of participants score within the 2.5th and 97.5th percentiles of the nomograms, with three PD patients and no controls scoring lower, or two controls and four PD patient scoring higher than those boundaries. All estimations were corrected for head size.

| | No. of Voxels | 1-p max | MAX X (vox) | MAX Y (vox) | MAX Z (vox) | COG X (vox) | COG Y (vox) | COG Z (vox) |
|----------------------------|---------------|---------|----------------|----------------|----------------|----------------|----------------|----------------|
| Total BDI | 34083 | 0.998 | 132 | 99 | 58 | 91.4 | 113 | 87.7 |
| Total BDI Control | 6616 | 0.968 | 109 | 167 | 80 | 97.7 | 140 | 91.7 |
| Total BDI PD | - | n.s. | - | - | - | - | - | - |
| Total BDI + covariate MoCA | 39023 | 0.998 | 129 | 90 | 51 | 90.7 | 111 | 87.2 |
| BDI depression | 29220 | 0.99 | 118 | 48 | 73 | 97 | 103 | 90 |
| BDI dep. Control | 41496 | 0.996 | 109 | 165 | 80 | 89.2 | 109 | 90.1 |
| BDI dep. PD | - | n.s. | - | - | - | - | - | - |
| BDI apathy | 1180 | 0.96 | 130 | 83 | 66 | 127 | 89.8 | 72.7 |
| BDI apathy Control | - | n.s. | - | - | - | - | - | - |
| BDI apathy PD | - | n.s. | - | - | - | - | - | - |
| HADS anxiety | 28233 | 0.984 | 112 | 115 | 82 | 88.6 | 97.4 | 87.8 |
| HADS anx. Control | 31108 | 0.984 | 115 | 145 | 52 | 87.3 | 109 | 88 |
| HADS anx. PD | - | n.s. | - | - | - | - | - | - |

Table 6.3 – Statistics for TBSS results.

There was a negative relationship between FA and mood scores, especially within posterior regions like the splenium of the corpus callosum, posterior thalamic radiation, and posterior corona radiata, but also across the wider white matter skeleton. By looking at individual group effects it emerged that this effect was significant only in controls, although a similar trend was found in PD patients (**Table 6.3 lower panel**). Mean FA values within the significant voxels were further plotted against total BDI scores to examine this relationship (**Figure 6.6**).

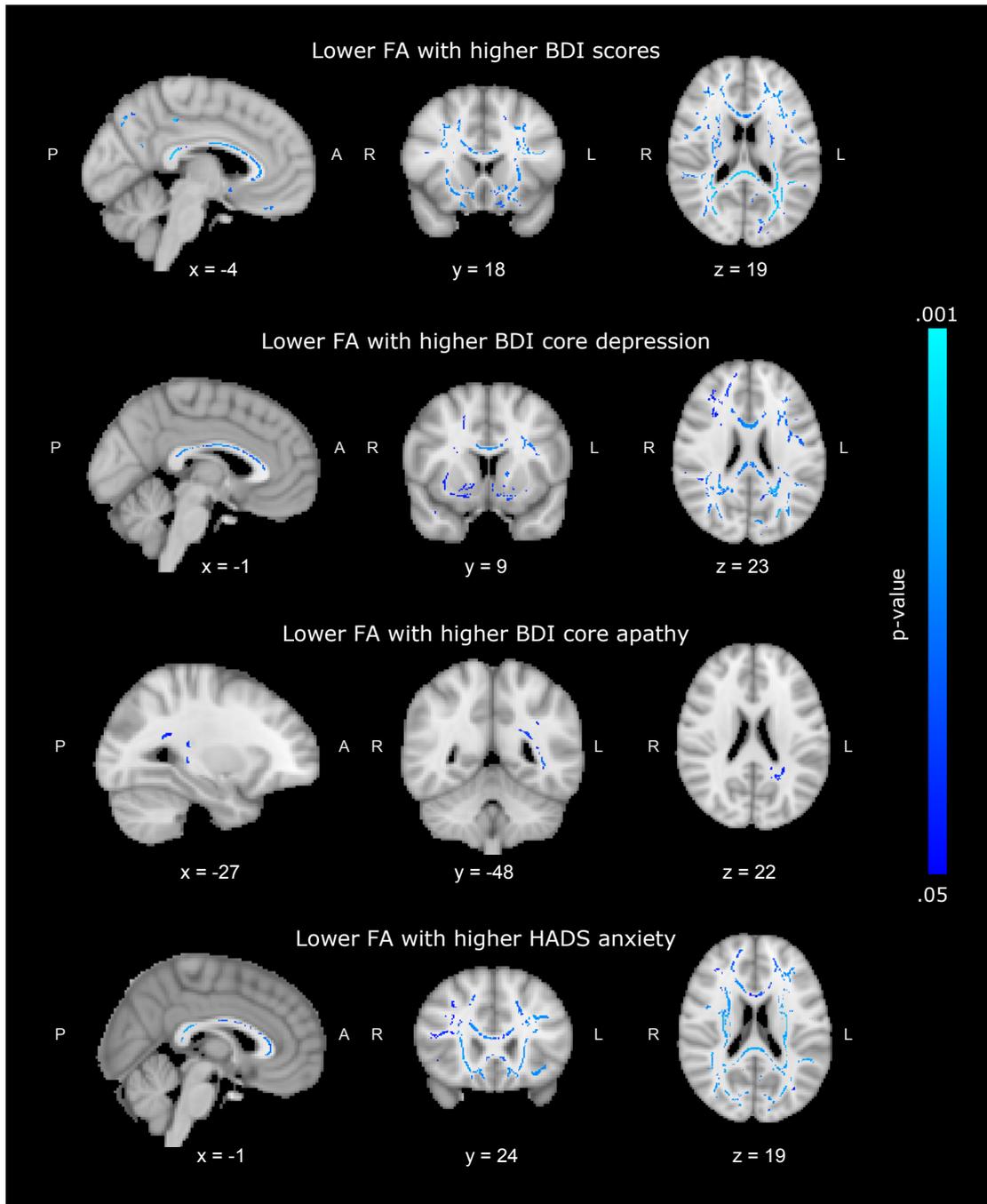


Figure 6.5 – TBSS in OPDC dataset shows lower FA values with higher mood symptom scores. There was a negative relationship between total BDI scores, core apathy, core depression, and anxiety with FA across much of the white matter skeleton, and primarily the posterior tracts. For all mood scores, more severe symptoms correlated with lower FA values (lower white matter integrity). Closer inspection of the groups revealed that this interaction was driven by controls, as the effect was not significant in only the PD patients.

Across the range of BDI scores, higher depression ratings were associated with lower FA values, with some extreme cases particularly driving this effect. As controls and PD patients

differed slightly in cognitive status, this analysis was rerun with an additional covariate for MoCA scores. This additional covariate did not affect the significance of the previous effects, and was not significant (**Table 6.3**).

6.3.5 VBM in OPDC cohort reveals smaller motor cortex volume in PD

Analysing T1-weighted images using VBM resulted in significant clusters within the motor cortex on each hemisphere (**Figure 6.7**). In these clusters, PD patients were found to have smaller volumes than healthy controls. This result did not change based on whether or not

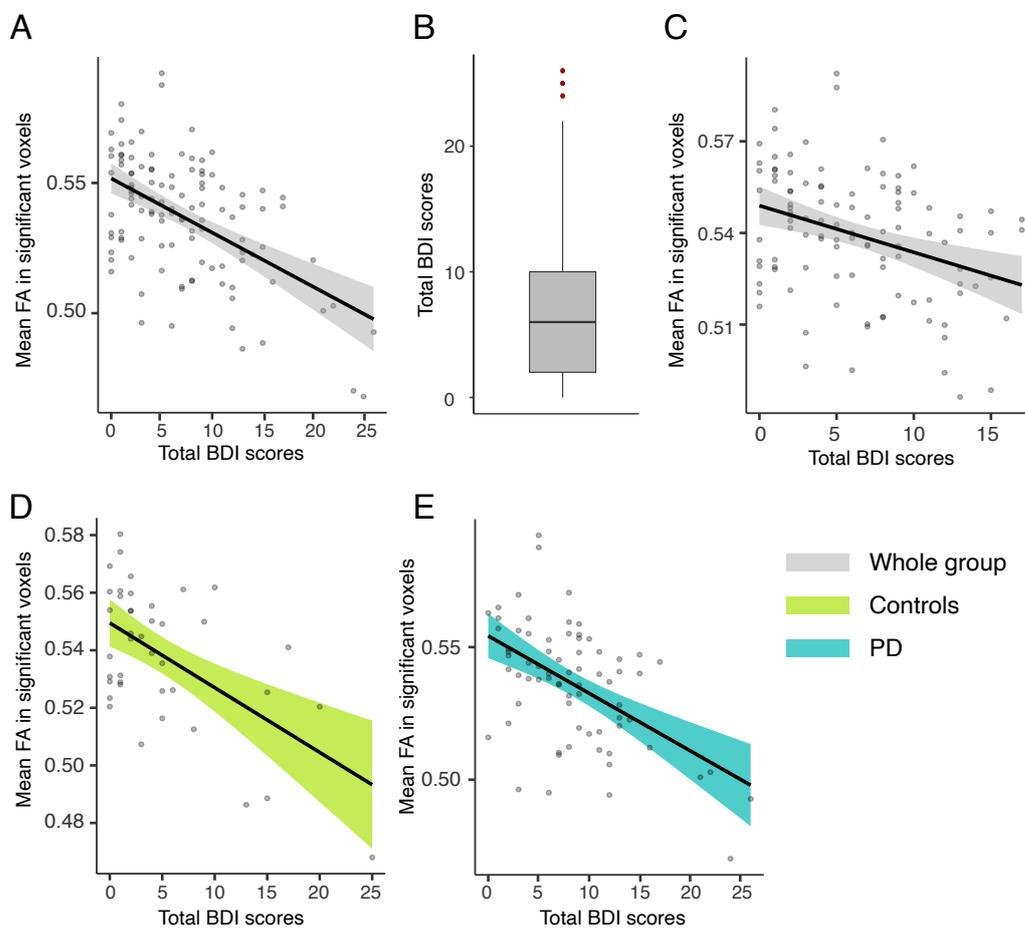


Figure 6.6 – Associations between mean FA values and BDI scores in OPDC. **A.** Correlation between mean FA in significant voxels with total BDI scores in the total group. **B.** Boxplot of total BDI scores with three potential outliers. **C.** Correlation between mean FA in significant voxels with total BDI scores up to 20. **D.** Correlation between mean FA in significant voxels with total BDI scores in controls. **E.** Correlation between mean FA in significant voxels with total BDI scores in PD patients. Although the BDI scores are strongly skewed towards the right, the negative association holds when removing the most extreme BDI scores.

age and sex were included as covariates. There were no other significant clusters, nor any areas where PD patients had larger volumes than healthy controls. Detailed information about the significant clusters is given in **Table 6.4**. As controls and PD patients differed slightly in cognitive status, this analysis was rerun with an additional covariate for MoCA scores. This additional covariate did not affect the significance of the previous effect, and was not significant (**Table 6.4**).

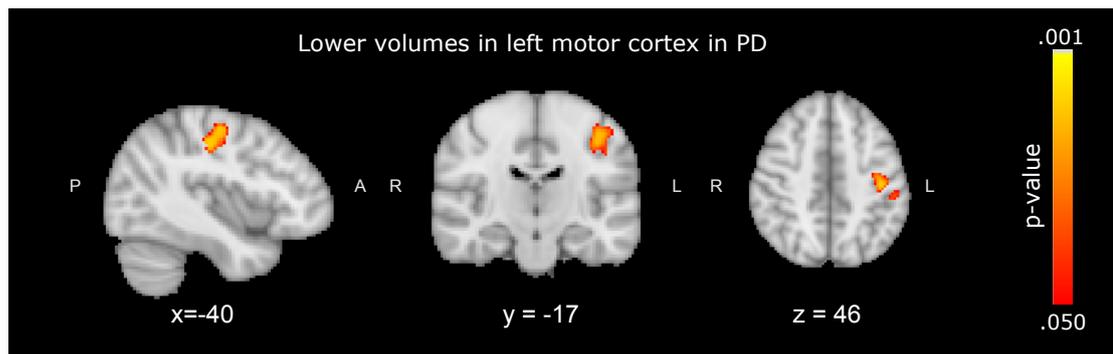


Figure 6.7 – VBM indicates lower left motor cortex volume in PD patients from OPDC cohort. Compared to controls within OPDC, and with covariates for age, sex, and scanning date, PD patients had lower volumes in the red highlighted areas in the left motor cortex.

| | No. of Voxels | 1-p max | MAX X (vox) | MAX Y (vox) | MAX Z (vox) | COG X (vox) | COG Y (vox) | COG Z (vox) |
|-----------------------------|---------------|---------|-------------|-------------|-------------|-------------|-------------|-------------|
| Left motor cortex | 318 | 0.990 | 65 | 52 | 58 | 66.0 | 54.6 | 59.9 |
| Left motor cortex with MoCA | 329 | 0.992 | 65 | 52 | 58 | 65.7 | 54.7 | 59.5 |

Table 6.4 – VBM motor cortex cluster information in OPDC dataset. Number of total voxels in significant cluster, maximum significance value, as well as MNI coordinates and voxel coordinates of the maximum cluster value are given.

6.3.6 VBM in UK Biobank cohort reveals smaller volume in temporal and parietal areas in PD

Similarly, VBM in the UK Biobank cohort also resulted in significant clusters where PD patients presented lower volumes than healthy controls. However, in this dataset, these voxel

clusters were found in the bilateral parahippocampal/fusiform gyri, the precuneus cortex, and the left inferior/middle temporal gyrus (**Figure 6.8**). Information on number of voxels and maximum significance are detailed in **Table 6.5**. These clusters were significant with and without correcting for age and sex using covariates. There were no other significant clusters for other contrasts testing for larger volumes in PD patients compared to control.

| | No. of Voxels | 1-p max | MAX X (vox) | MAX Y (vox) | MAX Z (vox) | COG X (vox) | COG Y (vox) | COG Z (vox) |
|--------------------------------|---------------|---------|-------------|-------------|-------------|-------------|-------------|-------------|
| Left parahippocampal gyrus | 1202 | 0.998 | 54 | 55 | 20 | 58.2 | 56.2 | 21.5 |
| Inferior/middle temporal gyrus | 449 | 0.981 | 76 | 46 | 27 | 75.1 | 45.7 | 26.7 |
| Right parahippocampal gyrus | 404 | 0.989 | 37 | 57 | 22 | 34.1 | 57.2 | 22.2 |
| Precuneus cortex | 243 | 0.982 | 46 | 34 | 48 | 46.0 | 32.5 | 48.1 |

Table 6.5 – VBM cluster information for OPDC dataset Number of total voxels in each cluster, maximum significance value, as well as MNI coordinates and voxel coordinates of the maximum cluster value are given for each of the four clusters presented in **Figure 7**.

6.3.7 No voxel-wise correlations between cortical volume and mood symptoms in either cohort

Running VBM models with the different mood symptom variables of interest as continuous independent variables did not result in any significant slopes or interactions in either of the two cohorts.

6.3.8 Some overlap between voxel-wise and IDP significance tests in UK Biobank

In the OPDC dataset, t-tests revealed significant grey matter differences with medium effect size in the superior temporal gyrus and planum temporale, with smaller volumes in PD patients. PD patients also had lower FA in the cerebral peduncle, posterior limb of the internal capsule and superior corona radiata, but higher FA in the sagittal stratum (**Table 6.6**).

In the UK Biobank cohort, testing for differences in grey matter regions of interest using IDPs

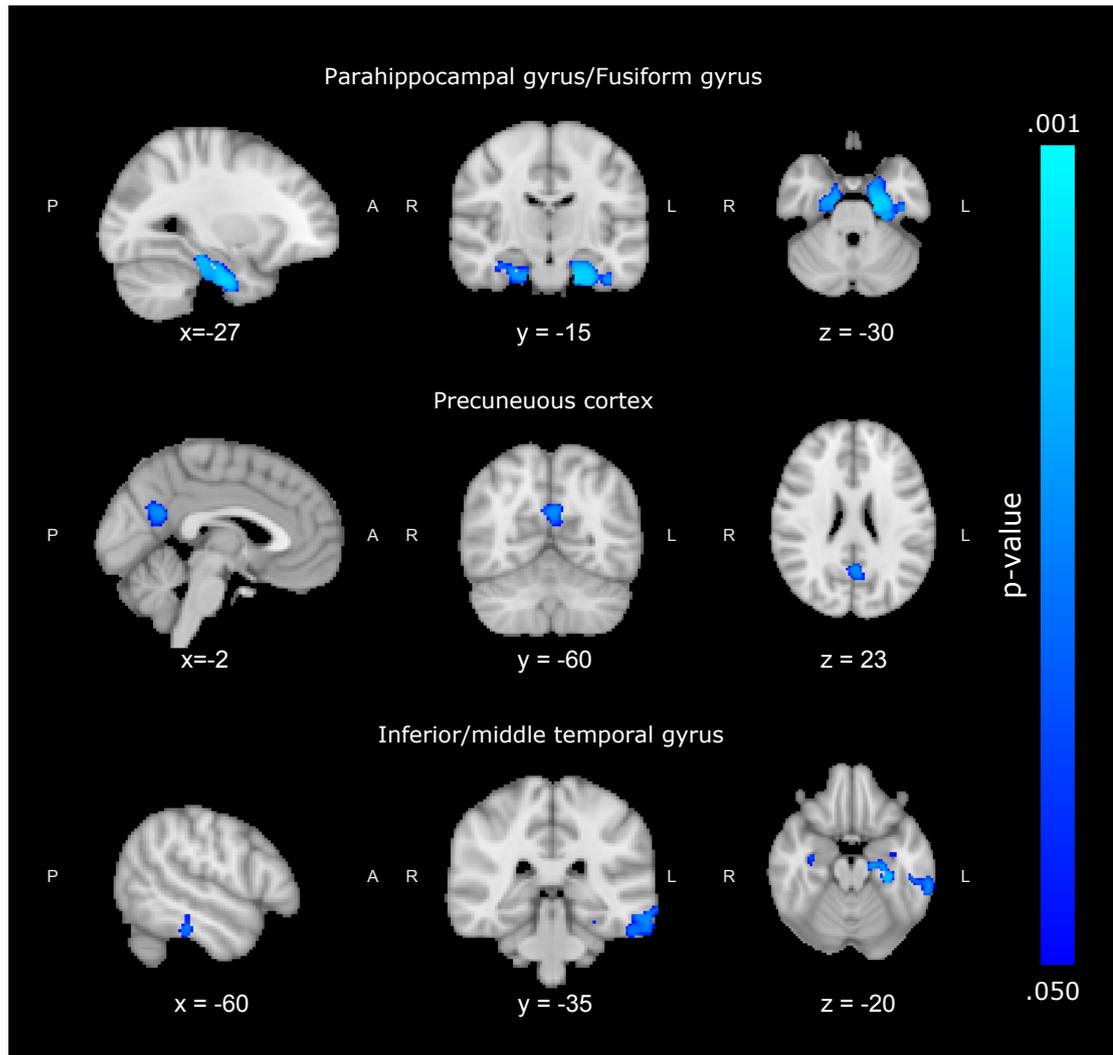


Figure 6.8 – VBM indicates lower volumes in PD patients in the UK Biobank in multiple areas. Compared to matched controls, with covariates for age, sex, and scanning date, PD patients were found to have lower volumes in bilateral parahippocampal/fusiform gyri, the precuneus cortex, and the inferior/middle temporal gyrus.

resulted in a number of significant cortical, subcortical, and cerebellar areas (**Table 6.7**). As shown with VBM, IDP analysis also revealed smaller left inferior temporal gyrus, precuneus cortex, and parahippocampal gyrus volumes in PD compared to controls.

| | IDP | HC mean | PD mean | p-value | Hedges' g |
|-----------------------|-------------------------------------------|------------------|------------------|---------|-----------|
| Volume of grey matter | Superior temporal gyrus, anterior (left) | 1414.71 ± 237.93 | 1511.71 ± 219.45 | 0.0117 | 0.42 |
| | Planum temporale (left) | 1448.15 ± 228.38 | 1534.70 ± 290.49 | 0.0398 | 0.34 |
| Mean FA | Cerebral peduncle (right) | 0.73 ± 0.02 | 0.72 ± 0.03 | 0.0051 | -0.47 |
| | Posterior limb of internal capsule (left) | 0.70 ± 0.02 | 0.69 ± 0.02 | 0.0177 | -0.39 |
| | Superior corona radiata (left) | 0.53 ± 0.02 | 0.52 ± 0.02 | 0.0437 | -0.33 |
| | Sagittal stratum (left) | 0.62 ± 0.03 | 0.63 ± 0.03 | 0.0244 | 0.37 |

Table 6.6 – Significant IDP differences from OPDC cohort. Grey matter volume in temporal areas and four IDPs for FA were significantly different in PD. However, no significant outcome survived correction for multiple testing ($p_{\text{corr}} = 0.05/124 = .00023$).

| | IDP | PD mean | HC mean | p-value | Hedges' g |
|--------------------------|---------------------------------------------------|----------------------|-----------------------|---------|-----------|
| Volume of grey matter | Peripheral cortical grey matter | 451343.53 ± 30794.03 | 463237.70 ± 463237.70 | 0.0204 | -0.38 |
| | Hippocampus (left) | 3585.78 ± 527.12 | 3760.54 ± 3760.54 | 0.0339 | -0.35 |
| | Brain stem + 4th ventricle | 23329.69 ± 2345.25 | 22387.36 ± 22387.36 | 0.0110 | 0.42 |
| | Temporal pole (left) | 8738.79 ± 1100.28 | 9092.07 ± 9092.07 | 0.0460 | -0.33 |
| | Inferior temporal gyrus, anterior division (left) | 1320.38 ± 233.35 | 1414.31 ± 1414.31 | 0.0221 | -0.38 |
| | Superior parietal lobule (right) | 4204.91 ± 733.72 | 4548.36 ± 4548.36 | 0.0141 | -0.40 |
| | Angular gyrus (left) | 3764.61 ± 642.58 | 4065.30 ± 4065.30 | 0.0077 | -0.44 |
| | Angular gyrus (right) | 4936.25 ± 941.73 | 5459.99 ± 5459.99 | 0.0007 | -0.56 |
| | Subcallosal cortex (left) | 2762.17 ± 291.64 | 2866.46 ± 2866.46 | 0.0469 | -0.33 |
| | Precuneus cortex (left) | 9353.76 ± 1112.45 | 9829.90 ± 9829.90 | 0.0098 | -0.43 |
| | Precuneus cortex (right) | 9724.02 ± 1322.79 | 10140.56 ± 10140.56 | 0.0449 | -0.33 |
| | Parahippocampal gyrus, anterior division (right) | 2833.30 ± 469.86 | 3001.34 ± 3001.34 | 0.0189 | -0.39 |
| | Occipital fusiform gyrus (left) | 3565.61 ± 533.50 | 3786.47 ± 3786.47 | 0.0123 | -0.41 |
| | Thalamus (left) | 2734.56 ± 266.95 | 2639.96 ± 2639.96 | 0.0246 | 0.37 |
| | Putamen (left) | 1819.92 ± 342.88 | 1670.86 ± 1670.86 | 0.0198 | 0.39 |
| | Putamen (right) | 2234.42 ± 390.51 | 2018.10 ± 2018.10 | 0.0015 | 0.53 |
| | I-IV cerebellum (left) | 1873.85 ± 289.78 | 1756.30 ± 1756.30 | 0.0069 | 0.44 |
| | V cerebellum (left) | 2602.49 ± 381.53 | 2464.86 ± 2464.86 | 0.0195 | 0.38 |
| | Crus II cerebellum | 411.23 ± 67.27 | 380.58 ± 380.58 | 0.0069 | 0.45 |
| | VIIb cerebellum | 136.67 ± 23.92 | 127.01 ± 127.01 | 0.0193 | 0.38 |
| VIIa cerebellum | 886.08 ± 169.77 | 830.97 ± 830.97 | 0.0356 | 0.34 | |
| VIIIa cerebellum (right) | 3834.08 ± 716.02 | 3585.03 ± 3585.03 | 0.0261 | 0.37 | |
| VIII cerebellum | 448.51 ± 90.08 | 418.68 ± 418.68 | 0.0271 | 0.36 | |
| IX cerebellum | 441.83 ± 91.61 | 408.92 ± 408.92 | 0.0180 | 0.39 | |
| Mean FA | Cerebral peduncle on FA skeleton (left) | 0.71 ± 0.03 | 0.70 ± 0.70 | 0.0471 | 0.34 |

Table 6.7 – Significant IDP differences from UK Biobank cohort. A number of grey matter volume and one FA IDP were significantly different between PD and Controls, with PD generally showing smaller volumes. However, no significant outcome survived correction for multiple testing ($p_{corr} = 0.05/124 = .00023$).

6.4 Discussion

The objective in this final chapter was to assess the generalisability and replicability of structural MRI findings related to PD. This was achieved by analysing scans from two separate cohorts of patients and controls in the UK Biobank and OPDC, using the same processing pipelines. The results indicate limited overlap both between previous and across the two current analyses, calling into question the validity of structural MRI biomarkers in PD. However, a robust association between white matter integrity and mood symptoms was found in PD and controls in the OPDC cohort, potentially supporting the vascular depression theory. While this was not found in the UK Biobank cohort, this may be due to the less well validated questionnaires used in this dataset. In addition, one limitation of this study is the relatively small number of cases in each dataset.

I plotted hippocampal volumes for PD patients and controls in either cohort over the nomograms that were created in **Chapter 3**, in order to assess generalisability of estimates from automated brain segmentation (**Figures 6.1-6.4**). In both datasets, the vast majority of cases scored within the 2.5th and 97.5th percentiles, with higher density of cases around the 50th percentiles. A few single participants scored lower or higher than that, which is in line with the number of outliers one would expect based on a normal distribution of brain volume in the general population. However, when comparing the overall fit of cases over the nomograms in the OPDC cohort to the UK Biobank cohort, it becomes evident that UK Biobank cases seem to cluster more around the 50th percentiles, especially for men. In contrast, a surprising number of PD patients in the OPDC cohort score higher than the 50th percentile when compared to controls. This might indicate a better generalisation of the nomograms for the UK Biobank cohort. This is on the one hand unsurprising, as data from the UK Biobank was used to create these nomograms. However, on the other hand, as the OPDC scans were analysed using the same processing pipeline, this highlights the lack of harmonisation resulting from different acquisition pipelines. Although PD is not necessarily associated with brain or hippocampal atrophy early in the progression of PD, higher than average volumes may indicate harmonisation issues. If MRI-derived biomarkers like hippocampal volume and the nomograms are to be used in clinical practice, this is an issue that needs to be addressed in

future research.

Using TBSS, I found no evidence for differences in white matter integrity measured by FA between PD patients and controls in either of the two cohorts. However, total BDI scores, as well as levels of core depression, core apathy, and core anxiety correlated negatively with FA in the corpus callosum in the whole group (**Figure 6.5**). This negative relationship was significant on a voxel-based level only in controls, although a similar trend was found for the PD group (**Figure 6.6 E**). No such effect was found in the UK Biobank cohort. This may be due to the low variance in the three mood question ratings between the patient and control groups in this cohort. As these were single questions rather than validated questionnaires, with only limited severity rating, the data may not have contained the necessary level of detail to uncover a relationship with white matter measures. In addition, patients with PD in the UK Biobank were selected based on either a self-reported diagnosis of PD, or a linked medical record of a PD diagnosis. Thus, the diagnoses in the UK Biobank may not have been made according to exactly the same guidelines between patients within this and the OPDC cohort, resulting in potentially higher rates of misdiagnoses in the UK Biobank PD group. It is also conceivable that disease duration plays a role in whether or not structural effects on the brain can be detected (Lewis et al., 2016; Oxtoby et al., 2021; Sarasso et al., 2020). However, this hypothesis could not be tested in the present study as this information was missing for a large number of PD patients within the UK Biobank.

White matter integrity abnormalities have previously been linked to depression, though the affected tracts differ widely. In a recent investigation in depressed individuals from the UK Biobank, Shen et al. (2017) document reduced FA in depression in association fibres, thalamic radiation, and longitudinal fasciculus. In contrast, other studies note relationships between FA in the cingulum and uncinate fasciculus and depression (Wu et al., 2018), or no associations at all (Hollocks et al., 2015). In PD specifically, depression has been linked to white matter abnormalities in the anterior corona radiata, thalamic radiation, cingulum, longitudinal fasciculus, sagittal stratum, or uncinate fasciculus (Wu et al., 2018). While the direction of the effects – higher levels of depression and lower levels of white matter integrity – matches the current findings, the tracts in which they were found differ. The variability in results may

be due to a number of different factors in these reports, such as scanning sequence and analysis pipeline used, small or heterogeneous samples, and the previously mentioned difficulty with diagnosing or measuring depression. It has been demonstrated that different analysis approaches to MRI data can have considerable influence on results (Botvinik-Nezer et al., 2020), especially since processing of this data is often highly complex involving many possible choices. However, one report investigating the reliability of FA using different methods found relatively high reproducibility ($ICC = 0.7$, Duan et al., 2015). Although the same MRI processing pipeline was used for most of the data in the UK Biobank and OPDC cohorts, this was not the case for diffusion-weighted images, as the acquisition sequences differed substantially between the two.

Yet, the fairly robust association between depression, apathy, and anxiety with white matter integrity within the OPDC cohort reported here further supports the hypothesis of a vascular type of mood disorder in older age that has been introduced in earlier chapters. Especially the lack of a distinctive relationship, or any relationship, in the PD group suggests that the significantly more severe mood symptoms (**Table 6.3**) in this group may underlie a different mechanism. For example, neurotransmitter dysfunction like reduced levels of serotonin, directly associated with PD, may introduce mood symptoms that would not be related to white matter integrity (Tan et al., 2011).

By applying VBM to structural T1-weighted images, group differences between controls and PD patients emerged in different brain regions across the two cohorts. In the OPDC dataset, VBM indicated significantly smaller left motor cortex volume in patients with PD as compared to healthy controls (**Figure 6.7**). In contrast, PD patients in the UK Biobank were found to have smaller grey matter volumes in the parahippocampal/fusiform gyrus, precuneus cortex, and inferior/middle temporal gyrus than their matched controls (**Figure 6.8**). In neither of the two datasets did grey matter volume correlate with mood symptoms. A previously analysed subset of the OPDC participants, comprised of 20 PD patients and 19 controls, did not display any grey matter differences using VBM (Menke et al., 2014). In contrast, a recent meta-analysis of 63 VBM studies with almost 3000 PD patients and 2000 controls documented significantly reduced grey matter volumes in PD patients in the insula, putamen, temporal lobe,

striatum, amygdala, angular gyrus, anterior cingulate, superior frontal gyrus, and fusiform gyrus, but not in motor cortex (Xu et al., 2020). Thus, there is some overlap of previous findings with the current results from the UK Biobank cohort, like the reduced grey matter volume in PD that was found in the fusiform gyrus and temporal gyrus. However, overall, VBM findings are highly variable across reports and datasets. As is the case with TBSS, VBM too may be affected by lack of statistical power due to small or heterogeneous samples, because of its requirement for normality and parametric test methods (Scarpazza et al., 2016). Results from VBM also seem to be sensitive to the choice of acquisition sequence and preprocessing steps, especially in relation to image contrast-to-noise ratio and signal-to-noise ratio (Tardif et al., 2009).

Finally, as an alternative approach to identifying voxel-wise grey and white matter differences between the groups, I compared IDP values using multiple testing-corrected paired t-tests. The IDPs included a variety of grey matter volumes summarised over atlas-based partial brain regions, as well as FA summarised over atlas-based white matter tract parcellations. While VBM and TBSS are more powerful for detailed, voxel-wise detection of differences, the use of cluster enhancement and multiple testing corrections in these methods can result in false negative results (Smith et al., 2006). In contrast, IDPs can be useful for capturing changes within wider brain regions that only become apparent by summarising over many voxels. Indeed, analysing IDPs resulted in a larger number of significantly different areas for both grey and white matter between PD patients and controls. In the OPDC cohort, grey matter differences were found in temporal regions, but not in the motor cortex as reported based on VBM.

PD patients also had smaller IDP estimations for FA than controls in a number of white matter tracts, like the cerebral peduncle or internal capsule (**Table 6.6**). This is in contrast to the TBSS results, where no significant differences in FA were found. In the UK Biobank dataset, a large number of grey matter IDPs were significantly smaller in PD than in controls, with the strongest effect sizes for the bilateral angular gyrus, right putamen, and precuneus cortex (**Table 6.7**). Again, there is some overlap with previous findings discussed above, though arguably not to an extent that would satisfy reproducibility concerns.

Generally, the variability in white and grey matter abnormalities in the literature may be due to different disease stages and severity of mood symptoms within the various study samples. It may be that PD affects the structure of the brain only in later stages of the disease, as the current study sample in the OPDC cohort had rather short disease duration, or that it can only be observed with MRI when more severe damage has occurred. However, this would result in further complications for the interpretation of findings, as it becomes more difficult to attribute any structural changes to PD itself rather than any secondary effects, such as reduced mobility. It also casts doubt on the feasibility of structural neuroimaging markers in PD, because it seems that grey or white matter changes are simply not the primary observable pathological manifestations of the disease. One exception to this may be PD with dementia, where structural neuroimaging findings too are variable, but seem to generally involve a common hippocampal network (Weil et al., 2019).

The number of studies on neuroimaging markers on PD, and the little convergence between them, also highlight that it is not sufficient to merely establish correlates of symptoms or diagnoses. Given the often fairly small and heterogeneous sample in clinical neuroimaging studies, some correlations and associations will always be present. However, these analyses are often not sufficient to conclude whether findings are causes, effects, or manifestations of symptoms. Thus, alternative methods that do allow for causal interpretations, such as metabolic PET or SPECT scans after pharmacological manipulation, may be worth investing more in for future research. In addition, combining neuroimaging with carefully designed, theory-based behavioural paradigms – as opposed to questionnaire sum scores – may also improve confidence in potential correlations and allow for faster translation to clinical practice (Niv, 2020).

Chapter 7

General discussion

This thesis set out with the aim to characterise effects of ageing on brain health. This was performed in two parts, first focusing on what may be considered “normal” changes in healthy ageing, then investigating differences to pathological ageing in the special case of PD.

7.1 Summary of findings

In **Chapter 2**, data from older adults in the UK Biobank were analysed to estimate the average trajectory of mood symptom severity across age. Both changes in neuropsychiatric symptoms over time, as well as common symptom profiles, were investigated. In this chapter, sub-clinical neuropsychiatric symptoms in a group of healthy older adults were contrasted with clinical symptoms in a group of older adults with psychiatric diagnoses. These results were then extended by investigating the symptom distribution in patients with PD in **Chapter 4.2**.

The findings indicated that on average mood and happiness generally improved with ageing, starting at 50 years or earlier (**Figure 2.3**). This effect was found in both the healthy group, and patients with psychiatric diagnoses. People’s happiness about their health too increased around age 60, but decreased again by 70 years (**Figure 2.4**). This supports the often-reported positivity effect in mid-to-older age, which suggests a general improvement in emotional well-being with age, potentially through positive attentional biases ([Mather et](#)

al., 2005). As participants with any kind of medical diagnosis (other than psychiatric in the patient group) were excluded from this analysis, and I did not find an increase in mood symptoms with age, these findings may also be in line with theories around vascular mechanisms of worsening mood symptoms in older age (Camus et al., 2004). Since many of the disorders associated with vascular pathology, such as stroke, were excluded, it could be argued that only those participants experiencing the positivity effect remained in the sample.

I further showed that similar types of symptoms – such as tiredness and anxiety – were among the most common in both healthy older adults and psychiatric patients, but to larger extent in the psychiatric group. Lastly, a factor analysis of individual mood questionnaire items revealed different symptom clusters between the groups of healthy adults and those with a psychiatric disorder. The item pairings within the mood questionnaire factors suggested that symptoms of sub-clinical depression and anxiety, such as worry or tiredness, explained the most variance in the healthy group. In contrast, more severe symptoms like feelings of inadequacy or suicidality were more common in the patient groups.

In **Chapter 3**, I described how neuroimaging-derived phenotypes like hippocampal volume change with age, by analysing the large cross-sectional dataset from the UK Biobank. The results of two different types of analysis revealed a slight acceleration of hippocampal volume loss around age 60-65 years for women, whereas for men the rate of hippocampal volume loss may increase earlier around 50 years (**Figures 3.4 and 3.5**). This may underlie the specific vulnerability of hippocampal volume loss in older age (Jack Jr. et al., 2000). To further demonstrate the extent and distribution of these age-related volume losses, I created norm values (nomograms) that hint at how MRI-based biomarkers may be applied in clinical practice in the future. These were inspired from growth charts commonly used to track children's development, where an individual's measurement can be plotted based on the percentile that they are scoring in.

In addition, I tested for differences in several structural IDPs, such as hippocampal volume, between participants with and without mood symptoms. Because of the large sample size and repeated testing, a large number of significant differences was found, distributed widely across the brain. However, after accounting for age, only very few associations were retained.

These were present when comparing people who reported feelings of loneliness (bilateral thalamus), worry (bilateral temporal poles), sensitivity (right precuneus), or taking risks (left superior lateral occipital cortex). Although the quality and detail of the mental health questionnaire in the UK Biobank are not ideal, the lack of clinically relevant structural differences suggests that other research avenues, such as focusing on network and neurotransmitter function, may provide more useful results.

Results from **Chapter 2** were complemented in the first two sections of **Chapter 4**, by investigating how neuropsychiatric symptoms are distributed, and what symptom clusters may be present, in PD specifically. I found that in PD, higher sum-scores in the BDI were mainly driven by somatic symptoms such as loss of energy, fatigue, sleep disturbances, and loss of libido. In addition, symptoms related to apathy, such as loss of interest, loss of pleasure, and indecisiveness, were more common than sadness or suicidal ideation in this sample. This supports the hypothesis that PD is more often associated with symptoms of apathy rather than sad mood.

The analysis in section two of **Chapter 4** further highlighted that patients with PD experience more neuropsychiatric symptoms, both somatic and psychological, than patients with similar disability (osteoarthritis) and healthy controls. Thus, the high rates of mood symptoms in PD seem to be a result of PD-associated monoamine and basal ganglia network pathology, rather than just a secondary reaction to the PD diagnosis and associated physical impediments.

In section three of **Chapter 4**, I tested whether one potential mechanism in the development and maintenance of major depressive disorder – negative affective bias – is also found in PD. This negative attention bias may be treated with SSRIs, thereby alleviating depressive symptoms (Harmer, Goodwin, et al., 2009). In PD without depression, it was hypothesised that the same dysfunctional neural circuits that may underlie the development of apathy, are also involved in a potential facial emotion recognition impairment. Indeed, while we found no differences in FERT performance between patients with PD, patients with RBD, and healthy age-matched control participants, participants scoring higher on the Emotional Sensitivity subscale of the AMI (i.e., more emotional apathy), performed worse for disgusted and sur-

prised faces. This is consistent with the hypothesis that apathy, rather than depression, may be associated with facial emotion recognition abilities. Taken together, these results support the possibility that neuropsychiatric symptoms in PD are primary, specific features of the disease itself, with potentially underlying dopaminergic and serotonergic dysfunction (Ballanger et al., 2012; Picillo et al., 2017; Schrag et al., 2016; Ye et al., 2017).

This potential role of serotonergic dysfunction in motivation and emotion processing was examined in **Chapter 5**. Here I investigated how administration of citalopram (20mg) for seven days may affect emotion and motivation processing in twenty patients with PD. Twenty healthy controls were additionally tested without medication to assess any baseline differences between the two groups. Results indicated that PD patients were overall less motivated than controls on an effort- and reward-based decision-making task (**Figure 5.9**). On this task, citalopram increased or decreased willingness to exert effort for reward, depending on whether baseline motivation was high or low, respectively (**Figure 5.11**). This was the case especially for low effort or low reward offers.

A task assessing decision-making under risk revealed higher levels of risk aversion for potential losses in PD patients (**Figure 5.15**), which neither serotonin, nor the patient's regular dopaminergic medication seemed to restore in this study. However, citalopram in PD patients was associated with more risk-seeking choices for gains, although patients and controls did not differ on this at baseline. Citalopram also affected reaction time in a reversal learning task (**Figure 5.18**), producing faster responses that did not seem to be related to changes in reward or punishment learning rates. While PD did not differ from control on any of the facial emotion recognition measures, apathy decreased patient's confidence in their response, for all stimuli except happy expressions (**Figure 5.19**). Thus, the motivational and decision-making deficit in PD that has been reported previously (Le Heron, Plant, et al., 2018; Muhammed, Manohar, et al., 2016) could be replicated here. In addition, the results suggest that the serotonergic system influences these processes, although a potential interaction with dopaminergic baseline function and medication needs to be considered in future research.

Chapter 6 addressed whether any consistent structural brain effects across the OPDC and

UK Biobank cohorts could be observed when using the same analysis pipeline. To assess usability of the nomograms created in **Chapter 3**, hippocampal volumes from controls and PD patients in each of the cohorts were created and plotted over their corresponding norm values. In both datasets, the vast majority of cases scored within the 2.5th and 97.5th percentiles, with higher density of cases around the 50th percentiles, but also a few extreme outliers.

While there were no baseline differences in FA between patients and controls in either cohort, an association between FA and mood symptoms was found in PD and controls in the OPDC cohort (**Figure 6.5**). This result potentially supports the vascular depression theory, although no such effect was present in the UK Biobank sample. Next to white matter changes, I tested for any effects of PD on grey matter by applying VBM to structural T1-weighted images. This yielded slightly different results in the OPDC and UK Biobank samples. In the OPDC dataset, patients with PD had significantly smaller left motor cortex volumes as compared to healthy controls (**Figure 6.6**). However, in the UK Biobank, PD was associated with smaller grey matter volumes in the parahippocampal/fusiform gyrus, precuneus cortex, and inferior/middle temporal gyrus (**Figure 6.7**).

Finally, in addition to TBSS and VBM, IDP estimates were compared between the groups, too. The IDPs included a variety of grey matter volumes summarised over atlas-based partial brain regions, as well as FA summarised over atlas-based white matter tract parcellations. In contrast to voxel-wise and cluster-enhanced signals from the TBSS and VBM analyses, IDPs average signals across a region of interest. Since running TBSS and VBM is time-intensive and requires expert knowledge, IDPs may offer a simpler solution to testing for structural brain changes. However, analysing IDPs resulted in a larger number of significantly different areas for both grey and white matter between PD patients and controls than what was found in TBSS and VBM, with only limited overlap. Generally, the results of this chapter indicated limited overlap between the two cohorts. Since the data were analysed using the same processing pipelines (except for diffusion-weighted image preprocessing), this lack of cohesion suggests a sensitivity of these methods to subtle differences in patient cohorts, which may be overrepresented in the literature due to publication bias.

7.2 Methodological considerations

7.2.1 The Big Data conundrum in clinical research

Significant outcomes from analyses using the large dataset from the UK Biobank in **Chapters 3 & 6**, for example when testing for associations between IDP estimates and mood symptoms, proved difficult to interpret for several reasons.

First, with a sample size large enough, even *very* small, clinically insignificant effects will appear significant using traditional null-hypothesis testing, because the strength of the p-value is directly related to the sample size (Thiese et al., 2016). For example, Miller et al. (2016) found significant canonical correlations between several resting state, grey matter, and white matter IDPs with dietary information such as “dried fruit intake” or “yoghurt intake”. It is of course possible that there truly exists a link between these, but whether they may have any real-life consequence needs to be critically assessed. Similarly, in this thesis, I found several statistically significant associations with small effect sizes and questionable clinical significance, such as larger right precuneus volume in people who reported being sensitive.

Second, even a large sample may be unrepresentative of the population which it was aimed at. For example, it has been suggested that due to sampling bias, participants within the UK Biobank are more educated, healthier, and less commonly smokers than what would be expected in the general population (Fry et al., 2017). However, as big data like in the UK Biobank are often viewed as representing the most accurate picture, this bias can have unfortunate consequences when it is being overlooked. For example, in **Chapter 3** I noted that out of a number of brain areas, only the hippocampus and parahippocampal gyrus appeared to have a strong non-linear age-related volume loss, suggesting that these two regions should be paid special attention to in future research. However, since the UK Biobank sample is unusually healthy, it is possible that other brain areas would have emerged in a more representative sample. Thus, if these results were to be used for the development of new clinical guidelines, such as the tracking of hippocampal volumes over age in people at risk for dementia, these may only serve those who fit the demographics within the UK Biobank dataset.

Third, in the case of the UK Biobank dataset analysed here, each participant had about 14,000 unique variables of information. This included hundreds of IDPs, but also vast amounts of questionnaire responses regarding lifestyle, environment, nutrition, mental health, and more. While this seems a luxury, having too many options is challenging and holds potential for bad scientific practices, such as p-hacking. Even when correcting for multiple testing, blindly testing for any possible association between this many variables will result in larger amounts of false positives than in smaller samples (Kaplan et al., 2014). To prevent this, I selected a limited subset of variables for each analysis, for example including only mental health questionnaire items related to depression, anxiety, and apathy, but not psychosis or addiction. Yet, because even small differences in large datasets are more likely to be statistically significant, this practice in turn may lead to a confirmation bias in the reported findings.

However, despite these challenges, the analyses presented here produced findings of a selective vulnerability of the hippocampus in ageing, a general increase in emotion well-being in ageing, and distinct neuropsychiatric symptom profiles in PD, all of which may not have been discovered with a small, underpowered sample. The need for large sample sizes has also become apparent very recently with the roll-out of COVID-19 vaccines. While numerous large clinical trials with tens of thousands of participants were powerful enough to assess the general safety and efficacy of the vaccines, only with much more data available, from hundreds of thousands to millions of people, have some extremely rare side effects been detected (Greinacher et al., 2021; Schultz et al., 2021).

7.2.2 New avenues for neuroimaging in PD

The analysis of neuroimaging data in groups of PD patients and healthy controls was not a novel one. Many previous studies have tested for differences in structural brain measures between these groups, in the hope to find neuroimaging-based biomarkers for PD (Guimarães et al., 2018; Lanskey et al., 2018; Li et al., 2017; Rosenberg-Katz et al., 2016; Sarasso et al., 2020; Zeighami et al., 2015). However, the results from these investigations have been highly variable, which informed the attempt at a replication of previous results across two datasets from the OPDC and UK Biobank that is presented in **Chapter 6**. Indeed, I could neither replicate effects from previous analyses, nor between the two cohorts, and associations with mood

symptoms were uninformative. One conclusion that follows could be that PD is generally not associated with pronounced structural effects in the brain, and that published reports of such effects are representing false positives and small cohort effects. This lack of structural brain findings in PD is interesting especially when considered in the larger context of neurodegeneration, where dementia – such as AD (Leung et al., 2013; Lo et al., 2011) – show strong structural effects on the brain. An example for a powerful neuroimaging marker in AD is of course hippocampal volume loss (Teipel et al., 2017), which was also covered in **Chapter 3**. In Frontotemporal dementia, assessing typical structural neuroimaging signs of atrophy in the frontal lobe are also already part of the diagnostic process (Piguet et al., 2011). Thus, while memory or behavioural impairments in dementia may be more closely tied to individual structures such as the hippocampus or frontal lobes, motor and non-motor symptoms in PD may be related to damage across wider neurotransmitter systems (Ji et al., 2018; Muñoz et al., 2020). As a result, conventional structural MRI techniques and analyses may not be suited to detect these effects. Instead, novel data-driven and multimodal approaches look promising (Cope et al., 2021).

For example, a relatively new MRI technique called Quantitative Susceptibility Mapping (QSM) is receiving increasing attention for research in PD. Using QSM, researchers can measure the level of deposition of magnetic substances, such as iron or calcium, in the brain (Thomas et al., 2020), which can indicate microbleeds or tissue changes (Haacke et al., 2015). In PD, levels of brain tissue iron have already been repeatedly linked to cognitive decline and striatal innervation (Wang et al., 2021), and cooccurs with amyloid and tau pathology (Thomas et al., 2020).

Apart from covert functional brain changes, a strong influence of individual differences in terms of environmental factors on behaviour may also play a role in the lack of coherent neuroimaging markers in PD and pathological ageing in general. In fact, only about 25% of variation in ageing seems to be explained by genetic information, leaving 75% to other, potentially environmental factors (Kirkwood, 2003). With increasing availability of big data, some researchers are now using machine learning approaches to find data-driven progression or diagnostic patterns that can take into account both neuroimaging and other environmental

variables (Oxtoby et al., 2017; Verdi et al., 2021). For instance, a recent report suggested building an AD disease progression model using temporally continuous self-modelling regression with a number of different variables, such as CSF measures, FDG-PET, brain volume, and cognitive test outcomes (Oxtoby et al., 2017). If such a model performs well enough, it may then be used to predict a new patient's disease stage based on their own data (Oxtoby et al., 2017). A similar approach was taken for a model of progression in PD, including variables spanning structural and diffusion imaging, QSM, vision tests, and cognitive function (Oxtoby et al., 2021). Thus, paired with the increasing availability of big data and machine learning, it may be possible to translate these methods into a precision-medicine approach in the near future (Verdi et al., 2021).

7.2.3 The value in behavioural paradigms

Although big data analyses may uncover some new neuroimaging findings not previously reported, well-designed behavioural paradigms should not be undervalued (Niv, 2020). One example of how behavioural paradigms can shed light on neural processes is the discovery of classical conditioning and prediction errors (Niv, 2020). Kamin (1967) first demonstrated that animals could learn the association between a reward (e.g., food), and a stimulus (e.g., a light), but did not learn the association between the reward and a second stimulus (e.g., a tone), if the first is sufficient to predict the outcome. This informed the understanding of prediction error and its association with phasic dopamine signals (Niv, 2020; Schultz et al., 1997). Now, many years later, other behavioural tasks that are based on the current understanding of reward processing are being used in decision-making research (Bonnelle et al., 2015; Le Heron, Holroyd, et al., 2018). In **Chapter 5**, several such paradigms were tested in relation to serotonergic modulation in PD, the results of which have implications for the design of future neuroimaging studies. For example, the interaction between citalopram treatment and baseline motivation on performance on the *Apples* task hints at a dopaminergic involvement. This hypothesis of course will need to be tested using neuroimaging, such as SPECT or PET in future research. Thus, a combination of neuroimaging with behavioural assessments that operationalise complex behaviours into individual cognitive processes may be especially useful for attempts at understanding heterogeneous syndromes like depression, or complicated

disorders like PD.

7.3 How can the study of neuropsychiatric symptoms advance our understanding of neurodegeneration?

Investigating specific brain processes is also important for the characterisation of neuropsychiatric symptoms in PD. In this thesis, a key focus was on apathy and depression, due to their high prevalence and likely connection to primary PD pathology. As discussed in previous chapters, there is growing evidence that apathy and depression are distinct syndromes that can exist independently of each other, but with overlapping symptoms. Breaking down these individual symptoms into their underlying cognitive mechanisms and relating these to potentially separate neural correlates may help further disentangle these two syndromes.

For example, apathy appears to be particularly common in PD and has been linked to underlying dopaminergic and serotonergic dysfunction as well as anterior cingulate cortex-VTA connections (Kirsch-Darrow et al., 2017). In contrast, core depression may be less common than previously thought (Kirsch-Darrow et al., 2006), and while the literature on neuroimaging correlates of depression in PD is less clear, dysfunction in the orbitofrontal cortex has been commonly reported (Thobois et al., 2017). In this context, orbitofrontal cortex function has been related to reward-processing and control of goal-directed behaviour (Schultz et al., 2000). Since these cognitive mechanisms have been linked to both apathy and depression (Le Heron, Holroyd, et al., 2018; Ubl et al., 2015), more research is needed to understand which components of dysfunctional reward processing may be involved in each symptom, and how they relate to PD pathology. Some evidence for different mechanisms underlying apathy and depression also emerged from **Chapter 5**, where serotonergic modulation in PD seemed to have affected decision-making processes associated with apathy, but not emotion processing normally associated with depression.

Considering individual neuropsychiatric symptoms and their neural mechanisms may also be useful beyond research in PD, and facilitate correct distinctions between different types of neurodegeneration. It has previously been suggested that similar to the high rates of apa-

thy in PD, other symptoms like anhedonia may be more common in some forms of dementia (Shaw et al., 2021). Anhedonia is a cardinal symptom of major depressive disorder and is usually defined as a loss of pleasure in previously rewarding activities (Der-Avakian et al., 2011; Dichter, 2010; Husain et al., 2018). It overlaps with apathy in that it can involve a lack of interest in pursuing previously pleasurable goals, but unlike isolated apathy, it also blunts the experience of pleasure once an activity has been initiated (Husain et al., 2018). A recent report suggested that in Frontotemporal dementia, what is often diagnosed as apathy may in fact be anhedonia as the loss of motivation was often also comorbid with loss of hedonic tone (Shaw et al., 2021). In contrast, this was not the case in AD. In this study, anhedonia and apathy were further associated with different neural correlates. While anhedonia was linked to reduced grey matter volume in mesocorticolimbic circuits that are known for their involvement in feelings of pleasure, apathy was associated with areas involved in decision-making and reward processing, such as the anterior cingulate cortices or orbitofrontal areas. However, it is not yet clear what role these areas play in the primary pathology of Frontotemporal dementia, or how damage to these areas might progress. In addition, Frontotemporal dementia has also been linked to widespread white matter deterioration (Coloigner et al., 2019; Yang et al., 2017), which may also impact the development of neuropsychiatric symptoms, such as vascular depression (Valkanova et al., 2013). Thus, understanding these nuances is important to inform studies of neurodegenerative disease progression and treatment avenues.

7.4 When does healthy ageing become pathological?

One objective of this thesis was to contribute to the understanding of mood and brain changes in healthy ageing, and how it differs from neurodegeneration, such as PD. It is currently estimated that neurodegenerative processes that diverge from normal ageing trajectories initiate years before a diagnosis is made, but it is not clear when and where to draw the line between healthy and pathological ageing (Dubois et al., 2016; Schapira et al., 2017). After all, age is the biggest risk factor for neurodegeneration (Hou et al., 2019), occurring simultaneously for those affected.

In **Chapter 3**, I showed that the hippocampus seemed to have a specific vulnerability to age-

ing, with accelerated volume loss around the 5th and 6th decades of life. Since hippocampal atrophy has been identified as a potential biomarker for AD, this might suggest that AD represents accelerated ageing to the hippocampus that is already visible to a smaller extent in healthy ageing. In addition, hippocampal volume loss is correlated with the extent of AD-related pathology, such as amyloid or tau depositions (Schuff et al., 2009). Thus, tracking individual's hippocampal volumes and comparing them to age-adjusted norm values may facilitate earlier diagnosis of neurodegeneration. However, these associations cannot predict the presence of AD perfectly. Some older people without any cognitive decline were found to have signs of AD-pathology, while others with cognitive decline were not (Hedden et al., 2016; Murray et al., 2014). Again, an explanation for this may be found in the 75% of variation between ageing adults not explained by genetics (Kirkwood, 2003). What causes earlier age of onset of neurodegeneration in some people may be due to the accelerating effects of a complex interaction between genes and environment on normal ageing processes. Even in absence of neurodegeneration, these normal ageing processes are estimated to increase an individual's risk of dementia to virtually 100% by the (for now) hypothetical age of 130 years (Terry et al., 2001),

I also suggested that while cognitive changes with age have received much attention in research, tracking the effects of age on mood and neuropsychiatric symptoms may prove equally useful, especially in the case of early PD diagnoses. In the analysis in **Chapter 2**, I found evidence for the hypothesised positivity effect in older age, with continuous improvements in mood, happiness, and neuropsychiatric symptoms in healthy older adults, but also older adults with formal psychiatric diagnoses. In addition, some results also supported the idea for a vascular type of depression, stating that older adults who acquire white matter damage with age may be at higher risk for depression (der Kooy et al., 2007). In PD however, neuropsychiatric symptom profiles seemed to be qualitatively, not just quantitatively, different from those healthy controls. Especially the presence of a lack of pleasure or interest seemed to distinguish the group of PD patients from people without PD. Together with findings on the involvement of serotonin in neuropsychiatric symptoms in PD from previous investigations and **Chapter 5**, this suggests that changes in mood in PD could be directly associated with specific PD-related pathology. Although some decline in neurotransmitter function too

is normal in healthy ageing (Karrer et al., 2017), the specific loss of dopaminergic and serotonergic receptors may explain these qualitatively different mood symptom profiles in PD (Fox et al., 2009; Politis et al., 2010). This can have important implications for treatment, especially as the main medication for depression, SSRIs, may have some complex effects when interacting with a dysfunctional dopaminergic system in PD (Fischer et al., 2017).

As already touched on, there are many aspects that influence the trajectory of healthy and pathological ageing not discussed here, especially those relating to environmental factors. For example, increased risk for PD has been linked to exposure to toxins such as heavy metals, paint fumes, or pesticides (Ascherio et al., 2016; de Lau et al., 2006; Lock et al., 2013). Reduced risk on the other hand may be associated with physical activity, caffeine intake, and even smoking (Ascherio et al., 2016). In addition, traumatic brain injury seems to have a strong link with future neurodegeneration, such as development of parkinsonism (Acosta et al., 2015; Wong et al., 2013) or dementia (Gardner et al., 2014).

7.5 Conclusion

In summary, this thesis provided evidence for:

- (A) A general improvement of mood and neuropsychiatric symptoms in healthy ageing
- (B) A selective vulnerability of the hippocampus to ageing, even in healthy older adults
- (C) Specific neuropsychiatric symptoms as direct effects of PD-related pathology
- (D) A role for serotonin in dysfunctional decision-making in PD
- (E) Large variability in structural neuroimaging features in PD patients

Although new developments in neuroimaging may still produce robust biomarkers for PD and for neuropsychiatric symptoms with, future research in specific patient groups should continue to utilise behavioural paradigms. This may improve confidence in potential correlations and allow for faster translation to clinical practice (Niv, 2020). In addition, focusing on more detailed estimations of the severity, rather than estimating just the presence of neu-

ropsychiatric symptoms, may be useful for future investigations. Finally, with the further development of very large datasets like the UK Biobank, small effects on the brain may be identified using neuroimaging in combination with improved quality control practices.

Appendix A

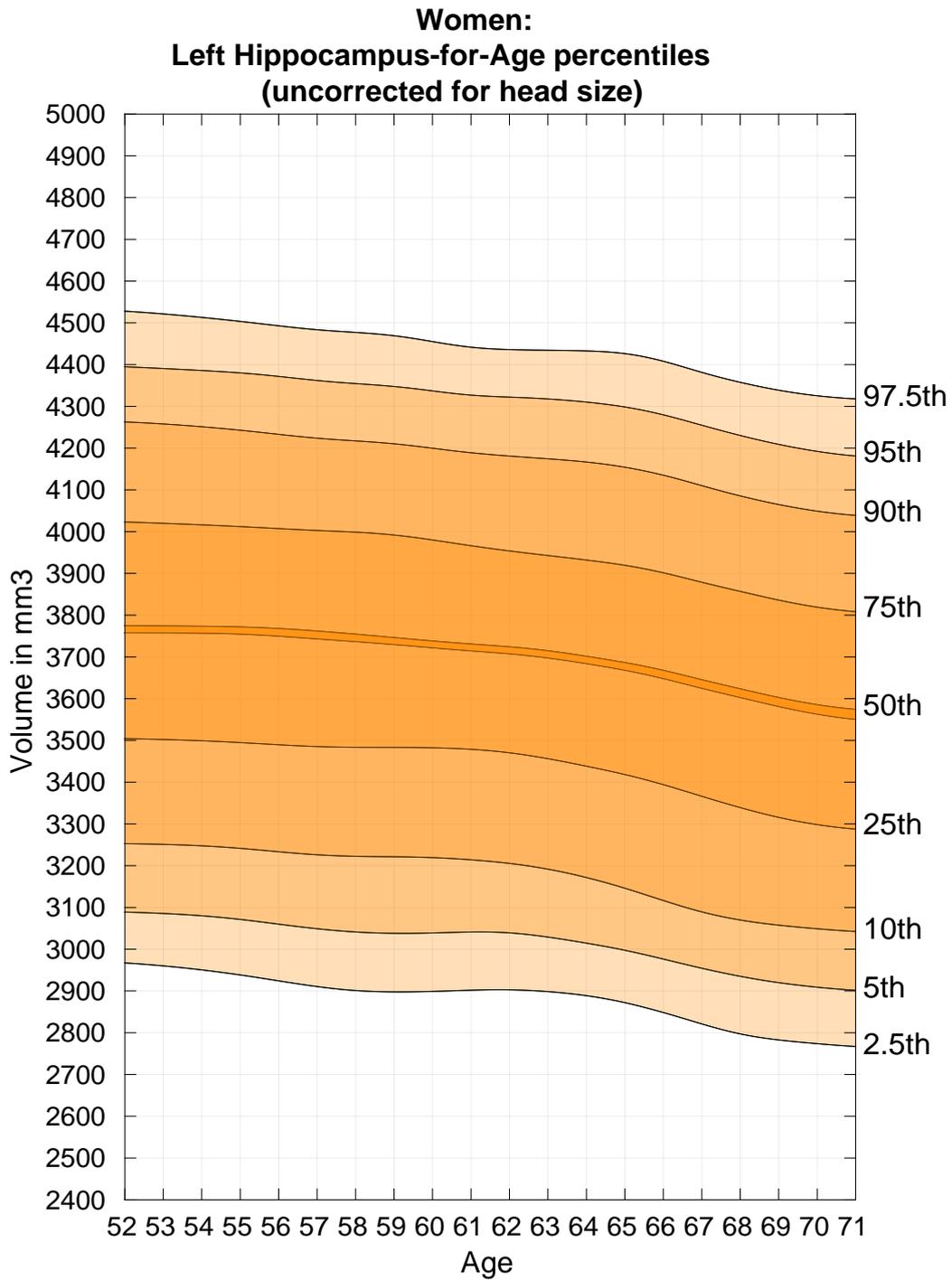


Figure A.1 – Nomogram of left hippocampus for women, uncorrected for head size

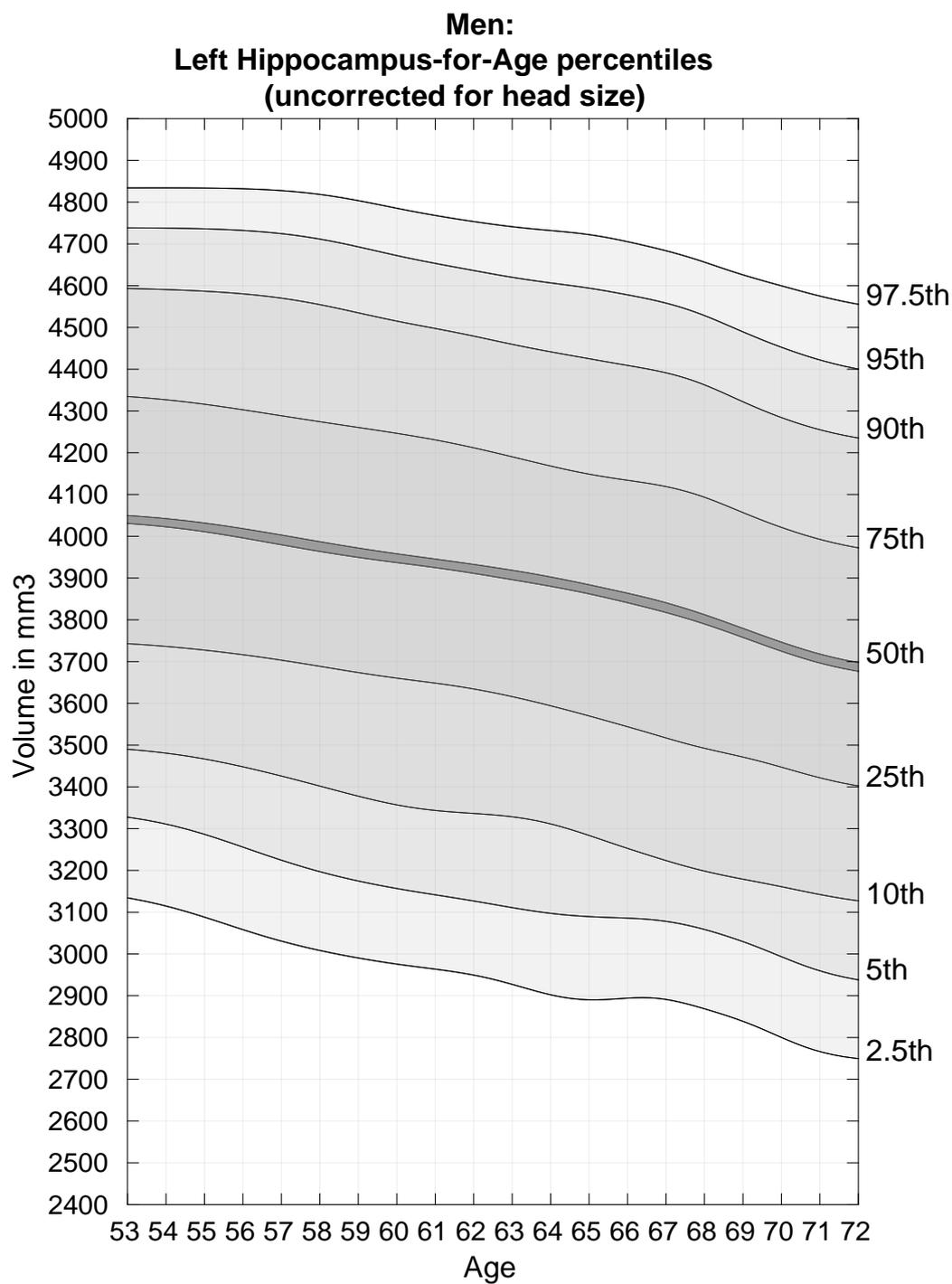


Figure A.2 – Nomogram of left hippocampus for men, uncorrected for head size

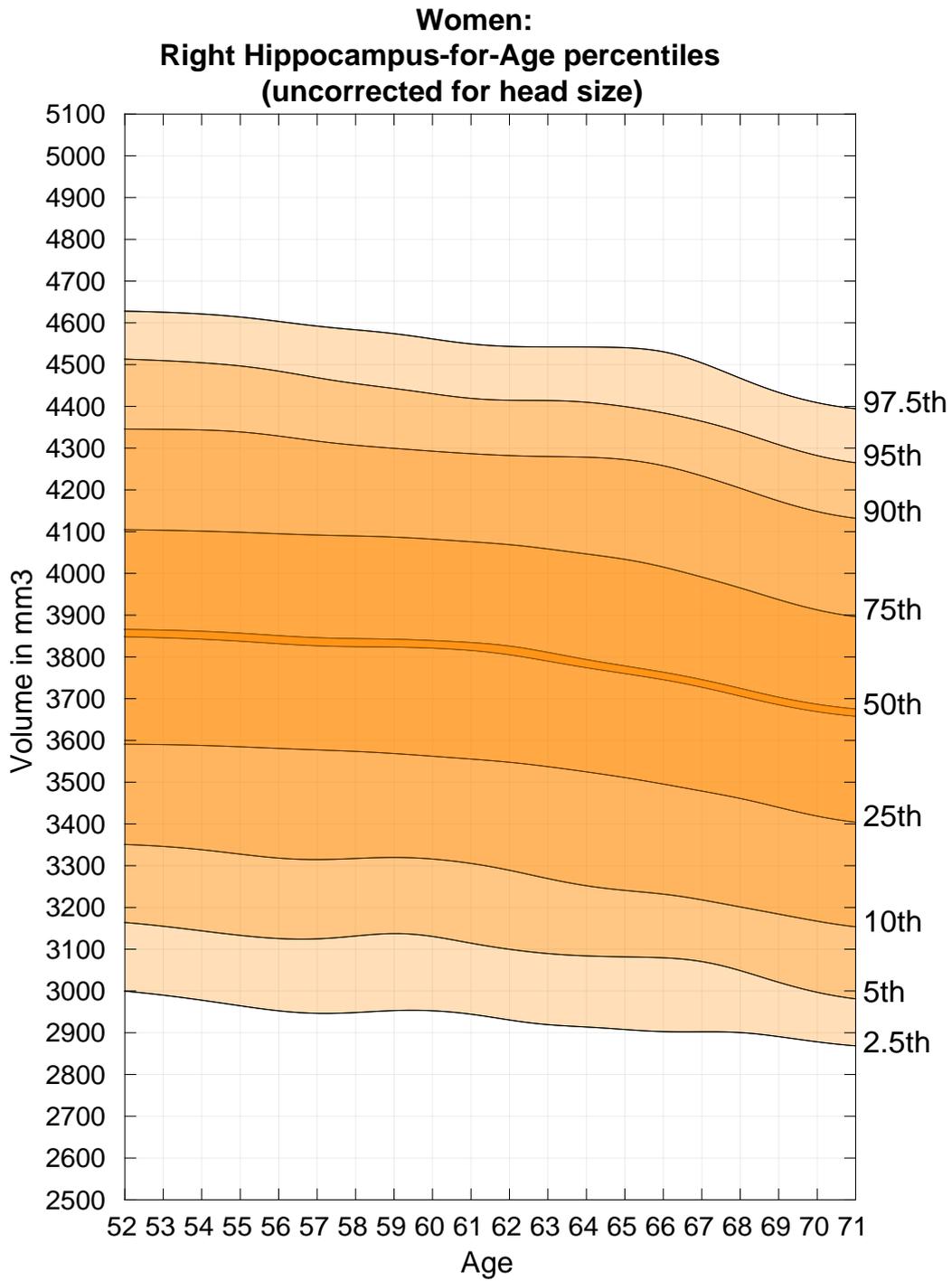


Figure A.3 – Nomogram of right hippocampus for women, uncorrected for head size

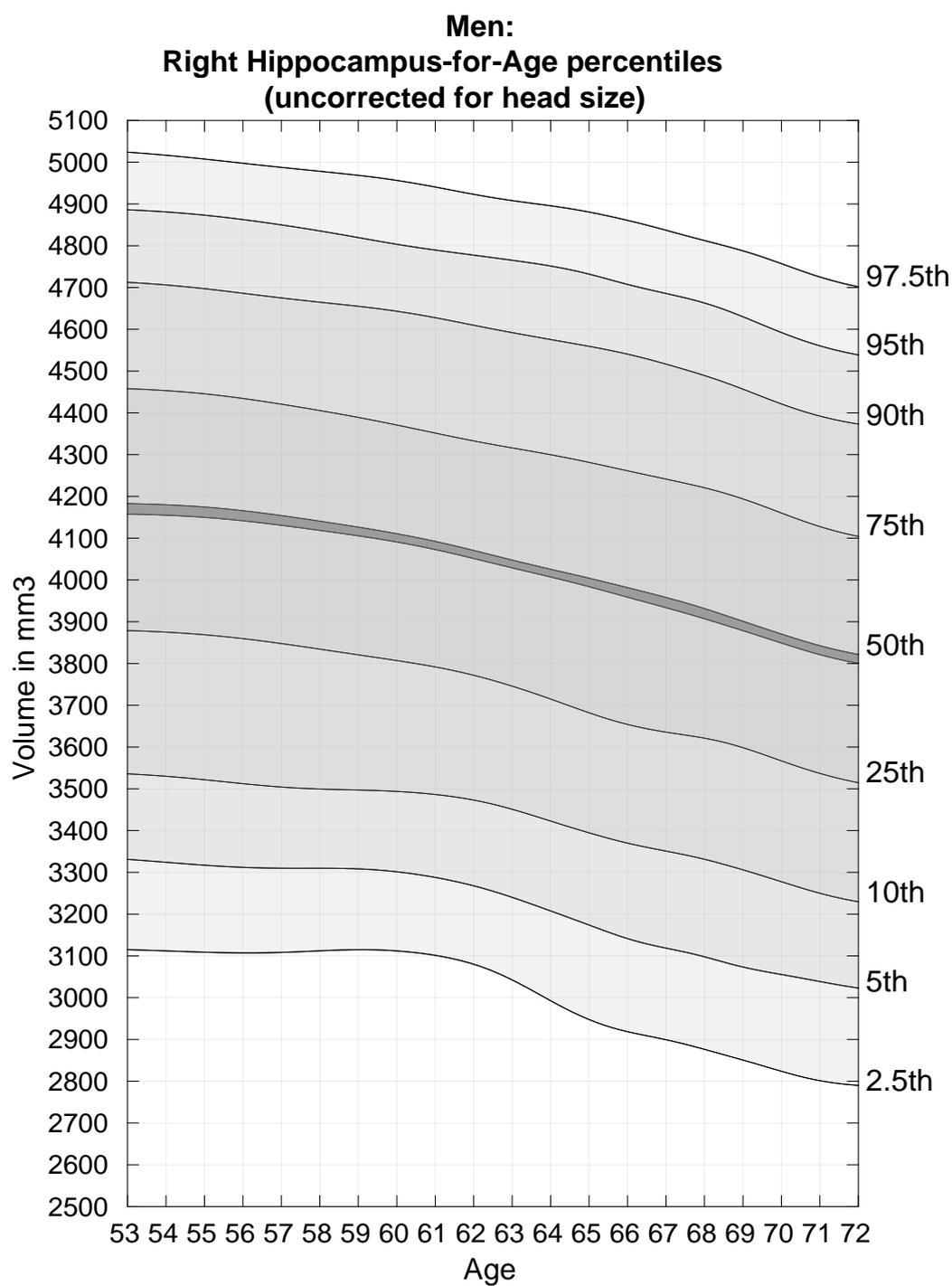


Figure A.4 – Nomogram of right hippocampus for men, uncorrected for head size

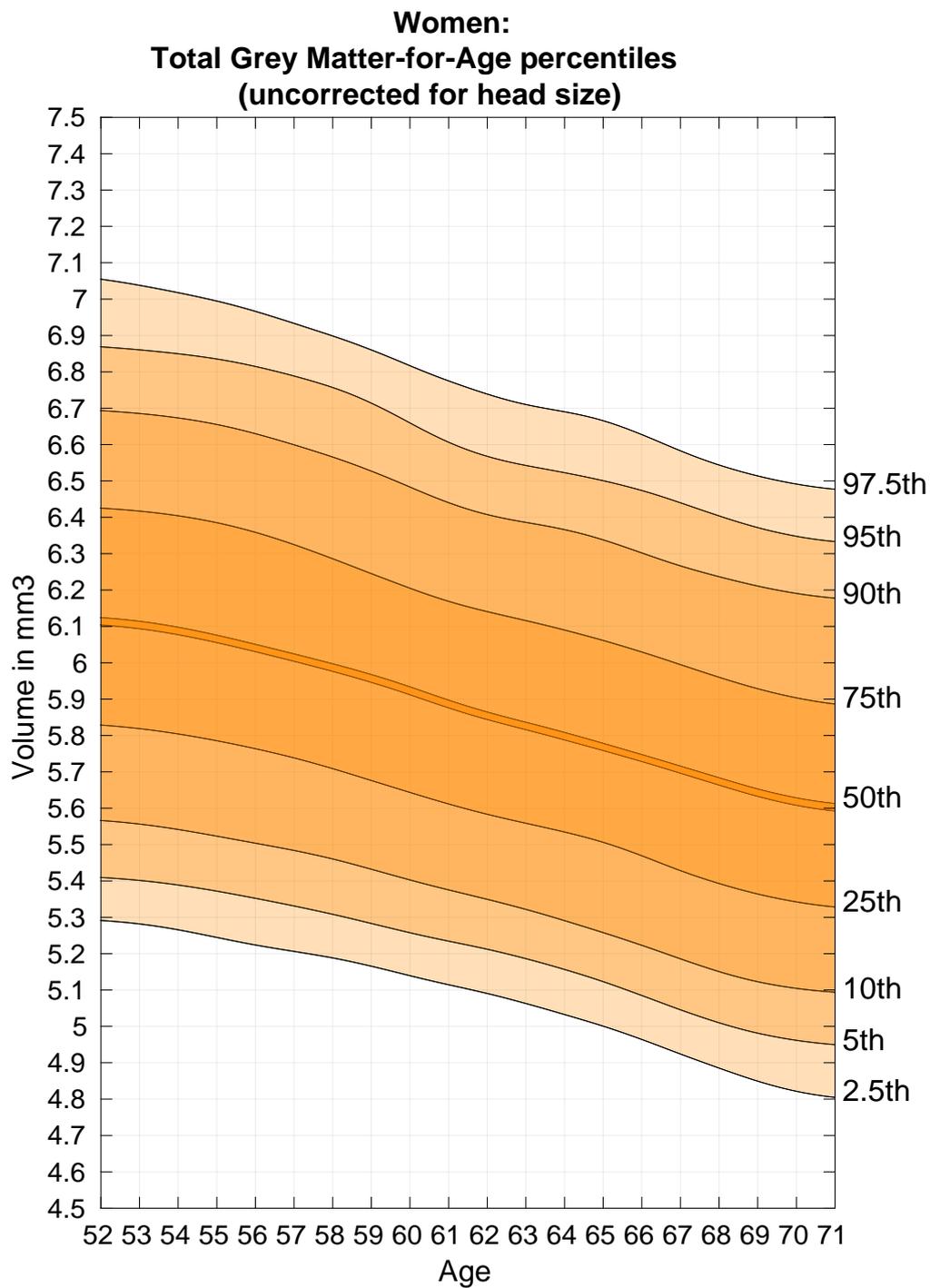


Figure A.5 – Nomogram of total grey matters for women, uncorrected for head size

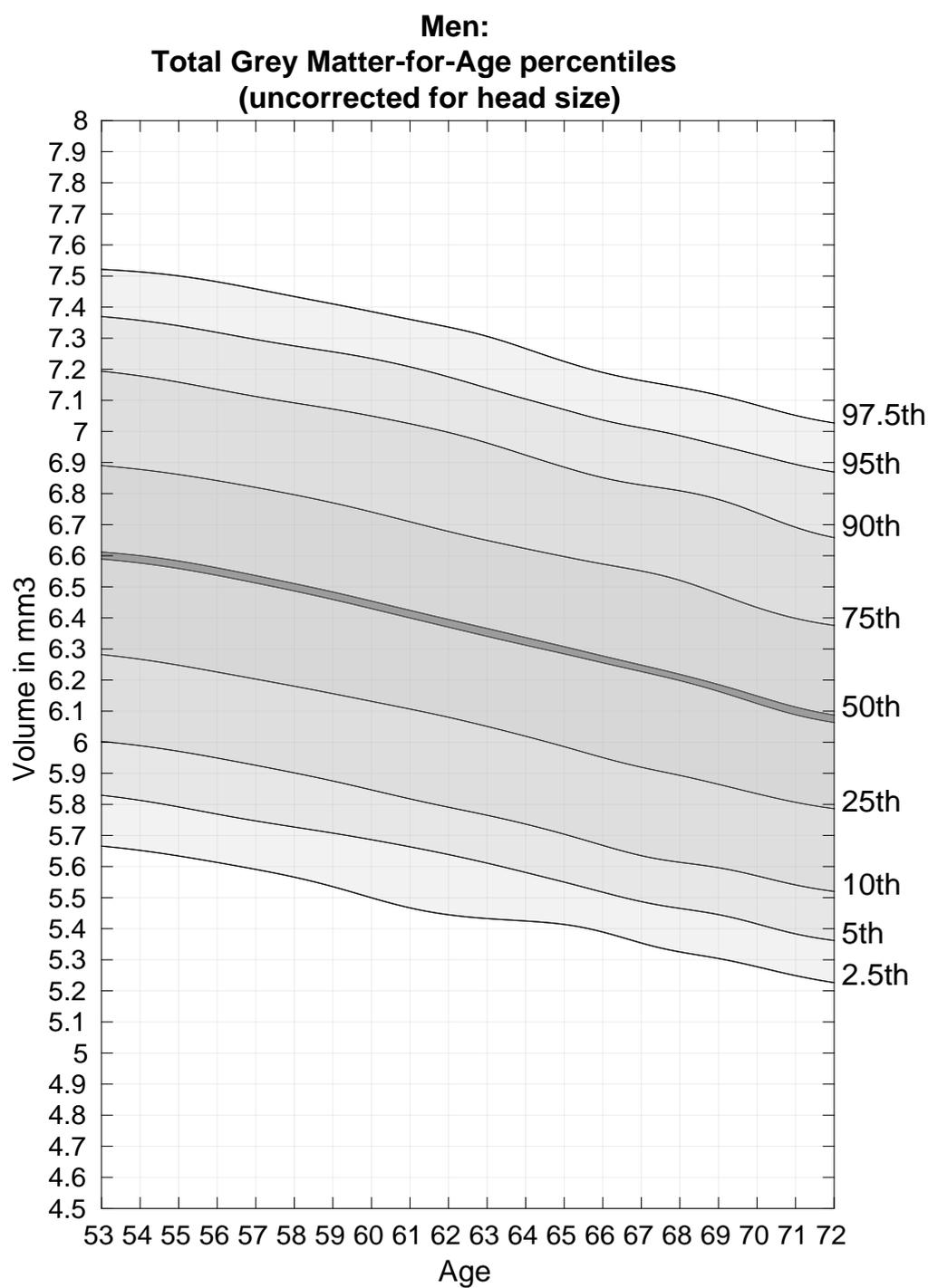


Figure A.6 – Nomogram of total grey matter for men, uncorrected for head size

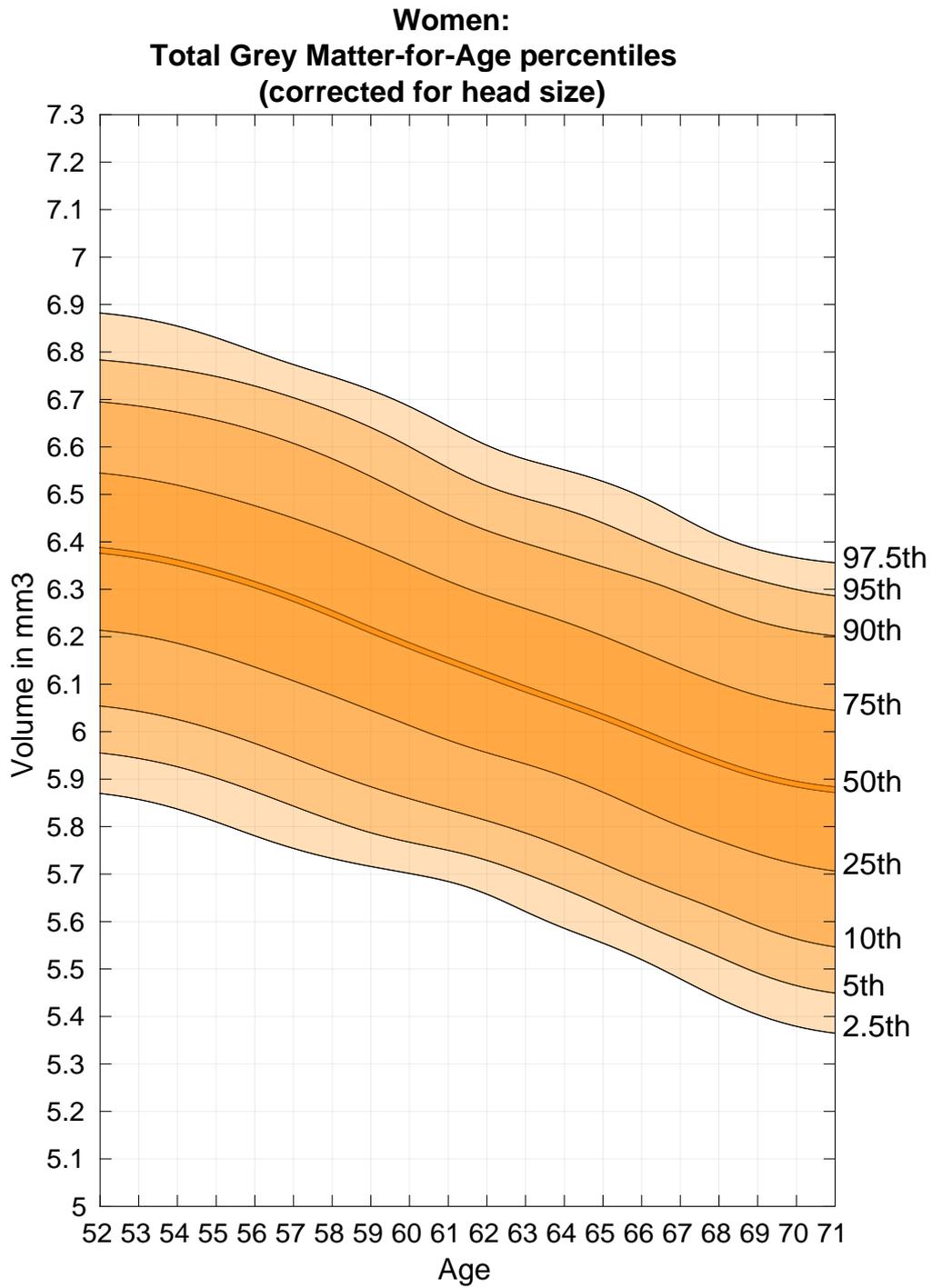


Figure A.7 – Nomogram of total grey matters for women, corrected for head size

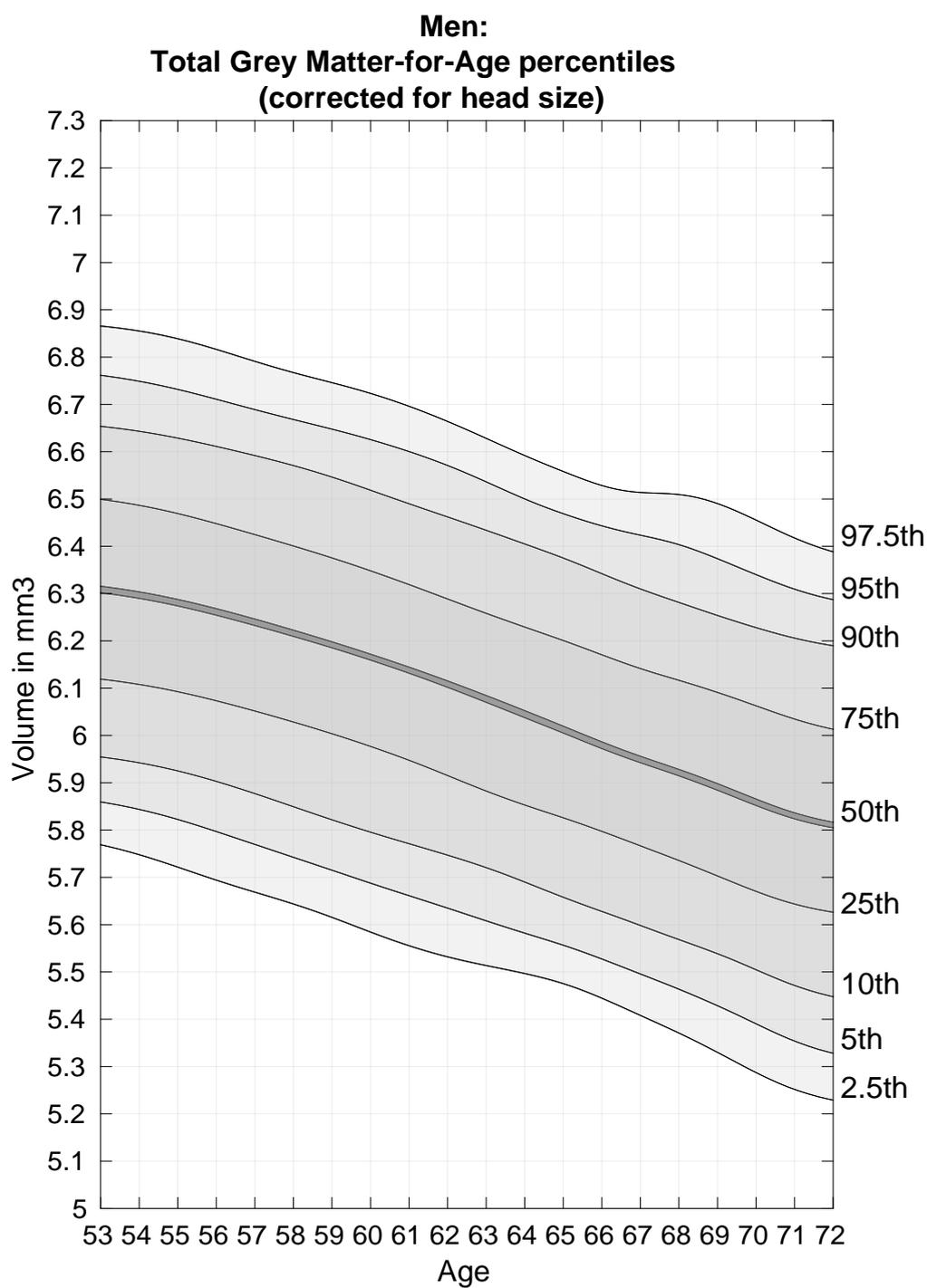


Figure A.8 – Nomogram of total grey matter for men, corrected for head size

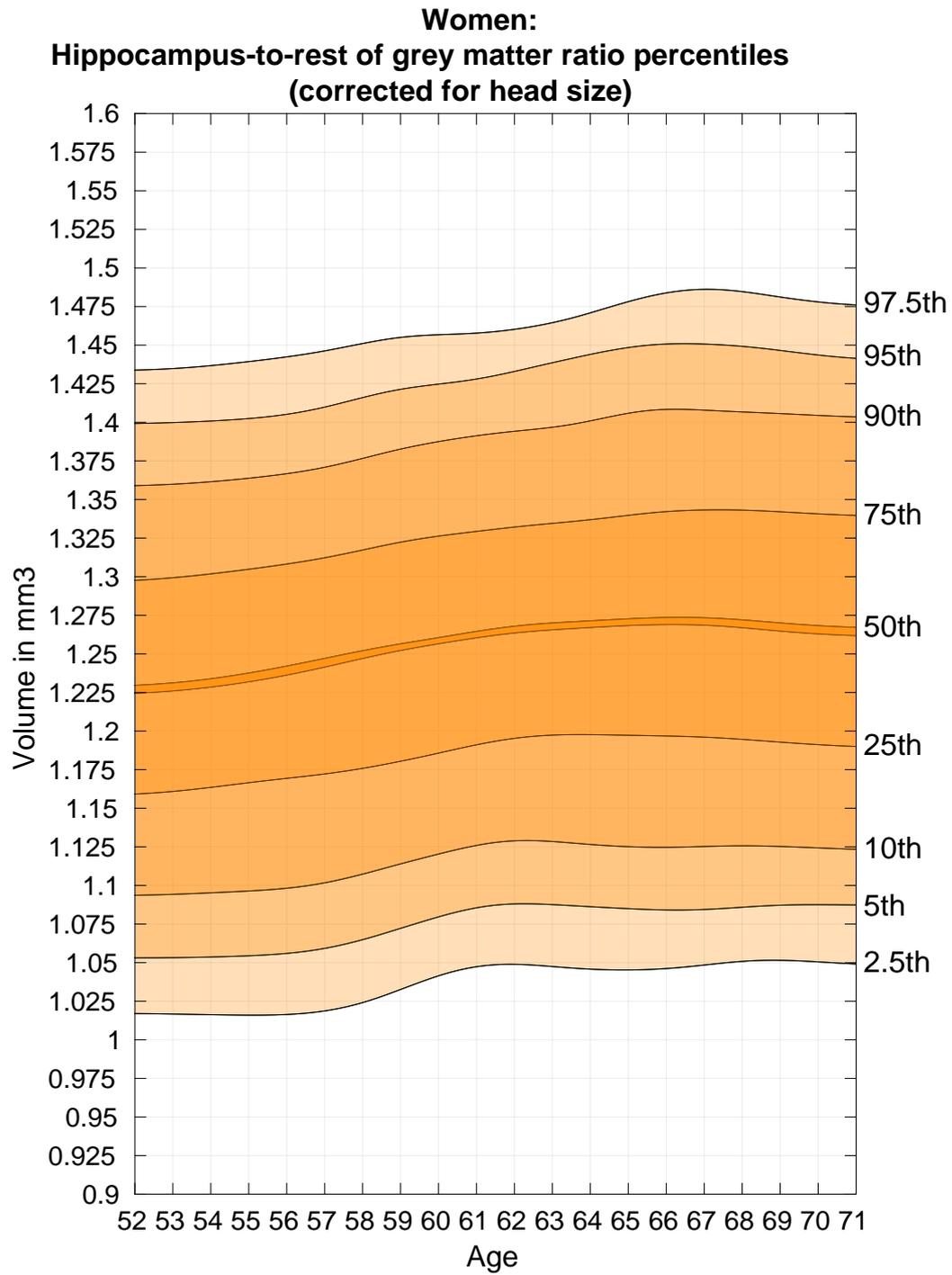


Figure A.9 – Nomogram of hippocampus-to-total grey matter ratio for women, corrected for head size

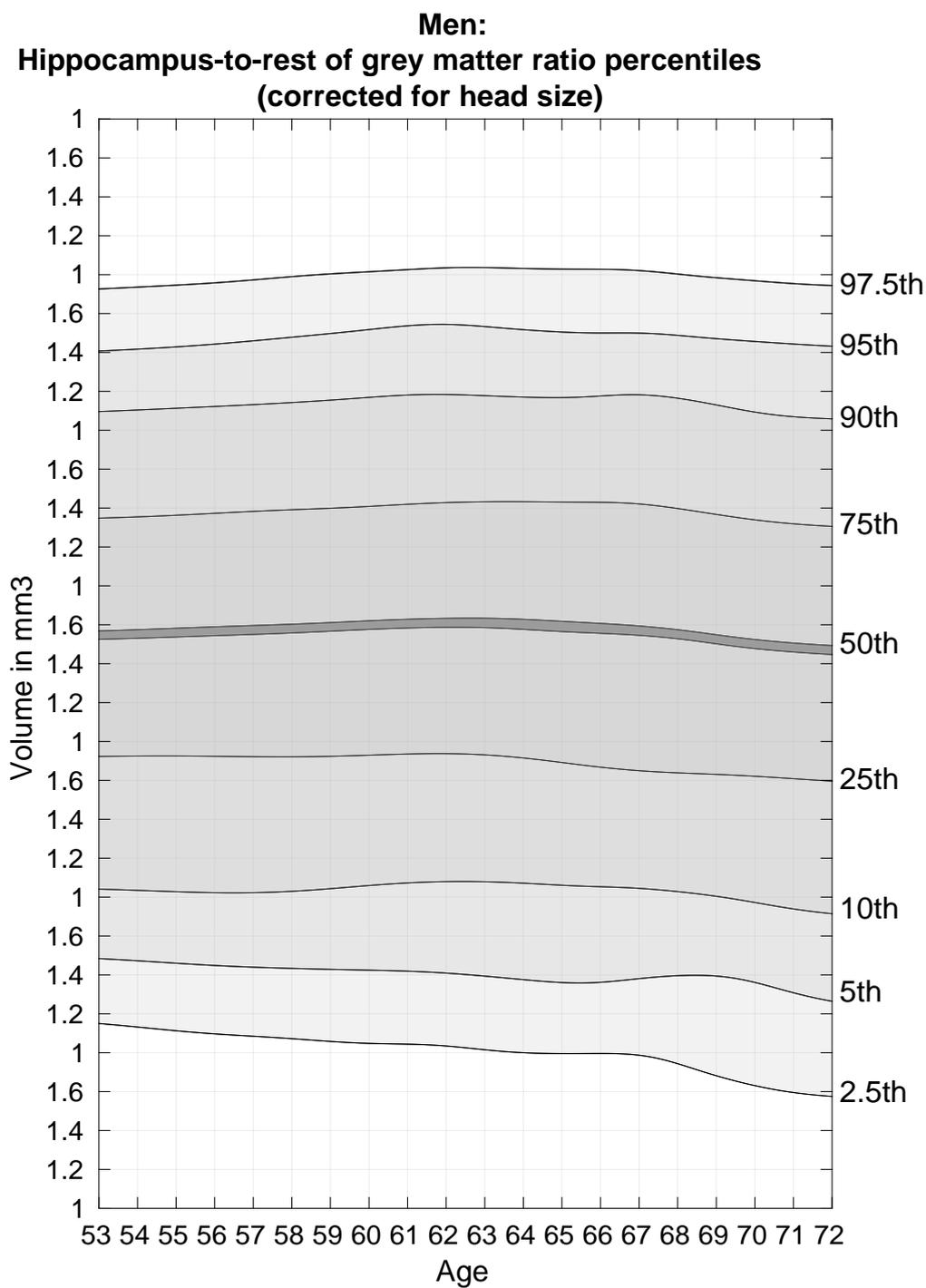


Figure A.10 – Nomogram of hippocampus-to-total grey matter ratio for men, corrected for head size

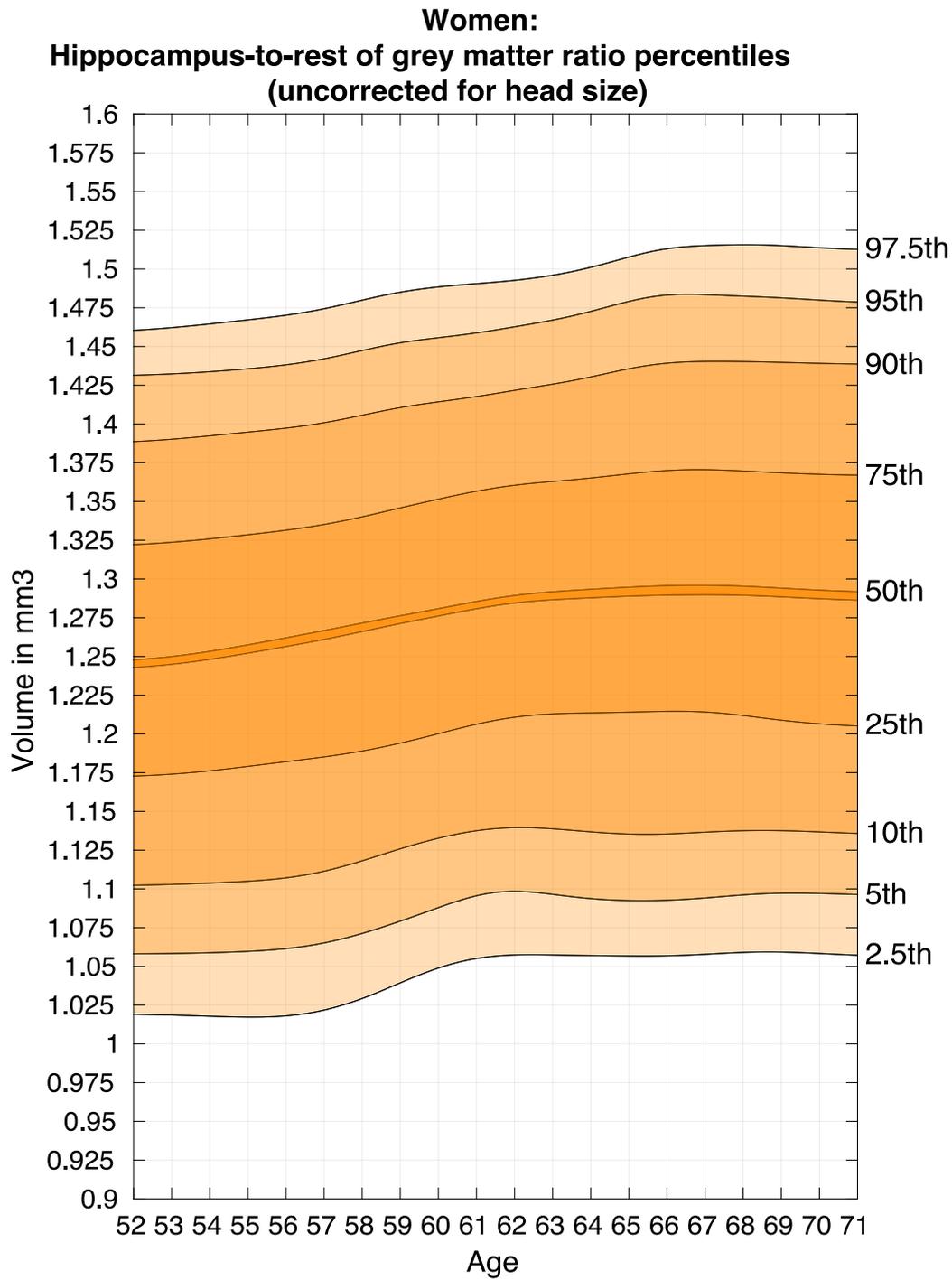


Figure A.11 – Nomogram of hippocampus-to-total grey matter ratio for women, uncorrected for head size

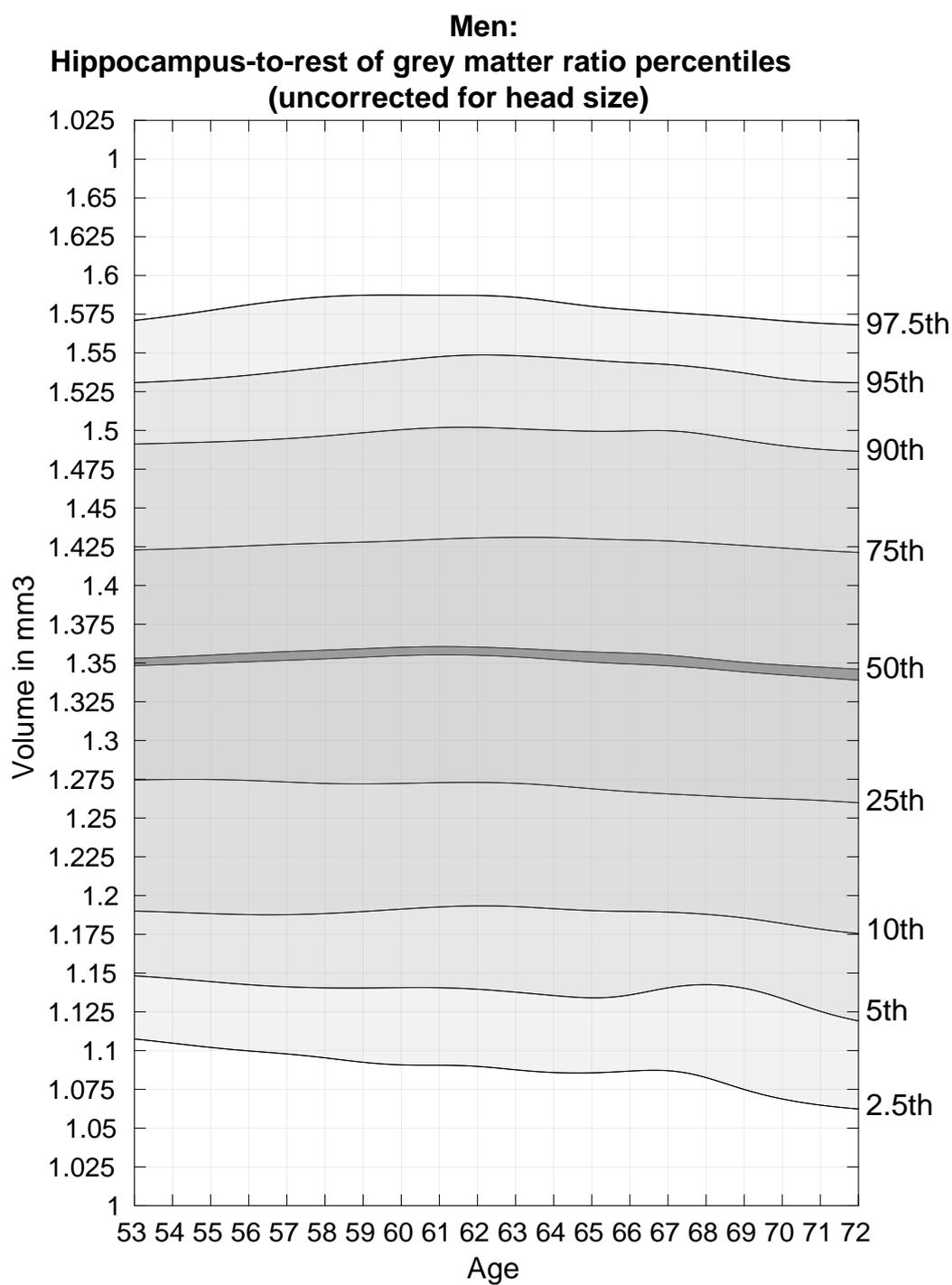


Figure A.12 – Nomogram of hippocampus-to-total grey matter ratio for men, uncorrected for head size

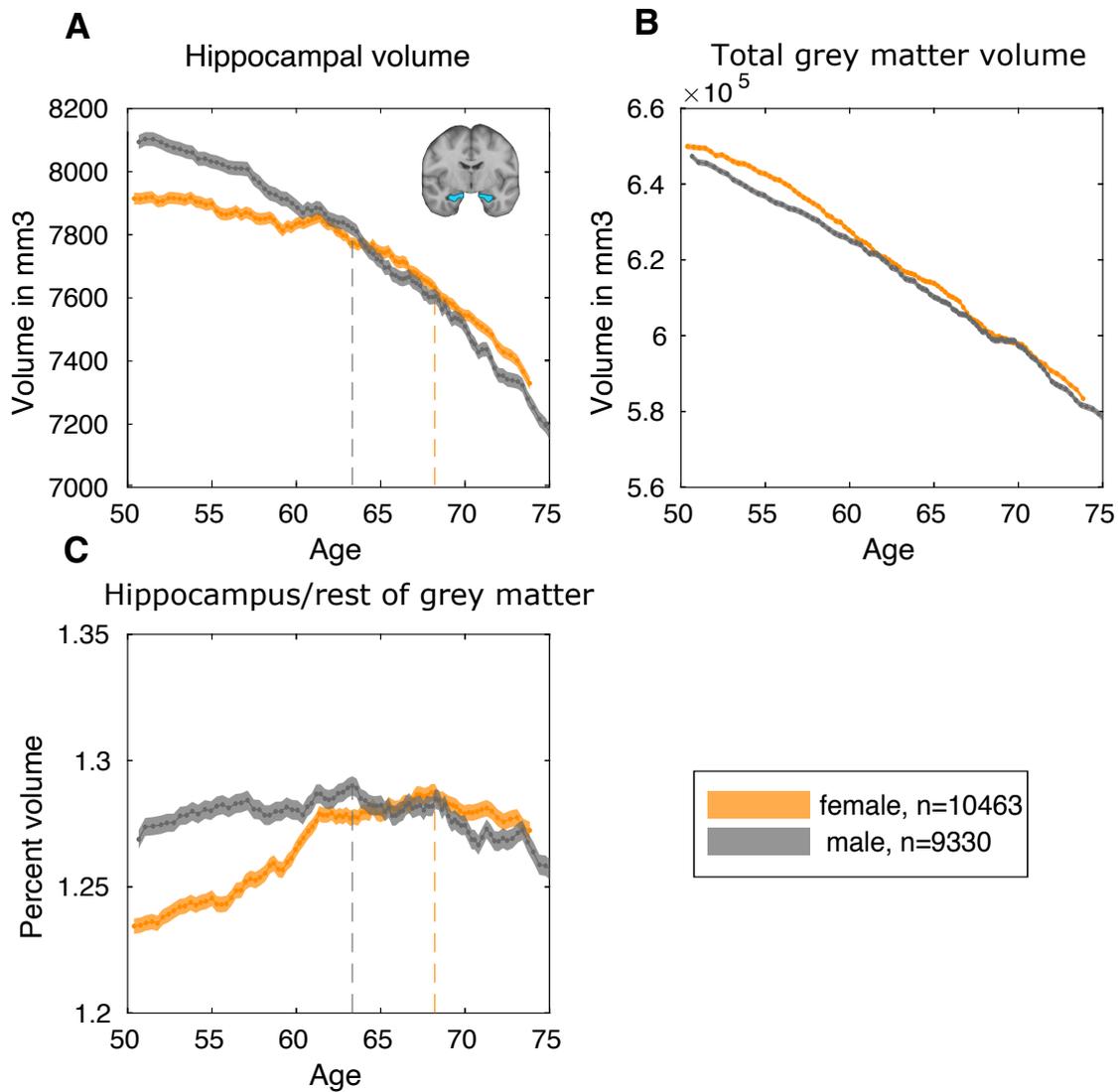


Figure A.13 – Sliding-window curves for hippocampus without smoothing. Dashed lines indicate points of maximum ratio. **A.** Mean bilateral hippocampal volume including standard errors as a function of age, corrected for head size. **B.** Mean total grey matter volume including standard errors as a function of age, corrected for head size. **C.** Mean hippocampal volume to rest of grey matter ratio including standard errors as a function of age.

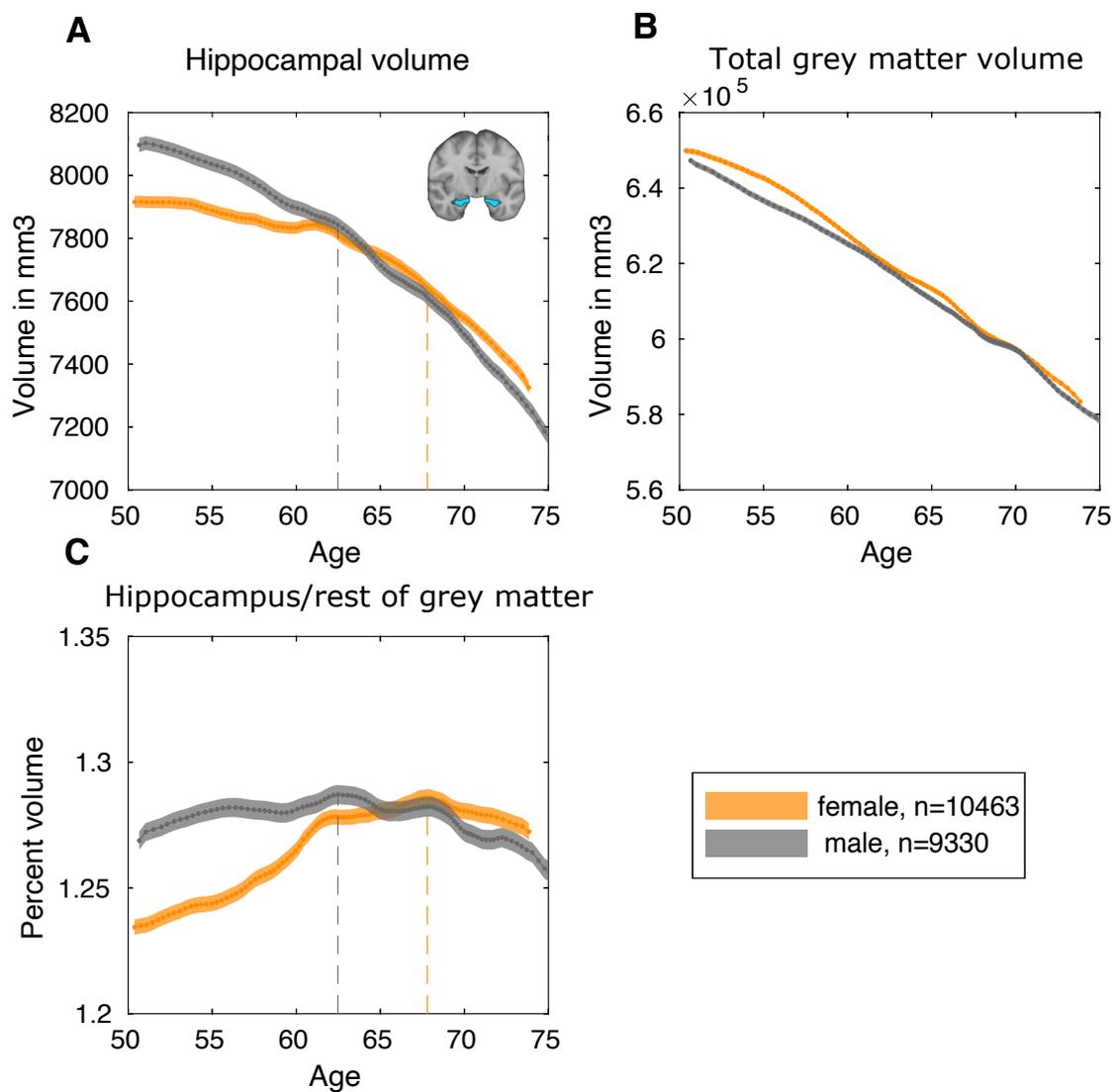


Figure A.14 – Sliding-window curves for hippocampus with smoothing kernel 10. Dashed lines indicate points of maximum ratio. **A.** Mean bilateral hippocampal volume including standard errors as a function of age, corrected for head size. **B.** Mean total grey matter volume including standard errors as a function of age, corrected for head size. **C.** Mean hippocampal volume to rest of grey matter ratio including standard errors as a function of age.

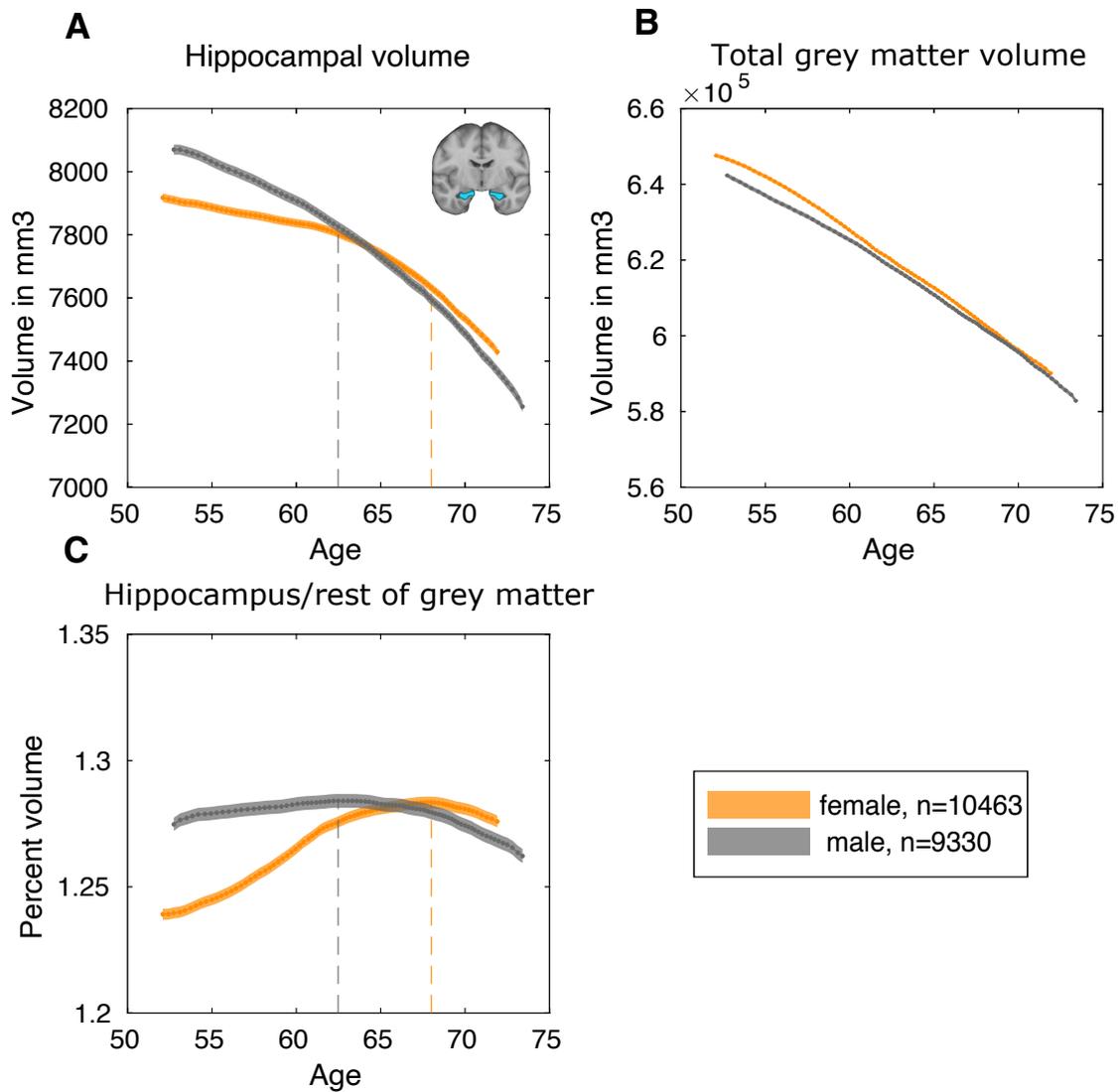


Figure A.15 – Sliding-window curves for hippocampus with 20% quantile width and smoothing kernel 20. Dashed lines indicate points of maximum ratio. **A.** Mean bilateral hippocampal volume including standard errors as a function of age, corrected for head size. **B.** Mean total grey matter volume including standard errors as a function of age, corrected for head size. **C.** Mean hippocampal volume to rest of grey matter ratio including standard errors as a function of age.

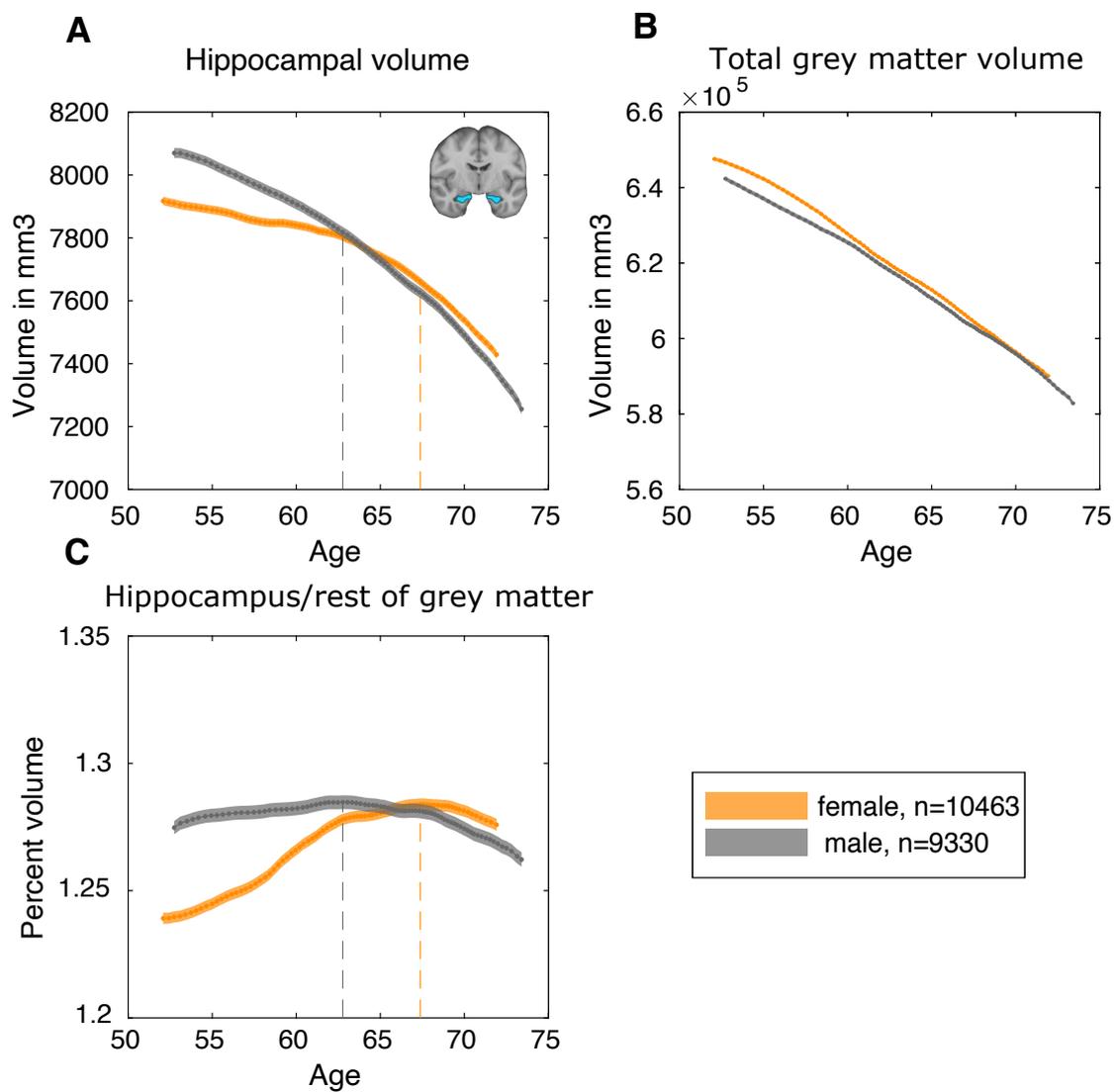


Figure A.16 – Sliding-window curves for hippocampus with 20% quantile width and smoothing kernel 10. Dashed lines indicate points of maximum ratio. **A.** Mean bilateral hippocampal volume including standard errors as a function of age, corrected for head size. **B.** Mean total grey matter volume including standard errors as a function of age, corrected for head size. **C.** Mean hippocampal volume to rest of grey matter ratio including standard errors as a function of age.

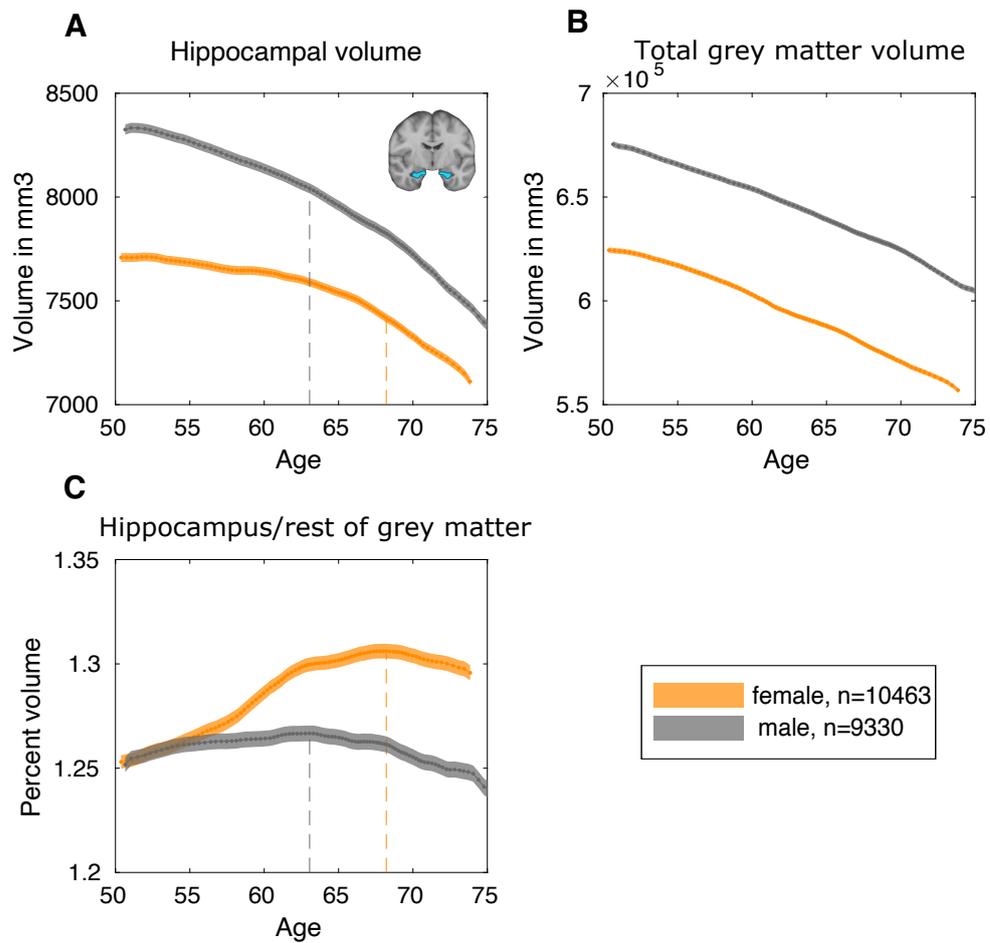


Figure A.17 – Sliding-window curves for hippocampus, uncorrected for head size. Dashed lines indicate points of maximum ratio. **A.** Mean bilateral hippocampal volume including standard errors as a function of age, not corrected for head size. **B.** Mean total grey matter volume including standard errors as a function of age, not corrected for head size. **C.** Mean hippocampal volume to rest of grey matter ratio including standard errors as a function of age.

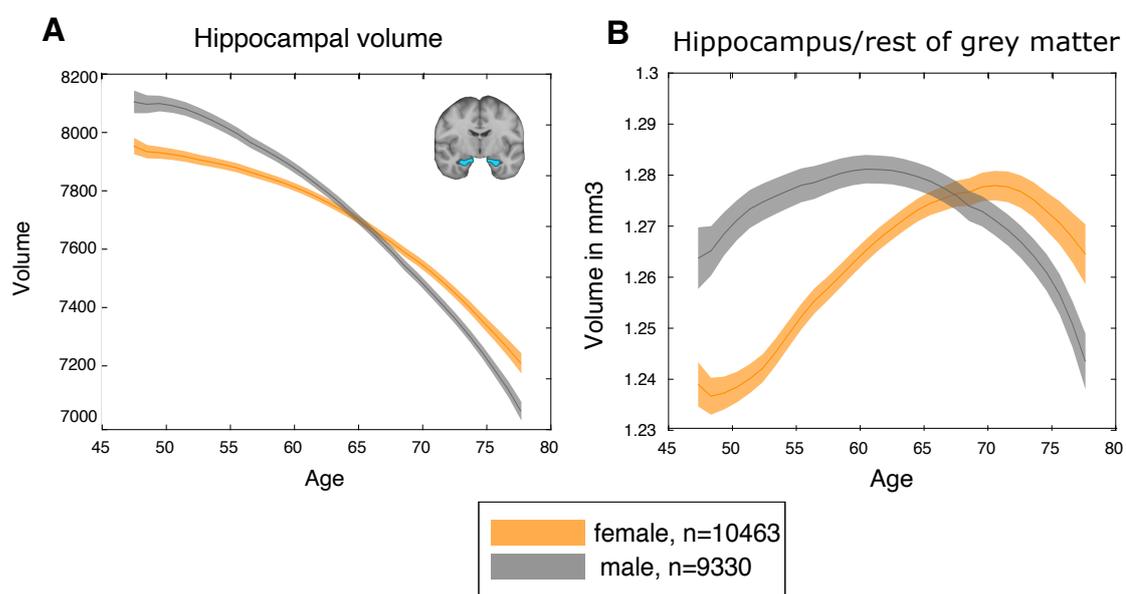


Figure A.18 – Sliding-window curves for hippocampus with fixed age-bins, corrected for head size. A. Mean bilateral hippocampal volume including standard errors as a function of age, corrected for head size. **B.** Mean hippocampal volume to rest of grey matter ratio including standard errors as a function of age.

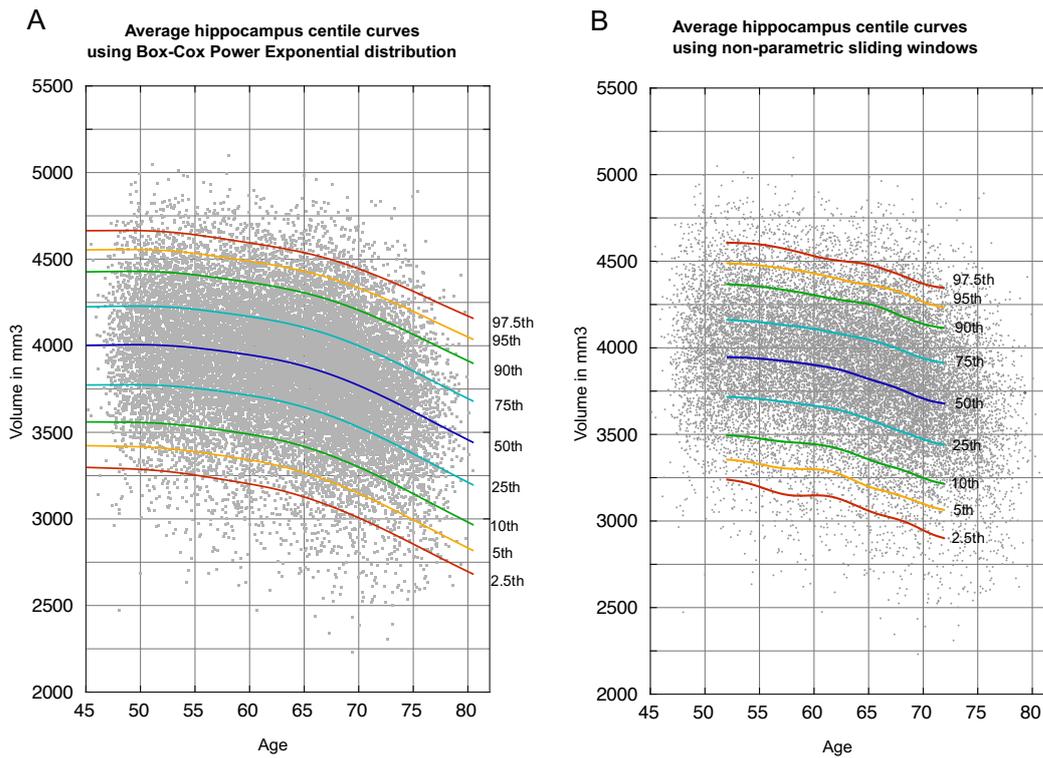


Figure A.19 – Nomograms of head size corrected average hippocampus, calculated with sliding-window and LMS method. A. Average hippocampus centile curves estimated using Box-Cox Power Exponential distribution, and plotted over raw data. Average hippocampal volume has been corrected for head size and is analysed for men and women combined. The model was fitted using the `lms()` function in RStudio version 1.1.383. The function selects the best distribution according to Generalized Akaike Information Criterion with penalty $k = 2$, in this case BCPE. **B.** Average hippocampus centile curves using non-parametric sliding window analysis, corrected for head size and plotted over raw data.

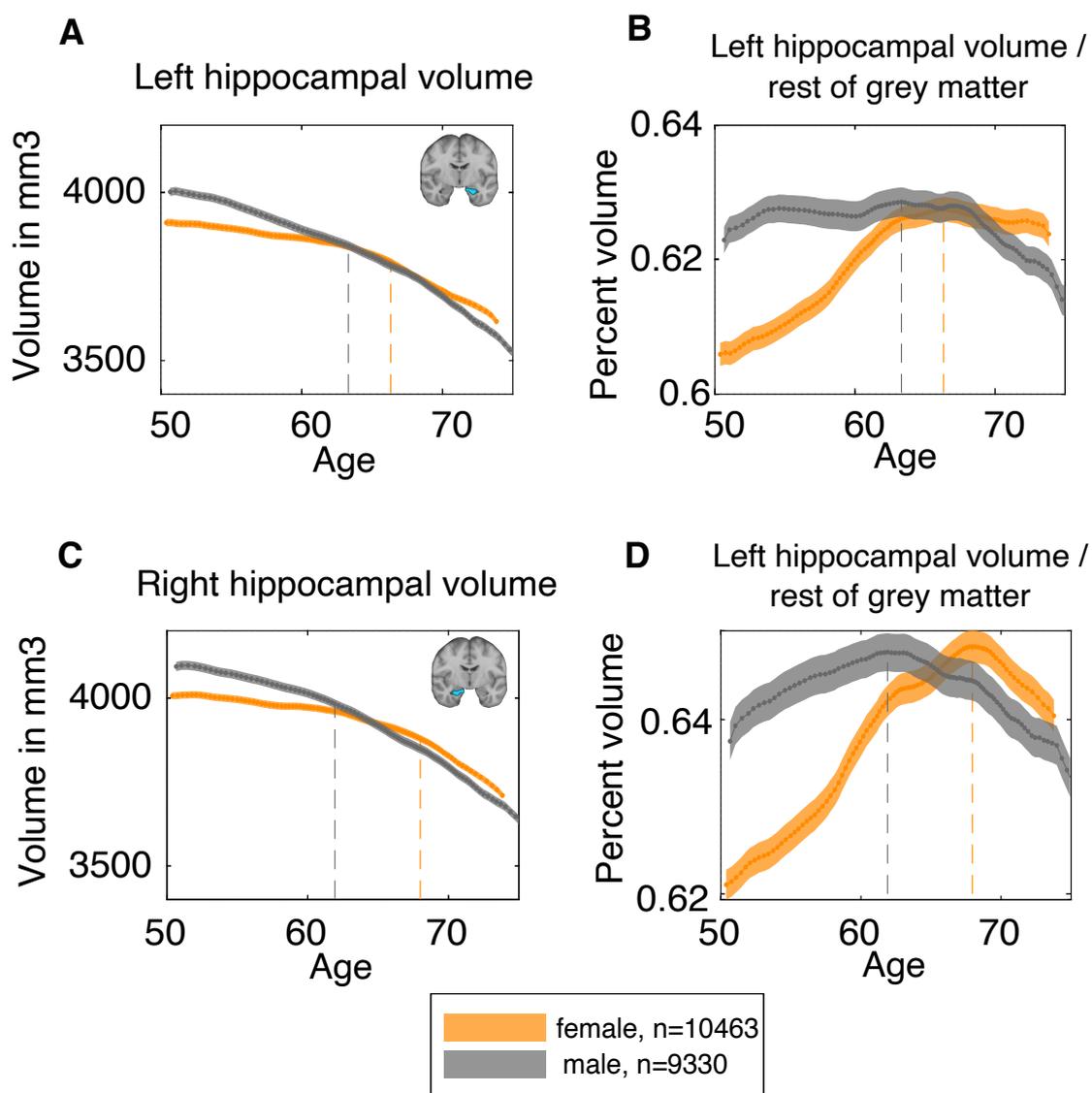


Figure A.20 – Sliding-window curves for left and right hippocampal volume across age. A. Mean left hippocampal volume including standard errors as a function of age, corrected for head size. B. Mean left hippocampal volume to rest of grey matter ratio including standard errors as a function of age. C. Mean right hippocampal volume including standard errors as a function of age, corrected for head size. D. Mean right hippocampal volume to rest of grey matter ratio including standard errors as a function of age.

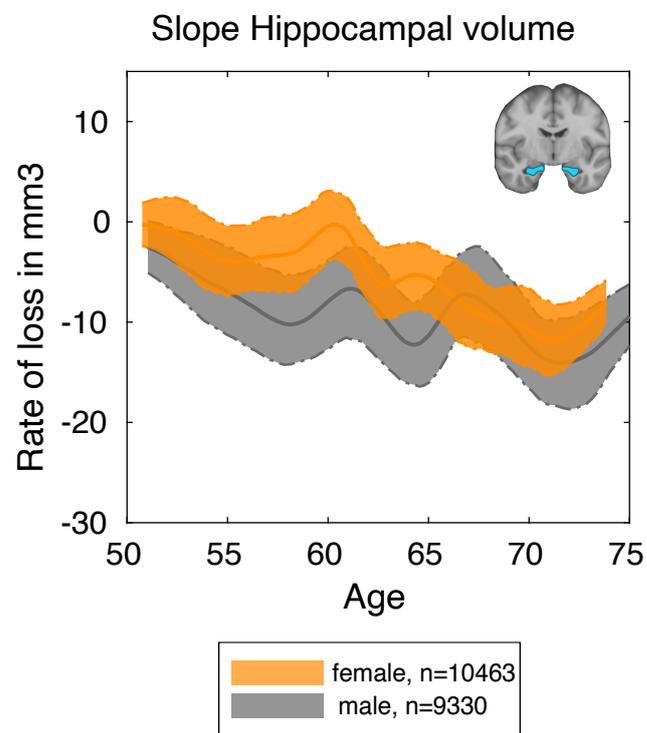


Figure A.21 – Mean slope of bilateral hippocampal volume as a function of age, including 95% bootstrapped confidence intervals.

Appendix B

Post Hoc Comparisons - Emotion

| Comparison | | Mean Difference | SE | df | t | Ptukey |
|------------|-------------|-----------------|--------|------|--------|--------|
| Emotion | Emotion | | | | | |
| Happy | - Surprised | 0.1792 | 0.0279 | 16.0 | 6.422 | <.001 |
| | - Disgusted | 0.3133 | 0.0364 | 16.0 | 8.602 | <.001 |
| | - Sad | 0.1403 | 0.0329 | 16.0 | 4.262 | 0.007 |
| | - Afraid | 0.4667 | 0.0210 | 16.0 | 22.180 | <.001 |
| | - Angry | 0.5226 | 0.0332 | 16.0 | 15.730 | <.001 |
| Surprised | - Disgusted | 0.1341 | 0.0466 | 16.0 | 2.878 | 0.095 |
| | - Sad | -0.0389 | 0.0419 | 16.0 | -0.929 | 0.933 |
| | - Afraid | 0.2876 | 0.0328 | 16.0 | 8.764 | <.001 |
| | - Angry | 0.3435 | 0.0324 | 16.0 | 10.607 | <.001 |
| Disgusted | - Sad | -0.1730 | 0.0351 | 16.0 | -4.924 | 0.002 |
| | - Afraid | 0.1534 | 0.0366 | 16.0 | 4.196 | 0.007 |
| | - Angry | 0.2094 | 0.0499 | 16.0 | 4.194 | 0.007 |
| Sad | - Afraid | 0.3265 | 0.0340 | 16.0 | 9.598 | <.001 |
| | - Angry | 0.3824 | 0.0431 | 16.0 | 8.871 | <.001 |
| Afraid | - Angry | 0.0559 | 0.0380 | 16.0 | 1.473 | 0.685 |

Table B.1 – FERT post-hoc tests for accuracy in patients

Post Hoc Comparisons - Emotion

| Comparison | | Mean Difference | SE | df | t | p | Ptukey | Pbonferroni |
|------------|-------------|-----------------|------|------|-------|-------|--------|-------------|
| Emotion | Emotion | | | | | | | |
| Happy | - Surprised | 10.49 | 1.89 | 16.0 | 5.55 | <.001 | <.001 | <.001 |
| | - Disgusted | 8.83 | 2.37 | 16.0 | 3.72 | 0.002 | 0.019 | 0.028 |
| | - Sad | 16.91 | 2.12 | 16.0 | 7.99 | <.001 | <.001 | <.001 |
| | - Afraid | 21.35 | 2.87 | 16.0 | 7.43 | <.001 | <.001 | <.001 |
| | - Angry | 25.94 | 2.81 | 16.0 | 9.23 | <.001 | <.001 | <.001 |
| Surprised | - Disgusted | -1.66 | 1.63 | 16.0 | -1.02 | 0.322 | 0.904 | 1.000 |
| | - Sad | 6.41 | 1.96 | 16.0 | 3.27 | 0.005 | 0.046 | 0.073 |
| | - Afraid | 10.86 | 2.53 | 16.0 | 4.29 | <.001 | 0.006 | 0.009 |
| | - Angry | 15.44 | 2.57 | 16.0 | 6.01 | <.001 | <.001 | <.001 |
| Disgusted | - Sad | 8.08 | 2.68 | 16.0 | 3.01 | 0.008 | 0.074 | 0.125 |
| | - Afraid | 12.52 | 2.92 | 16.0 | 4.29 | <.001 | 0.006 | 0.008 |
| | - Angry | 17.10 | 2.97 | 16.0 | 5.77 | <.001 | <.001 | <.001 |
| Sad | - Afraid | 4.44 | 1.56 | 16.0 | 2.84 | 0.012 | 0.101 | 0.177 |
| | - Angry | 9.03 | 2.19 | 16.0 | 4.12 | <.001 | 0.009 | 0.012 |
| Afraid | - Angry | 4.58 | 1.94 | 16.0 | 2.37 | 0.031 | 0.224 | 0.461 |

Table B.2 – FERT post-hoc tests for Question 1 in patients

Post Hoc Comparisons - Emotion

| Comparison | | Mean Difference | SE | df | t | p | Ptukey | Pbonferroni |
|------------|-------------|-----------------|------|------|--------|-------|--------|-------------|
| Emotion | Emotion | | | | | | | |
| Happy | - Surprised | 6.74 | 2.37 | 17.0 | 2.840 | 0.011 | 0.098 | 0.170 |
| | - Disgusted | 12.69 | 2.69 | 17.0 | 4.720 | <.001 | 0.002 | 0.003 |
| | - Sad | 3.29 | 2.11 | 17.0 | 1.561 | 0.137 | 0.632 | 1.000 |
| | - Afraid | 14.16 | 3.07 | 17.0 | 4.608 | <.001 | 0.003 | 0.004 |
| | - Angry | 19.24 | 3.56 | 17.0 | 5.406 | <.001 | <.001 | <.001 |
| Surprised | - Disgusted | 5.95 | 2.44 | 17.0 | 2.434 | 0.026 | 0.199 | 0.394 |
| | - Sad | -3.45 | 1.43 | 17.0 | -2.409 | 0.028 | 0.208 | 0.415 |
| | - Afraid | 7.41 | 2.82 | 17.0 | 2.631 | 0.018 | 0.143 | 0.263 |
| | - Angry | 12.49 | 3.28 | 17.0 | 3.803 | 0.001 | 0.015 | 0.021 |
| Disgusted | - Sad | -9.40 | 2.51 | 17.0 | -3.744 | 0.002 | 0.017 | 0.024 |
| | - Afraid | 1.46 | 1.69 | 17.0 | 0.867 | 0.398 | 0.949 | 1.000 |
| | - Angry | 6.54 | 2.08 | 17.0 | 3.143 | 0.006 | 0.056 | 0.089 |
| Sad | - Afraid | 10.86 | 2.56 | 17.0 | 4.238 | <.001 | 0.006 | 0.008 |
| | - Angry | 15.94 | 3.32 | 17.0 | 4.804 | <.001 | 0.002 | 0.002 |
| Afraid | - Angry | 5.08 | 1.55 | 17.0 | 3.276 | 0.004 | 0.043 | 0.067 |

Table B.3 – FERT post-hoc tests for Question 2 in patients

Post Hoc Comparisons - Emotion

| Comparison | | Mean Difference | SE | df | t | P _{Tukey} |
|------------|-------------|-----------------|-------|------|---------|--------------------|
| Emotion | Emotion | | | | | |
| Happy | - Surprised | -0.8574 | 0.223 | 16.0 | -3.8474 | 0.015 |
| | - Disgusted | -0.9570 | 0.227 | 16.0 | -4.2089 | 0.007 |
| | - Sad | -1.2498 | 0.196 | 16.0 | -6.3890 | <.001 |
| | - Afraid | -1.5607 | 0.314 | 16.0 | -4.9673 | 0.002 |
| | - Angry | -1.5486 | 0.300 | 16.0 | -5.1691 | 0.001 |
| Surprised | - Disgusted | -0.0996 | 0.246 | 16.0 | -0.4044 | 0.998 |
| | - Sad | -0.3924 | 0.192 | 16.0 | -2.0387 | 0.364 |
| | - Afraid | -0.7034 | 0.252 | 16.0 | -2.7923 | 0.110 |
| | - Angry | -0.6912 | 0.348 | 16.0 | -1.9852 | 0.391 |
| Disgusted | - Sad | -0.2928 | 0.244 | 16.0 | -1.2019 | 0.830 |
| | - Afraid | -0.6037 | 0.341 | 16.0 | -1.7718 | 0.509 |
| | - Angry | -0.5916 | 0.356 | 16.0 | -1.6594 | 0.575 |
| Sad | - Afraid | -0.3109 | 0.327 | 16.0 | -0.9497 | 0.927 |
| | - Angry | -0.2988 | 0.295 | 16.0 | -1.0136 | 0.907 |
| Afraid | - Angry | 0.0122 | 0.424 | 16.0 | 0.0287 | 1.000 |

Table B.4 – FERT post-hoc tests for reaction time in patients

Post Hoc Comparisons - Emotion

| Comparison | | Mean Difference | SE | df | t | Ptukey |
|------------|-------------|-----------------|--------|------|--------|--------|
| Emotion | Emotion | | | | | |
| Happy | - Surprised | 0.2326 | 0.0242 | 37.0 | 9.602 | <.001 |
| | - Disgusted | 0.2854 | 0.0248 | 37.0 | 11.497 | <.001 |
| | - Sad | 0.1123 | 0.0250 | 37.0 | 4.501 | <.001 |
| | - Afraid | 0.5241 | 0.0274 | 37.0 | 19.127 | <.001 |
| | - Angry | 0.5111 | 0.0332 | 37.0 | 15.383 | <.001 |
| Surprised | - Disgusted | 0.0527 | 0.0306 | 37.0 | 1.720 | 0.528 |
| | - Sad | -0.1203 | 0.0296 | 37.0 | -4.070 | 0.003 |
| | - Afraid | 0.2914 | 0.0369 | 37.0 | 7.888 | <.001 |
| | - Angry | 0.2785 | 0.0348 | 37.0 | 7.999 | <.001 |
| Disgusted | - Sad | -0.1730 | 0.0279 | 37.0 | -6.207 | <.001 |
| | - Afraid | 0.2387 | 0.0306 | 37.0 | 7.801 | <.001 |
| | - Angry | 0.2257 | 0.0373 | 37.0 | 6.047 | <.001 |
| Sad | - Afraid | 0.4118 | 0.0363 | 37.0 | 11.333 | <.001 |
| | - Angry | 0.3988 | 0.0380 | 37.0 | 10.484 | <.001 |
| Afraid | - Angry | -0.0130 | 0.0358 | 37.0 | -0.363 | 0.999 |

Table B.5 – FERT post-hoc tests for accuracy in controls and patients

Post Hoc Comparisons - Emotion

| Comparison | | Mean Difference | SE | df | t | P _{Tukey} |
|------------|-------------|-----------------|------|------|-------|--------------------|
| Emotion | Emotion | | | | | |
| Happy | - Surprised | 14.540 | 2.13 | 37.0 | 6.841 | <.001 |
| | - Disgusted | 14.770 | 2.43 | 37.0 | 6.072 | <.001 |
| | - Sad | 21.708 | 2.62 | 37.0 | 8.298 | <.001 |
| | - Afraid | 28.963 | 3.02 | 37.0 | 9.603 | <.001 |
| | - Angry | 37.245 | 4.17 | 37.0 | 8.937 | <.001 |
| Surprised | - Disgusted | 0.230 | 1.79 | 37.0 | 0.128 | 1.000 |
| | - Sad | 7.168 | 2.13 | 37.0 | 3.360 | 0.021 |
| | - Afraid | 14.423 | 2.46 | 37.0 | 5.861 | <.001 |
| | - Angry | 22.705 | 3.24 | 37.0 | 7.001 | <.001 |
| Disgusted | - Sad | 6.939 | 2.17 | 37.0 | 3.202 | 0.031 |
| | - Afraid | 14.193 | 2.22 | 37.0 | 6.388 | <.001 |
| | - Angry | 22.475 | 2.96 | 37.0 | 7.589 | <.001 |
| Sad | - Afraid | 7.254 | 1.80 | 37.0 | 4.025 | 0.003 |
| | - Angry | 15.537 | 2.93 | 37.0 | 5.295 | <.001 |
| Afraid | - Angry | 8.282 | 2.50 | 37.0 | 3.310 | 0.024 |

Table B.6 – FERT post-hoc tests for Question 1 in controls and patients

Post Hoc Comparisons - Emotion

| Comparison | | Mean Difference | SE | df | t | P _{tukey} |
|------------|-------------|-----------------|------|------|--------|--------------------|
| Emotion | Emotion | | | | | |
| Happy | - Surprised | 9.425 | 2.08 | 37.0 | 4.531 | <.001 |
| | - Disgusted | 5.412 | 2.49 | 37.0 | 2.177 | 0.273 |
| | - Sad | 20.761 | 2.70 | 37.0 | 7.681 | <.001 |
| | - Afraid | 21.569 | 2.40 | 37.0 | 8.982 | <.001 |
| | - Angry | 30.013 | 2.89 | 37.0 | 10.384 | <.001 |
| Surprised | - Disgusted | -4.013 | 1.99 | 37.0 | -2.017 | 0.352 |
| | - Sad | 11.336 | 2.73 | 37.0 | 4.146 | 0.002 |
| | - Afraid | 12.144 | 2.12 | 37.0 | 5.715 | <.001 |
| | - Angry | 20.589 | 2.53 | 37.0 | 8.126 | <.001 |
| Disgusted | - Sad | 15.349 | 2.87 | 37.0 | 5.355 | <.001 |
| | - Afraid | 16.157 | 2.17 | 37.0 | 7.438 | <.001 |
| | - Angry | 24.601 | 2.83 | 37.0 | 8.701 | <.001 |
| Sad | - Afraid | 0.808 | 2.42 | 37.0 | 0.334 | 0.999 |
| | - Angry | 9.253 | 2.68 | 37.0 | 3.451 | 0.016 |
| Afraid | - Angry | 8.445 | 1.69 | 37.0 | 4.997 | <.001 |

Table B.7 – FERT post-hoc tests for Question 2 in controls and patients

Post Hoc Comparisons - Emotion

| Comparison | | Mean Difference | SE | df | t | P _{Tukey} |
|------------|-------------|-----------------|-------|------|--------|--------------------|
| Emotion | Emotion | | | | | |
| Happy | - Surprised | -0.6006 | 0.169 | 35.0 | -3.548 | 0.013 |
| | - Disgusted | -0.5425 | 0.225 | 35.0 | -2.414 | 0.179 |
| | - Sad | -0.8736 | 0.150 | 35.0 | -5.811 | <.001 |
| | - Afraid | -1.5765 | 0.288 | 35.0 | -5.467 | <.001 |
| | - Angry | -1.3350 | 0.198 | 35.0 | -6.725 | <.001 |
| Surprised | - Disgusted | 0.0582 | 0.199 | 35.0 | 0.293 | 1.000 |
| | - Sad | -0.2730 | 0.182 | 35.0 | -1.503 | 0.664 |
| | - Afraid | -0.9758 | 0.298 | 35.0 | -3.274 | 0.027 |
| | - Angry | -0.7343 | 0.242 | 35.0 | -3.039 | 0.047 |
| Disgusted | - Sad | -0.3312 | 0.205 | 35.0 | -1.614 | 0.595 |
| | - Afraid | -1.0340 | 0.329 | 35.0 | -3.147 | 0.036 |
| | - Angry | -0.7925 | 0.265 | 35.0 | -2.993 | 0.052 |
| Sad | - Afraid | -0.7028 | 0.270 | 35.0 | -2.603 | 0.123 |
| | - Angry | -0.4613 | 0.223 | 35.0 | -2.069 | 0.326 |
| Afraid | - Angry | 0.2415 | 0.345 | 35.0 | 0.700 | 0.981 |

Table B.8 – FERT post-hoc tests for reaction time in controls and patients

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”Human knowledge is never contained in one person. It grows from the relationships we create between each other and the world, and still, it is never complete.”

—Paul Kalanithi, *When Breath Becomes Air*

