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Neurocognitive Mechanisms & Genetic Variants Underlying Apathy in Neurodegenerative Dementias

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Abstract

Apathy refers to a reduction in self-initiated, goal-directed behaviour and is present in many neurodegenerative dementias, including Alzheimer's disease (AD), frontotemporal dementia (FTD), Lewy Body dementia (LBD), and Parkinson's disease (PD). There are no robustly effective treatments for symptoms of apathy present in these dementias; this is, in part, because apathy is phenotypically diverse, yet is often understood and clinically treated as a single, homogenous syndrome. The current thesis aimed to use a combination of behavioural, genetic, and imaging data to better characterize the neurocognitive and genetic underpinnings of apathy across neurodegenerative dementias. Study One leveraged data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to examine associations between single nucleotide polymorphisms and 3T MRI structural imaging data in a cohort of patients with apathy and mild cognitive impairment (MCI) or AD. A partial least squares correspondence analysis (PLS-CA) revealed a novel genotype of minor homozygosity for the DAT1 gene and the possession of one APOE ε4 allele associated with significant brain atrophy in frontal, temporal, parietal, insular, and subcortical brain regions in patients with apathy. Study Two used computer-based tasks to index core cognitive and behavioural components of apathy, including option generation, amotivation, and avolition deficits. These computer tasks were employed in patients with neurodegenerative dementias, including AD, FTD, LBD/PD, and healthy controls. Results showed significant deficits in an option generation task related to a subtype of apathy characterized by impairments in initiation, option generation, and effort. Study Three involved 3T structural imaging data, collected at the Centre for Functional and Metabolic Mapping (CFMM), from participants who completed the computer tasks in Study Two. Based on findings from Study Two, deficits in the option generation task and an apathy latent factor (comprised of initiation, option generation, and effort indices) were expected to predict atrophy in the dorsal anterior cingulate cortex (dACC), anterior prefrontal cortex (PFC), medial PFC, and dorsolateral PFC. Results revealed a significant association between the apathy predictors and atrophy in the ACC. Overall, this thesis demonstrates novel genetic and cognitive underpinning of apathy in neurodegenerative dementias that can be used to inform future clinical trials for apathy.

Keywords

Apathy, Neurodegeneration, Frontotemporal Dementia, Lewy Body Dementia, Alzheimer's Disease, Parkinson's Disease, Option Generation, Initiation, Effort-Based, Decision Making, Motivation, Volition, Social Reward

Summary for Lay Audience

Apathy is a debilitating symptom that occurs widely in neurodegenerative dementias. The presence of apathy in dementia is associated with accelerated cognitive decline and increased morbidity in patients. There are currently no widely available treatment options for apathy in neurodegenerative dementias. This is largely due to a lack of understanding of the mechanisms in the brain and the genetic factors that give rise to apathy symptoms. As such, this thesis aims to elucidate the processes in the brain and genetic variants that underlie apathy in a population of patients with neurodegenerative dementias, including frontotemporal dementia (FTD), Lewy Body Dementia (LBD), Parkinson's Disease (PD), and Alzheimer's Disease (AD). The first study uses neuroimaging and genetic data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to assess the relationship between genetic polymorphisms and brain atrophy patterns as they relate to apathy in a cohort of patients with AD and mild cognitive impairment (MCI). The second study used computer-based tasks to examine deficits in option generation, motivation, and volition related to apathy in patients with FTD, AD, LBD/PD, and healthy controls. The third study used structural MRI scans to assess patterns of brain atrophy associated with the apathy deficits found in study two. Together, our results point to a novel genotype involving a dopamine transporter gene and deficits in option generation related to atrophy in the anterior cingulate cortex (ACC) that may give rise to apathy in neurodegenerative dementias.

Co-Authorship Statement

All chapters were written by Rubina Malik with input from Dr. Elizabeth Finger. Sophie Henke Tarnow, Maryam Berih, Janet Chen, Kristy Coleman, Sarah Jesso, Carolina Silveira, Miguel Restrepo, Ramiro Ruiz, and Soojung Yu were involved in data collection.

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List of Abbreviations

Aβ: beta-amyloid

ACC: anterior cingulate cortex

AD: Alzheimer’s disease

AD+A: AD with apathy

AD-A: AD without apathy

ADHD: attention deficit hyperactivity disorder

ADNI: Alzheimer's disease neuroimaging initiative

AES: apathy evaluation scale

ALS: amyotrophic lateral sclerosis

aMCI: amnestic mild cognitive impairment

AMI: apathy motivation index

APOE: apolipoprotein E gene

ApoE: apolipoprotein E

ART: align rank transform

BD: bipolar disorder

BDNF: brain-derived neurotrophic factor gene

BIN1: bridging integrator 1 gene

BRS: brain reward system

BSR: boot strap ratio

bvFTD: behavioural variant frontotemporal dementia

CBS: corticobasal syndrome

CDR: clinical dementia rating scale

CEU: Utah residents with ancestry from northern and western Europe

CN: cognitively normal

CN+A: CN with apathy

CN-A: CN without apathy

COMT: Catechol-O-methyltransferase gene

CSF: cerebrospinal fluid

C9orf72: chromosome 9 open reading frame 72

DA: dopamine

dACC: dorsal anterior cingulate cortex

DAS: dimensional anhedonia scale

DApS: dimensional apathy scale

DLPFC: dorsolateral prefrontal cortex

DNA: deoxyribonucleic acid

DRD2: dopamine receptor D2

DRD3: dopamine receptor D3

DRD4: dopamine receptor D4

DAT1: dopamine transporter 1

EBDM: effort-based decision making

FDG-PET: Fluorodeoxyglucose positron emission tomography

FrSBe: frontal systems behavior scale

FTD: Frontotemporal dementia

FTD-ALS: Frontotemporal dementia - amyotrophic lateral sclerosis

fMRI: functional magnetic resonance imaging

FUS: fused in sarcoma

GBA: glucocerebrosidase gene

GDB: goal-directed behaviour

GDS: geriatric depression scale

Glu: glutamate

Gln: glutamine

GRM3: Glutamate Metabotropic Receptor 3

GRN: progranulin gene

GWAS: genome-wide association study

HC: healthy control

I-FP-CIT SPECT: ^{123}I-N-3-fluoropropyl-2beta-carbomethoxy-3beta-4-iodophenyl tropane SPECT

IB: intentional binding

LARS: Lille apathy rating scale

LBD: Lewy body dementia

LRRK2: leucine-rich repeat kinase 2 gene

LV: latent variable

MAF: minor allele frequency

MAPT: microtubule associated protein tau gene

MCI: mild cognitive impairment

MCI+A: MCI with apathy

MCI-A: MCI without apathy

MDD: major depressive disorder

MFA: maximum force applied

MMSE: mini mental state examination

MOCA: Montreal cognitive assessment

mOFC: medial orbitofrontal cortex

MPRAGE: Magnetization-Prepared Rapid Acquisition Gradient Echo

MRI: magnetic resonance imaging

MVC: maximum voluntary contraction

NFTs: Neurofibrillary tangles

nfvPPA: non-fluent variant primary progressive aphasia

NMDA: N-methyl-d-aspartate

NPI: neuropsychiatric inventory

NPI-Q: NPI-questionnaire

OFC: orbitofrontal cortex

OPRD1: Opioid Receptor Delta 1

OPRM1: Opioid Receptor Mu 1

OXT: Oxytocin/Neurophysin I Prepropeptide

OXTR: oxytocin receptor

PACT: Philadelphia Apathy Computerized Test

PCA: principal component analysis

PCC: posterior cingulate cortex

PD: Parkinson's disease

PET: positron emission tomography

PFC: prefrontal cortex

PLS: partial least squares

PLSR: partial least square regression

PLS-CA: partial least squares correspondence analysis

PPA: primary progressive aphasia

PPN: parts per newton

Pre-SMA: pre-supplementary motor area

PRPF4B: Pre-MRNA Processing Factor 4B

PSP: progressive supranuclear palsy

ROI: region of interest

REACT: rTMS Apathy Clinical Trial

rTMS: repetitive transcranial magnetic stimulation

rTPJ: right temporo-parietal junction

SoA: sense of agency

SPECT: single-photon emission computerized tomography

SNCA: alpha-synuclein gene

SNPs: single nucleotide polymorphisms

SNRI: selective norepinephrine reuptake inhibitor

SSRI: selective serotonin reuptake inhibitor

ST: search time

svPPA: semantic variant primary progressive aphasia

TDP-43: TAR DNA-binding protein 43

TIV: total intracranial volume

TMEM175: transmembrane protein 175 gene

TMS: transcranial magnetic stimulation

TSI: Toscani in Italia

TH: tyrosine hydroxylase

vmPFC: ventromedial prefrontal cortex

VS: ventral striatum

VTA: ventral tegmental area

1 Chapter 1: Introduction

1.1 What is Apathy?

Apathy is a complex clinical construct. In the past decade, questions surrounding the clinical characterization and neurobiological underpinnings of apathy have emerged. Today, apathy is commonly characterized as a neuropsychiatric syndrome that can occur in late-life depression, neurological disorders, and neurodegenerative diseases (Steffens & Krishan, 1998; Fahed & Steffens, 2021). The earliest conceptions of apathy describe the condition as lack of motivation, not attributable to diminished levels of consciousness, cognitive impairment, or emotional distress (Marin, 1991). More recent ideas of apathy posit a multi-dimensional construct; apathy can be defined as a quantitative reduction in goal-directed activity compared with a patient's previous level of functioning, in at least two of the following domains: behaviour/cognition, emotion, social interaction (Robert et al., 2018). The definition of apathy has rapidly evolved to include elements of impaired self-initiation and/or lack of novelty-seeking behaviour or curiosity (Miller et al., 2021; Lanctot et al., 2023).

Clinical diagnostic criteria for apathy in brain disorders have advanced in the past decade. In 2008, the European Psychiatric Association congress assigned a task force to operationalize and rank criteria for diagnosis of apathy in Alzheimer's disease (AD) and neurodegenerative dementias (Robert et al., 2009). Experts in the neuropsychiatry of neurodegenerative diseases, from within Europe, Austria, and North America, proposed that the core criterion for apathy (Criterion A) is a loss of motivation, relative to a lifelong level of functioning (and accounting for standards concerning patient age and culture). Criterion B stipulates that at least one symptom in two of the three following domains must occur for a period of at least four weeks: B1. loss of goal-directed behaviour (GDB), B3. loss of goal-directed cognitive activity, B3. and/or loss of emotion. Diminished activity within these domains can be observed by a change in the patient's responsiveness to internal or external stimuli. These symptoms should cause clinically

significant impairment in personal, social, occupational, or other important areas of functioning (Criterion C), and not be attributable to diminished levels of consciousness, physical or motor disabilities, or the direct physiological effects of a substance (Criterion D). Fulfilment of criteria A-D indicates a clinical diagnosis of apathy in AD and other neurodegenerative dementias. More recently, the International Society for CNS Clinical Trials Methodology Apathy Work Group refined the diagnostic criteria for apathy, notably to broaden the three domains or "dimensions" of apathy in Criteria B and incorporate more specific examples of symptoms within these dimensions (Miller et al., 2021). The following dimensions replaced domains in Criteria B: diminished initiative, diminished interest, and diminished emotional responsiveness.

Although apathy may arise in disorders with different pathologies, recent approaches to understanding the neurobiological and cognitive features of apathy have adopted a transdiagnostic approach. A review by Husain and Roiser (2018) outlines the utility of investigating symptoms of apathy within the framework of effort-based decision making (EBDM) for rewards. They propose that isolating the cognitive mechanisms involved in, and leading up to, the decision to engage in an effortful activity in order to obtain a reward can elucidate deficits in cognition that give rise to symptoms of apathy. This can also help disentangle apathy as an independent construct from commonly overlapping phenomena, such as depression and anhedonia.

1.2 Neurocognitive Mechanisms Underlying Apathy

In a model of effort-based decision-making in goal-directed behaviour, apathy can arise from deficits in option generation, reward processing, effort discounting, effort initiation, and/or volition. The following section outlines current knowledge on the link between effort-based decision making in goal-directed behaviour.

1.2.1 Goal-Directed Behaviour

Goal-directed behaviour (GDB) refers to an action that is executed with the objective of achieving a specific outcome (Robbins & Costa, 2017). Within the framework of GDB, there is an implicit action-outcome contingency; the performer initiates an action with the intent of obtaining a particular goal. The action can be self-initiated or in response to

external, environmental factors. Goal-directed behaviour is distinguished from habits. Habits encompass actions initiated as a stimulus-response. In this way, a particular stimulus evokes a specific response, but the outcome of the response is not crucial (Robbins & Costa, 2017). Although both GDB and habits may be driven by the same motor mechanisms in the brain and daily habits may also be disrupted by apathy (e.g., having a snack when hungry), most studies investigating behaviour in apathy have adopted a GDB approach; this is because GDB is easier to examine in an experimental setting, where goals and rewards can be manipulated by task protocols.

1.2.2 Effort-Based Decision Making (EBDM) for Rewards

Effort-based decision making (EBDM) models for GDB examine an individual's willingness to exert a certain amount of effort to gain a reward (Husain & Roiser, 2018). In this way, GDBs are experimentally manipulated such that the goal of the action or behaviour is to obtain the reward. The effort needed to reach a goal can also be rewarding in itself (Inzlicht et al., 2018). In the simplest model of EBDM, the agent must engage in two consecutive steps: 1) anticipating the effort needed to obtain the reward, and 2) expending the effort (Zhang & Zheng, 2022). In step 1, anticipation of the effort includes weighing the personal cost of the effort (e.g., time it takes to complete, any risks of performing the effort) to the subjective value of the reward to be gained. Once a decision for action is made, step 2 can occur. Traditionally, impairments resulting in effort discounting or reward devaluation are mechanistic disruptions leading to apathy, or amotivation.

Recently, Husain & Roiser (2018) proposed an extended model of EBDM to encompass key steps leading up to the effort versus reward computation and steps that follow. First, before an action is initiated, an agent must be able to generate potential options for behaviour. These options can be self-generated or cued by the external environment. Next, in complex scenarios, with multiple potential options generated, the options are evaluated in terms of their costs and anticipated benefits. An option is then selected. Anticipation of the reward and preparation for the action is associated with a physiological signature of motivational arousal (change in heart rate and pupil dilation). The action is then initiated and sustained. The goal is obtained and there is an interaction

with the goal, or reward, which may lead to a positive (hedonic) or negative impact. Lastly, the agent learns from the action-outcome coupling and alters future weighting of effort costs and reward benefits. A deficit in any one of these steps can give rise to apathy.

1.2.2.1 Neuroanatomical Correlates of EBDM

Fronto-striatal networks are known to be involved in motivated behaviour. Functional neuroimaging studies in healthy human adults identify several brain regions involved in performing effort-based decision-making tasks (Pessiglione et al., 2018). In particular, the medial orbitofrontal (mOFC) or ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), and basal ganglia, specifically the ventral striatum (VS; Pessiglione et al., 2018). Within this network, activation of the mOFC and VS has been shown to correlate positively with increasing magnitude of reward (Croxson et al., 2009). Evidence suggests that the ACC is implicated in computing the decision by integrating reward and effort signals (Bonnelle et al., 2016). Lesions within this fronto-striatal network are therefore thought to give rise to clinical apathy.

1.2.3 Option Generation

Patients with amotivational syndromes may sometimes be able to perform actions when prompted, but unable to initiative activities by themselves (Husain & Roiser, 2018). Previous studies have employed option generation tasks to quantify the ability to do so in EBDM. In a cohort of patients with schizophrenia, Hartmann et al. (2015) used a verbal protocol to investigate the quantity of options generated in ill-structured real-world scenarios. An example of one of these scenarios is “It’s a sunny day. What could you do?”, and the number of options generated was the primary outcome. The authors found that the number of options generated was inversely correlated with negative symptoms (one of which includes apathy). In another study of patients with Parkinson’s disease, Ang et al. (2018) leveraged a novel motor task to assess option generation deficits associated with apathy. Participants were instructed to draw as many different paths (options) as they could between two points within a fixed time. Uniqueness (how individually different their options were) and fluency (number of options generated) were

the variables of interest in the task. A comparison between patients with PD when ON versus OFF dopaminergic medication, and healthy controls revealed the following results: 1) highly motivated healthy individuals generated more options that were less unique, and a dopamine agonist increased fluency but not uniqueness, 2) in apathetic healthy individuals, the dopamine agonist improved both fluency and uniqueness for a given fluency of generation, and 3) in patients with PD, neither apathy nor its interaction with dopamine levels influenced the fluency or uniqueness of options generated. These findings suggest that option generation may contribute to apathy in healthy human adults, but may not underlie apathy in all pathological conditions. Associations between option generation and apathy have not been previously explored in other neurodegenerative dementias such as Alzheimer's disease or Frontotemporal Dementias.

1.2.3.1 Neuroanatomical Correlates of Option Generation

Few studies have directly examined the neuroanatomical correlates of option generation in health and disease. Some findings suggest the role of the presupplementary motor area (pre-SMA) and possibly the dorsolateral prefrontal cortex (DLPFC; Nachev et al., 2008; Husain & Roiser, 2018). In a study with healthy adults, Kaiser et al. (2013) employed a task similar to Hartmann et al. (2015) in which participants were asked to generate verbal options for real-world scenarios. Using an fMRI analysis, the authors found that the left anterior prefrontal cortex was associated with generating options in contrast to reading available options. Additionally, option selection of self-generated options versus externally provided options was associated with the dorsal anterior cingulate cortex (dACC). The authors also propose that retrieval of options from long-term memory is a relevant process for option generation.

1.2.4 Volition

Deficits in action initiation have been previously implicated in apathy (Levy & Dubois, 2006). An important prerequisite to intentional self-generated actions is the sense of agency, commonly referred to as volition. The sense of agency (SoA) refers to the subjective feeling of control over voluntary actions and the subsequent outcomes of those actions (Haggard et al., 2002, Moore and Obhi, 2012). The experience the sense of

agency often occurs in the absence of conscious awareness of our actions and their effects. For instance, when we tie our shoes, we perform a series of complex finger movements without having to recite instructions to ourselves along every step of the way. Actions such as this are performed with near automaticity. Despite a lack of conscious awareness during performance, individuals are able to recall the outcomes of their actions with confidence in their causal role. How humans experience agency for actions that are registered at the unconscious level has been an imperative question in SoA research for nearly two decades. To the best of our knowledge the question of whether the SoA is related to inaction in apathetic patients has been largely unexplored.

1.2.4.1 Intentional Binding

Researchers have devised tools to measure conscious (explicit) and unconscious (implicit) experiences of the SoA. Explicit measures of the SoA ask subjects to make voluntary actions to produce effects and then indicate, often using a Likert scale or verbal reports, to what extent they felt in control over the action–outcome event (e.g., to what extent do you agree with the statement, "I caused X to move"?). A widely leveraged implicit index of the SoA is intentional binding (IB). IB is a temporal illusion in which the time interval between a voluntary action and its subsequent effect is perceived as being compressed. A seminal study by Haggard and colleagues (2002), found that compared to when the same action was made involuntarily by applying transcranial magnetic stimulation (TMS) to the motor cortex, participants perceived their voluntary actions, in the form of a single keypress, to be shifted forward in time; the subsequent effect of the keypress, in the form of a single auditory tone, was perceived as being attracted backwards in time towards to the action (i.e., the keypress). The magnitude of the temporal compression (i.e., an increase in intentional binding) was purported to be proportional to the sense of agency. The key finding of the study was that the attraction of action to effect (i.e., action binding), and effect to action (i.e., outcome or tone binding), occurred only for intentional, voluntary actions. This led to a new era of intentional binding studies in the investigation of the SoA.

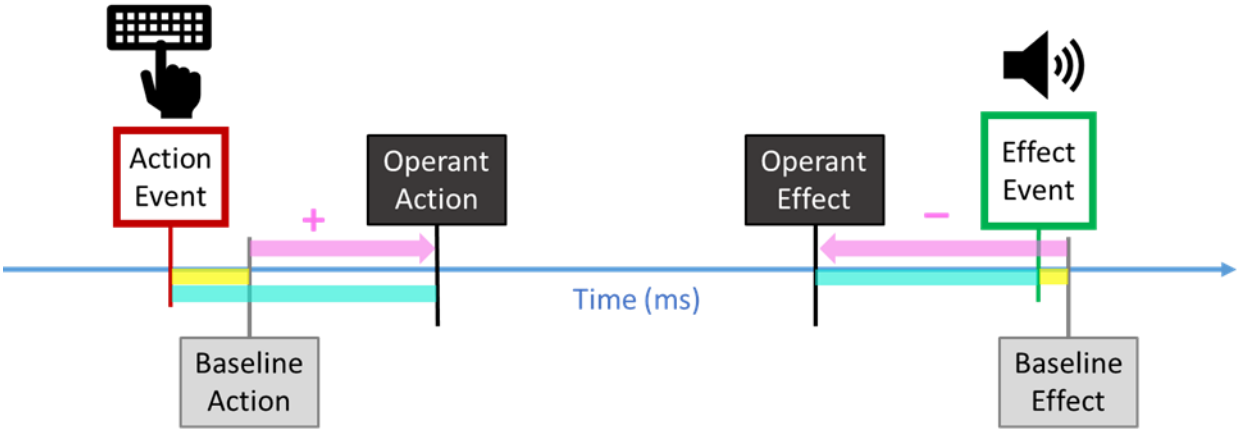

Figure 1-1 Intentional binding visualization. A critical comparison is made between action operant and action baseline conditions, as well as outcome operant and outcome baseline conditions. A perceptual shift of an event (i.e., action or outcome) forward in time occurs when the difference between the mean judgment errors (where the mean judgment error is the difference between the actual and estimated onset of the judged event) of the operant condition and the baseline condition yields a positive value. A perceptual shift of an event backwards in time occurs when the difference between the mean judgment errors of the operant and baseline condition yields a negative value. In the case of perceived timing of a voluntary action, "action binding" (i.e., the attraction of the action towards the outcome) occurs when there is a positive perceptual shift. "Tone binding" (i.e., the attraction of the outcome back towards the action) occurs when there is a negative value assigned to perceptual shift. Intentional binding is thus a combination of action and tone binding.

1.2.4.2 Neuroanatomical Correlates of Volition

A theoretical framework for assessing the cognitive mechanisms associated with the SoA has been recently proposed by Malik and colleagues (2022). Within this framework, processing of cues related to action execution/initiation is localized to the dorsal premotor cortex. The right temporo-parietal junction (rTPJ) is implicated in integrating sensory information regarding social agents in scenarios and connections between the rTPJ and subcortical limbic and thalamic structures are implicated in learning intention-effect contingencies. The dorsolateral prefrontal cortex is involved in action selection processes and the angular gyrus has been shown to be related to dysfluency in action selection processes. Additionally, in a recent commentary by Chirchiglia et al. (2019), the authors describe a "prefrontal dorsolateral syndrome" that mimics apathy, presenting as a loss of

interest or initiative. Chirchiglia et al. propose that damage to the DLPFC is responsible for the reduction or free will or volition, and this is the cause of the apathetic syndrome.

1.3 Apathy as a Neuropsychiatric Syndrome

1.3.1 Apathy and Depression

Apathy is a distinct neuropsychiatric syndrome that shares features of depression. Depression is also a common syndrome found in neurocognitive disorders. In fact, apathy and depression can co-occur in disorders, such as in neurodegenerative diseases. Symptoms of depression include depressed mood and/or markedly diminished interest or pleasure in activities (i.e., anhedonia; Lanctot et al. 2023). Depression and apathy have overlapping symptoms, including reduced interest and initiative and decreased motivation. However, unlike apathy, depression has elements of sadness and/or anhedonia. Two common tools for assessing depression in a clinical setting, The Hamilton Depression Scale and The Geriatric Depression Scale (GDS), include items that have been validated to assess apathy (Lanctot et al., 2023). As such, features specific to an apathetic syndrome may be masked, and instead contribute to, or overestimate, signs of depression clinically.

Distinguishing between apathy and depression has important implications, particularly in dementia research. Recent research suggests that in a prodromal state of Alzheimer's disease, the presence of apathy, and not depression, is associated with a higher risk for conversion to Alzheimer's disease (Ruthirakuhan et al., 2019). While diagnostic criteria for depression are well characterized in the DSM-5, with disease-specific variations such as for Alzheimer's disease and Parkinson's disease, assessments for apathy continue to develop. Research into the distinct phenotypic features of apathy, transdiagnostically and disease-specific, is an important research endeavor for improving early clinical detection of neurocognitive disorders.

1.3.2 Clinical Assessments of Apathy

The apathy evaluation scale (AES) and Lille apathy rating scale (LARS) are the oldest clinical tools used to assess apathy. The AES is an 18-item scale, with cognitive,

behavioural, and emotional responsivity subscales. The AES can be administered directly to patients or completed by an informant (Marin, 1999), and has been validated for use in patients with stroke, Alzheimer's disease, depression, and community-dwelling older adults. The Lille apathy rating scale is a clinician-administered interview. It includes 33 items that are divided into the following nine domains: everyday productivity, interests, taking initiative, novelty seeking, motivation, emotional responses, concern, social life, and self-awareness (Sockeel et al., 2006). The LARS has been validated for use in patients with Parkinson's disease and early mild-to-moderate dementia. In 1994, the Neuropsychiatric Inventory (NPI) was validated for use in patients with Alzheimer's disease and other types of dementia. The NPI is a comprehensive inventory of neuropsychiatric symptoms, with a subsection devoted to symptoms of apathy. A short version of the NPI (NPI-Q: NPI Questionnaire) uses a binary measure for the presence or absence of apathy (as indicated by an informant). All three of these measures are commonly used in clinical and research settings.

More recent assessments of apathy include the Apathy Motivation Index (AMI) and the Dimensional Apathy Scale (DApS). The AMI is an 18-item scale with subscales for behavioural activation, emotional sensitivity, and social motivation (Ang et al., 2017). It has been validated for use by patients with alcohol-use disorders and Parkinson's disease. The DApS includes 24 items to assess apathy symptoms across the following three subscales: executive function, emotional, and behaviour/cognitive initiation (Radakovic & Abrahams, 2014) The DApS has been validated for use in patients with Alzheimer's disease, Parkinson's disease, and Amyotrophic lateral sclerosis (ALS). The novelty in the AMI lies in its inclusion of a subscale for indexing apathy within a social setting. The DApS includes an executive scale that recognizes an "executive" deficit, whereby attentional and working memory difficulties may contribute to symptoms of apathy.Neuroanatomical Correlates of Apathy

Most studies of the neuroanatomical correlates of apathy have employed neuroimaging techniques within disease cohorts, such as Alzheimer's disease, acute strokes, or schizophrenia. A few recent studies and reviews have alluded to neuroanatomical changes that are shared across patient groups exhibiting symptoms of apathy. Striatal,

subcortical limbic, and frontal lobe regions have been implicated in giving rise to apathy. Specifically, studies comparing individuals with dementia to cognitively normal controls have found reduced cortical thickness in the orbitofrontal cortex (OFC; Jenkins et al., 2022). The OFC is responsible for facilitating the learning of stimulus-reinforcement associations, whereby the reinforcer is a reward or punishment (Rolls, 2004). This is done by representation of the reinforcer and correcting reward-related behaviour. In the context of goal-directed behaviour and apathy, disruptions in the OFC may play a vital role in integrating reward and behaviour information for execution of appropriate goal-directed activity.

The anterior cingulate cortex (ACC) is also frequently reported in studies of apathy (Jenkins et al., 2022; Lanctot et al., 2007). The ACC has extensive connections with areas known to be important for emotion (e.g., amygdala), autonomic function (e.g., lateral hypothalamus, brainstem centers), memory (e.g., hippocampal region), and reward-related functions (e.g., orbitofrontal cortex, ventral striatum; Stevens et al., 2011). It therefore is a region highly, and uniquely, involved in emotion and cognitive regulation, with its connections to the limbic system and prefrontal cortex, respectively. Experimental studies have shown that subregions of the ACC may have distinct functions. Of relevance to apathy, the dorsal ACC (dACC) is known to be associated with reward-based decision making (Bush et al., 2001), and the anterior cingulate gyrus is involved in processing social information (Apps et al., 2016). Additionally, a meta-analysis of fMRI studies in a healthy population of individuals found that the ACC and the anterior insula are involved in signaling effort costs in goal-directed behaviour, where the ACC positively correlates with effort costs and correlates negatively with reward value (Pessiglione et al., 2018; Heron et al., 2019). Additionally, it was found that the ventral medial prefrontal cortex (vmPFC), ventral striatum (VS), and ventral tegmental area (VTA) are involved in representing and signaling reward valuation (Pessiglione et al., 2018). In later sections, neuroimaging findings related to disease-specific apathy will be discussed.

1.3.3 Genetic Variants of Apathy

Few studies have explored genetic variants associated with apathy. One study by Mitaki et al. (2013) examined the effects of gene polymorphisms associated with the dopaminergic system on apathy in a healthy population of adults in Japan. The authors reasoned abnormalities in the dopaminergic transmission, which is highly involved in the brain reward and motivation system, could give rise to apathy, and that these abnormalities may have a genetic basis. As such, they selected candidate genes and single nucleotide polymorphisms (SNPs) with the following criteria: 1) genes in pathways implicated in the neurobiology of the dopamine pathway, and 2) within these genes, polymorphisms with well-documented functional effects (in vitro or in vivo) in dopamine transmission. Results revealed the minor allele and minor allele-containing genotype for SNP in the Catechol-O-methyltransferase (*COMT*) gene (rs4680) were associated with lower risk of apathy. The authors concluded that since *COMT* is the major mammalian enzyme involved in the degradation of released dopamine in the brain, this SNP may result in increased availability of dopamine in the prefrontal cortex.

In the following section, key neurotransmitter systems in processes related to apathy, such as motivation, will be discussed. In particular, we outline biological substrates previously found to be associated with neurotransmission in effort-based decision making to obtain rewards in humans.

1.3.3.1 Dopaminergic System

The dysfunction of dopaminergic transmission has been hypothesized as a new player in the pathophysiology of AD (Nam et al., 2018). Dopamine acts through five different types of receptors within two major classes: D1-like class receptors comprise the dopamine 1 receptor (D1R) and the dopamine 5 receptor (D5R), and D2-like class receptors comprise the dopamine 2 receptor (D2R), dopamine 3 receptor (D3R) and the dopamine 4 receptor (D4R; Kumar and Patel, 2007). Generally, dopamine receptors are highly expressed in the limbic system and cortex, which are responsible for regulating mood and emotions. Dopamine also plays a key role in the brain reward system (BRS). Rewards are cognitive or biological stimuli that generate and increase the frequency of

behavior that contributes to a positive emotional state; amotivational syndromes, such as apathy, can result from a loss of reward sensitivity related to BRS dysfunction (Mitchell et al., 2011), or exertion of effort and effort-related decision making (Salamone et al., 2016). Genetic variants underlying dopaminergic dysregulation may therefore present promising candidates for links with apathy in AD.

1.3.3.2 Glutamatergic System

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system. It is extensively distributed in the brain and is almost exclusively located intracellularly. Glutamatergic N-methyl-d-aspartate (NMDA) receptors play a crucial role in synaptic functioning and in activating neuronal survival pathways and inhibiting neuronal apoptosis (Wang & Reddy, 2017). The glutamate hypothesis for AD posits that the progressive cognitive decline seen in AD patients is due to neuronal cell death caused by over-activation of NMDA receptors and the subsequent pathological increase in intracellular calcium (Wang & Reddy, 2017). A recent study by Strasser et al. (2020) suggests the involvement of glutamate in motivation. In particular, the study examined whether levels of glutamate (Glu), glutamine (Gln), GABA or their ratios predict interindividual differences in effort-based motivated task performance in healthy adults. Results revealed higher Gln-to-Glu ratios in the nucleus accumbens predicted better task performance and reduced effort perception. In particular, the higher Gln-to-Glu ratio was related to the capacity to maintain performance over long periods of time, or effort sustenance. As such, the glutamatergic system may be important in effort cost computations within the framework of effort-based decision making for goal-directed behaviour.

1.3.3.3 Oxytocinergic System

Oxytocin has recently gained attention because of its role in the pathophysiology and potential management of neuropsychiatric disorders. Oxytocin is a peptide hormone that is synthesized in the hypothalamus and is released into different brain regions, acting as a neurotransmitter. Receptors for oxytocin are present in many areas of the brain, including the hypothalamus, amygdala, and nucleus accumbens. Oxytocin dysregulation in these

areas is involved in the pathophysiology of depression and anxiety (Saiz-Rodríguez et al., 2022). In healthy adults, oxytocin administration has been shown to increase cooperative behaviour, as indexed by economic decision-making tasks (Kosfeld et al., 2005; Baumgartner et al., 2008). It has also been shown to improve social cue processing, such as improved theory of mind performance (Dome et al., 2007). In study examining the effects of a single dose of intranasal oxytocin in frontotemporal dementia, a significant improvement in scores on the Neuropsychiatric Inventory (NPI) was observed on the evening of oxytocin administration compared with placebo and compared with baseline ratings. Oxytocin was also associated with reduced recognition of angry facial expressions by patients (Jesso et al., 2011). Oxytocinergic modulation could thus play a role in the processing of social rewards, within the context of effort-based decision making.

1.4 Apathy in Neurodegenerative Dementias

1.4.1 Apathy in Alzheimer's Disease & Mild Cognitive Impairment

1.4.1.1 Alzheimer's Disease (AD)

Alzheimer’s disease (AD) is the leading cause of dementia, accounting for 60–80% of cases (Thies and Bleiler, 2013). There are an estimated 50 million people with AD worldwide; this number is projected to double every 5 years and will increase to reach 152 million by 2050 (Breijyeh et al., 2020). Thus, AD presents one of the greatest global health crises of the 21st century. The total annual cost for AD and other dementias in Canada is $10.4 billion (Alzheimer’s Society Cananda, 2022). This substantial economic burden includes not only healthcare and hospice support for patients with AD, but also lost productivity from patients and overworked caregivers (Alzheimer’s Society Canada, 2022; Porsteinsson, 2023). Clinically, AD is characterized by a progressive loss of episodic memory and cognitive changes, with later deficits in language and visuospatial abilities (Grober et al., 2009). Such changes are often accompanied by behavioral disorders such as apathy, aggressiveness, and depression (Silva et al., 2019).

1.4.1.2 Neuropathology of AD

Alzheimer's disease is associated with structural alterations in the brain, including significant atrophy in the medial temporal regions, particularly in the hippocampi (Harper et al., 2017). Primary neuropathologic features of AD include a build-up of extracellular beta-amyloid plaques, intracellular neurofibrillary tangles, and cell-death of cholinergic neurons that innervate the hippocampus (Lui et al., 2013; Reinvang et al., 2013). Beta-amyloid (Aβ) plaques contribute to cell-death by interfering with cell-to-cell communication at synapses, while neurofibrillary tangles block the transport of nutrients inside cholinergic cells (Reinvang et al., 2013). Early-onset AD, defined as symptom onset before age 65 years of age, is sometimes linked to autosomal dominant inheritance of genes that cause an over-production of Aβ plaques. The more commonly occurring variant of AD is late-onset AD , defined as symptom onset after age 65 (Reinvang et al., 2013). Research demonstrates that environmental factors, such as aging, in combination with genetic factors, including APOE genotype, increase risk for developing late-onset AD (Alzheimer's Association, 2019; Mur et al., 2020; Rabinovici, 2019).

1.4.1.3 Genetics of AD

The apolipoprotein E gene (*APOE*) is located on chromosome 19 (Lui et al., 2013). It has two single nucleotide polymorphisms (SNPs) in its fourth exon, defining three alleles, ε2, ε3, and ε4, resulting in the production of three isoforms of the apolipoprotein E (apoE) protein, apoE2, E3, and E4, respectively (Lui et al., 2013). Humans inherit any two of these 3 alleles from their parents to form an *APOE* genotype. All possible combinations of the three alleles establish 6 different *APOE* genotypes in the human population, three of which include the ε4 allele (ε4/ε2, ε4/ε3, ε4/ε4). Individuals who inherit at least one ε4 allele are termed *APOE* ε4 "carriers". Linked to AD pathology, the ε4 allele is associated with reduced clearance of Aβ plaque build-up in the aging brain (Lui et al., 2013). Additionally, neuroimaging studies demonstrate that increased hippocampal volume loss in patients with AD is associated with possession of the ε4 allele (Hashimoto et al., 2001). As such, it is well-established that the ε4 allele of the *APOE* gene is associated with increased risk, as well as earlier age of onset, of AD (Alzheimer's Association, 2019).

1.4.1.4 Treatments for AD

Until the very recent FDA approval of two antibody therapies targeting beta-amyloid to slow disease progression, there were no disease modifying treatments for AD. Up until this point, therapies for AD have been limited to alleviating symptoms by counterbalancing neurotransmitter disturbances causing observed behavioural and cognitive changes. For example, cholinesterase inhibitors and dopamine regulators are used to manage changes in memory and psychosis, respectively (Yiannopoulou & Papageorgiou, 2012). Additionally, memantine, an NMDA receptor antagonist is approved for use in the United States and in Canada; memantine has demonstrated moderate significant effects on cognition and behavioural function in patients with mild to severe Alzheimer's disease (Robinson & Keating, 2006). The stage at which AD is diagnosed can impact the therapy that is advised. Early intervention in the disease course of AD has the potential to slow the progression the disease and prolong quality of life. As such, identifying early, or prodromal and disease-advancing symptoms of AD, can aid in the early detection and intervention of AD.

Accumulation of Aβ and tau tangles are widely accepted to be early markers of AD. Accordingly, anti-amyloid antibody therapies, such as Lecanemab, that target Aβ plaques have recently generated interest (Ramanan & Day, 2023). In a phase 3 clinical trial, Lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in modestly less decline on measures of cognition and function than placebo at 18 months (Van Dyck et al., 2023). Additionally, several anti-tau immunotherapies that target intracellular tau aggregation or inhibit tau expression are approved for use in clinical trials in Canada, but more research is underway to examine the safety and efficacy of anti-tau therapies for AD (Ramanan & Day, 2023).

1.4.1.5 Mild Cognitive Impairment (MCI) & AD

Mild cognitive impairment (MCI) refers to emerging cognitive impairment that is often seen as a transition or boundary stage between aging and dementia. In community-dwelling older adults, aged 71 years and older, prevalence rates of MCI are 22% (Campbell et al. 2013). Progression to clinically diagnosable dementia occurs at a 3 to 5

times higher rate from MCI than from normal cognition (Campbell et al., 2013; Roberts and Knopman, 2013). In particular, amnestic MCI (aMCI) is often seen as a precursor to AD. In aMCI, recent episodic memory loss is predominant and associated with a considerable risk of further development to AD (Albert et al. 2011), whereas non-amnestic MCIs can often progress to non-Alzheimer's disease dementias. As a key transitional stage, attention has been focused on identifying modifiable risk factors to prevent or delay the progression of MCI to AD. Common factors that increase risk of progression include older age, lower educational attainment, and ε4 allele possession (Campbell et al., 2013). Several studies have shown that the presence of apathy in MCI is a robust and common neuropsychiatric predictor of progression to AD (Teng & Cummings, 2007; Palmer et al., 2010; Richard et al. 2012).

1.4.1.6 Apathy in AD

Apathy is the most common neuropsychiatric symptom in patients with Alzheimer's disease (Zhao et al., 2016). A recent meta-analysis of 25 studies reported a prevalence of apathy in AD ranging from 19% to 88% across the studies, with an overall mean prevalence of 49% (Zhao et al., 2016). Apathy is associated with accelerated cognitive decline, increased morbidity, reduced compliance with treatment in AD, and increased caregiver burden. A recent study by Wei and colleagues (2020) investigated the cognitive and behavioural distinction of apathy in AD, compared to frontotemporal dementia and healthy older adults. The study examined a multi-dimensional model of apathy, with emotional apathy (i.e., emotional blunting and reduced empathy), executive apathy (i.e., difficulties in planning and organizing goals for the future), and initiation apathy (i.e., inactivity or lack of inertia). Consistent with previous findings, results revealed the presence of executive and initiation apathy in the early stages of AD (< 5 years since diagnosis), with the development of emotional apathy in later stages of AD, if at all (> 5 years of disease duration; Wei et al, 2020; Radakovic et al., 2014; Quaranta et al, 2012). These studies suggest a behavioural inactivation subtype of apathy may be predominant in patients with AD.

1.4.1.7 Neuroanatomical Correlates of Apathy in AD

The Wei et al. (2020) study, discussed above, revealed significant patterns of atrophy associated with apathy in patients with AD. Executive apathy in AD was correlated with atrophy in the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC). The DLPFC is linked with capacity for planning, problem solving and rule-based behaviour. Within the context of effort-based decision-making, the OFC is shown to be involved in processing stimulus-reward contingencies. Initiation apathy in patients with AD was associated with lower grey matter intensity in the medial prefrontal cortex and anterior cingulate. Atrophy or lesions in these brain regions is correlated with decreased spontaneity in goal-directed behaviour and impaired motor activity.

Other recent studies similarly implicate frontal-subcortical regions of the brain in giving rise to apathy in AD. In an FDG-PET study, apathy in patients with AD was related to hypometabolism in the right anterior cingulate (Fernández-Matarrubia et al., 2018). In a small sample of patients with AD (n=28), brain amyloid-beta was imaged using PET and a positive correlation between severity of apathy, indexed by the NPI, and amyloid-beta deposition in the medial and orbitofrontal areas, insula, and right ACC was found (Mori et al, 2014). Interestingly, there was no difference in apathetic versus non-apathetic patients in cognitive function and disease duration, suggesting that the relationship between apathy and amyloid deposition may not be simply mediated by disease severity in AD. Neuroimaging studies of apathy in AD have also pointed to the involvement of the basal ganglia in giving rise to apathy (Rosenberg et al., 2015, Theleritis et al., 2014). As such, fronto-striatal connections, including the ACC, PFC, and basal ganglia are potential circuits affected in apathy in patients with AD. Indeed, studies have shown that links between the ventral striatum and dACC via the ventral pallidum and thalamus are involved in effort-based decision-making and executive functioning (Nobis & Husain, 2018).

1.4.1.8 Genetic Contributors to Apathy in AD

Genetic contributors to apathy in AD have not been widely studied. Recent work demonstrates that the possession of the APOE ε4 allele and the presence of apathy in

MCI confer an additive risk for conversion to AD (Pink et al., 2015). However, whether there are genetic variants associated with apathy, regardless of disease severity or outcome remains elusive. Similarly, past research investigating CSF biomarkers associated with apathy in AD has been inconclusive. Lanctot and colleagues (2017) concluded in their literature review that amyloid protein burden is a marker of apathy in the early stages of AD, whereas tau protein burden is associated with higher apathy throughout AD progression. In a mixed sample of people with different dementias, lower levels of CSF amyloid beta 1–42 (Aβ1–42) was associated with increasing apathy over a 5-year period, while higher levels of CSF tau and phosphorylated tau were associated with decreased levels of apathy over time (Banning et al., 2020).

1.4.2 Apathy in Parkinson's Disease and Lewy Body Dementia

1.4.2.1 Parkinson's Disease (PD) & Lewy Body Dementia (LBD)

Parkinson's disease (PD) is the second most common neurodegenerative disease, after AD, with a prevalence of 1.2% in men and 0.6% in women, aged 65 or older, in Canada (Statistics Canada, 2011). The population-based incidence of Lewy body dementia (LBD) is between 0.5 and 1.6 per 1000 person-years, accounting for 3 to 7% of dementia cases (Hogan et al., 2016). Parkinson's disease and Lewy body dementia (LBD) share many diagnostic and neuropathological features. Clinically, PD and LBD are distinguished based on the time at which motor and cognitive symptoms occur. In LBD, early cognitive impairment typically precedes motor symptoms, and the opposite pattern is true in PD (Jellinger & Korczyn, 2018). LBD is characterized by dementia with moderate memory impairment, deficits in attention, executive dysfunction and visuospatial ability, fluctuating cognition, and recurrent visual hallucinations that are well-formed and detailed (Jellinger & Korczyn, 2018; Gromperts, 2016). Additionally, REM sleep behaviour disorder is a core feature of LBD that may precede cognitive impairment by decades, and motor symptoms, such as bradykinesia and rigidity may occur later in the disease course (in approximately 85% of cases; Postuma et al., 2015). Tremors are less common in LBD, but are a core motor feature of PD. Moreover, the cognitive symptoms associated with PD, although different in timing and frequency of occurrence, are virtually indistinguishable from LBD (Postuma et al., 2015; Jellinger & Korczyn, 2018).

1.4.2.2 Neuropathology of PD & LBD

Both PD and LBD share pathological features, namely the inclusion of alpha-synuclein protein aggregates. Alpha-synuclein is a small protein and under pathological conditions aggregates into β-sheet-rich oligomers and fibrils predominantly in neuronal cells and their processes (termed Lewy bodies and Lewy neurites respectively; Serpell et al. 2000). The pathological delineation of PD compared to LBD lies in the stage of progression of pathology through the brain; patients with PD generally have inclusions restricted to the brainstem and limbic regions, while patients with LBD have inclusions in cortical regions (Walker et al., 2019). Specifically, LBD cases have higher burden of Lewy bodies/neurites in limbic and neocortical regions, including the temporal lobe and hippocampus compared to PD cases. In PD, dopaminergic cell loss in the substantia nigra is reportedly higher (mainly affecting the dorsolateral regions), compared to LBD (where medioventral regions are most affected; Walker et al., 2019; Jellinger, 2018). These findings align with the predominant cognitive impairment seen in patients with LBD and more pronounced motor disorder in PD.

Although primarily classed as synucleinopathies, LBDs are heterogeneous disorders with pathologic substrates including synaptic degeneration, vascular pathology, neuronal loss and basal forebrain cholinergic degeneration (Walker et al., 2019). In both PD and LBS, AD-related pathologies are also a common feature, with hyperphosphorylated tau and amyloid-beta contributing to cognitive decline. Concurrent AD-related and alpha-synuclein pathologies can occur at more advanced stages in patients with LBD, when compared to patients with PD (Walker et al., 2019).

1.4.2.3 Genetics of PD & LBD

Most PD cases are sporadic, with only 5% of patients presenting a genetic form (Tran et al., 2020). The most common genetic variants associated with PD are located close to the leucine-rich repeat kinase 2 (*LRRK2*) gene, alpha-synuclein gene (*SNCA*), and microtubule associated protein tau (*MAPT*) gene, as well as low-frequency coding variants in the glucocerebrosidase (*GBA*) gene (Billingsley et al., 2018). Mutations in *LRRK2* are associated with increased kinase activity and are the most common cause of

autosomal dominant PD (Rui et al., 2018). The SNCA gene codes for alpha-synuclein and *GBA* codes for an enzyme involved in lysosomal function; mutations associated with these genes in PD are thought to cause disruptions in regulating alpha-synuclein (Billingsley et al., 2018; Simon-Sanchez et al., 2009; Chia et al., 2021).

A recent genome-wide association study (GWAS) identified risk alleles associated with Lewy body dementia, including GBA, bridging integrator 1 (*BIN1*), transmembrane protein 175 (*TMEM175*), *SNCA* and *APOE* (Chia et al., 2021). *APOE* and *BIN1* are risk loci that affect the accumulation of amyloid-beta and neurofibrillary tangles in AD (Seshadri et al., 2010). The question of whether the *APOE* ε4 allele independently drives alpha-synuclein pathology or contributes to AD pathology in complex cases of LBD + AD remains unclear. In alpha-synuclein transgenic mice expressing human *APOE* isoforms, the *APOE* ε4 allele was found to regulate synucleinopathies directly and independently of amyloid-beta deposition (Davis et al., 2020). However, a recent study by Kaivola et al. (2022) stratified a group of patients with LBD into three groups based on extent of concomitant AD pathology. Results revealed that APOE ε4 was associated with LBD + AD and LBD + intermediate, but not with pure dementia with Lewy bodies. Additionally, the study revealed an interplay between the *APOE* ε4 allele and *GBA*, such that *GBA* was associated with risk for LBD in patients without *APOE* ε4, but not with patients with *APOE* ε4.

1.4.2.4 Treatments for PD & LBD

Currently, symptomatic treatments for PD and LBD are available. To treat cognitive symptoms, acetylcholinesterase inhibitors, donepezil and rivastigmine, have been demonstrated to be effective in LBD and PD, respectively (Wang et al., 2015). Acetylcholinesterase inhibitors, and low-dose atypical anti-psychotics, such as quetiapine and clozapine, are first-line treatment options for visual hallucinations and delusions (Gomperts, 2016). Carbidopa/levodopa are dopamine agonists often used to improve motor function and reduce tremors in PD and LBD (Molloy et al., 2005). To date, there are no known disease-modifying treatments for either PD or LBD.

1.4.2.5 Apathy in PD & LBD

Apathy is reported in 54% and 57% of patients with PD and LBD, respectively (Milan-Tomas et al., 2021). Just as in patients with AD, apathy in PD and LBD is associated with more severe symptoms and quicker cognitive decline. Radakovic et al. (2017) leveraged the dimensional apathy scale to investigate subtypes of apathy in a cohort of patients with PD. Results revealed that on the caregiver-rated DAS, executive apathy was significantly greater than in healthy controls, and in the self-rated DAS, both executive and initiation apathy were significantly different from controls. The authors concluded that, unrelated to motor impairments, patients with PD demonstrate a lack of motivation for planning, organization and attention, and lack of initiation of thoughts or behaviors. In line with an executive apathy profile in PD, Mole et al. (2022) recently assessed the ability of patients with PD to perform on the Brixton Spatial Anticipation Task (Brixton), a measure of inductive reasoning. Results demonstrated that apathy, indexed by the LAS, predicted Brixton errors associated with a failure to generate either correct or incorrect rules. The authors reason that deficient reasoning in apathy may be underpinned by impaired option generation.

In the context of effort-based decision making, Muhammed et al. (2016) assessed reward sensitivity in patients with PD, ON and OFF dopaminergic medication. Pupillary dilation to increasing levels of monetary reward was used to index reward sensitivity. Results revealed that decreased pupillary dilation was predictive of apathy in patients with PD compared to healthy controls, and this effect was independent of motor impairment and autonomic dysfunction. Reward sensitivity was modulated by dopaminergic state, with blunted sensitivity when patients were OFF dopaminergic drugs.

Few studies have examined the nature of apathy in LBD. A recent study compared cognitive function in patients with LBD and apathy and those with AD and apathy (Breitve et al., 2018). Specifically, they investigated the association between apathy, indexed by the NPI, and the Mini Mental State Examination (MMSE), over a 4-year period. They found that apathy was associated with a faster global cognitive decline (MMSE) over 4 years in patients with LBD compared to patients with AD. The authors

reasoned that apathy was associated with worse executive outcomes in patients with LBD compared to patients with AD.

1.4.2.6 Neuroanatomical Correlates of Apathy in PD & LBD

Given the involvement of the basal ganglia in PD and apathy, Carriere et al. (2014) compared striato-frontal brain changes in patients with PD and apathy, PD without apathy, and healthy controls. Results revealed a positive correlation between the severity of apathy and atrophy of the left nucleus accumbens. Additionally, there was greater atrophy of the dorsolateral head of the left caudate in apathetic patients than in nonapathetic patients, and greater atrophy in the bilateral nucleus accumbens in apathetic patients than in healthy controls. Martinez-Horta et al. (2017) used MRI and voxel-based morphometry to quantity grey matter volume changes in patients with PD and apathy versus those without apathy. In their analysis, clusters of cortical grey matter volume decreases were found in the parietal cortex, lateral prefrontal cortex, and orbitofrontal cortex. The second largest cluster of grey matter volume loss was found in the left nucleus accumbens. These structures are key nodes in the human brain reward circuit, and align with behavioural findings indicating reduced reward sensitivity in PD (e.g., Muhammed et al., 2016).

A SPECT study found dopaminergic neuronal loss in the bilateral putamen of patients with apathy, including those with Alzheimer's disease and dementia with Lewy bodies (David et al., 2008). Another study that included both patients with LBD and AD, investigated the relationship between apathy and striatal dopamine uptake, using (123)I-FP-CIT SPECT (Aalten et al., 2008). They found that higher apathy was associated with a reduced dopaminergic binding potential in the right putamen (Aalten et al., 2008). As a core structure in the basal ganglia, the putamen plays a key role in regulating movement planning and execution (Zapparoli et al., 2017). As such, patients with LBD and apathy may experience a lack of behavioural initiation or avolition that gives rise to symptoms of apathy.

1.4.2.7 Genetic Contributors to Apathy in PD & LBD

One study in a Polish sample of patients with PD investigated the link between SNPs in the brain-derived neurotrophic factor (BDNF) gene and the presence of apathy (Gorzkowska et al., 2021). The BDNF gene is widely expressed in the human brain and maintains the survival of dopaminergic neurons. Neuroimaging studies have shown an association between the Val66Met polymorphism of BDNF gene and gray matter volume in the anterior cingulate cortex and dorsolateral prefrontal cortex (Matsuo et al., 2009); both of these brain regions have been implicated in the pathogenesis of apathy. Results revealed that patients carrying the AA (Met/Met) genotype of the BDNF polymorphism were more likely to be apathetic, but these results were not significant, perhaps owing to the small sample size of the study (Gorzkowska et al., 2021). To date, there are no established genetic variants associated apathy in patients with LBD.

1.4.3 Apathy in Frontotemporal Dementia

1.4.3.1 Frontotemporal Dementia (FTD)

Frontotemporal dementia (FTD) comprises a group of heterogeneous neurodegenerative disorders characterized by changes in behaviour, language, and motor function (Greaves & Rohrer, 2019). The estimated point prevalence of FTD is 15–22/100000 (Onyike & Diehl-Schmid, 2013). FTD is considered a rare disease, but it is the second most common form of neurodegenerative dementia in individuals under the age of 60 (Coyle-Gilchrist et al., 2016). The behavioural variant (bvFTD) is the most frequently diagnosed type of FTD, accounting for nearly 60% of cases, and is characterized by stark changes in personality and decline in social function (Onyike & Diehl-Schmid, 2013; Piguet & Hodges, 2013). Some commonly cited symptoms of bvFTD include the following: behavioural disinhibition (socially inappropriate behavior, loss of manners, impulsivity, rash actions), apathy or inertia, loss of empathy or social disinterest, perseverative or compulsive/ritualistic behaviour, hyperorality and dietary changes, executive dysfunction with relative sparing of episodic memory and visuospatial ability (Young et al., 2018).

The language variant (known as primary progressive aphasia, PPA) is typically associated with progressive speech production or comprehension difficulties (Mesulam,

2003; Gorno-Tempini et al., 2011). PPA is further subdivided into semantic variant PPA (svPPA) and nonfluent agrammatic PPA (nfvPPA; Young et al., 2018). Patients may be diagnosed with the semantic variant of PPA if they exhibit impaired confrontation naming (i.e., difficulty naming or recognizing objects or drawings) and impaired single-word comprehension. Patients with svPPA generally have at least three of the following symptoms: impaired object knowledge, surface dyslexia (i.e., inability to recognize words as a whole) or dysgraphia, spared repetition, or spared speech production (Young et al., 2018). Patients with nfvPPA exhibit agrammatism in language production or effortful speech that is not consistent with apraxia of speech. They may also experience at least two of the three following symptoms: impaired comprehension of complex sentences, spared single-word comprehension, or spared object knowledge (Young et al., 2018).

People with FTD can also develop motor deficits, either amyotrophic lateral sclerosis (FTD-ALS) or Parkinsonism, in the latter case often with specific features of a corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP; Greaves & Rohrer, 2019). Frontotemporal dementia symptoms are found in up to 15-30% of patients diagnosed with amyotrophic lateral sclerosis (ALS; Ringholz et al., 2005). Patients with FTD-ALS have behavioral changes consistent with bvFTD or dysexecutive function, including verbal fluency deficits, as well as hallucinations and delusions (Strong et al., 2017). Patients with features of CBS often exhibit apraxia and/or alien limb phenomenon, frontal deficits, and extrapyramidal motor symptoms, such as myoclonus or rigidity (Armstrong et al., 2013). In patients with PSP, it is common to see behavioural symptoms such as apathy, disinhibition, anxiety, dysphoria, and stereotypic or repetitive behaviors. Patients with PSP may also present with primary apraxia of speech, combined apraxia of speech and progressive non-fluent aphasia (Höglinger et al., 2017).

1.4.3.2 Neuropathology of FTD

FTDs are divided into subtypes based on their respective protein-based inclusions. Accumulations of tau or TAR DNA-binding protein 43 (TDP-43) account for most of the pathologically confirmed cases of FTD, with fused in sarcoma (FUS) inclusions common in the remaining 10% (Finger, 2016). The TPD-43 protein normally helps regulate gene expression in the brain. Under pathological conditions, cleavage, hyperphosphorylation

and ubiquitination of TDP-43 can occur (Jo et al., 2020). These posttranslational modifications lead to cytoplasmic aggregation of TDP-43 (Jo et al., 2020). Previous studies found that TDP-43 neuropathology is present in GRN mutations, and the brain pathology of MAPT mutation carriers is characterized by tau-positive inclusions (Bang et al., 2015; Irwin et al., 2015).

Neuroimaging studies of FTD have shown distinct brain atrophy patterns associated with the different variants. BvFTD is characterized mainly by frontal and anterior temporal lobe atrophy, which tends to be asymmetric between hemispheres; more posterior cortical areas are relatively spared in bvFTD (Warren et al., 2013). In svPPA, there is a characteristic pattern of asymmetrical, usually left greater than right, atrophy of the temporal lobes, particularly in the anterior and inferior regions (Rohrer & Rosen, 2013). Imaging studies of nfvPPA demonstrate that atrophy is most prominent in the left inferior frontal lobe, insula and premotor cortex (Rohrer & Rosen, 2013).

1.4.3.3 Genetics of FTD

FTD is a heritable neurodegenerative disorder, with strong family history presenting in 10-48% of cases (Greaves & Rohrer, 2019). There are three common autosomal dominant genetic mutations in three genes that account for most of the heritability of FTD. These three genes are progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), and chromosome 9 open reading frame 72 (*C9orf72*). Most cases of genetic FTD are of the behavioural variant. Patients with the *C9orf72* expansion mutation may exhibit an atypical neuropsychiatric presentation of bvFTD with hallucinations or delusions (Devenney et al., 2018). Additionally, family members of *C9orf72* carriers have a greater risk of psychiatric disorders, including autistic spectrum disorders, psychotic illnesses including schizophrenia, mood disorders and suicide (Devenney et al., 2018; Greaves & Rohrer, 2019).

The majority of Individuals with the *MAPT* mutation have either behavioral changes associated with bvFTD or, less commonly, a parkinsonian syndrome (i.e., progressive supranuclear palsy, corticobasal syndrome, or Parkinson disease; Rohrer et al., 2000). In rare cases, *MAPT* mutation carriers may also have prominent semantic impairment, CBS

or, in rare cases, PSP may both occur, although never FTD-ALS (Greaves & Rohrer, 2019). In contrast, *GRN* mutations can present with PPA, either a non-fluent variant of PPA or a mixed phenotype, not clearly fitting into one of the three described. PPA is a rare phenotype but is usually a non-fluent variant when present, and similarly parkinsonian disorders can occur but are infrequent as a presenting syndrome (Greaves & Rohrer, 2019).

Neuroimaging studies have shown unique patterns of atrophy for genetic FTD. *MAPT* mutation carriers exhibit relatively symmetrical anterior temporal lobe atrophy with lesser involvement of the orbitofrontal cortices (Rohrer et al., 2010). *GRN* mutations are associated with strongly asymmetrical atrophy affecting either the left or right hemispheres maximally and involving the temporal, inferior frontal and inferior parietal lobes. In patients with the *C9ORF72* gene mutation, imaging studies have shown relatively symmetrical involvement of the frontal and temporal lobes, as well as posterior cortical involvement (Mahoney et al., 2012). Compared to *MAPT* and *GRN* mutation carriers, *C9ORF72* gene mutation carriers demonstrate involvement of the thalamus and cerebellum (Mahoney et al., 2012).

1.4.3.4 Treatments for FTD

Treatments for FTD are tailored to managing cognitive, behavioural, and language symptoms, but success in clinical trials has shown modest or variable improvements. Cholinesterase inhibitors for FTDs are not commonly used and have been found to exacerbate behavioural symptoms (Tsai & Boxer, 2014). Unlike in AD, memantine was found to not be an effective treatment for cognitive symptoms in FTD and accelerated cognitive decline in some patients (Boxer et al., 2013). Limited evidence suggest that severity of compulsions, agitation, aggressiveness, impulsivity, and aberrant eating behavior can improve with certain SSRIs, such as trazadone, in FTD, but there are no significant improvements in cognition (Boxer et al., 2013). Dopamine receptor antagonists (i.e., antipsychotic medications) are used clinically to treat the behavioral symptoms of FTD, including agitation and disinhibition (Huey et al., 2006). Currently, there are no established disease-modifying treatments of FTD. However, clinical trials targeting tau protein aggregates or aiming to restore granulin levels are currently

underway, and are expected to be completed by the end of the decade (Jadhav et al., 2019).

1.4.3.5 Apathy in FTD

Apathy is common neuropsychiatric syndrome occurring in approximately 90% of FTD cases (Mendez et al., 2000). A recent study using the DApS to categorize apathy subtypes in patients with bvFTD and PPA, compared to AD was recently conducted (Radakovic et al., 2021). The authors found that patients with bvFTD had significantly higher emotional apathy (indifference or emotional/affective neutrality) than patients with AD and PPA. Additionally, lower self-awareness for executive apathy (lack of motivation for planning, organization, or attention) differentiated bvFTD from PPA. Another study of caregiver- and self-ratings of apathy in a sample of patients with FTD found nfvPPA and svFTD did not differ from healthy controls and their informants. In the patients with bvFTD, caregiver apathy scores were not correlated with general cognitive screening or depression scores but were significantly correlated with social cognition and executive function measures (Eslinger et al., 2012).

In a longitudinal study of pre-symptomatic carriers of *MAPT*, *GRN* or *C9orf72* mutations, the motivation subscale of the caregiver-reported Cambridge Behavioural Inventory revised was used to assess changes in apathy over time (Malpetti et al., 2021). In a two-year period, the study found that pre-symptomatic carriers had greater apathy scores compared to non-carriers. Additionally, in pre-symptomatic mutation carriers, baseline apathy severity predicted cognitive decline over the two-year period (Malpetti et al., 2021). Future studies should aim to differentiate apathy profiles within genetic FTD group to better elucidate genetic variants giving rise to apathy in FTD.

Recently, a group of researchers explored apathy in bvFTD within the framework of effort-based decision making (Le Bouc et al., 2023). Their primary finding was elevated effort aversion, but not reduced reward appetence, as a core dysfunction related to apathy in patients with bvFTD. Another study leveraged the Philadelphia Apathy Computerized Test (PACT) to assess apathy, specifically within the initiation, planning, and motivation domains, in a cohort of patients with bvFTD. The authors found that patients with bvFTD

showed significant impairments in each of the three domains of apathy (Massimo et al., 2015). Collectively, these findings highlight apathetic symptoms in the heterogeneous bvFTD disorder may relate to specific neuroanatomical correlates of effort-based decision making and affected brain regions.

1.4.3.6 Neuroanatomical Correlates of Apathy in FTD

In the same study by Massimo et al. (2015) that explored apathy in bvFTD using PACT, neuroanatomical correlates of apathy were examined. Specifically, the authors found that poor initiation was associated with grey matter atrophy in the anterior cingulate. Planning impairment was associated with atrophy in the dorsolateral prefrontal cortex (DLPFC), and motivation impairment was related to atrophy of the orbitofrontal cortex (OFC). In the study conducted by Le Bouc et al. (2023), effort avoidance was associated with atrophy in the dorsal anterior cingulate cortex, within the bvFTD group. Using Voxel-based morphometry, Eslinger et al. (2012), found that caregiver apathy ratings in bvFTD were related to prominent atrophy in the right caudate (including the ventral striatum), the right temporo-parietal junction, right posterior inferior and middle temporal gyri, and left frontal operculum-anterior insula region.

1.4.4 Clinical Trials for Apathy in Neurodegenerative Dementias

Recent clinical trials for apathy in neurodegenerative dementias have investigated the potential effects of dopamine agonists in alleviating symptoms. In a multicenter randomized placebo-controlled clinical trial, Mintzer et al. (2021) measured whether methylphenidate compared with placebo decreases the severity of apathy in individuals with AD. Indexed by the NPI, more improvement was found from baseline to 6 months in the apathy sub score in those receiving methylphenidate compared with those receiving placebo. The largest improvement in apathy scores was observed within the first 100 days, and there were no adverse events related to methylphenidate in the AD cohort. Safinamide, a drug that increases dopamine in the brain by inhibiting the monoamine oxidase B enzyme involved in metabolizing dopamine, was tried in a cohort of patients with PD. In a prospective, 24-week, two-site, randomized, double-blind, placebo-controlled trial, Kulisevsky et al. (2021) found a trend towards a significant decrease in

apathy scores on safinamide versus placebo. The drug was safe and well-tolerated, but the limited sample size failed to produce significant results. A clinical trial of intranasal oxytocin for FTD assessed the effectiveness of the treatment on apathy, loss of interest, and lack of empathy (Jesso et al., 2011). The primary outcome of the study was the change in the apathy/indifference score of the NPI. The authors found that a single dose of intranasal oxytocin administration was associated with significant improvement in the NPI apathy score compared to placebo and compared to baseline score (Jesso et al., 2011).

Previously, Gauthier et al. (2002) explored the effect of a cholinesterase inhibitor, donepezil, on behavioural symptoms in AD in a large, double-blind, placebo-controlled trial. The primary outcome measure was the NPI total score. Changes in NPI sub scores, including the apathy sub-score were measured at Week 24, and significant improvements in apathy, as well as the other 11 sub scores on the NPI, were found with donepezil treatment. However, apathy was not a primary outcome in the study, and the effect size was small. Additionally, more recent investigations of cholinesterase inhibitors in trials for apathy were unable to replicate these results (Ruthirakuhan et al., 2018). A more recent non-pharmacological trial for apathy in dementias is exploring the use of repeated transcranial magnetic stimulation (rTMS), the rTMS Apathy Clinical Trial (REACT) out of the Toronto Dementia Network. In a previous 8-week, double-blind, randomized, sham-controlled cross-over pilot study on 9 patients with MCI and apathy, there was a significantly greater improvement in the AES cognitive domain with rTMS compared to sham treatment at 2 weeks. The stimulation site was the left dorsolateral prefrontal cortex (DLPFC), and the authors concluded that enhanced dopamine transmission in the prefrontal cortex, the ipsilateral anterior cingulate, and medial orbitofrontal cortex, as detected in prior studies, could explain the improvement in apathy (Padala et al., 2018; Cho and Strafella, 2009).

1.4.5 Psychosocial Interventions for Apathy

With limited options and efficacy of pharmacological interventions for apathy, psychosocial interventions for apathy in neurodegenerative dementias are often employed. A recent review of non-pharmacological approaches to apathy indicated that

emotional and stimulation-oriented therapies were useful for individuals with mild cognitive impairment (MCI) or mild-to-moderate dementia (Oba et al., 2022). One study found that reminiscence group therapy was effective in reducing cognitive apathy on the AES (Hsieh et al., 2010). This therapy involved 12 sessions, 40-50 minutes per week, of reminiscing, and telling others, about past life experiences, and has been associated with improving self-esteem, life satisfaction, and social interactions. In a sample of individuals with dementia-related symptoms, recruited from a nursing facility in China, Tang and colleagues (2018) demonstrated the efficacy of a 12-week music therapy intervention in improving AES total score. Music therapy includes sensory stimulation by listening to music, singing nostalgic songs, and playing musical instruments. In individuals with amnestic MCI, a cognitive training intervention, using a memory task adapted to an iPAD game, was found to help stabilize AES total score over a 4-week period in a treatment group, compared to controls (Savulich et al., 2017). Collectively, these findings have shown the potential benefits of continuous emotional and cognitive stimulation therapies for apathy in patients with dementia and dementia-related symptoms.

1.5 Critical Gap

Behavioural, cognitive, and neuroanatomical correlates of apathy, as they manifest within and across neurodegenerative disorders, are novel research pursuits that have gained traction in the past decade. Apathy, as a distinct, multidimensional construct, has only recently gained appreciation in clinical neuroscientific research. An effort-based decision-making model for goal-directed behaviour offers a nuanced experimental approach for exploring the neurocognitive mechanisms that correlate with apathetic symptoms. To date, few studies have examined whether impairments in EBDM in the context of GDB underlie apathy in neurodegenerative dementias. Additionally, option generation has only recently become introduced into the apathy literature, with only one study investigating option generation in a neurodegenerative disorder (Ang et al., 2019). To our knowledge, no studies have examined the relationship between intention binding (a measure of the sense of agency) and apathy. Critically, understanding whether and how deficits in option generation, effort discounting, reward valuation, and volition, as

well as the neural and genetic basis of these impairments, contribute to apathy in neurodegenerative dementias will help inform future therapies for apathy. Particularly, discovering whether apathy manifests as a result of unique disease-specific pathologies or similarly across diseases is a crucial step informing future clinical trials targeting apathy and their selection of inclusion criteria (pathology based vs. cognitive deficit focused or neurotransmitter based) as well as their treatment targets.

1.6 Thesis Objectives & Hypotheses

The overall purpose of this thesis is to explore the neurocognitive mechanisms and genetic variants that underlie apathy in neurodegenerative dementias. Three studies were conducted to achieve this goal. The central hypothesis of this thesis is that deficits in option generation, motivation (effort and/or reward sensitivity), and/or volition will be associated with apathy in neurodegenerative dementias. These deficits will relate to focal atrophy in cortical and subcortical structures associated with brain regions known to underlie option generation, motivation, and/or volition, specifically fronto-striatal structures. The results of these studies expand upon existing work in the field of effort-based decision making, apathy, and neurodegenerative dementias, and outline recommendations for potential treatment targets for apathy.

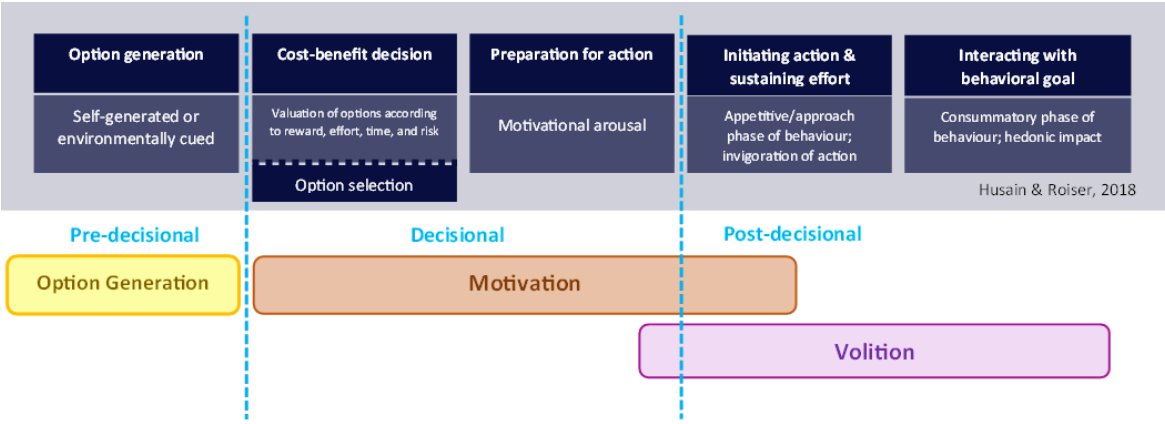

Figure 1-2 Model of neurocognitive mechanisms giving rise to apathy in neurodegenerative dementias.

1.6.1 Study 1: Neural correlates and genetic variants underlying apathy in Alzheimer's Disease

Little is known about how genetic variants and focal brain atrophy patterns interact to give rise to apathy in health and in disease. In study 1, candidate single nucleotide polymorphisms (SNPs) associated with neurotransmitter systems potentially involved in apathy were selected for analysis. Similarly, structural imaging data across the whole brain was leveraged for the analysis. Apathy was a binary variable, indicating the presence or absence of symptoms of apathy, using the Neuropsychiatric Inventory (NPI). A partial least squares correspondence analysis was used to explore interactions in SNPs and ROI cortical thickness and subcortical volume measures in a cohort of patients with mild cognitive impairment and Alzheimer's disease, with versus without apathy. We hypothesized that SNPs associated with dopaminergic regulation in the brain would correlate with significant patterns of atrophy in fronto-striatal brain structures in patients with apathy, compared to those without apathy.

1.6.2 Study 2: Neurocognitive mechanisms of apathy in neurodegenerative dementias

An effort-based decision making framework that includes option generation and volition has not been explored across neurodegenerative dementias. In study 2, behavioural tasks were created to index option generation, effort-based decision making for rewards, and volition. In the EBDM tasks, cognitive and motor effort were assessed in relation to obtaining money, candy, and social rewards. Patients with FTD, LBD, AD, and healthy controls were included in the study. All participants completed apathy questionnaires and the behavioural tasks. A partial least squares (PLS) analysis was used to find outcomes across our behavioural tasks that cluster together and reflect apathy items corresponding to cognitive components of our EBDM model. We hypothesized that deficits in one or more of these tasks (i.e., option generation, cognitive EBDM, motor EBDM, intentional binding) would give rise to distinct, transdiagnostic apathy profiles across the patient groups.

1.6.3 Study 3: Neural correlates of apathy in neurodegenerative dementias

Informed by the findings of study 2, the objective of study 3 is to determine the neuroanatomical correlates underlying the neurocognitive profiles of apathy that emerge from the PLS. Participants in study 2 completed 3T structural MRI scans. The scans were used to conduct a whole-brain region of interest (ROI) analysis, whereby multivariate regressions probed for links between the PLS apathy clusters and focal atrophy patterns. We hypothesized that patients with apathy and deficits in certain clusters would show patterns of reduced cortical thickness and subcortical volumes in fronto-striatal structures related to the cognitive processes that map onto the clusters. Specifically, we expected patients with apathy and deficits in option generation to show reduced cortical thickness in the dorsolateral prefrontal cortex. Patients with apathy and impairments in motivation were expected to demonstrate reduced cortical thickness in the orbitofrontal cortex, anterior cingulate cortex, and/or reduced volume of the ventral striatum. Additionally, we hypothesized that patients with apathy and a reduced sense of agency would demonstrate reduced cortical thickness in premotor areas, right temporoparietal junction, and/or the dorsolateral prefrontal cortex.

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2 Chapter 2: Neural Correlates & Genetic Variants Underlying Apathy in Alzheimer's Disease

2.1 Introduction

Alzheimer's disease (AD) is the leading cause of dementia, accounting for 60–80% of cases (Thies and Bleiler, 2013). More than 80% of patients exhibit at least one neuropsychiatric symptom, such as hyperactivity (aggression, disinhibition, irritability, aberrant motor behavior and euphoria), psychosis (delusions, hallucinations and sleep disorder), affective (depression and anxiety,) and apathy (apathy and appetite disorder), since the onset of cognitive impairment (Zhao et a., 2016). Apathy is the most common neuropsychiatric symptom in patients with Alzheimer's disease (Zhao et al., 2016) and is associated with accelerated cognitive decline, increased morbidity, reduced compliance with treatment, and increased caregiver burden. Apathy in AD is often refractory to pharmacologic interventions, though clinical trials have shown some benefit of dopamine agonists, such as methylphenidate (Mitchell et al., 2011). Whether specific genetic variants related to differential function of neurotransmitter systems relevant to apathy and AD are associated with the development of apathy, either directly or in interaction with regional atrophy has not been evaluated. This knowledge may inform prediction of individual patient's response to treatment.

In patients with AD, apathy is associated with atrophy in regions of prefrontal cortex and the basal ganglia. A recent meta-analysis of 25 studies reported a prevalence of apathy in AD ranging from 19% to 88% across the studies, with an overall mean prevalence of 49% (Zhao et al., 2016). A recent study by Wei and colleagues (2020) investigated the cognitive and behavioural distinction of apathy in AD, compared to frontotemporal dementia and healthy older adults. The study examined a multi-dimensional model of apathy, with emotional apathy (i.e., emotional blunting and reduced empathy), executive apathy (i.e., difficulties in planning and organizing goals for the future), and initiation apathy (i.e., inactivity or lack of inertia). Consistent with previous findings, results revealed the presence of executive and initiation apathy in the early stages of AD (< 5

years since diagnosis), with the development of emotional apathy in later stages of AD, if at all (> 5 years of disease duration; Wei et al, 2020; Radakovic et al., 2014; Quaranta et al, 2012).

Executive apathy in AD was correlated with atrophy in the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC). The DLPFC is linked with capacity for planning, problem solving and rule-based behaviour. Within the context of effort-based decision-making, the OFC is involved in processing stimulus-reward contingencies. Initiation apathy in patients with AD was associated with lower grey matter intensity in the medial prefrontal cortex and anterior cingulate. Lower volumes in these brain regions was correlated with decreased spontaneity in goal-directed behaviour and impaired motor activity.

Other recent studies similarly implicate frontal-subcortical regions of the brain in giving rise to apathy in AD. Apathy in patients with AD was related to hypometabolism in the right anterior cingulate (Fernández-Matarrubia et al., 2018), and amyloid-beta deposition in the medial and orbitofrontal areas, insula, and right ACC (Mori et al, 2014). Neuroimaging studies indicate the involvement of the basal ganglia in giving rise to apathy (Theleritis et al., 2014). As such, frontostriatal connections, including the ACC, PFC, and basal ganglia are potential circuits affected in apathy in patients with AD. Indeed, links between the ventral striatum and dACC via the ventral pallidum and thalamus are known to be involved in effort-based decision-making and executive functioning (Nobis & Husain, 2018).

The underlying neuropathophysiology of apathy in AD is not well understood. Disruptions in neurotransmitter systems related to the fronto-striatral structures are probable candidates for giving rise to apathy. Dopamine plays a key role in the brain reward system (BRS). Rewards are cognitive or biological stimuli that generate and increase the frequency of behavior that contributes to a positive emotional state; amotivational syndromes, such as apathy, can result from a loss of reward sensitivity related to BRS dysfunction (Mitchell et al., 2011), or exertion of effort and effort-related decision making (Salamone et al., 2016). The glutamate hypothesis for AD posits that the

progressive cognitive decline seen in AD patients is due to neuronal cell death caused by over-activation of NMDA receptors and the subsequent pathological increase in intracellular calcium (Wang & Reddy, 2017). Levels of glutamate (Glu) and glutamine (Gln) have been shown to predict interindividual differences in effort-based motivated task performance in healthy adults. Previous studies show that oxytocin dysregulation in the hypothalamus, amygdala, and nucleus accumbens are involved in depression and anxiety, and processing of facial expressions (Saiz-Rodríguez et al., 2022; Jesso et al., 2011). The cholinergic hypothesis for AD posits early degeneration of basal forebrain cholinergic neurons, which support memory, learning, and motivation, among other cognitive and autonomic functions involved in goal-directed behaviour (Chen et al., 2022). As such, dopaminergic, glutaminergic, cholinergic, and oxytocinergic modulation are potentially related to apathy in AD.

The major genetic risk factor for AD is the apolipoprotein E gene (APOE; Lui et al., 2013). Individuals who inherit at least one ε4 allele are termed APOE ε4 "carriers". Linked to AD pathology, the ε4 allele is associated with reduced clearance of Aβ plaque build-up in the aging brain (Lui et al., 2013). Additionally, neuroimaging studies demonstrate that increased hippocampal volume loss in patients with AD is associated with possession of the ε4 allele (Hashimoto et al., 2001). Evidence for genetic correlates of apathy is limited and inconclusive. The possession of the APOE e4 allele and the presence of apathy in MCI confer an additive risk for conversion to AD (Pink et al., 2015), but the causal role of the e4 allele in symptoms of apathy has not been established.

2.1.1 Objective & Hypothesis

The purpose of this study was to investigate the relationship between regional brain changes, genetic polymorphisms in neurotransmitter systems, and the presence of apathy in AD. We hypothesized that interactions between regional brain structures and genetic variants in dopaminergic, glutamatergic, or oxytocinergic neurotransmitter systems would be associated with symptoms or subtypes of apathy in AD. More specifically, we predicted that apathy in AD is predominantly caused by the interaction of medial frontal, subcortical, and striatal brain changes and genetic polymorphisms in dopaminergic, glutamatergic, cholinergic or oxytocinergic neurotransmitter systems.

2.2 Methods

2.2.1 ANDI Overview

Data collected for this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI is a longitudinal multicenter study, with sites across North America, that enrolls adults, ages 55-90 years, with mild cognitive impairment (MCI), Alzheimer's disease (AD), and cognitively normal (CN) controls. The principal investigator, Dr. Michael W. Weiner, MD, launched ADNI in 2003 as a longitudinal examination of progression from MCI to AD. The database includes various imaging, neuropsychology, genetic, and clinical indices made available to ADNI researchers for analysis. ADNI is comprised of 4 phases, ADNI 1, 2, GO, and 3. All participants in ADNI have comprehensive baseline assessments, including neuropsychological tests, structural MRI scans, and genetic tests. Participants then undergo repeat testing at pre-determined intervals (e.g., at months 6, 12, and 24) for the duration of 2-3 years. For up-to-date information, see www.adni-info.org.

2.2.2 Participants

Participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI), with AD, MCI, and cognitively normal controls, were included in this study. Participants with MCI scored between 24-30 on the Mini Mental State Exam (MMSE), 0.5 on the Clinical Dementia Rating (CDR) scale, had objective memory loss, and had preserved cognitive abilities. Patients with AD scored between 20-26 on the MMSE, 0.5 or 1 on the CDR, and met clinical (NINCDS/ADRDA) criteria for probable AD. CN participants scored between 24-30 on the MMSE, 0 on the CDR, and had preserved cognitive abilities and no objective memory loss. Data from participants enrolled in any of the ADNI1, ADNI2, ADNIGO, and ADNI3 phases, and who completed at least three study visits were included in the current study. All participants provided written informed consent at enrollment as approved by local ethics committees.

Participants were categorized into apathetic and non-apathetic subgroups based on endorsed symptoms of apathy as assessed by the Neuropsychiatric Inventory (NPI) or the Neuropsychiatric Inventory questionnaire (NPI-Q). Inclusion criteria for patients

endorsing symptoms of apathy included a clinical diagnosis of AD or MCI due to AD, at least one episode of apathy as assessed by either the NPI or NPI-Q apathy domain score, an available UCSF volumetric measurement of a 1.5T or 3T MRI scan at or after the first recorded onset of apathy, and genome wide analysis data. Inclusion criteria for control participants included a no clinical diagnosis of AD or MCI at the most recent recorded visit, an available UCSF volumetric measurement of a 1.5T or 3T MRI scan, and available genome wide analysis data. Exclusion criteria for both groups included a history of brain injury, other neurological disorders (e.g., dementia with Lewy Bodies, Parkinson's disease, etc.), psychiatric disorders (e.g., schizophrenia, bipolar disorder, etc.) or strokes, as determined based on clinical assessment, which could account for the presence of apathy.

2.2.3 Demographic & Behavioural Data

Demographic data, including age, sex, and years of education were collected for each participant. These data were used to adjust for effects of age, sex, and education in the main PLS-CA analysis and post-hoc analyses, when applicable. Given the potential involvement of neurotransmitter system disruptions in apathy, we report the proportion of participants on neuromodulating medications, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and different classes of antipsychotics.

Neuropsychiatric Inventory (NPI)

The NPI and NPI-Questionnaire (NPIQ; a self-administered version of the NPI interview) are informant-based indices of neuropsychiatric symptoms across several domains, over the previous month. The domains assessed by the NPI and NPIQ include hallucinations, delusions, agitation/depression, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, motor disturbance, sleep, and appetite. The presence of each symptom is recorded using a binary variable coding system, with 1 indicating presence, and 0 indicating absence. In the current study, the NPI and NPIQ were used to identify participants who did and did not endorse apathy throughout their enrollment in ADNI. Participants were binarily categorized into two groups: apathy present or apathy absent. For participants endorsing apathy on multiple visits, data from the first ADNI visit in

which apathy symptoms were present were included in the analysis. For the control group, the NPI and NPI-Q scores for all available ADNI visits were reviewed to ensure that participants did not develop apathy over the course of their enrollment.

Clinical Dementia Rating Scale (CDR)

The CDR is a semi-structured interview of patients and their informants, conducted to evaluate dementia severity. The rating assesses the patient's cognitive ability and function in six domains, including memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each domain is assessed with 5-point scale as follows: 0=no impairment, 0.5=questionable impairment, 1=mild impairment, 2=moderate impairment, and 3=severe impairment. A global CDR score between 0-3 is calculated for each participant. In the current study, the CDR was used as a covariate for disease severity.

Mini-Mental State Examination (MMSE)

The MMSE is widely used to screen for cognitive impairment. The MMSE total score is comprised of sub scores on the following cognitive domains: memory, orientation, attention, language, and construction. The tool uses 30 questions, to assign a total score ranging from 0-30, with a score of 25 or higher indicating normal cognition. In the current study, the MMSE was used to account for effects of cognitive impairment in the analyses.

2.2.4 Neuroimaging Data Preprocessing and FreeSurfer Analysis

All participants in the current study had undergone a 1.5T or 3T T1-weighted MRI scan. Images were pre-processed by the Mayo Clinic. A two-step quality control procedure was performed. The first step involved assessing adherence to defined ADNI MRI collection protocol. The second step ensured series-specific quality through procedures including gradient warping, scaling, and correction for image intensity and/or inhomogeneities. Scan quality was graded by trained analysts, with a grade of 1-3 being acceptable and 4 indicating failure (i.e., unusable). Preprocessed ADNI cross-sectional data [UCSFFSX] images were then analyzed by the UCSF ADNI group (Co-I Norbert Schuff) using FreeSurfer version 4.3 for images collected at 1.5T and FreeSurfer version 5.1 for images

collected at 3T. The 2010 Desikan-Killany and 2009 Destrieux atlases were used to process the T1-weighted images. The processing procedure included segmentation of grey matter, white matter, and subcortical structures, as well as cortical parcellation. Segmentation accuracy was assessed manually by visual inspection.

In the current study, a whole brain analysis, including 82 regions interest (ROIs) in cortical and subcortical structures, was performed. Cortical thickness or subcortical volumes from the 82 regions were obtained from the UCSF FreeSurfer cross-section ADNI data analysis. All subcortical volume measurements were adjusted for total intracranial volume (TIV) to account for inter-individual differences in brain size. All images were assessed for regional segmentation quality and were subsequently included in the analysis if they passed in the frontal, temporal, occipital and basal ganglia regions. For statistical analyses, volume and cortical thickness measurements were adjusted for sex, age or years of education, CDR global score, and MMSE total scores. All cortical and subcortical measurements were also scaled using Z-transformations before further analyses.

2.2.5 Genetic Data Acquisition and Preprocessing

Participants in ADNI had DNA information derived from either peripheral blood or immortalized lymphocyte cell lines. All genotyping and initial preprocessing was conducted by the ADNI Genetics Core group using Illumina genotyping array platforms (Illumina Human610-Quad BeadChip, Illumina HumanOmni Express BeadChip, and Illumina HumanOmni 2.5M BeadChip). Quality control and genotype imputation of the SNPs in the current study was performed by Dr. Nho Kwangsik and Dr. Andrew Saykin.

PLINK (www.cog-genomics.org/plink2/), was used to perform the standard quality control procedures for SNPs and samples, with the following cut-offs for exclusion in the study: 1) for SNPs, SNP call rate < 95%, Hardy-Weinberg p-value < $1´10^{-6}$, and minor allele frequency (MAF) < 1%, 2) for samples, sex inconsistencies, and sample call rate < 95%. To prevent spurious association due to population stratification, only non-Hispanic participants of European ancestry that clustered with HapMap CEU (Utah residents with Northern and Western European ancestry from the CEPH collection) or

TSI (Toscani in Italia) populations using multidimensional scaling analysis were included in the study.

Following the quality control procedures, genotype imputation was used to infer sequenced SNPs based on proximally related sequenced SNPs, or haplotypes. Haplotypes are groups of SNPs in the human population that are likely inherited together, as they tend to exist nearby on the same chromosome and recombination between these SNPs is rare. SNPs that have been sequenced act as markers for haplotypes are contained in a reference panel and are compared to participants' haplotypes. Identification of shared genotypes between the individual and the reference panel then allows for inference of un-sequenced SNPs in the individual. Drs. Nho and Saykin imputed un-sequenced SNPs using MaCH software with the Haplotype Reference Consortium data as a reference panel. In the current study, only imputed genotypes with r^2 association values above a 0.30 threshold were accepted and used in subsequent analyses.

2.2.6 Candidate SNP Selection

After conducting a thorough review of the literature, SNPs with known functional associations with neuropsychiatric symptoms in Alzheimer's Disease and related disorders were selected for the study. Concluding our review, we selected 22 candidate SNPS. Ultimately, 20 of the 22 SNPs were imputed; two SNPs (rs1799836 and rs25531) did not pass the imputation quality check.

Since there have not been many studies investigating SNPs in neurotransmitter systems associated with apathy in AD, the literature review was expanded to include SNPs meeting one of the following criteria: 1) implicated in the development of apathy or related conditions (e.g., depression, anhedonia, negative symptoms) in any human population, or 2) associated with AD and/or neurodegenerative or psychiatric disorders that have functional consequences on neurotransmitter-related transcripts or proteins. The neurotransmitter system, functional roles, and key literature associated with each of the 21 SNPs is found in table 2.1. Notably, although cholinergic disruption is known to contribute to AD disease pathology, no cholinergic SNPs were found to align with selection criteria at the time of the literature review.

SNP data were recoded into disjunctive format prior to additional analyses. Using this format, each SNP was treated as a categorical variable with three levels (i.e. homozygous dominant, heterozygous, homozygous recessive). The advantages of disjunctive coding are outlined in Beaton, Dunlop, & Abdi (2015) and are discussed in section 2.2.7.1. To ensure sufficient powering to assess the effects of different alleles/genotypes, homozygous recessive genotypes were checked to have frequencies > 5%, which all 20 SNPs had.

Table 2-1 Candidate single nucleotide polymorphisms (SNPs)

Gene	Chromosome	SNP GENBANK accession #	Source(s)	Key Findings
Catechol-O-Methyltransferase (COMT)	22	rs4680	Mitaki et al. (2013) Mitaki et al. (2012)	COMT gene is associated with reduced risk of apathy in healthy controls Associated with decreased enzymatic activity and dopamine catabolism – leads to increased dopamine availability in PFC Less frequent A allele associated with significantly lowered flexibility subset of FAB (frontal assessment battery) score Gene-gene interaction with DRD4 affects FAB score
Dopamine Receptor D2 (DRD2)	11	rs6277	Mitaki et al. (2013)	Affects mRNA stability, therefore receptor expression

Dopamine Receptor D3 (DRD3)	3	rs6280		Altered dopamine binding affinity
Dopamine Receptor D4 (DRD4)	11	rs1800955		Influences transcriptional efficiency
Dopamine Transporter (DAT1 or SLC6A3)	5	rs464049	Reith et al. (2021)	Alter DAT's density, DA reuptake activity, and the dynamics of DA neurotransmission Implicated in environment-sensitive neuropsychiatric disorders, including major depressive disorders (MDDs)
Tyrosine Hydroxylase (TH)	11	rs6356	Bademci, Vance & Wang (2012)	TH gene codes for tyrosine hydroxylase enzyme, involved in the synthesis of dopamine
Brain-derived neurotrophic factor (BDNF)	11	rs6265	Shumacher et al. (2005)	BDNF may be a susceptibility gene for MDD and schizophrenia
Oxytocin Receptor (OXTR)	3	rs53576	Webster et al. (2015) Viviani et al. (2011)	DNA variant within OXTR (rs53576) significantly predicted 19.4% of the variance in apathy severity as measured by the NPI-Apathy, while controlling for cognitive status and number of Apolipoprotein E (APOE) e4 alleles (AD study) oxytocinergic stimulation inhibits the amygdaloid efferents to the hypothalamus and brainstem that produce

				autonomic responses to social stimuli
		rs237902	Marit et al. (2016)	Associated with amygdala activation in response to fearful/angry faces only in patients with schizophrenia
Oxytocin/Neurophysin I Prepropeptide (OXT)	20	rs2740204	Bruno et al. (2016)	rs237887 has been reported to lie in a functional region of OXTR gene, required for transcriptional regulation of OXTR, and likely plays a role in oxytocin pathway dysregulation rs237887 G mutated allele found in MDD patients compared with BD patients and controls
Opioid Receptor Mu 1 (OPRM1)	6	rs1799971	Alfimova et al. (2019)	Observed nominally significant associations of rs1042114 genotypes and the rs1042114*rs1799971 interaction with behavioral apathy scores in schizophrenic patients (significant effects disappear after correction for multiple comparisons is applied)
Opioid Receptor Delta 1 (OPRD1)	1	rs1042114		
Pre-MRNA Processing Factor 4B (PRPF4B)	6	rs9392549	Ren et al. (2018)	Associated with anhedonia in patients with MDD
Glutamate Metabotropic Receptor 3 (GRM3)	7	rs274622	Bishop et al. (2005)	The GRM3 polymorphisms considered together explained 28% of the variance in negative symptom improvement after controlling for baseline negative symptom psychopathology
		rs724226		
		rs917071		
		rs1468412		

		rs1989796		
		rs1476455		

2.2.7 Statistical Analysis

Independent samples t-tests were used to compare age, years of education, MMSE total score and CDR global score for participants that did and did not endorse apathy, across the entire sample and within groups (AD, MCI, and CN). Chi-square tests of independence were used to compare apathetic versus non-apathetic participants (across the sample and within groups), on the distribution of sex, MRI scanner strength (1.5T versus 3T), and number of APOE e4 alleles.

2.2.7.1 Partial Least Squares Correspondence Analysis: Overview

The partial least squares (PLS) multivariate analysis is suited for analyzing two data tables from the same observations (Abdi, 2010), where explanatory variables may be correlated. PLS has been used in studies to integrate genetic and brain data, or genetic and clinical data. However, PLS approaches are met with the limitation of treating genetic variables as numerical data. In these cases, the major homozygote (AA), heterozygote (Aa), and minor homozygote (aa) SNP genotypes are assigned values based on the presence of a specific allele. For example, the major homozygote may be assigned a value of 2 to indicate the presence of two major alleles; the heterozygote is then assigned a 1, and the minor homozygote is assigned a value of 0. This coding scheme rests on two unrealistic assumptions about how SNPs contribute to the observed effects: 1) the statistical emphasis is placed on the one allele (e.g., the major allele in the former example), and 2) the effect of SNPs is uniform (i.e., each SNP contributes equally to the phenotype) and linear (i.e., each allele has an additive effect and in the same direction). These assumptions are particularly detrimental when considering the effects of combinations of SNPS, or haplotypes, that are inherited together, as well the directionality of SNPs. A salient example of this is the APOE gene, which consists of two SNPs, rs7412 and rs429358. The ApoE E4/E4 genotype confers a major risk for AD, and

is produced by a major homozygote (i.e., 0) from rs7412, and a minor homozygote (i.e., 2) from rs429358. Complexly, the ApoE E2 allele confers a protective effect in AD. Additionally, in candidate SNP studies, such as the current study, when sample sizes are typically small (N<5000), the minor allele in one sample is not guaranteed to be the minor allele in another cohort.

When the size of the effect of a SNP (non-uniform effect), the pattern of inheritance (e.g., haplotype), and directionality of the effect cannot be assumed, each genotype (AA, Aa, aa) can be treated as a level of a categorical variable (i.e., SNP). This can be accomplished with the partial least squares correspondence analysis (PLS-CA), a derivative of PLS. The PLS-CA, formalized by Beaton and colleagues (2015), is able to simultaneously analyze two data sets that contain both continuous (i.e. neuroimaging) and categorical (i.e. genetic) variables. This is done by first using an Escofier transformation to convert continuous variables, such as cortical thickness and subcortical volume measurements, into pseudo-categorical variables. PLS-CA uses generalized singular value decomposition to identify orthogonal pairs of underlying latent variables (LVs): LVY (to represent imaging data) and LVX (to represent SNPs data). Non-parametric inferencing methods, such as bootstrap resampling techniques are then used to identify significant principal components. The first two extracted LVs associated with Component 1 explain the greatest amount of covariance in the data sets. Overall, the PLS-CA approach can be used to identify group-level interactions between imaging and genetic latent variables associated with each significant component. These interactions are inferred through latent factor plots for each component, that load associated imaging ROIs and SNP genotypes in the same direction.

2.2.7.2 PLS-CA

A PLC-CA was conducted in a combined cohort of patients with AD and MCI, and cognitively normal (CN) participants. The purpose of the analysis was to identify interactions between brain regions of interest and genetic variants associated with the presence of apathy in the cohort. The NPI and NPI-Q were used to numerically binarize the presence or absence of apathy in the cohort (assigned value of 1 or 2, respectively). 82 ROIs and 20 SNPs were included in the analysis. The 82 regions of interest,

comprised of cortical thickness and subcortical volume values, were adjusted for participant age, sex, years of education, MMSE total score, CDR global score and MRI scanner strength. Subcortical volumes were adjusted for total intracranial volume to account for inter-individual differences in brain size. Significance of each component was tested using 1000 permutations ($p < 0.05$). Significance of the variables contributing to each component was assessed using 1000 bootstrapped samples (bootstrap ratio > 2.0, $p<0.05$).

PLS-CA was conducted using R (Version 3.5.2) and the related statistic packages, ExPosition and TExPosition (Beaton, Chin Fatt, & Abdi 2014; Beaton, Rieck, Fatt, & Abdi, 2013), using the pipeline proposed in Beaton et al., 2015.

2.2.7.3 Post-Hoc Group Level Analysis

Chi-square tests of independence and ANCOVAs were used to evaluate disease group level-based differences on the genetic and imaging latent variables, respectively, associated with significant PLS-CA components. Within the AD and MCI groups, chi-square tests were used to determine differences in the distribution of alleles for significant SNPs, between participants who did and those who did not endorse apathy. Additionally, group-based ANCOVAs were conducted to examine differences in significant imaging variables between participants with and without apathy. Sex, age, and MMSE total score were used as covariates in the ANCOVAs.

2.3 Results

2.3.1 Transdiagnostic PLS-CA: Presence or Absence of Apathy

2.3.1.1 Participant Demographics

A total of 1162 participants, across the ADNI phases (GO, 1, 2, and 3), met the inclusion criteria for the current study. This cohort included 491 participants who endorsed symptoms of apathy by the NPI or NPIQ (Apathy+), and 671 participants who did not endorse symptoms of apathy (Apathy-) (Table2.1). Independent Welch t-tests were used to compare age, years of education, CDR global score, and MMSE total scores between the Apathy+ and Apathy- groups. Participants who endorsed apathy were slightly older

(Apathy+ mean age: 75.18, Apathy- mean age: 73.97, $t(1005.3)=-2.78$, $p=0.005$), had fewer years of education (Apathy+ mean education: 15.61, Apathy- mean education: 16.44, $t(1012)=5.05$, $p<0.001$), higher global CDR scores indicating more impairment (Apathy+ mean CDR Global: 0.64, Apathy- mean CDR Global: 0.28, $t(842.43)=-16.72$, $p<0.001$), and lower MMSE total scores (Apathy+ mean MMSE: 25.31, Apathy- mean MMSE: 28.03, $t(733.88)=13.04$, $p<0.001$) than participants who did not endorse apathy.

Pearson's chi-squared tests of independence were used to compare the distribution of sex, MRI field strengths, and APOE e4 allele counts between the two groups. There was a larger proportion of males than females in the Apathy+ group compared to the Apathy- group (60.5% and 53.8% percent males respectively, $X^2(1)= 4.90$, $p=0.03$). In the Apathy- group, a larger proportion of the imaging data was obtained from 3T MRI scanners compared to the Apathy+ group ($X^2(1)= 6.74$, $p<0.01$). Lastly, there was a significant association between apathy endorsement and number of APOE e4 alleles ($X^2(2)= 56.13$, $p<0.0001$), with those in the Apathy+ group more likely to have 1 or two APOE e4 alleles in comparison to the Apathy- participants.

Participants enrolled in ADNI may often take non-study specific medication. Here, we report the percentage of individuals, with and without apathy, on medications that could affect symptoms of apathy. Approximately 36% of participants in the Apathy+ group, and 20% of participants in the Apathy- group, are listed as taking SSRIs, including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline ($X^2(1)= 6.29$, $p=0.01$). Approximately 11% and 5% of participants were taking SNRIs (Duloxetine and Venlafaxine) in the Apathy+ and Apathy- groups, respectively ($X^2(1)= 6.37$, $p=0.01$). Few participants were reported to use atypical antidepressants (19% Apathy+ and 11% Apathy-; $X^2(1)= 1.91$, $p=0.17$), including mirtazapine, trazadone, and bupriopion, as well as antipsychotics (2% Apathy+, <1% Apathy-; $X^2(1)= 3.27$, $p=0.07$), including haloperidol and aripiprazole. Approximately 1% of participants in both groups were taking dopamine agonists, such as methylphenidate, levodopa, pramipexole, ropinirole, and bromocriptine ($X^2(1)= 1.00$, $p=0.32$). Cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, were used by approximately 67% and 25% of participants with and without apathy, respectively ($X^2(1)= 53.24$, $p<0.001$). Lastly, nearly 43% of

participants with apathy, and 13% without apathy, were reported to take memantine, an NMDA receptor antagonist ($X^2(1)= 50.60$, $p<0.001$).

Table 2-2 PLS-CA sample demographics and apathy profiles.

	Apathy+				*Apathy-*					
N	491				671					
	Mean(sd), range				**Mean(sd), range**				***t*(df)**	***p*-value**
Age	75.18(6.95), 55-94				73.97(7.53), 55-92				-2.78(1005.3)	0.005
Years of Education	15.61(2.86), 6-20				16.44(2.67), 6-20				5.05(1012)	<0.0001
CDR Global Score	0.641(0.41), 0-3				0.276(0.30), 0-2				-16.72(842.43)	<0.0001
MMSE Total Score	25.31(4.13), 0-30				28.03(2.42), 16-30				13.04(733.88)	<0.0001
Sex(%)	**Male**	**Female**			**Male**	**Female**			**Pearson's Chi-squared Test**	
	297(60.5)	194(39.5)			361(53.8)	310(46.2)			0.03	
MRI Field Strength(%)	**1.5T**	**3T**			**1.5T**	**3T**			**Pearson's Chi-squared Test**	
	230	261(53.16)			262	409(60.95)			0.009	
# of APOE e4 Alleles	**0**	**1**	**2**		**0**	**1**	**2**		**Pearson's Chi-squared Test**	
	200	224	67		415	217	39		<0.0001	
Medications									**Pearson's Chi-squared Test**	
# on SSRIs (%)	176 (35.85)				132 (19.67)				0.01	
# on SNRIs (%)	53 (10.80)				30 (4.47)				0.01	
# on Atypical Antidepressants (%)	94 (19.14)				76 (11.33)				0.17	

# on Antipsychotics (%)	11 (2.24)	4 (0.60)	0.07
# on Dopamine Agonists	6 (1.22)	10 (1.49)	0.32
# on Cholinesterase Inhibitors	331 (67.41)	168 (25.04)	<0.0001
# on Memantine	211 (42.97)	88 (13.11)	<0.0001

2.3.1.2 SNP Allelic Frequencies

Minor allele frequencies were calculated for the 21 candidate SNPs across the entire sample (Table 2.3). All 21 SNPS had MAF > 1% and were kept for the PLS-CA.

Table 2-3 Minor allele frequencies for the 21 candidate SNPs across sample of 1162 participants.

Total Sample, N=1162			
Gene	**SNP**	**Minor Allele**	**Minor Allele Frequency**
OPRD1	rs1042114	G	0.14
OPRD1	rs533123	G	0.19
OXTR	rs53576	A	0.31
OXTR	rs237902	A	0.34
DRD3	rs6280	C	0.33
SLC6A3	rs464049	G	0.44
PRPF4B	rs9392549	A	0.02
OPRM1	rs1799971	G	0.13

GRM3	rs274622	C	0.33
GRM3	rs724226	A	0.35
GRM3	rs917071	T	0.29
GRM3	rs1468412	T	0.28
GRM3	rs1989796	T	0.43
KIAA1324L	rs1476455	A	0.11
DRD4	rs1800955	C	0.43
TH	rs6356	T	0.37
BDNF	rs6265	T	0.18
DRD2	rs6277	G	0.45
DRD2	rs1076560	A	0.16
AVP	rs2740204	T	0.41
COMT	rs4680	G	0.49

2.3.1.3 Transdiagnostic PLS-CA Results

Results of the PLS-CA identified three significant Principal Components of the 42 components: 1, 2 and 3 (59.07%, $p_{perm}<0.001$; 5.65%, $p_{perm}<0.001$; 4.68%, $p_{perm}=0.013$, respectively). Variance contributing to Components 2 and 3 were likely due to natural variation in the sample and were not used for the analysis. Interactions of ROIs and SNPs in Component 1 explained 59.07% of the variance in the dataset and was further explored (Figure 2.1A).

Bootstrap analysis revealed cortical thickness and subcortical volume values below the grand mean for bilateral frontal regions, right frontal pole, bilateral temporal regions, bilateral parietal regions, bilateral fusiform, bilateral entorhinal, bilateral lingual, bilateral isthmus cingulate, bilateral posterior cingulate, bilateral precuneus, bilateral insula, right accumbens area, left putamen, and right caudal anterior cingulate (Figure 2.1B; see table 2.4 for complete list of ROIs). Regions of interest that did not meet the significance threshold included the following: bilateral caudate, bilateral cerebellum cortex, bilateral thalamus, bilateral pallidum, bilateral putamen, right precuneus, left pericalcarine, left frontal pole, left rostral anterior cingulate, and the third ventricle. The bootstrap analysis also revealed that the presence of apathy was also associated with the minor homozygote of rs464049 in SLC6A3 and the presence of an APOE e4 allele (Figure 2.1C). This pattern of smaller brain volumes in the regions above was most prominent in apathetic participants with the genotypic combination of just one APOE e4 allele and minor homozygote of rs464049 in SLC6A3. Cortical thickness and subcortical volume values above the grand mean in the aforementioned ROIs were associated with possessing no APOE e4 alleles. This pattern of brain structure was most prominent in participants who did not endorse apathy.

A)

N=1162	
Component	**P-value**
1	<0.001
2	<0.001
3	0.013
4	0.99
5	1.00

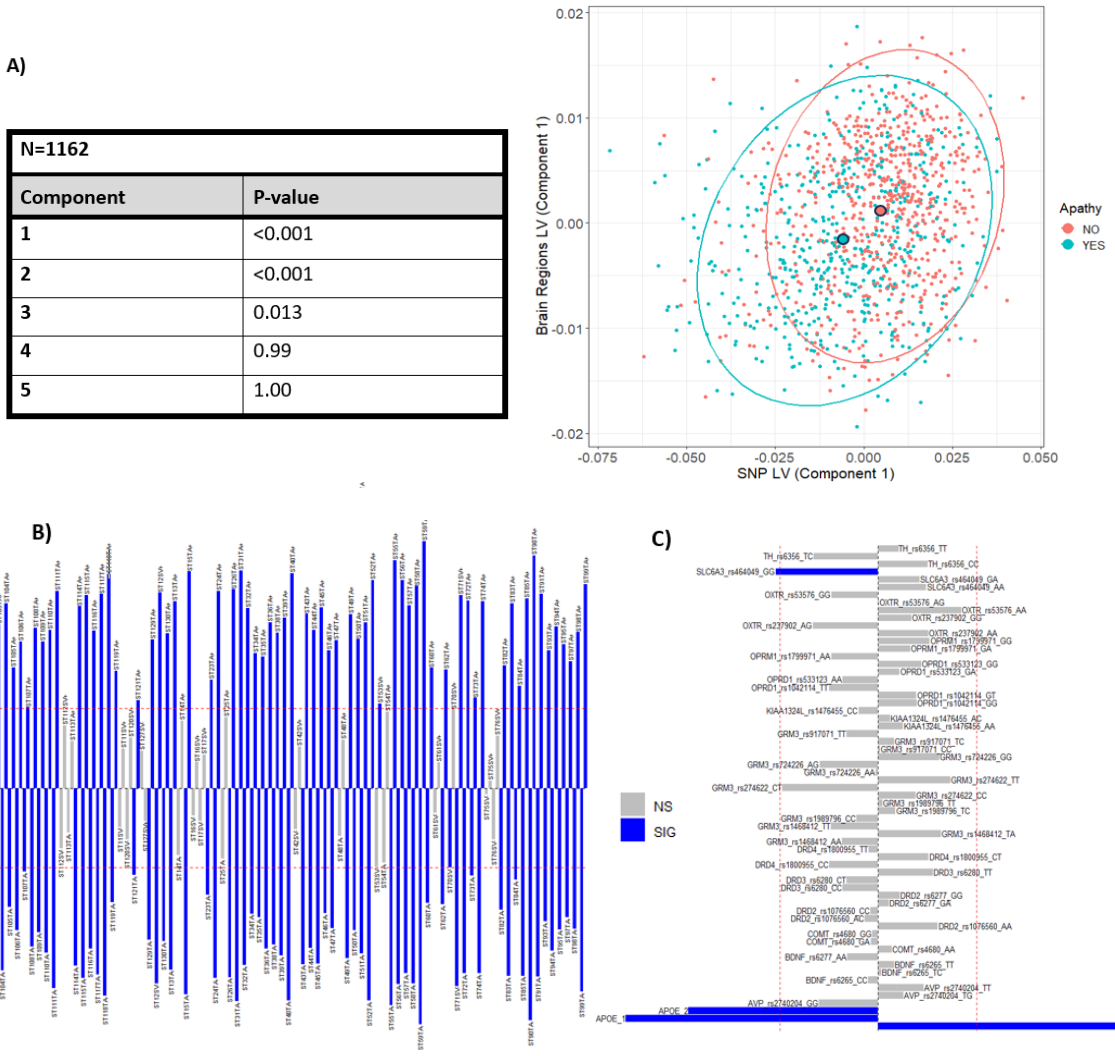

Figure 2-1 PLS-CA Results. A) Component p-values and latent variable (LV) plot for Component 1. The horizontal axis represents the latent variable composed of candidate SNP data and the vertical axis represents the latent variable composed of the imaging brain regions of interest. Ellipsoids represent boot-strap confidence intervals (95%). B) Neuroimaging boot-strap regression results for Component 1. Blue bars indicate brain regions with significantly greater cortical thickness or subcortical volume values than the grand mean (blue bars above the horizontal axis), and regions with significantly lower values than the grand mean (blue bars below the horizontal axis). The longer the bar associated with an item, the more variance the item contributes to the component. The red dashed line indicates the boot-strap ratio (BSR) threshold for significance (+2 and -2), for an α=0.05. C) Single nucleotide polymorphisms boot-strap regression results for Component 1. Blue bars indicate SNPs contributing significantly to variation in Component 1. The red dashed line indicates the boot-strap ratio (BSR) threshold for significance (+2 and -2), for an α=0.05. Blue bars to the left of the vertical axis are associated with the blue imaging items below the horizontal axis in panel B.

Table 2-4 PLS-CA Significant brain regions of interest below the grand mean for Component 1. Regions are colour-coded by lobe: yellow=frontal, orange=temporal, blue=parietal, green=insula, pink=occipital. Boot-strap ratios (BSRs) with greater magnitudes account for a greater amount of variance in Component 1.

Significant ROIs with cortical thickness and subcortical volume values below the grand mean			
Right Hemisphere	**BSR**	**Left Hemisphere**	**BSR**
ST102TA_RightParacentral	-3.56724	ST43TA_LeftParacentral	-4.38909
ST103TA_RightParahippocampal	-4.31663	ST44TA_Left Parahippocampal	-4.05646
ST104TA_RightParsOpercularis	-4.5416	ST45TA_LeftParsOpercularis	-4.24688
ST105TA_RightParsOrbitalis	-2.9769	ST46TA_LeftParsOrbitalis	-3.14755
ST106TA_RightParsTriangularis	-3.43039	ST47TA_LeftParsTriangularis	-3.5642
ST108TA_RightPostCentral	-3.98587	ST49TA_LeftPostCentral	-4.22321
ST109TA_Right Posterior Cingulate	-3.65294	ST50TA_LeftPosteriorCingulate	-3.63335
ST110TA_RightPrecentral	-3.97067	ST51TA_LeftPrecentral	-4.1281
ST111TA_RightPrecuneus	-5.0159	ST52TA_LeftPrecuneus	-5.35237
ST114TA_RightRostralMiddleFrontal	-4.40912	ST55TA_LeftRostralMiddleFrontal	-5.42389
ST115TA_RightSuperiorFrontal	-4.75832	ST56TA_LeftSuperiorFrontal	-5.42389
ST116TA_RightSuperiorParietal	-4.01319	ST57TA_LeftSuperiorParietal	-5.05548
ST117TA_RightSuperiorTemporal	-4.59497	ST58TA_LeftSuperiorTemporal	-4.64849
ST118TA_RightSupramarginal	-5.14279	ST59TA_LeftSupramarginal	-4.89194
ST119TA_RightTemporalPole	-2.92482	ST60TA_LeftTemporalPole	-5.92004

ST121TA_RightTransverseTemporal	-2.13874	ST62TA_LeftTransverseTemporal	-2.98164
ST130TA_RightInsula	-3.85577	ST129TA_LeftInsula	-3.76548
ST71SV_Right Amygdala	-4.97871	ST12SV_LeftAmygdala	-5.05542
ST99TA_RightMiddleTemporal	-5.08863	ST40TA_LeftMiddleTemporal	-5.36546
ST82TA_RightCuneus	-3.0542	ST23TA_LeftCuneus	-2.64981
ST72TA_RightBankSuperiorTemporalSulcus	-4.51808	ST13TA_LeftBankSuperiorTemporalSulcus	-4.5628
ST74TA_RightCaudalMiddleFrontal	-4.60068	ST15TA_LeftCaudalMiddleFrontal	-5.33723
ST83TA_RightEntorhinal	-4.59778	ST24TA_LeftEntorhinal	-4.82072
ST85TA_RightFusiform	-4.54299	ST26TA_Left Fusiform	-4.81771
ST90TA_RightInferiorParietal	-5.77935	ST31TA_LeftInferiorParietal	-5.45655
ST91TA_RightInferiorTemporal	-4.68393	ST32TA_LeftInferiorTemporal	-4.5314
ST93TA_RightIsthmusCingulate	-3.34149	ST34TA_LeftIsthmusCingulate	-3.16539
ST94TA_RightLateralOccipital	-4.09733	ST35TA_LeftLateralOccipital	-3.31779
ST95TA_RightLateralOrbitofrontal	-3.57231	ST36TA_LeftLateralOrbitofrontal	-3.8994
ST97TA_RightLingual	-3.22819	ST38TA_LeftLingual	-3.98889
ST98TA_RightMedialOrbitofrontal	-3.60838	ST39TA_LeftMedialOrbitofrontal	-4.21688
ST107TA_Right Pericalcarine	-2.09446	ST53SV_LeftPutamen	-2.11231
ST70SV_RightAccumbensArea	-2.03202		
ST73TA_RightCaudalAnteriorCingulate	-2.22487		

ST84TA_RightFrontalPole	-2.39145		

2.3.1.4 Group-Level Variance

A post-hoc exploration of disease group level variation in Component 1 was conducted. A stronger association between cortical thickness and subcortical volume values in the ROIs and the possession of one APOE e4 allele and minor homozygosity for the rs46409 SNP in SLC6A3 was found in participants with Alzheimer's Disease, compared to participants with Mild Cognitive Impairment and healthy controls. Participants with MCI showed an intermediate pattern on Principal Component 1, between the healthy controls and the participant with AD.

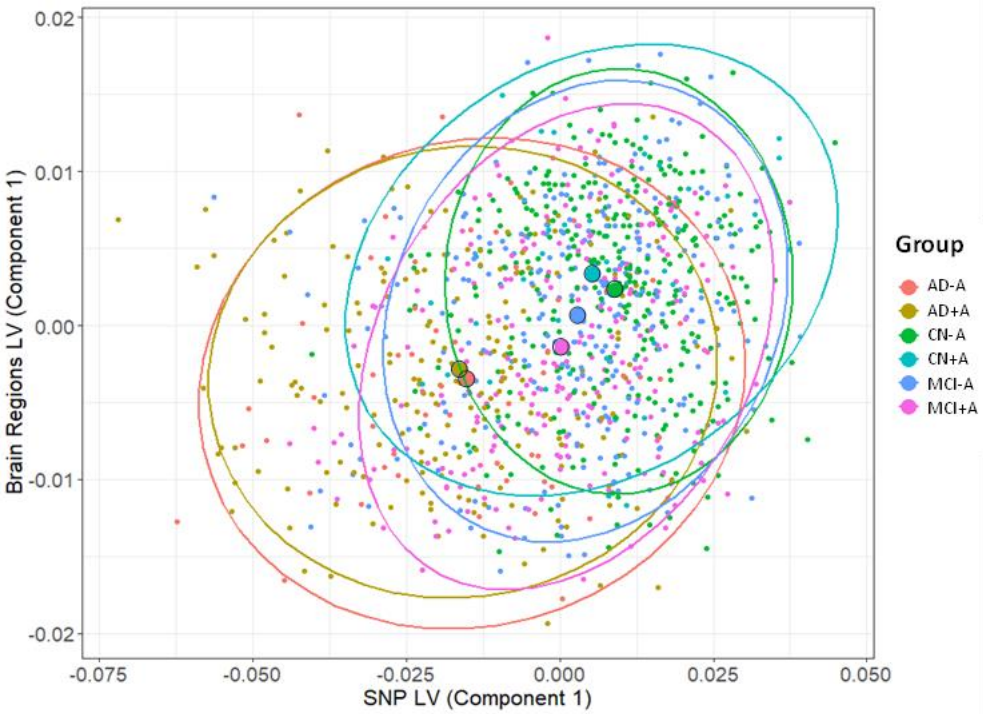

Figure 2-2 Latent variable (LV) plot for Component 1. The horizontal axis represents the latent variable composed of candidate SNP data and the vertical axis represents the latent variable composed of the imaging brain regions of interest. Ellipsoids represent boot-strap confidence intervals (95%). Disease and apathy subgroups are colour-coded: red = AD without apathy, brown = AD with apathy, green = cognitively normal without apathy, aqua = cognitively normal with apathy, blue = mild cognitive impairment without apathy, pink = mild cognitive impairment with apathy.

2.3.2 Disease Group Level Analysis

Given the significant association between the possession of one APOE e4 allele and a minor homozygous genotype for the rs46409 SNP in SLC6A3, and the consequent impact on brain structure in the entire sample, an exploration of genotypic variation within disease groups was warranted. As such, we examined APOE e4 allele and rs46409 allele distributions within each group (AD, MCI, and CN), and between patients with and without apathy, using chi-square tests of independence. ANCOVAs were leveraged to determine structural imaging differences in patients with and without apathy, within each group, and with MMSE total score as a covariate.

2.3.2.1 Alzheimer's Disease Cohort

2.3.2.1.1 Patient Demographics

A total of 266 participants met the inclusion criteria for Alzheimer's Disease in the current study. This cohort included 208 patients who endorsed symptoms of apathy by the NPI or NPIQ (Apathy+), and 58 patients who did not endorse symptoms of apathy (Apathy-) (Table 2.5). Independent Welch t-tests were used to compare age, years of education, CDR global score, and MMSE total score between the Apathy+ and Apathy- groups. There were no statistically significant differences in age or years of education between the two groups. AD patients with apathy had greater global CDR scores (Apathy+ mean CDR Global: 0.92, Apathy- mean CDR Global: 0.76, $t(141.96)=-3.18$, $p<0.01$), and lower MMSE total scores (Apathy+ mean MMSE: 22.19, Apathy- mean MMSE: 23.50, $t(121.52)=2.63$, $p<0.01$) than participants who did not endorse apathy.

Pearson's chi-squared tests were used to compare the distribution of sex, MRI field strengths, and APOE e4 allele counts between the two groups. In the Apathy+ group, a larger proportion of the imaging data was obtained from 3T MRI scanners compared to the Apathy- group ($X^2(1)=5.68$, $p=0.02$). There were no significant differences in ApoE4 allele frequency or sex for the AD Apathy+ group compared to AD Apathy- group.

Table 2-5 Demographics and apathy profile for Alzheimer's Disease cohort (N=266).

	AD Apathy+			*AD Apathy-*			
N	208			58			
	Mean(sd)			**Mean(sd)**			**t(df), *p***
Age	75.80(7.44)			76.19(8.62)			0.32(82.22), 0.76
Years of Education	15.42(3.03)			15.47(2.75)			0.11(99), 0.91
CDR Global Score	0.92(0.47)			0.76(0.30)			-3.18(141.96) ,0.002
MMSE Total Score	22.19(4.19)			23.50(3.09)			2.63(121.52), 0.009
Sex(%)	**M**	**F**		**M**	**F**		**Pearson's Chi-squared Test**
	117	91(43.75)		29	29(50)		0.49
MRI Field Strength(%)	**1.5T**	**3T**		**1.5T**	**3T**		**Pearson's Chi-squared Test**
	112	96(46.15)		42	16(27.59)		0.02
# of APOE e4 Alleles	**0**	**1**	**2**	**0**	**1**	**2**	**Pearson's Chi-squared Test**
	66	102	40	15	32	11	0.65

2.3.2.1.2 Post-Hoc Genotypic Analysis

Pearson's chi-square tests of independence or Fisher's exact test were used to examine distributions of APOE e4 alleles, DAT1 SNP (rs46409 SNP in SLC6A3) genotype between AD patients with and without apathy. Additionally, we examined the difference in frequency of the DAT 1 minor homozygote and one APOE e4 allele genotypic combination between the two groups. As mentioned in section 2.3.2.1.1, there was no significant association between apathy and APOE e4 allele frequencies, with 49% of

Apathy+ patients and 55% of Apathy- patients possessing exactly one copy of the e4 allele (Table 2.6). Results revealed no significant association between the presence of apathy and DAT1 genotype ($X^2(2)=0.96$, $p=0.62$), with 19% of Apathy+ patients and 24% of Apathy- patients being minor homozygotes. A Fisher's exact test revealed no significant association between apathy and the combination of DAT1 and APOE genotypes ($p=0.74$).

Table 2-6 Frequency table for APOE e4 alleles and DAT 1 genotypes in AD cohort.

AD	**Apathy+**	**Apathy-**
APOE e4 allele (%)		
0	31.73	25.86
1	49.04	55.17
2	19.23	18.97
DAT1 Genotype (%)		
Minor homozygous GG	19.23	24.14
Major homozygous AA	31.35	32.76
Heterozygous GA	49.52	43.10
DAT1 + APOE e4 (%)		
GG + 0 e4	5.77	5.17
GG + 1 e4	9.13	15.52
GG + 2 e4	4.33	3.45
AA + 0 e4	10.58	6.90
AA + 1 e4	16.82	17.24
AA + 2 e4	3.84	8.62
GA + 0 e4	15.38	13.80

GA + 1 e4	23.08	22.41
GA + 2 e4	11.06	6.90

2.3.2.1.3 Post-Hoc Imaging Analysis

An ANCOVA was conducted to investigate differences between Apathy+ and Apathy- patients with AD in the imaging latent variable from Component 1. Age, Sex, and MMSE total score were used as covariates in the analysis. Results revealed a significant interaction between apathy and MMSE total score ($F(1,250)=4.62$, $p=0.03$). While the imaging latent variable scores for patients with MMS < 25 were similar for both Apathy+ and Apathy- patients with AD, for patients with MMSE >= 25, the imaging latent variable score was lower for the Apathy- relative to the Apathy+ (Figure 2.3). The difference in structural imaging scores in the latent variable between patients with AD and apathy is smaller as a function of MMSE total score compared to patients without apathy. Additionally, patients with AD and apathy have a stronger negative association in the latent variable when MMSE total scores are below 25, compared to when they are 25 or above. Patients with AD and without apathy have a stronger negative association with the latent variable when MMSE total scores are 25 or greater compared to when MMSE total scores are below 25.

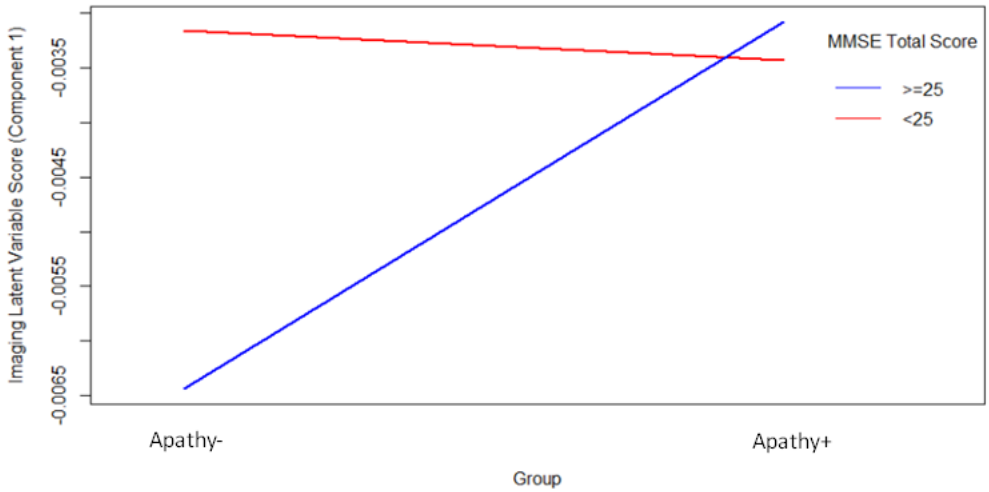

Figure 2-3 Interaction plot for MMSE total score and presence of apathy in AD cohort. The vertical axis represents mean scores for the imaging latent variable.

2.3.2.2 Mild Cognitive Impairment Cohort Results

2.3.2.2.1 Patient Demographics

A total of 518 participants met the inclusion criteria for mild cognitive impairment in the current study. This cohort included 236 patients who endorsed symptoms of apathy by the NPI or NPIQ (Apathy+), and 282 patients who did not endorse symptoms of apathy (Apathy-) (Table 2.7). Independent Welch t-tests were used to compare age, years of education, CDR global score, and MMSE total score between the Apathy+ and Apathy- groups. Patients with MCI and apathy were slightly older than MCI patients without apathy (Apathy+ mean age: 74.40, Apathy- mean age: 72.95, $t(495.38)=-2.11$, $p=0.04$). MCI patients with apathy had greater CDR global scores indicative of slightly more impairment (Apathy+ mean CDR Global: 0.50, Apathy- mean CDR Global: 0.47, $t(510.85)=-3.40$, $p<0.001$), slightly lower MMSE total scores (Apathy+ mean MMSE: 27.29, Apathy- mean MMSE: 27.80, $t(509.84)=2.65$, $p<0.01$), and less years of education than MCI patients without apathy (Apathy+ mean years of education: 15.61, Apathy- mean years of education: 16.54, $t(495.24)=3.80$, $p<0.001$).

Pearson's chi-squared tests were used to compare the distribution of sex, MRI field strengths, and APOE e4 allele counts between the two groups. There was an uneven distribution of e4 alleles between the Apathy+ and Apathy- groups ($X^2(2)=16.24$, $p<0.001$). This association is further explored in section 2.3.2.2.2.

Table 2-7 Demographics and apathy profile for Mild Cognitive Impairment cohort (N=518).

	MCI Apathy+	*MCI Apathy-*	
N	236	282	
	Mean(sd)	**Mean(sd)**	**t(df), *p***
Age	74.40(7.88)	72.95(7.68)	-2.11(495.38), 0.04

Years of Education	15.61(2.80)			16.54(2.73)			3.8(495.24), <0.001
CDR Global Score	0.50(0.10)			0.47(0.13)			-3.4(510.85), p<0.001
MMSE Total Score	27.29(2.09)			27.80(2.24)			2.65(509.84), p=0.008
Sex(%)	**M**	**F**		**M**	**F**		**Pearson's Chi-squared Test**
	150	86(36.44)		171	111(39.36)		0.55
MRI Field Strength(%)	**1.5T**	**3T**		**1.5T**	**3T**		**Pearson's Chi-squared Test**
	93	143(60.59)		97	185(65.60)		0.28
# of APOE e4 Alleles	**0**	**1**	**2**	**0**	**1**	**2**	**Pearson's Chi-squared Test**
	97	114	25	166	96	20	0.0003

2.3.2.2.2 Post-Hoc Genotypic Analysis

Pearson's chi-square tests of independence or Fisher's exact test were used to examine distributions of APOE e4 alleles, DAT1 SNP (rs46409 SNP in SLC6A3) genotype, and genotypic combinations of the two genes, between patients with MCI with and without apathy. As mentioned in section 2.3.2.2.1, there was a significant association between apathy and APOE e4 allele frequencies in the MCI cohort. Examination of the chi-square residuals reveals that the presence of one and two APOE e4 allele(s) are driving the observed difference in frequencies between the apathy groups (fig.2.4.a.). Results revealed no significant association between the presence of apathy and DAT1 genotype ($X^2(2)=1.42$, $p=0.49$), with 21% of Apathy+ patients and 21% of Apathy- patients being minor homozygotes. A Fisher's exact test revealed a significant association between apathy and the combination of DAT1 and APOE genotypes ($p=0.011$). Specifically, there is a strong positive association between MCI patients with apathy and the following two genotypic combinations: 1) possessing one APOE e4 allele and heterozygosity for DAT1, and 2) possessing one APOE e4 allele and minor homozygosity for DAT1. Conversely,

these two genotypic combinations have a strong negative association with MCI patients without apathy (fig.2.4.c).

A)

	Apathy+	Apathy-
APOE e4 allele (%)		
0	41.10	58.87
1	48.31	34.04
2	10.59	7.09
DAT1 Genotype (%)		
Minor homozygous GG	21.19	20.57
Major homozygous AA	32.27	27.54
Heterozygous GA	47.16	31.89
DAT1 + APOE e4 (%)		
GG + 0 e4	7.63	12.06
GG + 1 e4	11.02	7.45
GG + 2 e4	2.54	1.06
AA + 0 e4	11.86	17.73
AA + 1 e4	12.71	11.35
AA + 2 e4	2.97	3.19
GA + 0 e4	21.61	29.08
GA + 1 e4	24.58	15.25
GA + 2 e4	5.08	2.84

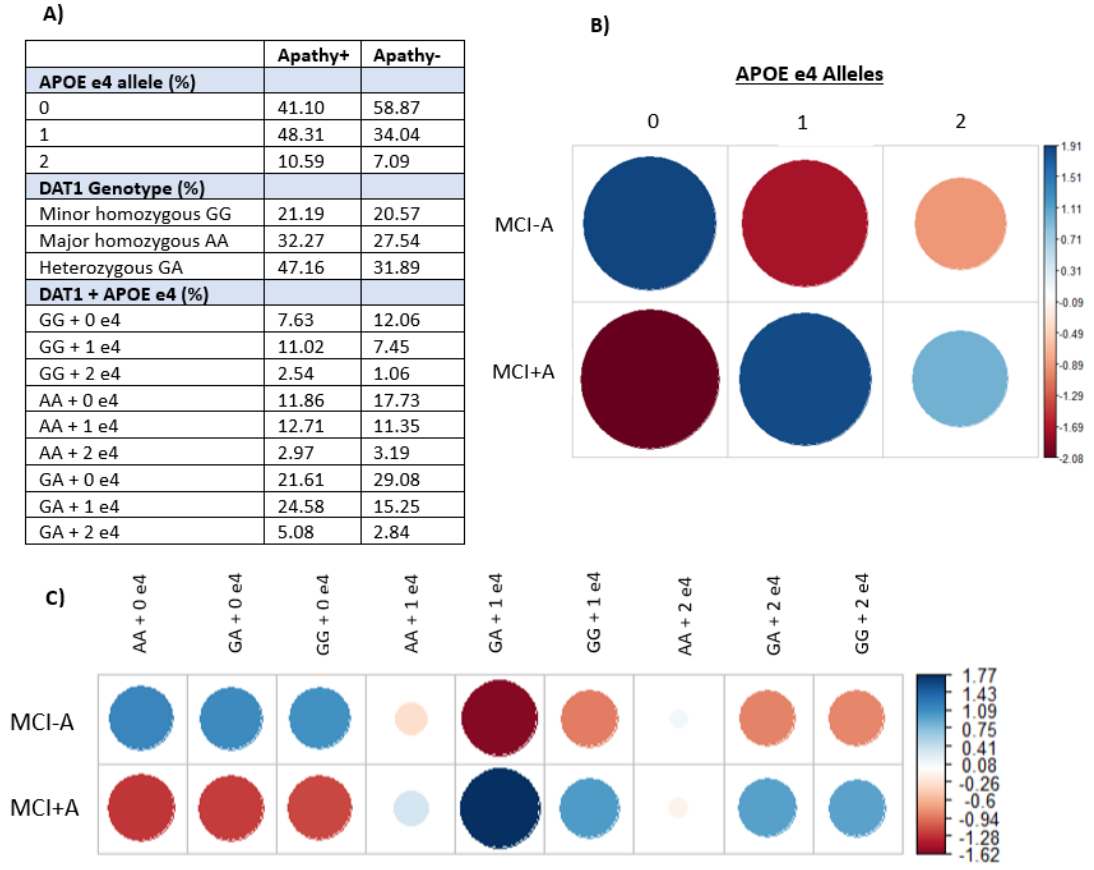

Figure 2-4 Post-Hoc Genotypic Results for MCI Cohort. A) Frequency table for APOE e4 alleles and DAT 1 genotypes in MCI cohort. B) Chi square residual plot for APOE e4 allele frequencies. The larger and darker the cell circle, the stronger the association between column and row. Blue represents positive associations and red represents negative associations. The larger the magnitude of the residual, the stronger the association. MCI+A = MCI with apathy, MCI-A = MCI without apathy C) Chi square residual plot for APOE e4 allele + DAT1 genotype combination frequencies.

2.3.2.2.3 Post-Hoc Imaging Analysis

An ANCOVA was conducted to investigate differences between Apathy+ and Apathy- patients with MCI in the imaging latent variable from Component 1. Age, Sex, and MMSE total score were used as covariates in the analysis. Results revealed a significant main effect of apathy ($F(2,502)=4.73$, $p<0.01$), and MMSE total score ($F(1,502)=19.02$, $p<0.0001$). Patients with MCI and apathy have reduced structural imaging values

(indicating greater atrophy) associated with the latent variable compared to patients with MCI and no apathy. Additionally, patients with MCI and MMSE total scores below 25 have reduced structural imaging values associated with the latent variable compared to patients with MCI and MMSE total scores if 25 or above.

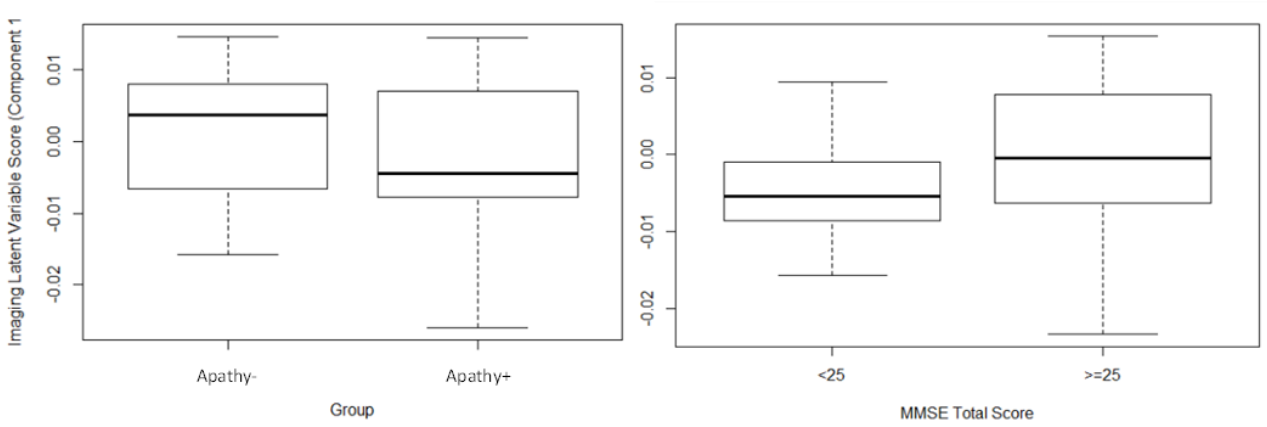

Figure 2-5 Post-Hoc Imaging Results for MCI Cohort. A) Boxplot for main effect of apathy on the structural imaging latent variable from Component 1. B) Boxplot for main effect of MMSE total score on the structural imaging latent variable from Component 1.

2.3.2.3 Cognitively Normal Cohort Results

2.3.2.3.1 Patient Demographics

A total of 378 participants met the inclusion criteria for cognitively normal in the current study. This cohort included 47 participants who endorsed symptoms of apathy by the NPI or NPIQ (Apathy+), and 331 participants who did not endorse symptoms of apathy (Apathy-) (Table 2.8). Independent Welch t-tests were used to compare age, years of education, CDR global score, and MMSE total score between the Apathy+ and Apathy- groups. Participants with apathy were older than those without apathy (Apathy+ mean age: 76.34, Apathy- mean age: 74.46, $t(60.57)=-2.15$, $p=0.04$). Participants with apathy also had greater CDR global scores (Apathy+ mean CDR Global: 0.11, Apathy- mean CDR Global: 0.03, t(50.54)=-2.5 4, $p=0.01$).

Pearson's chi-squared tests were used to compare the distribution of sex, and MRI field strengths between apathy groups. Fisher's exact test was used to examine APOE e4 allele

counts between the two groups. There were no significant associations between apathy and distributions of sex, MRI field strengths, and APOE e4 alleles in the cohort.

Table 2-8 Demographics and apathy profile for cognitively normal cohort (N=378).

	Apathy+			*Apathy-*			
N	47			331			
	Mean(sd)			**Mean(sd)**			**t(df), *p***
Age	76.34(5.60)			74.46(5.74)			-2.15(60.57), 0.04
Years of Education	16.40(2.17)			16.52(2.57)			0.34(65.67), 0.73
CDR Global Score	0.11(0.21)			0.03(0.12)			-2.54(50.54), 0.01
MMSE Total Score	29.15(0.93)			29.01(1.17)			-0.9(68.33), 0.37
Sex(%)	**M**	**F**		**M**	**F**		**Pearson's Chi-squared Test**
	30	17(36.17)		161	170(51.36)		0.07
MRI Field Strength(%)	**1.5T**	**3T**		**1.5T**	**3T**		**Pearson's Chi-squared Test**
	25	22(46.81)		123	208(62.84)		0.05
# of APOE e4 Alleles	**0**	**1**	**2**	**0**	**1**	**2**	**Fisher's Exact Test**
	37	8	2	234	89	8	0.25

2.4 Discussion

The biological mechanisms underlying apathy in Alzheimer's disease are not well understood. In the current study, we aimed to investigate interactions between regional brain changes and genetic polymorphisms that give rise to apathy in individuals with mild cognitive impairment and Alzheimer's disease. We leveraged a PLS-CA to simultaneously assess the relationship between 82 cortical and subcortical and regions of

interest and 20 SNPs in neurotransmitter systems to determine whether unique imaging-genetic patterns could separate individuals with and without apathy, across and within, disease groups.

The overall PLS-CA analysis, collapsed across groups, revealed a significant association between frontal, temporal, parietal, and subcortical brain regions and the possession of one APOE e4 allele and minor homozygosity for the DAT1 gene polymorphism (rs46409) in participants with apathy versus those without apathy. DAT1 is a dopamine transporter gene that codes for DAT (dopamine transporter protein). DAT is a plasma membrane protein that is expressed in all dopamine neurons, but in highest quantities in the striatum and nucleus accumbens. It is responsible for regulating intra- and extra-cellular concentrations of dopamine by synaptic reuptake of the neurotransmitter (Salatino-Oliveira, Rohde & Hutz, 2017). Previous research implicates the potential role of DAT dysfunction in neuropsychiatric disorders, such as ADHD and bipolar disorders. For instance, it has been shown that DAT1 gene variation is associated with structural differences in both the right lateral prefrontal cortex (PFC) and the cingulate cortex among patients with ADHD (Fernandéz-Jaén et al., 2015, 2016). To our knowledge, the current study is the first to report an association between the APOE e4 allele, the greatest genetic risk factor AD, and a DAT1 genetic variant in association with the presence of apathy and AD-related structural brain changes.

Post-hoc analyses were conducted to elucidate group-specific effects of the genetic variants on structural brain changes between those with apathy versus those without apathy. In doing so, we aimed to disentangle variation in the data caused by disease-specific versus apathy-specific factors. Within the AD cohort, there was no statistically significant difference in APOE e4 allele plus DAT1 minor homozygosity between patients with and without apathy. An examination of the imaging latent variable with respect to apathy, while accounting for age and MMSE, revealed a significant a significant interaction between apathy and MMSE total influencing brain structure, however the direction of this association was unpredicted and will require further replication. Specifically, in patients with apathy and AD, MMSE total had less of an association with cortical thickness and subcortical values associated with the imaging

latent variable, with an MMSE total score of less than 25 correlating with greater atrophy in the associated ROIs. In patients with AD without apathy, the magnitude of the interaction effect was greater and in the opposite direction; patients with MMSE scores less than 25 had better preserved cortical thickness and subcortical values in the latent variable ROIs than those with MMSE total scores above 25. This finding was not predicted and is not evident why patients with AD without apathy would not show an association of lower MMSE scores and more brain atrophy.

Within the MCI cohort, there was a statistically significant difference in APOE e4 allele plus DAT1 minor homozygosity as well as in APOE e4 allele plus DAT1 heterozygosity between patients with and without apathy. Results revealed a significant association between apathy and the combination of DAT1 and APOE genotypes. Apathy was strongly correlated with the combination of possessing one APOE e4 allele and either minor homozygosity or heterozygosity for the DAT1 SNP. Additionally, patients with apathy and MCI had a strong association with reduced cortical thickness and subcortical values in ROIs comprising the imaging latent variable, compared to patients with MCI and without apathy.

Together, these data point to a unique genotype-phenotype coupling in the MCI plus apathy group. Specifically, in the early stages of AD, in individuals with the signature APOE e4 allele and DAT1 rs46409 heterozygosity or minor homozygosity, there is an association between the presence of apathy and widespread structural brain changes. The implications of these findings are vast. Firstly, there could be a subgroup of individuals with this genotype that are predisposed to developing MCI and apathy. We know that MCI and apathy are associated with faster cognitive decline and progression to AD. As such, it could be the case that the APOE + DAT1 genotype is associated with an apathetic subgroup of individuals with MCI that convert to AD at a faster rate. Whether the presence of apathy, and resultant reduction in activity may accelerate cognitive decline and volume loss is not yet known. Future longitudinal studies of this cohort are required to understand the impact of the genotype and activity on disease progression.

Additionally, the biological implications of the DAT1 dopaminergic SNP on an apathetic phenotype are novel. To date, there are no well-established genetic biomarkers for apathy. However, dopaminergic dysregulation is a key mechanism thought to be involved in syndromes of motivation, such as apathy. Future PET imaging studies should explore specific symptoms of apathy related to the signature genotype in patients with cognitive impairment to assess whether a subtype of apathy with disruptions in dopaminergic reuptake exists. Doing so could point to a specific pharmacological target and patient subgroup most likely to benefit for prospect clinical trials for apathy in AD.

2.4.1 Limitations

In this study, we selected candidate SNPs for our PLS-CA, given the relatively small sample size. This, however, limited the options for exploring genetic variants, as selection depended largely on extant literature in a newly growing field. Future studies with similar sample sizes should adopt a machine learning approach for predictive modelling of a wider selection of SNPs with complex disease phenotypes. Additionally, in this study, apathy was treated as a binary variable, using the caregiver rated NPI. However, it is becoming increasingly recognized that apathy is a multidimensional and complex syndrome, with potentially heterogenous mechanisms giving rise to different apathy subtypes. As such, future studies should leverage an in-depth index for apathy, such as the dimension apathy scale, to tease apart apathy phenotypes within, and across, disease cohorts.

Additionally, some participants in this study were on prescription medications, prior to apathy endorsement, that could have contributed to the presence or absence of apathy. Previous research suggests that certain classes of anti-depressants, specifically SSRIs, can cause apathy in a reversible, dose-dependent manner (Masdrakis et al., 2023; Aydemir et al., 2018). A recent review of 50 studies examining SSRI-induced apathy identifies a predominantly affective/emotional subtype of apathy (Masdrakis et al., 2023). SSRIs influence serotonergic systems, which modulate midbrain dopaminergic systems that project to the prefrontal cortex; as such, SSRIs may induce apathetic symptoms by affecting dopamine release to areas of the PFC (Aydemir et al., 2018). In the current study, there was a significantly greater proportion of individuals with apathy versus those

without apathy taking SSRIs. As such, whether these medications contributed to the presence of apathy within the Apathy+ group remains unknown. Participants on dopamine antagonists or agonists may experience increases or reductions in symptoms of apathy, respectively. In the current study, there was no significant differences in the distribution of participants taking dopaminergic medications in the Apathy+ versus Apathy- group. Lastly, a significantly greater proportion of individuals in the Apathy+ group, compared to the Apathy- group, were taking cholinesterase inhibitors and memantine. A 2015 clinical trial investigating the efficacy of donepezil on apathy in individuals with AD suggests that cholinesterase inhibitors may be associated with improvements to cognitive apathy earlier on in the disease course (Rea et al., 2015). The authors suggest that increased levels of acetylcholine in the central nervous system can modulate dopaminergic neuron activity. NMDA receptor antagonists, such as memantine, are often used in AD to reduce heightened intracellular glutamate levels (Parsons et al., 2007). Glutamate-dopamine interactions are critical top-down control from PFC regions to the striatum; projections from the DLPFC to the caudate are thought to modulate striatal dopamine and glutamate systems (Arnsten, 2009). Future studies may benefit from accounting for concomitant medications in statistical analyses or creating exclusion criteria based on predicted neuromodulating effects of specific medication types/classes.

2.4.2 Conclusions

In summary, the results of this study provide preliminary evidence of a unique signature of genetic and structural imaging interactions which may be associated with the presence of apathy in the early stage of AD, MCI. Specifically, these results suggest that genetic variants in the dopaminergic system and the APOE e4 allele, along with regional brain changes, may uniquely predispose individuals to apathy. Although these findings did not extend to patients with diagnosed Alzheimer's disease, our results could point to a specific subtype of apathy in, or timeframe within aMCI in which these interactions occur. Overall, knowledge of the associations between SNPs in neurotransmitter systems and changes in particular brain regions may be useful for earlier detection of patients who may be susceptible to certain symptoms in AD, and may allow for the development of more specific and targeted treatment options.

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3 Chapter 3: Neurocognitive mechanisms of apathy in neurodegenerative dementias

3.1 Introduction

Apathy refers to reduced goal-directed behaviour (i.e., behaviour executed to achieve an outcome, in which the value of the outcome and cost of action are accounted for; Nobis & Husain, 2018; Husain & Roiser, 2018). It typically manifests in different domains of regular life, including a quantitative reduction in previously characteristic daily behaviours, cognition, emotional reactivity, and social interactions (Robert et al., 2018). For example, caregivers of patients with apathy often report a marked decrease in activities such as hobbies, work, socializing with friends, and/or personal hygiene (Nyatsanza et al., 2003). Apathy is one of the most prevalent and salient symptoms of neurodegenerative dementias. Mean prevalence rates of apathy in patients with dementias are as follows: 72% in patients with frontotemporal dementia , 49% in patients with Alzheimer's disease , and 40% in patients with Parkinson's disease or Lewy Body dementia (Husain & Roiser, 2018; Breitve et al., 2018). In fact, apathy is one of the first symptoms to occur in many cases (Taveres et al., 2019; Palmer et al., 2010; Martin et al., 2020) and can manifest decades prior to clinical presentation of a neurodegenerative disorder.

Apathy in these patient populations is associated with increased caregiver burden, accelerated cognitive decline, increased morbidity, and reduced quality of life (Nyatsanza et al., 2003; Taveres et al., 2019). Despite these adverse consequences, there is currently no widely available treatment for apathy. Previous pharmacological trials for apathy, including dopamine agonists, SSRIs, and cholinesterase inhibitors have been met with variable success and are generally disease-specific (Padala et al., 2007; Yuen et al., 2014; Rea et al., 2014). This difficulty in managing symptoms of apathy is attributed to an incomplete understanding of the underlying causes of apathy (Ruthirakuhan et al., 2018). As such, there is an evident need to identify the neurocognitive mechanisms that give rise to apathy (Ruthirakuhan et al., 2018; Husain & Roiser, 2018).

Whether apathy is qualitatively different within and across specific groups of neurodegenerative disorders, or whether common patterns of cognitive deficits and/or brain atrophy patterns underlie apathy across disorders is a crucial question. A review by Husain and Roiser (2018) outlines the utility of investigating symptoms of apathy across disorders, within the framework of effort-based decision making for goal directed behaviour. The authors propose that isolating the cognitive mechanisms involved in, and leading up to, the decision to engage in an effortful activity to obtain a reward can elucidate deficits in cognition causing apathy. The current study has chosen to focus on three key cognitive processes in effort-based decision making for goal directed behaviour: option generation, motivation, and volition. Option generation refers to the capacity to come up with options for behaviour in a given scenario (Kaiser et al., 2013). Here, motivation encompasses the weighting of costs to benefits in the decision-making process. Lastly, volition refers to the feeling of control over one's actions and the outcomes of those actions, as in the sense of agency (SoA; Malik et al., 2022). The SoA is a critical human experience that aids in the learning of action-outcome contingencies.

To date, little is known about whether and how option generation, motivational processes, and volition are impaired in patients with neurodegenerative dementias and apathy. Some recent evidence exists for effort aversion/discounting and reward devaluation in patients with apathy. For example, patients with behavioural variant FTD and AD have demonstrated increased sensitivity to effort in decision-making tasks (Le Bouc et al., 2023; Aschenbrenner et al., 2023). In patients with PD and apathy, a significant decrease in sensitivity to monetary rewards was found (Muhammed et al.,2016). One study found that that the capacity to generate options in a healthy adult population was associated with higher levels of motivation and this relationship was modulated by dopaminergic medication (Ang et al., 2018). To the best of our knowledge, no study has examined the relationship between apathy and volition in an experimental setting. Moreover, there have been no studies investigating option generation, motivation, and/or volition across neurodegenerative dementias.

The novelty of the current study also lies in its investigation of differences between motor and cognitive effort, as well as different types of rewards, during decision-making in

goal-directed behaviour. A recent study by Tran and colleagues (2021) investigated how cognitive and physical effort sensitivity differentially influence motivational deficits in individuals with major depressive disorder (MDD). Participants were required to press a button a certain number of times in a physical effort-based decision-making task and complete a letter variant of the N back task in a cognitive effort based decision-making task for monetary rewards. Results revealed that participants with higher levels of anhedonia were less willing to expend physical effort for rewards, but this was not the case for cognitive effort. However, reduced motivation to expend cognitive effort was associated with worse cognitive outcomes and impaired life functioning. These findings suggest that effort sensitivity is affected by the type of effort expended in effort-based decision making for goal directed behaviour.

Additionally, evidence suggests that different types of rewards are processed differently in the brain. The mesolimbic dopaminergic pathway plays a crucial role in brain's reward system (BRS). When rewarding stimuli are presented the dopaminergic pathway is activated and causes the release of dopamine from the ventral tegmental areas (VTA) to targeted nuclei (Lewis et al., 2021). Food, monetary, and erotic rewards have been shown to engage overlapping, but also distinct, nuclei in the basal ganglia; food rewards engage the left hemisphere basal ganglia, monetary rewards engage the basal ganglia bilaterally, while erotic rewards engage the right lateral globus and left caudate (Arsalidou, Vijayarajah & Sharaev, 2020). As such, there is reason to believe that effort allocation for different reward types may influence effort-based decision making for various reward types.

3.1.1 Objective & Hypothesis

The purpose of this study was to investigate the relationship between apathy and option generation, motivation, and volition. We hypothesized that apathy in neurodegenerative dementias will be associated with deficits in option generation, effort sensitivity, reward sensitivity, and/or volition. Additionally, we predicted that specific deficits may exist within disease groups. In patients with frontotemporal dementia and apathy, we expected to see effort discounting and heightened sensitivity to candy rewards based on common presentations of declines in cognitive and motor activity and heightened preferences for

sweets (Silvieria et al. 2023; Ahmed et al. 2014) . In apathetic patients with PD and/or LBD we expected to see effort discounting and reduced sensitivity to monetary rewards. In patients with AD and apathy, we expected effort discounting and perhaps an overall reduction in reward sensitivity.

3.2 Methods

3.2.1 Participant Characteristics & Recruitment

Participants with neurodegenerative dementias, including patients with Alzheimer's Disease (AD), frontotemporal dementia (FTD), and Lewy body dementia (LBD), as well as age-matched healthy controls (HC) were enrolled in this study. At time of recruitment, patients with AD met the National Institute on Aging-Alzheimer's Association criteria for probable AD (DeKosky et al., 2011), patients with LBD met the criteria of the Fourth Consensus Report of the LBD Consortium for probable LBD (McKeith et al., 2017), and patients with PD met the Movement Disorder Society's clinical diagnostic criteria for diagnosis of probable PD (Postuma et al., 2015). In the FTD group, patients met the criteria for the semantic variant, nonfluent/agrammatic variant (Gorno-Tempini et al., 2011), or the international consensus criteria for the behavioural variant of FTD (Rascovsky et al., 2011). Patients were recruited from the Cognitive Neurology and Alzheimer Research Centre (CNARC) at Parkwood Hospital in London, Ontario, Canada, and through advertisements in doctor's offices in the community. Healthy control participants were recruited from the community through word of mouth and posters. Patients and healthy control participants varied in apathy symptomatology, assessed by study questionnaire data.

Inclusion criteria for patients were the following: 1) age 30 to 90, and 2) diagnosis of frontotemporal dementia or related disorders (including progressive supranuclear palsy, corticobasal syndrome, Lewy body dementia, Parkinson's disease, Alzheimer's disease or a related disorder). Exclusion criteria included the following: 1) history of significant brain tumor, or other neurologic disease affecting cognition, apart from FTD, AD, or LBD, or related disorders, 2) cognitive or language impairment that prevents the

participant from understanding the nature of the study or the study task instructions, as assessed by the principle investigator, and 3) lack of a study partner or caregiver available to provide details about the patient's general functioning and symptoms. Healthy participants were eligible for the study if they met the following criteria: 1) age 30 to 90, 2) have no self-experienced persistent decline in cognitive capacity in comparison with a previously normal status, and 3) MoCA of 24 or greater (23 with <12 years of education). Exclusion criteria for healthy controls included history of a significant brain tumor, or neurologic or psychiatric disease judged to affect cognition by the investigators, inclusive of FTD, AD, LBD, or related disorders.

All study procedures were approved by Western University's Health Sciences Research Ethics Board. Participants, or their substitute decision makers, and their study partners (applicable only to patients), provided written informed consent prior to undertaking study procedures and were compensated for their time.

3.2.1.1 Sample Size Calculation

Using MANOVA procedures, a targeted sample size of N=22 per group was designed to maintain a minimum power (1-ß) of 0.90 and detect a medium effect size, with alpha = 0.05. Power calculations were determined using G* Power 3.1.7 (Faul et al., 2007) based on a MANOVA procedures with 4 groups and 6 response variables.

3.2.2 Neuropsychology Assessments

Self- and informant-administered questionnaires were completed by healthy controls and patients' caregivers, respectively. Two questionnaires were chosen to assess apathy and one questionnaire was used to assess anhedonia. The Montreal Cognitive Assessment (MoCA) was administered as a measure of overall cognitive ability.

Apathy Evaluation Scale (AES; *Marin et al., 1991)*: The Apathy Evaluation Scale includes 18 items to assess apathy across three domains, including cognitive, emotional, and behavioural. Self-rated and informant-based versions of the AES have been validated for use in healthy controls and patients with dementia. Participants or informants rate how characteristic each item is of the subject's behaviour and cognition from 1 (not at all

characteristic) to 4 (a lot characteristic), based on the previous four weeks, with a higher score indicating less apathy.

Apathy Motivation Index (AMI; Ang et al., 2017): The Apathy Motivation Index is a brief, 18-item, self-report measure of apathy and motivation. The AMI includes behavioural, emotional, and social domains and has been validated for use in a healthy population of adults. Each item on the index is rated based on the previous two weeks, and participants are asked to indicate how each item reflected their behaviours and attitudes, from 0 (completely true) to 4 (completely untrue). With higher scores indicating more apathy. The AMI is unique in its inclusion of items pertaining to motivation for social rewards.

Dimensional Anhedonia Scale (DAS; Rizvi et al., 2015): The Dimensional Anhedonia Scale is a 17-item questionnaire that measures desire, motivation, effort and consummatory pleasure across hedonic domains. It has been validated for use in healthy community-dwelling participants and unipolar and bipolar depressed patients. The DAS is used to measure anhedonia in the following four domains: hobbies, food/drink, social activities, and sensory experience.

Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005): The MoCA is a researcher or clinician administered screening tool for cognitive impairment in the following domains: visuospatial/executive abilities, memory, attention, language, abstraction, and orientation. Patients are given a total score out of 30, with a score of 26 or below indicating cognitive impairment. It is widely used, and validated for use, in neurodegenerative dementias, including FTD (Freitas et al., 2012), PD (Vásquez et al., 2019), LBD (Biundo et al., 2016), and AD (Freitas et al., 2012).

3.2.3 Computer Tasks

Four computer tasks were programmed, using MATLAB's Psychtoolbox, to assess neurocognitive mechanisms underlying apathy, including option generation, cognitive effort-based decision making for rewards, motor effort-based decision making for rewards, and volition.

3.2.3.1 Option Generation Task

Participants were asked to provide verbal responses to questions posed by the experimenter. In each trial of the task, the participant was shown a short, real-world scenario that the experimenter read to the participant off a computer screen. Participants were then prompted for answers to the question, "what could you do?" Participants were expected to generate behavioural options for each scenario. A 2x3 experimental design was used, with scenario type (goal-directed, open) and time (8 seconds, no limit, maximum time) as within-subjects factors. In goal-directed scenarios, participants are presented with a problem that needs to be overcome to achieve a certain goal; these goal-directed trials serve as a control for comprehension and language skills. An example of a goal-directed scenario is "You want to read but you cannot focus because your neighbour's music is too loud. What could you do?" Open scenarios provided ill-structured settings without any goal-based behavioural expectations. An example of an open scenario is "You missed your train and you have an hour to wait before the next train comes. What could you do? Scenarios were presented under three different time conditions; in "time-constrained" trials, participants were given eight seconds to verbally generate options for the scenario. The eight second constraint is based off previous work by Kaiser and colleagues (2013) and was meant to assess speed of comprehension and language production ability. In "unlimited" trials, participants were instructed to take as much time as needed to generate options and to let the experimenter know when they were done with their response. In the "prompted" condition, participants were prompted to keep thinking of options before the trial is over. The purpose of prompted condition was to assess impairments in self-initiated cognition. The option generation task, therefore, included the following six conditions across the scenario type and time factors: goal-directed & time-constrained, goal-directed and unlimited, goal-directed & prompted, open & time-constrained, open & unlimited, open & prompted. The task included a total of 18 trials, with three trials per condition. Trials were presented in random order across participants with random combinations of scenario type and time. MATLAB's random generator was used to assign time condition types to scenarios. Experimenters made audio recordings of the task sessions. Fluency, defined as the number of feasible options in each trial, was the primary outcome of the task.

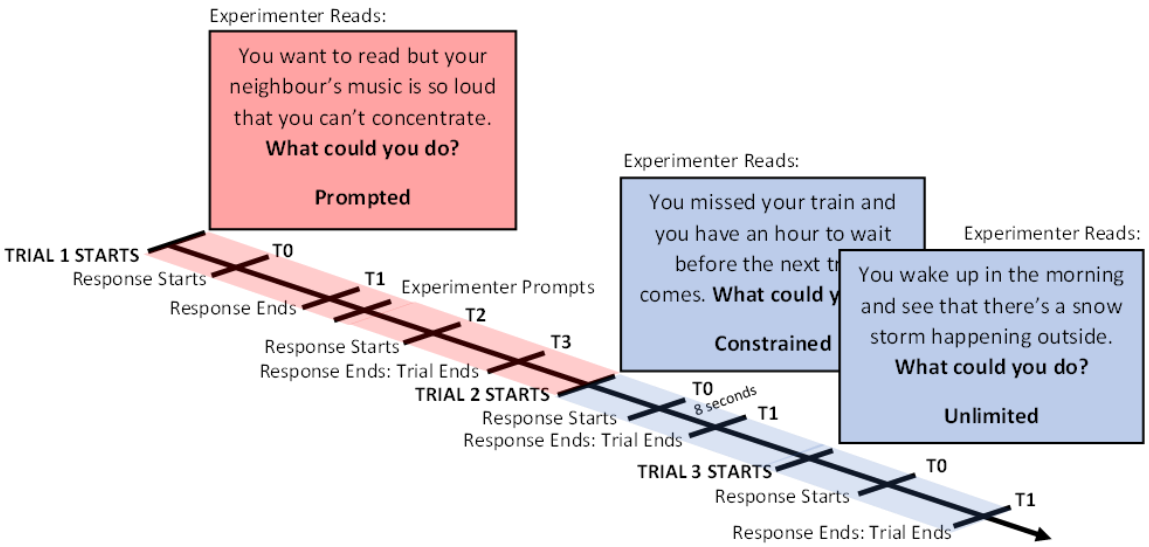


Figure 3-1 Option generation: Example trial structure. Red-coded prompt cards were used to indicate goal-directed scenarios. Blue-coded prompt cards were used to indicate open scenarios. Prompt cards indicated time trial, Prompted, Constrained, or Unlimited. Time intervals between participants' verbal response starts and ends were recorded.

3.2.3.2 Cognitive Effort-Based Decision-Making Task

A 3x2x3 (*effort*: high, medium, low; *reward value*: high, low; *reward type*: monetary, food, social) within-subjects experimental design was leveraged for this task. The experiment was programmed on a Lenovo touch-screen laptop, using MATLAB's Psychtoolbox. Participants engaged in a visual search task to obtain monetary, food, or social rewards. The visual search task included stimuli of black-shaded animal silhouettes on a white background. In all the stimulus pictures, there were two copies each animal (i.e., distractor animals), except for one (i.e., the target animal). In each trial of the experiment, participants were instructed to find and touch the target animal, on-screen. The touchscreen registered and recorded participant touch responses. Stimulus difficulty varied by number of distractor animals, to provide three levels of difficulty; easy trials included 4 distractor animals and 1 target animal, medium-difficulty trials included 16 distractor animals and 1 target animal, and hard trials included 30 distractor animals and

1 target animal. At the beginning of each trial, participants were shown the visual search stimulus for 1000ms, followed by the reward associated with successful completion of the trial. After the reward was revealed, participants were asked to accept or reject the trial. When a trial was accepted, the visual search stimulus reappeared on-screen and the participant was given unlimited time to complete the trial. When a trial was rejected, participants were re-directed to the start of the next trial. Upon successful completion of a trial, participants were informed that they won the associated reward. If the trial was unsuccessfully attempted, participants were informed that their answer was incorrect and instructed to move on to the next trial. Each participant engaged in 18 trials of the task. The main output variables of this task are: 1) the number of accepted trials, and 2) the time it took (in seconds) to choose an answer in the visual search task (i.e., search time). In a sensitivity analysis, the number of correct trials (i.e., accuracy) was accounted for as well.

Three reward types, including money, candy, and social rewards could be obtained by participants. Each reward type had two degrees of value: high reward and low reward. A high monetary reward was $1.25 CAD. A low monetary reward was $0.25 CAD. A high candy reward included one package of Rockets candy and one Smarties chocolate box. A low candy reward included one package of Rockets candy. Social rewards took the form of short video clips of staff members and their families saying complimentary phrases to the participants, such as “you’re a wonderful person.” In a high social reward trial, the video clips included a friendly gesture (e.g., thumbs up), smiling actor, and emphatic positive vocal expression. In a low social reward trial, there was no bodily gesture, the actor’s phase was expressionless, and the actor used a neutral vocal expression. All videos were recorded on a plain background and actors wore plain black or grey shirts to eliminate visual distractions from the subject of the video. Please see Appendix A (A.1) for more information about the stimuli used in this task.

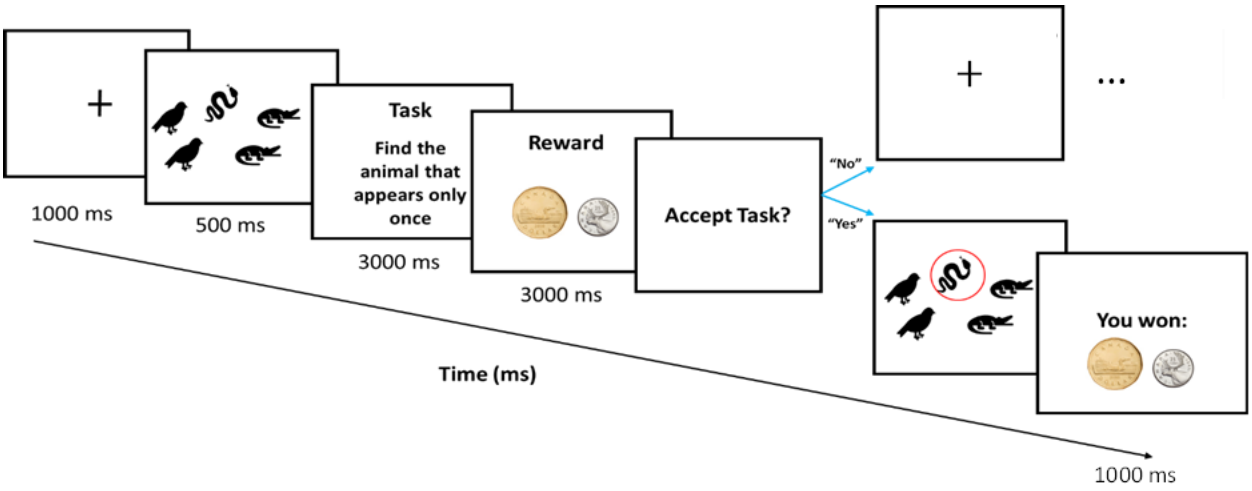


Figure 3-2 Trial structure for cognitive effort-based decision-making task. A fixation cross is followed by a presentation of a visual search task. Effort increases with number of animals in the stimulus. A low effort, high monetary reward trial type is pictured here. Participants are prompted to accept or reject the task. If accepted, participants complete the task by touchscreen and then receive feedback. If the participant rejects a trial, the task moves on to the next trial beginning with a fixation cross.

3.2.3.3 Motor Effort-Based Decision-Making Task

The experimental design for the motor EBDM task was similar to the cognitive EBDM task. A 3x2x3 (*effort*: high, medium, low; *reward value*: high, low; *reward type*: monetary, food, social) within-subjects experimental design was leveraged for this task. The experiment was programmed on a Lenovo touch-screen laptop, using MATLAB's Psychtoolbox. In order to obtain monetary, food, or social rewards, participants were required to apply a certain amount of grip force to a handheld dynamometer. The hand dynamometer was calibrated to each participant's maximum voluntary contraction (MVC). There were three levels of task difficulty (i.e., effort levels) that were set to a percentage of the participant's MVC; in high, medium, and low effort trials, 100%, 65%, and 25% of the participant's MVC was required, respectively. At the start of each trial, participants were shown a visual depiction of the force needed to successfully complete the trial and the associated award for 3000 ms. They were then prompted to either accept or reject the trial. When a trial was accepted, the task stimulus reappeared on-screen and the participant was given ten seconds to complete the trial. When a trial was rejected,

participants were re-directed to the start of the next trial. Upon successful completion of a trial, participants were informed that they won the associated reward. If the trial was unsuccessfully attempted, participants were informed that they did not apply enough force and instructed to move on to the next trial. Each participant engaged in 18 trials of the task. The reward types and reward magnitudes were identical to those used in the cognitive EBDM task. The main output variables task included: 1) the number of accepted trials, and 2) the maximum force (in parts per newton, ppn) applied in each trial.

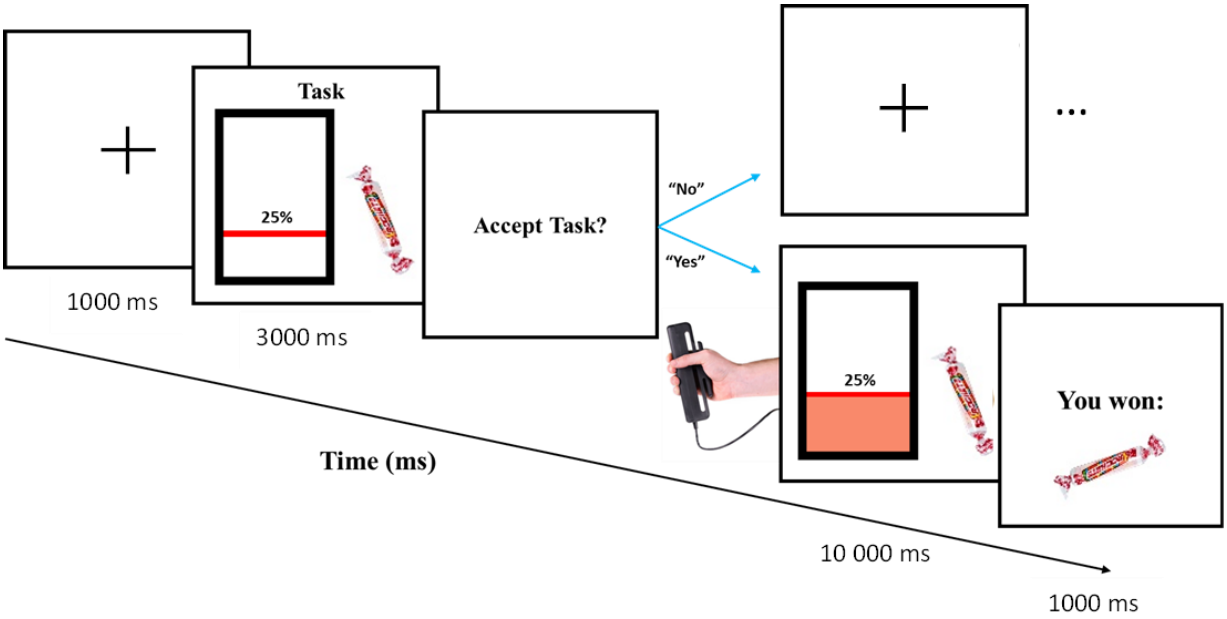


Figure 3-3 Trial structure for motor effort-based decision-making task. Each trial begins with a fixation cross, followed by a visual presentation of the trial task. Motor effort required is indicated by the height of the red horizontal line along the inner rectangle. A low motor effort, low monetary reward trial type is pictured here. Participants are then prompted to accept or reject the task. If accepted, participants complete the task by exerting motor effort in the form of clenching a hand-grip dynamometer that is calibrated to the participant's maximum voluntary contraction. Finally, participants receive feedback. If rejected, participants move on to the next trial beginning with a fixation cross.

3.2.3.4 Intentional Binding Task

Intentional binding was used to index volition. Intentional binding is a perceptual phenomenon that occurs when an individual makes a voluntary action; it manifests as a compression in the perceived time interval between a voluntary action and its subsequent effect (Moore & Obhi, 2012). Intentional binding is indicative of feelings of agency, which are strongly linked to volitional actions (Moore & Obhi, 2012). The task consists of two baseline and two operant conditions. In a baseline tone condition, participants watch a hand rotate (at a period of 2.56s) around a clockface, marked at regular intervals; in each trial a single auditory tone (1000Hz, 100ms) sounds and the participant is instructed to indicate the position of the hand on the clockface when they perceived the tone to have occurred (fig 3.4a). In baseline action condition, participants make a single voluntary action, in the form of a key press, in place of the tone, and are instructed to estimate the position of the hand on the clockface when they perceived the key press to have occurred (fig 3.4b). In operant trials, participants make voluntary key presses in each trial; each key press is followed by a tone (fig 3.4c). In operant action trials, participants are instructed to estimate the position of the hand on the clockface when they perceived the key press. In operant tone trials, participants are instructed to estimate the position of the hand on the clockface when they perceived the tone to have occurred. For each condition, mean judgment errors (judgment error = actual position of the hand during event–estimated position of the hand during event) will be calculated. Then, for each event (voluntary action and tone), mean judgment error of the baseline condition will be subtracted from the mean judgment error of the operant condition to yield a "perceptual shift measure." A positive perceptual shift value for the action event and a negative perceptual shift value for the tone event represents the intentional binding phenomenon. The main output variables are as follows: 1) magnitude of action binding (perceptual shift of action), and 2) magnitude of tone binding (perceptual shift of tone).

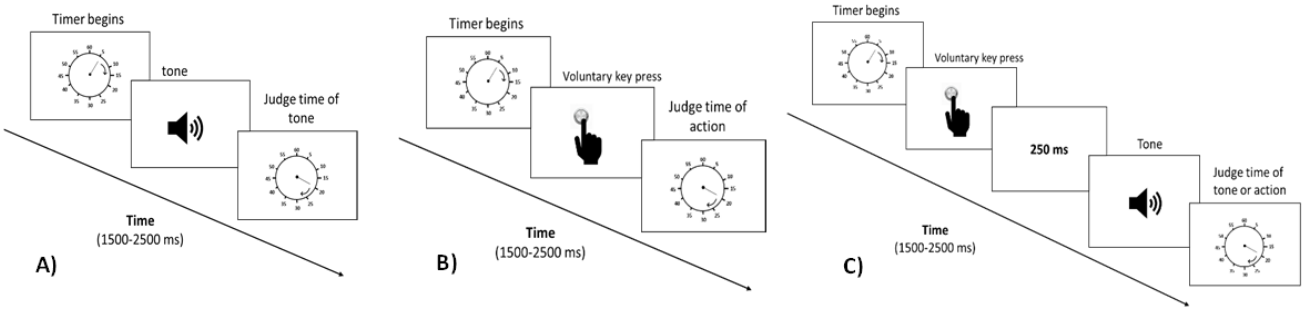


Figure 3-4 Intentional Binding Task Trial Structures. A) Trial structure for baseline tone condition. Participants watch a clock hand rotate around a clockface at a period of 2.56 seconds while a tone sounds. Participants estimate the position of the hand on the clockface of when they heard the tone. B) Trial procedure for baseline action condition. Trial structure is identical to baseline tone, with the exception that the tone is replaced by a voluntary action, in the form of a key press, that they are instructed to make at a time of their own choosing. Participants estimate the position of the hand of when they perceive their key press. C) Trial procedure for operant conditions. Participants watch a clock hand rotate around a clockface at a period of 2.56 seconds. At a time of their choosing, they make a key press. 250 ms following the key press, a single tone sounds. In operant action trials, participants estimate the position of the hand when they perceive the keypress. In operant tone trials, participants estimate the position of the hand when they perceive the tone.

3.2.4 Procedure

Participants were consented into the study by verbal written informed consent. Patients were required to have a study partner to provide informant-based questionnaire data. All study procedures took place at CNARC, located at Parkwood Hospital Main Building, London, Ontario. After consent was received, participants completed the MoCA to assess cognitive impairment. A neurological exam was then completed by a neurologist to account for any motor or physical conditions that could affect engagement in the study tasks. Following the neurological examination, participants completed the computer tasks, within a 1-2 hour timeframe. The order of tasks was randomly assigned, using a random number generator. The order of conditions within the intentional binding task was randomly assigned as well. Following the computer tasks, healthy control participants completed questionnaires, including the AES, AMI, and DAS. While patients were engaged in the computer tasks, their study partners completed the informant-based

AES, AMI, and DAS. At the end of the study, all participants received monetary compensation, and were provided with candy rewards, as depicted in the EBDM tasks.

3.2.5 Statistical Analyses

All data analyses were carried out in R Studio v1.3.959. All computer task data were examined for outliers, and values that differed from the mean by three or more standard deviations were removed from further analyses. Missing data points for individuals who were missing single data points due to brief technical glitches, but for whom the rest of the data was usable, were imputed using multivariate imputation by chained equations via the mice package v3.11.0.

3.2.5.1 Neuropsychological Assessments

Given the collinearity and size of the data from the AES, AMI, and DAS, a thematic data reduction approach was taken to group items across all three measures. In accordance with this study's a priori hypothesis regarding the mechanisms underlying apathy, items were extracted and grouped from the AES, AMI, and DAS, into the following apathy component indices: effort, social reward, food reward, other reward, initiation, and option generation. Since the AES and AMI are scaled in opposite directions, all AMI scores were reversed so that higher scores indicated less apathy. Composite component scores were created for each participant by first converting each item score to a Z score and then adding together relevant item scores to make composite scores of the six apathy components. These component scores were used as response variables for the partial least squares analysis. A full list of the AES, AMI, and DAS items comprising the component scores can be found in Appendix A (A.2).

3.2.5.2 Group Level Analyses

In order to better understand differences in our task measures that may be driven by specific neurodegenerative dementias, group-level analyses of variance were conducted. All participants were placed into one of four groups, based on disease profile. In the "FTD+", patients with a diagnosis of bvFTD, svPPA, nfvPPA, CBS, and PSP were included. The "AD/aMCI" group included patients with Alzheimer's disease and

amnestic mild cognitive impairment. The “LBD/PD” group included patients with a diagnosis of Lewy body dementia or Parkinson’s disease. Lastly, the “HC” group consisted of healthy, cognitively normal participants.

The align ranked transform (ART) for nonparametric factorial ANOVAs (as described by Wobbrock et al., 2011), was leveraged for exploring the cognitive and motor EBDM task data. Unlike typical non-parametric ANOVAs, such as the Friedman test, ART is sensitive to detecting interaction effects in factorial experimental designs. The ART relies on a preprocessing step that "aligns" data before applying averaged ranks, after which point common ANOVA procedures can be used. In the cognitive EBDM task, we explored average search time within each reward type x reward value x effort level condition in relation to disease group. As such, there were 18 response variables (table 3.1).

Table 3-1 Eighteen response variables included in the group-level EBDM analyses.

Reward Type	Reward Magnitude	Effort Level
Monetary	Low	Low Medium High
	High	Low Medium High
Candy	Low	Low Medium High
	High	Low

		Medium High
Social	Low	Low Medium High
	High	Low Medium High

The independent variable included four levels of disease group, including FTD+, LBD/PD, AD/aMCI, and HC. In the motor EBDM task, the same independent variable and levels were used. The response variable was maximum force applied for each of the 12 conditions listed above. Additionally, percentage of accepted trials, across the different conditions was explored for any group-specific patterns of effort or reward preference. Chi-square tests of independence or Fisher's exact tests were used to assess significant difference in accepted trials across disease groups and conditions.

A MANCOVA was used to assess group-level differences in the option generation task. The independent variable was disease group, including FTD+, LBD/PD, AD/aMCI, and HC as the four levels. The response measure was "fluency" (i.e., the number of options generated); fluency was measured across the following six trial types: goal-directed & time-constrained, goal-directed and unlimited, goal-directed & prompted, open & time-constrained, open & unlimited, open & prompted. Age, years of education, sex, and MoCA total score were included in the MANCOVA as covariates. In the intentional binding task, perceptual shift (in ms) was the response variable in a repeated measures

ANOVA. The between subjects variable was disease group and the within subjects variable was binding event (tone binding and action binding).

3.2.5.3 Partial Least Squares (PLS)

To identify whether patterns of performance on the tasks were associated with different aspects of apathy symptoms as rated by study partners, a partial least squares (PLS) analysis was used. PLS is a multivariate regression technique with the ability to reduce high dimensional data and deal with multicollinearity in both the predictor and response variables. The PLS is unique in its ability to unveil covariance between predictors and response measures, rather than just focusing on variance explained by multiple collinear predictors, as is the case with traditional data reduction methods such as principal component analyses. As such, the PLS can find relationships between dependent and independent variables when variables are expected to be correlated. Additionally, PLS is well-suited for data with a small number of observations relative to the number of variables in the study. In the present PLS, predictor variables were the outcome measures from the cognitive EBDM task, motor EBDM, and option generation task. Given the small sample of individuals able to complete the intentional binding task, it was excluded from the PLS analysis. Additional covariates, including age, years of education, sex, and MoCA total score, were added to the PLS analysis as predictors. The response variables were the composite component scores arising from the six AES, AMI, and DAS groupings.

3.3 Results

3.3.1 Participant Demographics

Due to the restrictions placed on data collection because of the COVID-19 lockdown, we were unable to reach our target sample size. Sixty-one participants participated in the study. However, as detailed below for each task, several participants were excluded from data analysis due to incomplete neuropsychological data or noncompliance with computer task instructions.

3.3.1.1 Cognitive Effort-Based Decision-Making Task Cohort

A total of 51 participants (30 males) completed all neuropsychological tests and the cognitive EBDM task. The mean age of participants was 70.36 years old (SD:7.46, range:49-86). Participants reported attending between 10 and 25 years of formal education (Mean:15.01, SD:2.59). For the cognitive EBDM task group-level analysis, 14 AD/aMCI (8 female), 15 FTD+ (5 female), 12 LBD/PD (1 female), and 8 HCs (5 female; Table 3.2) were included. Participants with AD/aMCI, FTD+, and LBD/PD had significantly less years of education than healthy controls ($F(3,45)= 7.73$, $p<0.001$), and had significantly lower MoCA total scores than healthy controls ($F(3,45)=11.28$, $p<0.001$).

3.3.1.2 Motor Effort-Based Decision-Making Task Cohort

For the motor EBDM task, a total of 50 participants (31 males) were included for subsequent analysis (Table 3.2). The mean age of participants was 69.84 years old (SD:2.85; range:49-86). Participants reported attending between 10 and 21 years of formal education (Mean:15.00, SD:2.55). The motor EBDM group-level analysis included 16 AD/aMCI, 14 FTD+, 12 LBD/PD, and 8 HC participants. Participants in the AD/aMCI, FTD+, and LBD/PD groups were slightly older than healthy control participants ($F(3,46)= 3.20$, $p=0.03$). Additionally, participants in the AD/aMCI, FTD+, and LBD/PD groups had significantly less years of education ($F(3,46)= 6.41$, $p<0.001$) and lower MoCA total scores ($F(3,46)= 15.98$, $p<0.001$) than healthy control participants.

3.3.1.3 Intentional Binding Task Cohort

The intentional binding task was completed by fewer participants, due to noncompliance with task instructions. A cohort of 38 participants (22 males) was eligible for the analysis (Table 3.2). The mean age of participants was 69.27 years old (SD:7.21, range:49-86). Participants in this cohort attended between 10 and 21 years of formal education (Mean:14.56, SD:2.15). In total, there were 8 participants in the AD/aMCI group, 13 in the FTD+ group, 7 in the LBD/PD group, and 10 participants in the HC group. Participants in the AD/aMCI, FTD+, and LBD/PD groups had significantly less years of

education ($F(3,34)= 9.49$, $p<0.001$) and lower MoCA total scores ($F(3,34)= 11.18$, $p<0.001$) than healthy control participants.

3.3.1.4 Option Generation Task Cohort

Forty-nine participants (30 males) completed the option generation task (Table 3.2). The mean age of participants was 70.40 years old (SD: 8.27, range: 49-86). Participants in this task completed between 10 and 25 years of formal education (mean: 14.87, SD: 3.09). Of the 49 participants, 10 participants were included in the aMCI/AD group, 15 were in the FTD+ group, 13 were included in the LBD/PD group, and there were 11 HCs. As with the other task cohorts, participants in the AD/aMCI, FTD+, and LBD/PD groups had significantly less years of education ($F(3,43)= 9.80$, $p<0.001$) and lower MoCA total scores ($F(3,43)= 19.38$, $p<0.001$) than healthy control participants.

Table 3-2 Participant Demographics Across Computer Task

Cognitive EBDM Task					
	aMCI/AD	**FTD+**	**LBD/PD**	**HC**	**Contrasts**
N	14	15	12	8	**--**
Sex	--	--	--	--	--
Male	6	10	11	3	--
Female	8	5	1	5	--
Age (SD; range)	71.29(9.47;53-86)	70.60(8.93;49-84)	74.17(5.25;66-86)	64.20(6.25;53-73)	F= 1.98 *p*= 0.13
Education (SD; range)	13.21(2.26;10-18)	13.93(2.74;10-21)	14.25(2.53;10-18)	18.66(2.84;15-25)	F= 7.73 ***p*<0.001***
MOCA (SD; range)	12.93(6.01;5-24)	18.93(6.33;4-28)	19.92(5.05;10-28)	27.45(2.49;23-30)	F=11.28 ***p*<0.001***
Motor EBDM Task					
	aMCI/AD	**FTD+**	**LBD/PD**	**HC**	**Contrasts**
N	16	14	12	8	--
Sex	--	--	--	--	--
Male	8	10	11	2	--
Female	8	4	1	6	--

Age (SD; range)	73.00(10.09;53-89)	69.64(8.43;49-81)	74.17(5.25;66-86)	63.75(6.14;58-73)	F= 3.20 ***p*= 0.03***
Education (SD; range)	13.44(2.45;10-18)	14.07(2.79;10-21)	14.25(2.53;10-18)	18.13(2.42;15-21)	F= 6.41 ***p*=0.001***
MOCA (SD; range)	11.88(6.42;1-24)	20.00(4.98;11-28)	19.92(5.05;10-28)	26.88(2.53;23-30)	F=15.98 ***p*<0.001***
Intentional Binding					
	aMCI/AD	**FTD+**	**LBD/PD**	**HC**	**Contrasts**
N	8	13	7	10	--
Sex	--	--	--	--	--
Male	4	9	7	2	--
Female	4	4	0	8	--
Age (SD; range)	72.13(11.13;53-86)	70.31(7.92;49-81)	71.43(3.60;66-77)	63.20(6.18;53-73)	F= 2.65 *p*=0.064
Education (SD; range)	13.50(2.33;12-18)	13.62(1.98;10-17)	13.43(2.30;10-16)	17.70(2.00;15-21)	F= 9.49 ***p*<0.001***
MOCA (SD; range)	14.63(7.89;1-24)	19.92(4.09;13-28)	21.43(2.88;16-24)	27.30(2.63;23-30)	F=11.18 ***p*<0.001***
Option Generation Task					
	aMCI/AD	**FTD+**	**LBD/PD**	**HC**	**Contrasts**
N	10	15	13	11	--

Sex	--	--	--	--	--
Male	5	10	11	3	--
Female	5	5	1	7	--
Age (SD; range)	71.90(10.19;53-86)	69.07(6.76;49-80)	74.75(6.15;66-86)	65.70(8.55;53-81)	F=2.69 *p*=0.06
Education (SD; range)	14.00(2.62;11-18)	13.60(1.80;10-17)	14.08(2.61;10-18)	18.60(2.95;15-25)	F=9.80 ***p*<0.001***
MOCA (SD; range)	12.00(5.14; 5-12)	20.53(5.03;11-28)	20.25(4.67;10-28)	27.5(2.59;23-30)	F=19.38 ***p*<0.001***

3.3.1.5 Partial Least Squares Cohort

The partial least squares analysis included participants who completed all of the computer tasks and who had complete neuropsychological testing (table 3.2). This included a cohort of 29 participants (18 males). The mean age of participants was 68.52 years old (SD: 7.13, range: 49-80). Participants in this task completed between 10 and 25 years of formal education (mean: 14.69, SD: 2.78). 4 participants were included in the aMCI/AD group, 11 were in the FTD+ group, 7 were included in the LBD/PD group, and there were 7 HCs. As with the other task cohorts, participants in the AD/aMCI, FTD+, and LBD/PD groups had significantly less years of education ($F(3,25)= 5.44$, $p<0.01$) and lower MoCA total scores ($F(3,25)= 8.71$, $p<0.001$) than healthy control participants. Healthy controls had significantly higher scores (lower apathy ratings) compared to all three disease groups ($F(3,25)=3.39$, $p=0.03$.

Table 3-3 Participant Demographics for PLS Analysis

	aMCI/AD	**FTD+**	**LBD/PD**	**HC**	**Contrasts**

N	4	11	7	7	--
Sex	--	--	--	--	--
Male	1	8	7	2	--
Female	3	3	0	5	--
Age (SD; range)	68.75 (10.26; 53-75)	69.09 (7.84; 49-80)	71.43 (5.27; 66-77)	65.38 (6.12; 58-73)	F=1.99 p=0.13
Education (SD; range)	14.00 (2.29; 12-18)	13.82 (2.09; 10-17)	14.27 (2.65; 10-16)	18.63 (3.34;15-25)	F=5.44 ***p*<0.01***
MOCA (SD; range)	14.50 (4.82; 7-21)	20.27 (4.36; 13-28)	21.43 (4.78; 16-24)	26.88 (2.53; 23-30)	F=8.71 ***p*<0.001***
AES (SD; range)	43.5 (1.00; 43-45)	44.00 (16.38; 24-72)	47.42 (14.75; 29-68)	62.43 (4.65; 57-68)	F=3.39 *P*=0.03*
AMI (SD; range)	34.50 (6.45; 30-44)	35.91 (13.61; 6-58)	39.00 (20.68; 1-68)	51.57 (6.48; 44-60)	F= 2.17 *P*=0.12
DAS (SD; range)	48.5 (9.47; 38-57)	49.91 (17.18; 26-85)	61.00 (13.38; 46-81)	60.71 (7.18; 47-69)	F=1.69 *p*=0.19

3.3.2 Group Level Task Results

3.3.2.1 Cognitive Effort-Based Decision-Making Results

3.3.2.1.1 Search Times

Search time (ST), the time it took in seconds for participants to find the correct animal in each trial, was the primary outcome of the task. The beginning of the measures (t1) began once the participant accepted the trial and the visual search tasks stimulus appeared on-screen. The end of the measure (t2) occurred when the participant's touch was registered by the touchscreen. Search time was therefore calculated as t2-t1. Within an *easy* effort level trial, a *shorter* search time was thought to indicate greater effort exerted in the trial task. In more *difficult* trials (i.e., medium and hard effort level trials), *longer* search times were indicative of greater effort exerted. The ST metric was split in this way based on previous findings. Pomplun and colleagues (2013) suggest that visual search strategies vary with number of distractors involved in the task. In as easy visual search task (e.g., 4 distractors), participants tend to process multiple display items within a single fixation, and saccades are typically directed towards the centers of item clusters rather than individual items, termed the "global effect." With more distractors, participants tend to engage in more nuanced visual search strategies, such as scanning a search display in reading direction, from left to right, and up to down. Additionally, Horstmann and colleagues (2016) suggest that when the visual target and distractors are more similar and there are more of them, engaging in less efficient search strategies, such as distractor dwelling and distractor revisiting, may occur. We reason that the combination of less efficient search strategies and more distractors in the harder trials indicate greater willingness to endure through the trial; as such, a longer search time would indicate greater effort sustenance.

The 4x3x3x2 (disease group x reward type x effort level x reward magnitude) ART factorial analysis revealed a significant 4-way interaction ($F(12,674.64)=2.21$, $p<0.01$). Post-hoc analyses of the interactions of interest revealed significant three-way and two-way interactions. A significant 3-way interaction between disease group, effort-level, and reward type was found ($F(12,674.05)=1.84$, $p=0.03$), where for each disease group and

reward type combination, search times were significantly longer for high effort level trials compared to low effort level trials (fig 3.5a). There were significant interactions between effort level and disease group ($F(6,75.89=5.95$, $p<0.001$), reward magnitude and disease group ($F(3,675.33)=9.64$, $p<0.001$), and reward type and disease group ($F(6,675.36=2.71$, $p=0.01$). A series of pairwise comparisons were performed, using Bonferroni corrections. Unpacking the reward type x disease group interaction revealed that participants in the FTD+ group had significantly longer search times for candy rewards than for social rewards ($t(673.84)=3.44$, $p=0.04$; figure 3.5b), collapsed across effort levels. A closer look at the reward magnitude x disease group interaction revealed while most groups had no significant differences in mean response times for high reward trials in comparison to low reward trials, there was a significant difference in ST between high and low magnitude rewards in the LBD/PD group, where there was greater mean search times for high magnitude rewards compared to low magnitude rewards ($t(678.07)=4.44$, $p<0.001$, figure 3.5c). Lastly, pairwise comparisons within the effort level x disease group interaction demonstrated faster ST for low effort trials, intermediate ST for medium effort trials, and the longest search times for high effort trials (figure 3.5d). Notably, within the aMCI/AD, HC, and FTD+ groups, there were significant differences in STs between all three levels of effort (aMCI/AD [low-med: $t(674.46)=-9.55$, $p<0.001$, low-high: $t(674.41)=11.86$, $p<0.001$, med-high: $t(674.42)=9.54$, $p<0.001$]; HC [low-med: $t(673.37)=-11.16$, $p<0.001$, low-high: $t(673.16)=18.72$, $p<0.001$, med-high: $t(673.21)=7.49$, $p<0.001$]; FTD+ [low-med: $t(70.72)=-6.98$, $p<0.001$, low-high: $t(685.27)=17.58$, $p<0.001$, med-high: $t(674.14)=3.84$, $p<0.01$]). However, participants in the LBD/PD group spent similar amounts of time in the medium and high effort level trials, but had faster STs in the low effort level trials compared to medium and high effort level trials (low-med: $t(675.11)=-13.45$, $p<0.001$; low-high: $t(674.84)=15.51$, $p<0.001$). Please refer to Appendix A (A.3) for mean search times across each of the 12 task conditions, within each group. Overall, all participants demonstrated shorter STs for low effort trials, across reward types. There was no indication of any reward type, or reward magnitude dependent difference in STs within the low effort level trials. Generally, longer STs were found for medium and high effort level trials across the disease groups. Longer STs for candy rewards appear in the FTD+ group compared to the other two

reward types and this is perhaps driven by more effort exerted for candy rewards (i.e., longer STs) in the medium effort level trials (fig 3.5a). Lastly, it appears that only the LBD/PD+ group showed sensitivity to reward magnitude, with longer search times for high magnitude rewards compared to low magnitude rewards. Although the LBD/PD group did show the greatest difference in mean search times between high reward-high effort and low reward-high effort trials (see Appendix A (A.4)), this difference did not reach significance and conclusion regarding effort exerted on high versus low magnitude trials for the LBD/PD cannot be ascertained.

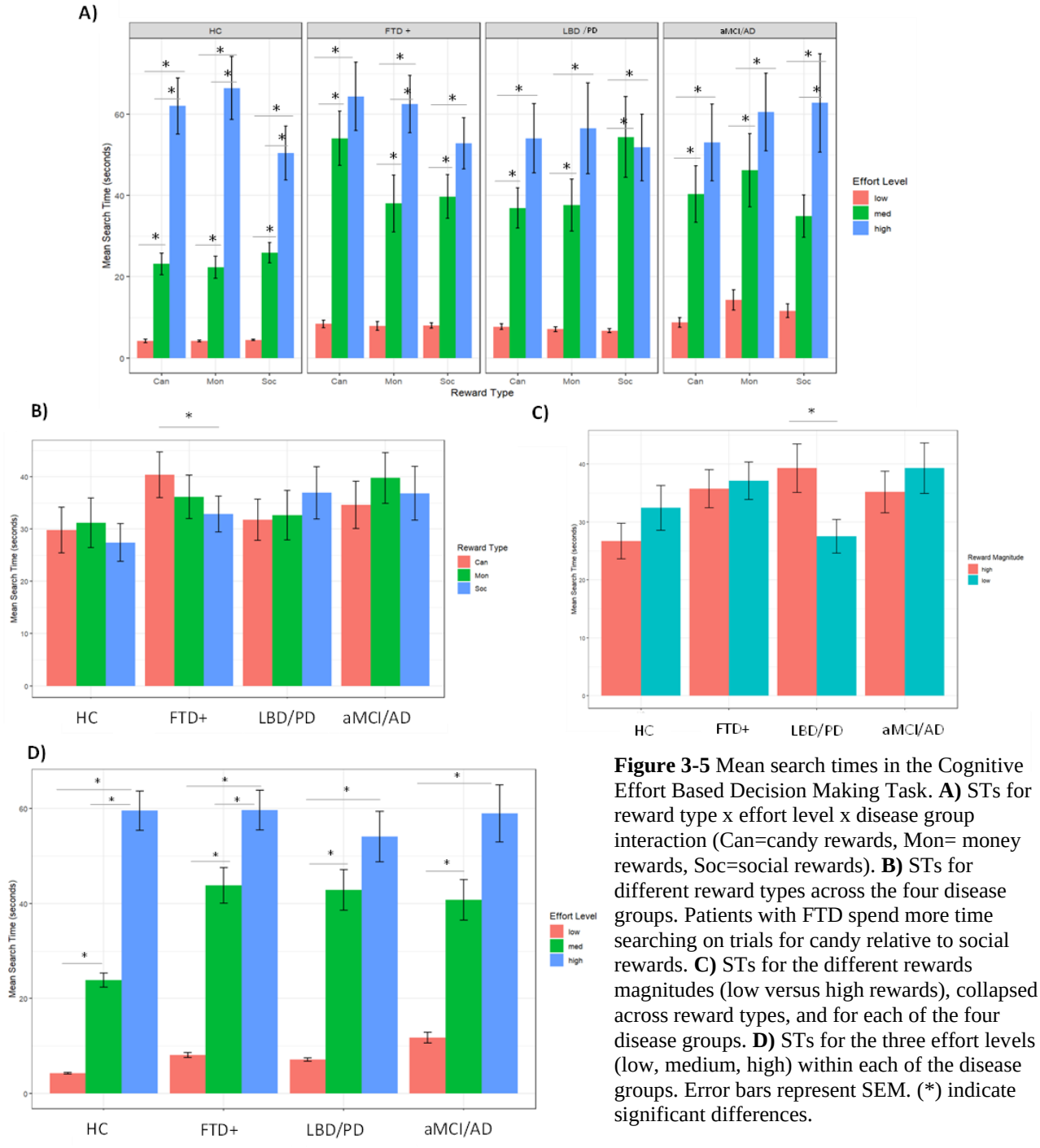


Figure 3-5 Mean search times in the Cognitive Effort Based Decision Making Task. **A)** STs for reward type x effort level x disease group interaction (Can=candy rewards, Mon= money rewards, Soc=social rewards). **B)** STs for different reward types across the four disease groups. Patients with FTD spend more time searching on trials for candy relative to social rewards. **C)** STs for the different rewards magnitudes (low versus high rewards), collapsed across reward types, and for each of the four disease groups. **D)** STs for the three effort levels (low, medium, high) within each of the disease groups. Error bars represent SEM. (*) indicate significant differences.

To further explore whether shorter search times reflected greater cognitive effort (and more efficient detection of the target) within an effort level, a sensitivity analysis was conducted with search times for correct trials only. STs for correct trials were expected to reflect concerted engagement with the task, perhaps due to greater desire for the corresponding trial reward. The same significant three- and two-way interactions were found for the sensitivity analysis. Pairwise comparisons within the disease group x effort level interaction revealed the same pattern of significant group-level differences (figure 3.5d). However, in the reward type x disease group interaction, the significant difference between STs in candy and social rewards did not remain for the FTD+ group. Instead, there was a significant difference in STs for social rewards and monetary rewards in the LBD/PD group, such that more time was spent searching for the animal when a social reward was to be gained ($t(384.42)=-3.92$, $p<0.01$; figure 3.6a). Additionally, further analysis of the disease group x reward magnitude interaction revealed significantly greater STs for low magnitude rewards versus high magnitude rewards in HCs ($t(385.71)=-4.30$, $p<0.01$; figure 3.; interestingly, greater STs were seen for low magnitude rewards compared to high magnitude rewards.

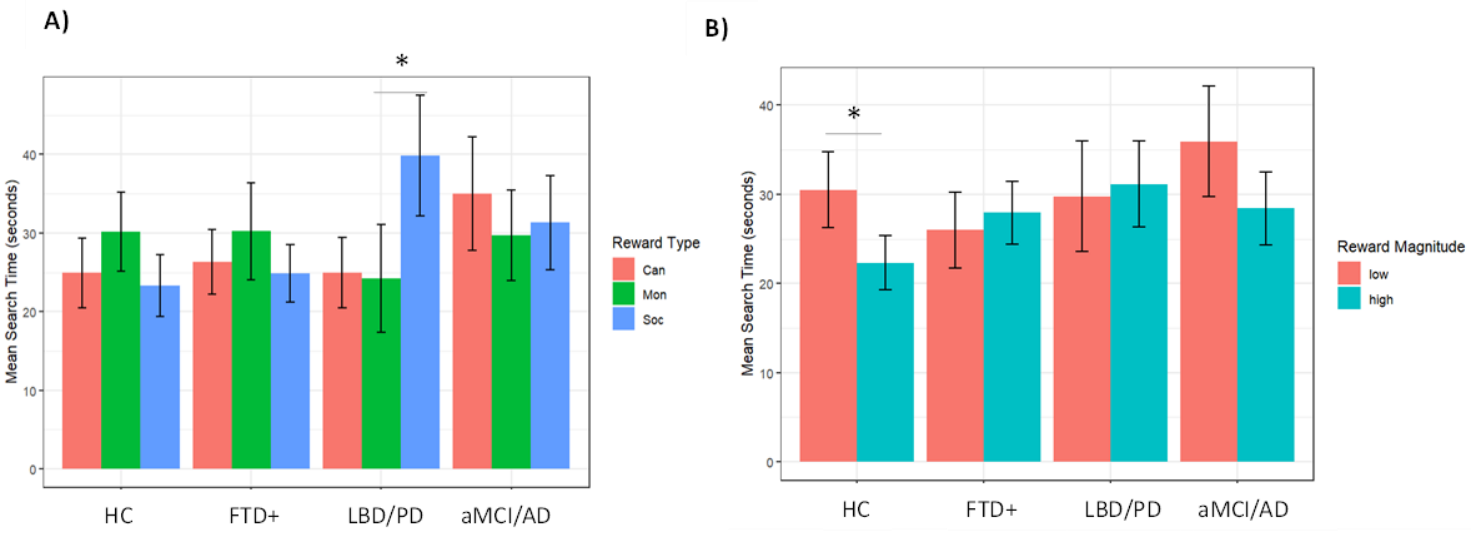


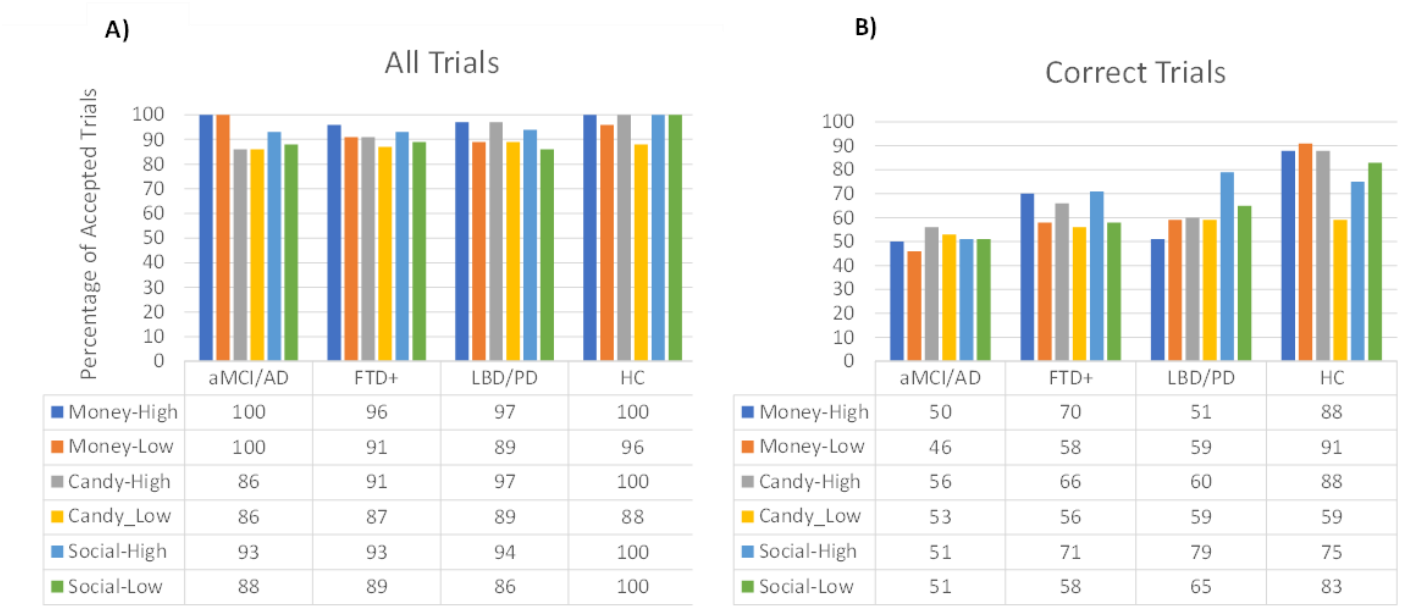
Figure 3-6 Mean search times for correct trials only. A) STs for different reward types (Can=candy rewards, Mon= money rewards, Soc=social rewards), across the four disease groups. B) STs for the different rewards magnitudes (low versus high rewards), collapsed across reward types, and for each of the four disease groups. Error bars represent SEM. (*) indicate significant differences.

3.3.2.1.2 Percentage of Accepted Trials

The percentage of accepted trials within each reward type-reward magnitude combination (i.e., money-high, money-low, candy-high, cany-low, social-high, social-low) and within each effort level (i.e., low, medium, high) was calculated to explore the effect of reward sensitivity and effort discounting on decision making. As a sensitivity measure, the percentage of accepted trials that resulted in obtaining a reward (i.e., "correct accepted" trials) was calculated to assess whether effort exerted was distributed with preference for a certain reward type-magnitude combination. Similarly, the percentage of correct accepted trials for each effort level was examined.

All participants in the study accepted at least 86% of trials within each reward type-magnitude trial type in the cognitive EBDM task (range: 86%-100%). Chi-square tests of independence did not find an association between reward type-magnitude combination and number of accepted trials across disease groups ($X^2(15)=0.59$, $p=0.99$; see figure 3.7a for proportion of accepted trials). Success rates in obtaining the rewards varied from 46%

to 91% within a reward type-magnitude condition. On average, the aMCI/AD group had the lowest overall success rate, across conditions, and the HC group had the highest success rate. However, there was no statistically significant association between number of correct accepted trials and reward type-magnitude across the disease groups ($X^2(15)=3.31$, $p=0.99$; see figure 3.7b for proportion of accepted correct trials).



	aMCI/AD	FTD+	LBD/PD	HC
Money-High	100	96	97	100
Money-Low	100	91	89	96
Candy-High	86	91	97	100
Candy_Low	86	87	89	88
Social-High	93	93	94	100
Social-Low	88	89	86	100

	aMCI/AD	FTD+	LBD/PD	HC
Money-High	50	70	51	88
Money-Low	46	58	59	91
Candy-High	56	66	60	88
Candy_Low	53	56	59	59
Social-High	51	71	79	75
Social-Low	51	58	65	83

Figure 3-7 Percentage of accepted trials across cognitive EBDM task reward type-magnitude conditions and within disease groups. A) Percentage of accepted trials between the aMCI/AD, FTD+, LBD/PD, and HC groups. Colours represent the task reward type-reward magnitude condition. A data table with numerical percentage values is provided. B) Percentage of accepted trials that resulted in obtaining a reward (i.e., correct trials). Colours represent the task reward type-reward magnitude condition. Data table represents numerical percentage values.

All participants accepted at least 86% of trials across the three effort levels, including low effort, medium effort, and high effort trials (range: 86%-99%). Chi-square tests of independence did not find an association between effort level and number of accepted trials across disease groups ($X^2(6)=0.56$, $p=1.00$; see figure 3.8a for proportion of accepted trials across effort levels and between disease groups). Success rates in obtaining the rewards varied from 24% to 100% between different effort levels. On average, the low effort level trials had the greatest success rates (range:85%-100%), the

high effort level trials had the lowest success rates (range: 24%-66%), and the medium effort level trials had an intermediate success rate (42%-87%); this pattern was preserved across the four disease groups. The HC groups demonstrated the highest success rates across effort levels compared to the other three group (correct low effort trials: 100%, correct medium effort trials: 87%, correct high effort trials: 66%). A chi square test of independence demonstrated a trend toward a significant association between effort level and number of correct accepted trials between the disease groups, with the LBD/PD and aMCI/AD groups demonstrating relatively lower success rates in the high effort level trials compared to the FTD+ and HC groups ($X^2(6)=12.53$, $p=0.05$; see figure 3.8b for proportion of accepted correct trials across effort level trials and disease groups).

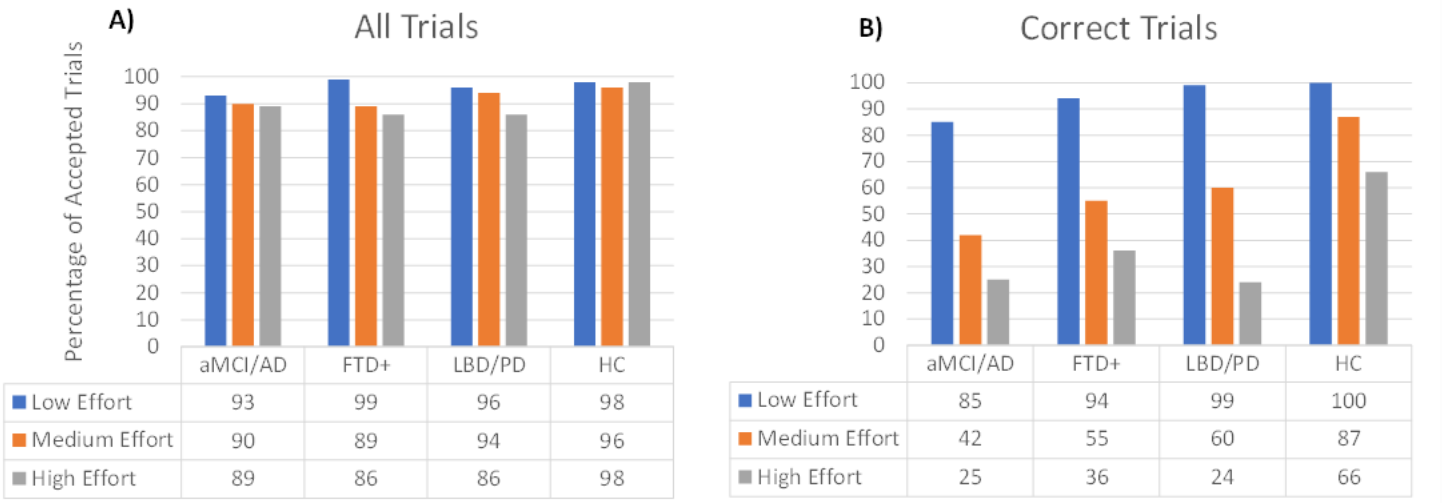


Figure 3-8 Percentage of accepted trials across cognitive EBDM task effort levels and within disease groups. A) Percentage of accepted trials between the aMCI/AD, FTD+, LBD/PD, and HC groups. Colours represent the task effort level condition. A data table with numerical percentage values is provided. B) Percentage of accepted trials that resulted in obtaining a reward (i.e., correct trials). Colours represent the task effort level condition. Data table represents numerical percentage values.

3.3.2.2 Motor Effort-Based Decision-Making Results

3.3.2.2.1 Maximum Force Applied (MFA)

Maximum force applied (MFA), measured in parts per newton (ppn), to the hand dynamometer was the primary outcome of the task. The 4x3x3x2 (disease group x reward type x effort level x reward magnitude) ART factorial analysis revealed a significant 3-

way interaction between reward type, reward magnitude, and disease group ($F(6,740.91)=2.70$, $p=0.01$). Bonferroni-corrected post-hoc analyses of interactions of reward magnitude and disease group revealed a significant difference in MFA between high social rewards and low social rewards in the FTD+ group ($t(740.36)=-3.87$, $p=0.03$; figure 3.9a). Additionally, a significant two-way interaction between effort level and disease group ($F(6,740.98)=6.68$, $p<0.001$) was revealed, with pairwise, Bonferroni corrected comparisons showing that MFA for each group was lowest for low effort trials, intermediate for medium effort trials, and highest for high effort trials (figure 3.9b; aMCI/AD [low-med: $t(741.12)=-16.76$, $p<0.001$, low-high: $t(740.94)=-27.62$, $p<0.001$, med-high: $t(740.97)=-11.13$, $p<0.001$]; HC [low-med: $t(740.26)=-10.05$, $p<0.001$, low-high: $t(740.46)=-18.34$, $p<0.001$, med-high: $t(740.28)=-8.34$, $p<0.001$]; FTD+ [low-med: $t(740.04)=-15.16$, $p<0.001$, low-high: $t(742.49)=-28.88$, $p<0.001$, med-high: $t(742.30)=-14.05$, $p<0.001$]; LBD/PD [low-med: $t(740.22)=-12.36$, $p<0.001$, low-high: $t(741.18)=-27.83$, $p<0.001$, med-high: $t(741.14)=-15.55$, $p<0.001$]). A sensitivity analysis was performed with trials in which participants applied enough force to obtain the reward (i.e., correct trials). No changes in significant results were found. Please refer to Appendix A (A.5) for mean max force applied across each of the 12 task conditions, within each group.

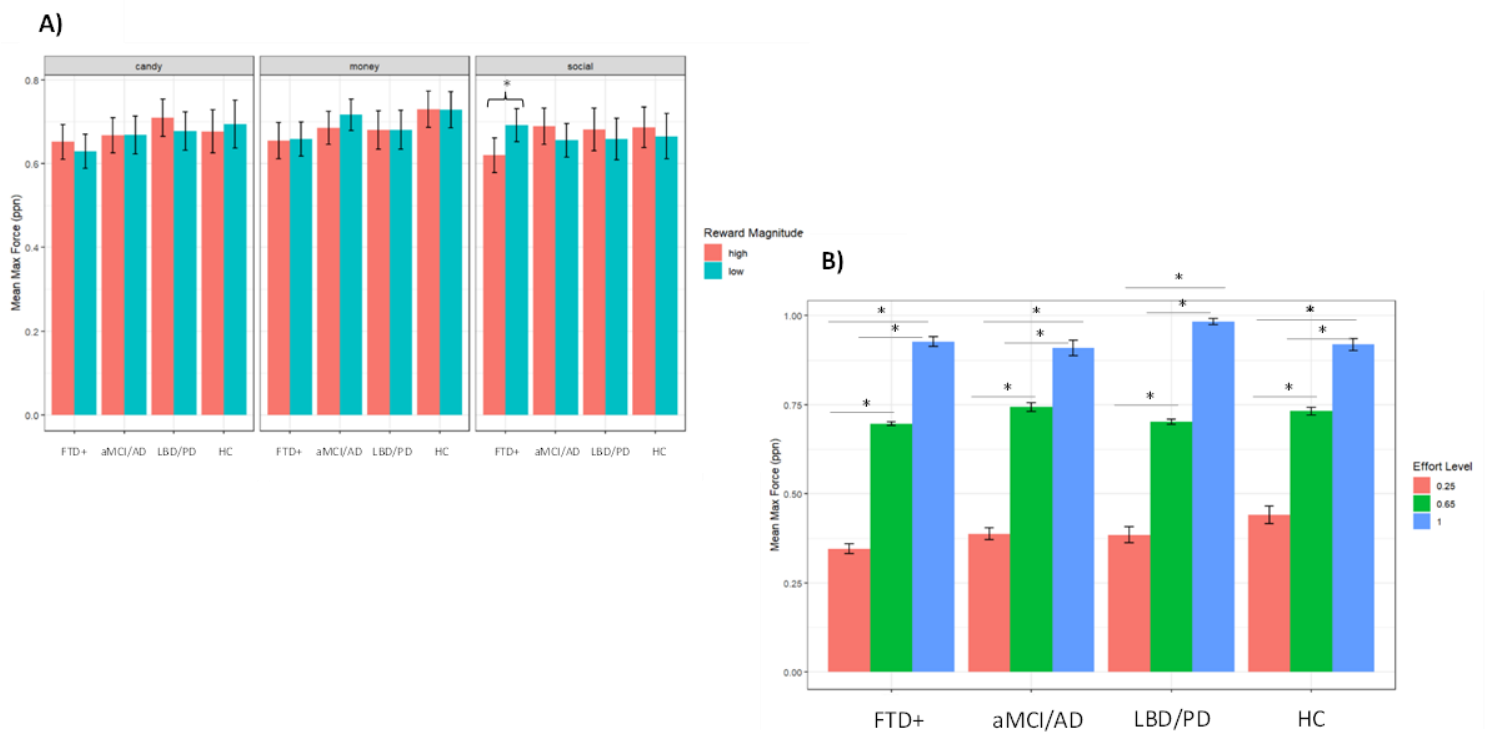
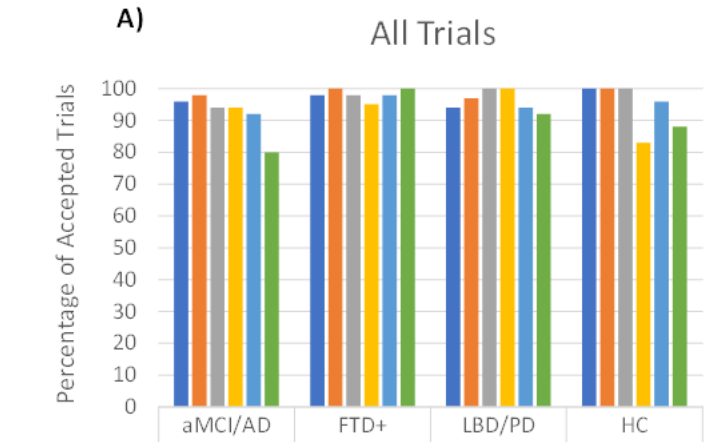


Figure 3-9 Mean max force applied (MFA). A) MFA for different reward types (Can=candy rewards, Mon= money rewards, Soc=social rewards), and reward magnitudes (high versus low), across the four disease groups. B) MFA for the different the three effort levels (low, medium, high) within each of the disease groups. Error bars represent SEM. (*) indicate significant differences.

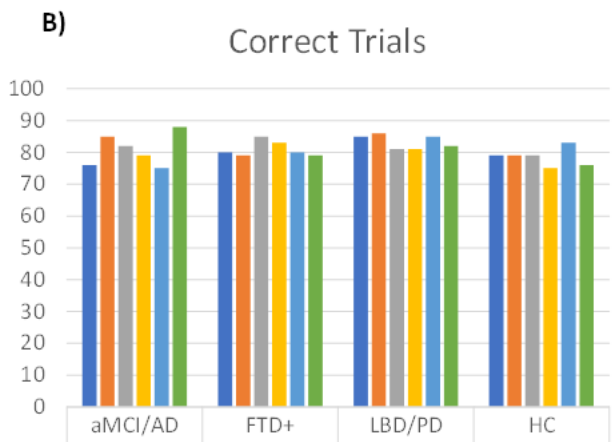
3.3.2.2.2 Percentage of Accepted Trials

All participants in the study accepted at least 80% of trials within each reward type-magnitude trial type in the motor EBDM task (range: 80%-100%). Chi-square tests of independence found a statistically significant association between reward type-magnitude combination and number of accepted trials across disease groups ($X^2(15)= 27.47$, $p=0.03$; see figure 3.10a for proportion of accepted trials in the different reward type-magnitude conditions and between disease groups). Post-hoc 4x1 chi-square tests, performed for each reward type-magnitude combination (6 tests total; α-level= 0.0083), were used with Bonferroni corrections to identify significant pairs of associations. Results revealed a significant association between accepted trials between reward type-magnitude conditions within the aMCI/AD groups ($X^2(5)= 31.38$, $p<0.0001$), where participants in this groups accepted less low social rewards compared to the other conditions. Success rates in obtaining the rewards in the motor EBDM task varied from 75% to 88% within a

reward type-magnitude condition. However, there was no statistically significant association between number of successful (i.e., correct) accepted trials and reward type-magnitude across the disease groups ($X^2(15)= 1.51$, $p=0.99$; see figure 3.10b for proportion of accepted successful trials).



	aMCI/AD	FTD+	LBD/PD	HC
Money-High	96	98	94	100
Money-Low	98	100	97	100
Candy-High	94	98	100	100
Candy_Low	94	95	100	83
Social-High	92	98	94	96
Social-Low	80	100	92	88

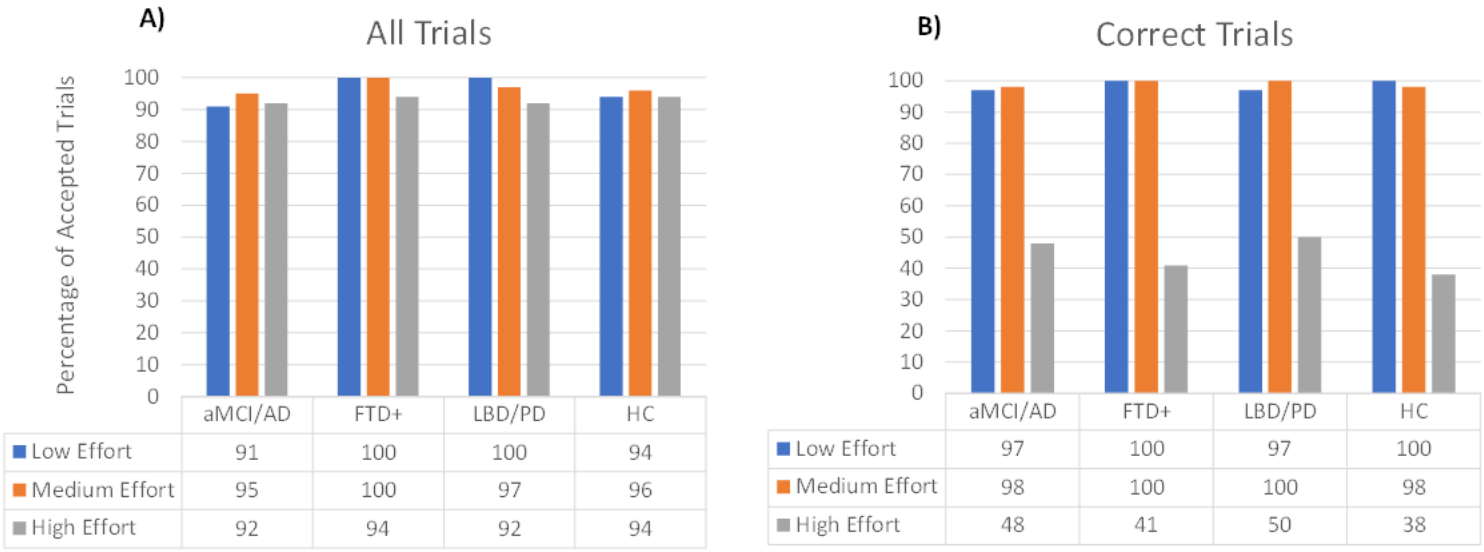


	aMCI/AD	FTD+	LBD/PD	HC
Money-High	76	80	85	79
Money-Low	85	79	86	79
Candy-High	82	85	81	79
Candy_Low	79	83	81	75
Social-High	75	80	85	83
Social-Low	88	79	82	76

Figure 3-10 Percentage of accepted trials across motor EBDM task reward type-magnitude conditions and within disease groups. A) Percentage of accepted trials between the aMCI/AD, FTD+, LBD/PD, and HC groups. Colours represent the task reward type-reward magnitude condition. A data table with numerical percentage values is provided. B) Percentage of accepted trials that resulted in obtaining a reward (i.e., correct trials). Colours represent the task reward type-reward magnitude condition. Data table represents numerical percentage values.

All participants accepted at least 91% of trials across the three effort levels, including low effort, medium effort, and high effort trials (range: 91%-100%). Chi-square tests of independence did not find an association between effort level and number of accepted trials across disease groups ($X^2(6)= 0.21$, $p=1.00$; see figure 3.11a for proportion of accepted trials across effort levels and between disease groups). Success rates in obtaining the rewards varied from 38% to 100% between different effort levels. On average, the low effort level and medium effort level trials had the greatest success rates (range:97%-100%), compared to the high effort level trials with relatively lower success rates (range: 38%-50%); this pattern was seen in all four disease groups. A chi square test

of independence found no significant association between effort level and number of successful accepted trials between the disease groups ($X^2(6)= 1.36$, $p=0.97$; see figure 3.11b for proportion of accepted correct trials across effort level trials and disease groups).



	aMCI/AD	FTD+	LBD/PD	HC
Low Effort	91	100	100	94
Medium Effort	95	100	97	96
High Effort	92	94	92	94

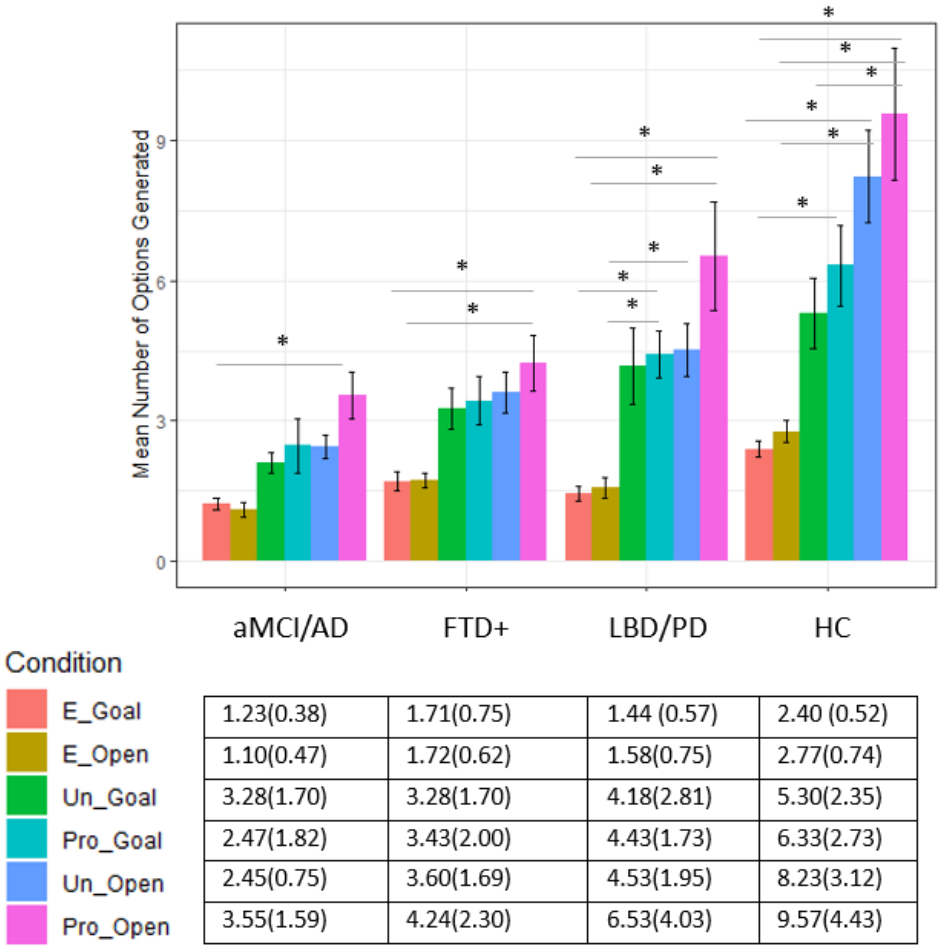
	aMCI/AD	FTD+	LBD/PD	HC
Low Effort	97	100	97	100
Medium Effort	98	100	100	98
High Effort	48	41	50	38

Figure 3-11 Percentage of accepted trials across motor EBDM task effort levels and within disease groups. A) Percentage of accepted trials between the aMCI/AD, FTD+, LBD/PD, and HC groups. Colours represent the task effort level condition. Data table represents numerical percentage values. B) Percentage of accepted trials that resulted in obtaining a reward (i.e., correct trials). Colours represent the task effort level condition. Data table represents numerical percentage values.

3.3.2.3 Option Generation Results

The results of the MANCOVA, using Pillai's Trace test statistic, revealed a significant effect of group on fluency ($F(18, 117)= 2.66$, $p<0.001$). There were no significant associations between the dependent variable and the covariates of MoCA total score, age, sex, or level of education. Overall, open ended scenarios were associated with more responses than goal-directed ones, and prompted conditions were associated with more responses than prompted conditions. Patients with AD generated the fewest options on average, followed by FTD, then LBD/PD, with healthy controls generating the most options (Figure 3.12). A series of ANOVAs were conducted, using the Holms-Bonferroni

correction, to identify specific disease group-level differences in the number of options generated across the six conditions. Results revealed a significant main effect of disease group on fluency in all 6 conditions (Figure 3.12). Eight seconds-goal directed: $F(3,2.62)= 8.10$, <0.001; Eight seconds-open scenario: $F(3,96)=12.07$, $p<0.001$; Unlimited-goal directed: $F(3,18.88)=4.42$, $p<0.01$; Unlimited-open scenario: $F(3,64.43)=15.89$, $p<0.001$; Prompted-goal directed: $F(3,28.18)=7.45$, $p<0.001$; Prompted-open scenario: $F(3,78.38)=7.50$, $p<0.001$). Post-hoc Tukey HSDs were used to conduct pairwise comparisons of fluency between conditions and within each disease group. In the aMCI/AD group, significantly less options were generated in the Eight Second-Open ($p<0.001$) and Eight Second-Goal ($p<0.001$) conditions compared to the Prompted-Open condition. Similarly, in the FTD+ group, significantly less options were generated in the generated in the Eight Second-Open ($p<0.001$) and Eight Second-Goal ($p<0.001$) conditions compared to the Prompted-Open condition, and less options were also generated in the Eight Second-Open compared Unlimited-Open condition ($p=0.03$). In the LBD/PD group, more options were generated in the Prompted-Open condition compared to Eight Second-Goal ($p<0.001$) and Eight Second-Open ($p<0.001$), in the Prompted-Goal condition compared to Eight Second-Goal ($p=0.03$) and Eight Second-Open ($p=0.04$), and in the Unlimited-Open condition compared to the Eight Second-Open condition ($p=0.03$). Lastly, in the HC group, significantly more options were generated in the Prompted-Goal condition compared to the Eight second-Goal condition ($p=0.02$), in the Prompted-Open condition compare to the Eight second-Goal condition ($p<0.001$), Eight second-Open condition ($p<0.001$), and Unlimited-Goal condition ($p<0.01$). More options were generated in the Unlimited-Open condition compared to Eight Second-Goal ($p<0.001$), and Eight Second-Open ($p<0.01$) conditions. Generally, the main effect of group showed an overall patter of number of options generated across conditions in the following descending order: HC > LBD/PD > FTD+ > aMCI/AD.



1.23(0.38)	1.71(0.75)	1.44 (0.57)	2.40 (0.52)
1.10(0.47)	1.72(0.62)	1.58(0.75)	2.77(0.74)
3.28(1.70)	3.28(1.70)	4.18(2.81)	5.30(2.35)
2.47(1.82)	3.43(2.00)	4.43(1.73)	6.33(2.73)
2.45(0.75)	3.60(1.69)	4.53(1.95)	8.23(3.12)
3.55(1.59)	4.24(2.30)	6.53(4.03)	9.57(4.43)

Figure 3-12 Number of options in each condition across disease groups. Conditions: E_Goal = eight seconds and goal directed, E_Open = eight seconds and open scenario, Un_Goal = unprompted and goal directed, Un_Open = unprompted and goal directed, Pro_Goal = prompted and goal directed, Pro_Open = prompted and goal directed. Error bars represent SEM. (*) indicate significant differences. Data table shows mean fluency (standard deviation) per disease group and within conditions.

3.3.2.4 Intentional Binding Results

Results of the repeated measures ANOVA revealed a significant interaction between disease group and condition ($F(3,31)=5.01$, $p<0.001$). Pairwise comparisons, with Bonferroni corrections, confirmed significant action and tone binding within each group (all $p<0.001$; figure 3.13). Additionally, there was a significant difference in action binding between the HC and LBD/PD groups ($p=0.03$) and a significant difference in

tone binding between aMCI/AD and FTD+ groups (p=0.01), although neither of these differences survived Bonferroni correction (p=0.19 and p=0.07, respectively). This would suggest that individuals in the LBD/PD group perceived their key press to happen closer to the tone than did healthy controls (i.e., greater action binding effect). The FTD+ group reported the tone to occur close to their key press compared to the aMCI/AD group (i.e., greater tone binding).

A)

	Mean tone shift in ms (sd)	Mean action shift in ms (sd)
AMCI/AD	-70.78 (150.24)	37.74 (51.44)
FTD+	-46.48(137.52)	90.13(129.23)
LBD/PD	-87.92(154.05)	147.02(45.94)
HC	-220.41(50.84)	6.02(50.92)

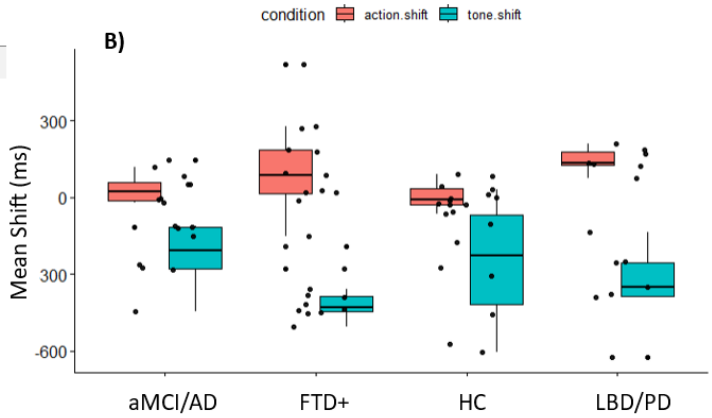


Figure 3-13 Intentional binding across disease groups. A) Mean perceptual action and tone shifts (in ms) across the four disease groups. B) Boxplot depicting mean action and tone shifts.

3.3.3 Partial Least Squares Results

Informed by the results of the group-level analyses across the tasks above, a partial least squares analysis was performed with the six apathy components from the AES, AMI, and DAS as the response variables. The predictor variables included the demographic variables of the MoCA total score, age, sex, level of education, and the following task variables: search time for cognitive effort based decision making task and mean max force for the motor effort task for each of the combinations of two of the different types of reward (candy, social) and the three different effort levels (low, medium, high), number of options generated in the option generation task for the open unprompted and the 8 second goal directed scenarios, and for the intentional binding task, the mean action binding and mean tone binding, for a total of 20 variables. For this analysis, search times were collapsed across reward magnitudes, as the interaction effects with reward

magnitudes were small or within the healthy control group. The monetary reward conditions for both the cognitive and motor EBDM tasks were not included because search times and max force applied for these trials did not vary significantly within disease groups. Candy reward trials were retained, as one of the apathy component response variables was “sensitivity for food rewards.” From the option generation, fluency in the eight second goal directed and prompted open conditions were included in the PLS because these conditions produced large contrasts in fluency within each of the disease groups.

The PLS produced a one-component model that was able to explain 15.50% of the variance in the predictor variables and 83.22% of the variance in the response variables. Predictor variables with factor loadings >0.40 were retained in the component. This included a single predictor from the option generation task- fluency in the Promoted Open Scenario condition, and MoCA total score. The response variables retained in the PLS model included the following apathy components: effort, option generation, and initiation. The predictive performance of the one-component PLSR model was evaluated on a test set. The PLSR model was able to predict effort, initiation, and option generation responses with a correlation coefficient of r^2=0.67.

3.4 Discussion

The purpose of this study was to elucidate the neurocognitive mechanisms underlying apathy in neurodegenerative dementias. Four computer-based tasks were used to investigate the following key mechanisms implicated in apathy: option generation, motor effort-based decision making, cognitive effort-based decision making, and volition. To the best of our knowledge, the current study is novel in several aspects. First, this is the first study to experimentally examine components of effort-based decision making across the main types of neurodegenerative dementias, including patients with amnestic mild cognitive impairment, Alzheimer’s disease, Lewy body dementia, Parkinson’s disease, and frontotemporal dementia, as well as healthy control participants. Moreover, though some studies have examined EBDM within disease groups, this study is the first to take a transdiagnostic analytical approach to experimentally examining the mechanisms underlying apathy. Lastly, the current study puts forth a novel three-faceted

neurocognitive framework for assessing apathy, including option generation, motivation, and volition as three key critical pillars of goal-directed behaviour. Although volition, and more specifically intentional binding, has been explored in the context of brain disorders, there have been no studies investigating the relationship between IB and apathetic behaviour.

As a proof of concept, the computer tasks were analyzed at the group level to determine whether the tasks were sensitive to detecting behavioural patterns within the context of goal-directed behaviour. In the cognitive EBDM task, search time was used to index effort sustenance for monetary, candy, and social rewards. This interpretation is supported by research demonstrating that arousal can facilitate faster performance on visual search tasks (Park et al., 2012). In an effort-based decision making for reward scenario, after a decision for action is made, anticipation of reward and preparation for action are associated with physiological changes (e.g., in heart rate and pupil dilatation) linked to motivational arousal (Husain & Rosier, 2018). As such, our results suggest that all participants in the study, on average, expended more effort (i.e., spent significantly more time) on the most difficult visual search task trials compared to the easy trials. It is worth noting that there was no disease group, reward type or reward magnitude dependent effects on STs within the low effort trials, meaning there was less variation overall in these trials; as such, the low effort trials were likely too easy, and this interpretation is bolstered by the high percentage of correct trials across disease groups in low effort conditions.

In the aMCI/AD, FTD+, and HC groups, there were also significant differences in ST between medium and high effort trials. However, medium versus high effort level difference in search time was not seen in the LBD/PD group; it is possible that this is due to issues with visuospatial ability commonly observed in patients with LBD and the visual nature of this task. The FTD+ groups demonstrated greater effort working for candy rewards compared to social rewards, as they spent significantly more time on the visual search task on candy reward trials compared to social reward trials. These findings are consistent with increased appetite for sweets and reduced emotional processing as key features of FTD (Kumfor & Piguet, 2012; Finger, 2016). Lasty, participants in the

LBD/PD group demonstrated greater sensitivity to reward magnitude, as they spent significantly more effort on high magnitude reward trials compared to low magnitude reward trials. This could perhaps be interpreted as a more nuanced strategy for effort allocation; because the visual search task may be more taxing to this groups compared to the others, they may choose to forgo spending effort on low reward trials and reserve effort for greater reward possibilities.

Unexpectedly, in the sensitivity analysis of only the correct trials, HCs spent significantly more time on the low magnitude than high magnitude reward trials. The LBD/PD group followed a similar, but non-significant, pattern, whereas the FTD+ and aMCI/AD groups showed the inverse pattern (i.e., more time spent searching in the high reward magnitude trials compared to low magnitude reward trials). This could be because HCs experience less arousal during the low reward magnitude tasks (and therefore experience less of a cognitive boost). Alternatively, this result could simply reflect a general preference for low magnitude rewards; for example, the low magnitude candy reward included a hard candy, whereas the high magnitude reward included hard candy and chocolate, and some individuals may have a preference for the hard candy over chocolate. The lack of difference in STs across the three reward types in the HC group may reflect that the task in itself is rewarding to cognitively healthy adults (Inzlicht et al., 2018). Future studies may benefit from administering a post-task survey investigating subjective reports of reward desire and valuation.

In the motor EBDM task, the maximum force applied in a given trial was used to index effort sustenance. A significant three-way interaction demonstrated that participants in the FTD+ group had greater sensitivity to low versus high magnitude social rewards, as they expended significantly more effort to obtain high social rewards compared to low social rewards. This may indicate that for patients with FTD, social interactions that are not overtly very positive are not rewarding, such as in the the neutral facial and vocal emotional valence used in the low reward stimuli (Keane et al., 2002). These results also offer support for behavioural interventions for patients with FTD that may use very positive social cues as to motivate specific behaviours. Additionally, sensitivity to effort level across the low, medium, and hard difficulty trial types was seen across all disease

groups, signifying preserved ability/desired to allocate effort effectively in motor EBDM for goal directed behaviour.

Next, we examined patterns of option generation in different time- and goal-dependent scenarios. Interestingly, all of the disease groups demonstrated similar trends in which fluency was generally better in the prompted conditions compared to the eight-second conditions, with unlimited unprompted conditions producing an intermediate level of fluency. There was less variation in fluency across the trial types within the aMCI/AD and FTD+ groups compared to the significant variation withing the LBD/PD and HC groups. This finding could be related to recent findings of individuals with LBD demonstrating comparable abilities in linguistic tasks, such as verbal semantic fluency, to cognitively normal adults (Yamada et al., 2022). Overall, the results indicate that deficits in option generation, particularly in situations with little structure or routine, may contribute to apathy in FTD and AD.

The intentional binding task revealed significant action and tone binding across all four groups, indicating preserved sense of agency or volition. However, the magnitude of binding may differ between groups; future studies with greater statistical power may be able to shed light on group-based IB differences. Our findings, although not significant, suggest that individuals with LBD/PD may show increased action binding compared to controls, and those with FTD+ may demonstrate increased tone binding compared to individuals with aMCI/AD. Tone binding has been shown to be a more reliable measure of the intentional binding effect (Haggard et al., 2002). As such, it may be the case that the FTD+ group experiences a hyper-binding effect, perhaps due to strong, egocentric causal beliefs about self-initiated actions and subsequent outcomes (Malik, Galang & Finger, 2022). Alternatively, there may be hypo-binding in the aMCI/AD group; this could be due to dysfluency in the link between the goal of the action (i.e., keypress), and subsequent initiated action.

Lastly, a partial least squares analysis was employed to identify significant factors, made up of task-based predictors and apathy questionnaire data, that could predict deficits in the three core neurocognitive mechanisms we hypothesize to underlie apathy (i.e., option

generation, motivation, and volition). Task outcomes demonstrating sensitivity to group-level analyses were chosen as predictors and the response variables included apathy questionnaire items grouped in to six variables representing effort, social reward sensitivity, food reward sensitivity, other reward sensitivity, initiation, and option generation. The PLS produced a one-component model that included the prompted-open scenario predictor, and the *effort*, *initiation*, and *option generation* response variables. The prompted-open scenario allowed participants to generate options at their own pace and without time restrictions; as such, there is a large amount of variation in fluency seen in this condition, and is perhaps the purest measure of uninhibited *option generation*. Additionally, a post-hoc examination of the time spent generating options in each condition revealed that participants spent more time coming up with options in this condition compared to the others (see Appendix A (A.7) for mean option generation times across conditions), suggesting that more *effort* and effort sustenance is needed to complete trials in this condition. Lastly, in the prompted condition, participants were encouraged to continue generating options after they indicated completing the task. The prompting may be associated with items related to *initiation* in the apathy questionnaire items. Overall, results from this analysis indicate that deficits in option generation contribute to apathy in dementias.

3.4.1 Limitations

The current study involved controlled experimental paradigms with human participants. Participants were provided with frequent breaks throughout the experimental session. However, given the older age of the population and uncontrollable disease-related factors, it was difficult to account for the effects of fatigue on effortful tasks. In the cognitive effort-based decision-making task, it was not possible to account for any interindividual fluctuations in attention to the visual search task. Future studies may benefit for employing an eye-tracker to investigate patterns of eye movement indicative of active search versus passive viewing. Additionally, without an eye-tracker, it was not possible to determine if, and what, certain visual search strategies were used by participants and how this could affect variability in search time. A measure of pupil dilation would be beneficial in confirming anticipatory arousal in participants during

different reward type and reward magnitude trials (Husain & Roiser, 2018). Asking participants for subjective value or desirability ratings of the monetary, candy, and social rewards is a future direction that would help discern whether participants were truly aiming to obtain certain rewards versus being inherently interested or disinterested in completing the task. In a cohort of participants with cognitive impairments, it is also difficult to discern whether participants are aware of, and following, task instructions. A modification of the intentional binding task, with simpler task instructions, could help with data collection from a larger cohort of participants with cognitive impairments.

3.4.2 Conclusion

Overall, this research is the first to experimentally investigate a novel three-component neurocognitive model of apathy across neurodegenerative dementias. Group-level differences found in the computer task outcomes were used to inform a transdiagnostic analytical approach to predict option generation, motivation, and volition deficits related to apathy in neurodegenerative dementias. Our results were the first to substantiate an option generation metric as an important predictor of apathy in brain disorders.

3.5 References

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4 Chapter 4: Neural correlates of apathy in neurodegenerative dementias

4.1 Introduction

A few recent studies have shed light on neuroanatomical correlates of apathy across neurodegenerative dementias. In bvFTD, anatomical changes in frontal, temporal, and limbic structures have been shown to correlate with apathy on a Frontal Systems Behavior (FrSBe) Scale (Sheelakumari et al., 2020). Previous studies of PD have implicated the involvement of the cingulate gyrus and inferior frontal gyrus, with atrophy in these regions correlating with apathy severity measures (Reijnders et al., 2010). Patients with AD and apathy demonstrate significant hypoperfusion or cortical thinning in the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), putamen, and posterior cingulate (PCC; Fernández-Matarrubia et al., 2018; Mori et al, 2014). In review of neuroimaging studies examining neural correlates of apathy across neurodegenerative disorders, acquired brain injury and psychiatric disorders, alterations in several areas including frontal, striatal, anterior cingulate, and parietal regions were involved in apathy within disease groups and across groups (Kos et al., 2016).

Given the diversity of neuroanatomical regions involved in apathy in various disorders, more recent research has focused on understanding the neural correlates of mechanisms that underlie specific subtypes of apathy (Husain & Roiser, 2018; Kos et al., 2016). The general goal of this line of research is to elucidate whether transdiagnostic behavioural manifestations of apathy occur as a result of alterations in specific neural circuits. To achieve this, assessing different cognitive domains of apathy and their associated neural substrates is crucial. For instance, Moretti and Signori (2016) propose that different fronto-striatal neural networks may underlie "emotion affective" apathy (i.e., diminishment of emotional responsiveness or involvement), "cognitive" apathy (i.e., dysexecutive alteration leading to an inability to motivate behaviour), and "auto-activation" apathy (i.e., difficulty beginning new actions). Specifically, emotion affective apathy may be related to the orbitomedial prefrontal cortex (PFC) and ventral striatum, cognitive apathy may result from disruptions in the lateral PFC and dorsal caudate nuclei,

and auto-activation apathy is presumed to be associated with bilateral lesions of the internal portion of globus pallidus, bilateral paramedian thalamic lesions, or the dorsomedial portion of PFC.

A recent model for exploring the cognitive mechanisms of apathy was proposed by Husain and Roiser (2018). The model highlighted cognitive processes involved in effort-based decision making (EBDM) in the context of goal-directed behaviour. In exploring apathy across disorders, the authors recommend future research examining deficits in EBDM and focal brain regions that can give rise to such deficits. In Chapter 3 of the current thesis, a simplified, testable model of apathy including option generation, cognitive and motor EBDM, and volition was utilized in a group of patients with neurodegenerative dementias. Results revealed that across the patient groups, significant effort-based, option generation, and initiation deficits related to facets of apathy were associated with poor performance in an option generation task. Although the neural correlates of this unique combination of cognitive deficits related to apathy is yet to be explored, past research has implicated the involvement of the anterior cingulate cortex (ACC) and PFC in effort processing, initiation, and option generation (Kaiser et al., 2013; Bonnelle et al., 2016). Specifically, previous research on intentional or self-generated action has emphasized the role of medial prefrontal areas (Passingham, Bengtsson, & Lau, 2010), and the anterior prefrontal cortex has been implicated in scenarios where many possible solutions can exist for option generation (Kaiser et al., 2013). The dorsolateral PFC is involved in retrieval of episodic memory, and the dorsal ACC plays a crucial role in selecting self-generated options.

4.1.1 Objective & Hypothesis

The purpose of the current study was to determine the neuroanatomical correlates of facets of apathy underlying neurodegenerative dementias. In chapter 3, deficits in effort sustenance, initiation, and option generation were found to overlap with poor fluency in the prompted, open scenario condition from the option generation task. The covariance shared by these indices produced a component or factor that was well-represented across the neurodegenerative dementias. This apathy factor is used as the primary response variable in the current study. We hypothesized that regions of the brain implicated in

option generation, effort, and initiation would show significant atrophy, and this atrophy would be associated with this apathy factor. Specifically, cortical thinning in the dorsal ACC and the anterior, medial, and dorsolateral PFC were expected to be significantly associated with the apathy factor.

4.2 Methods

4.2.1 Participants

Participants for the current study consisted of individuals who were included in the partial least squares analysis from Chapter 3 (see section 3.2.1). This involved participants who completed the cognitive and motor effort-based decision-making task, option generation task, and volition task, and who also had completed data from the apathy evaluation scale, apathy motivation index, and dimensional apathy scales. Eligible participants included those who also underwent an MRI structural brain scan at the Centre for Functional and Metabolic Mapping (CFMM) at Robarts Research Institute in London, ON, Canada, as part of the study.

4.2.2 Neuroimaging Data

4.2.2.1 MRI Acquisition & Pre-processing

All anatomical MRI scans were acquired on a Siemens 3T scanner at the CFMM. T1-weighted images were acquired using a Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence ([TR]= 2400 ms, [TE]= 2.28 ms, flip angle = 8°). T1-weighted images were automatically segmented using the FreeSurfer recon-all command and the Desikan-Killiany atlas (Desikan et al., 2009). This includes the following steps: motion correction, intensity normalization, skull stripping, registration, subcortical segmentation, white matter segmentation, and cortical parcellation. As a quality control measure, all images were manually inspected for accurate segmentation and parcellation. Subcortical brain structure volumes and cerebral cortical thickness values were extracted to produce 76 whole-brain regions of interest (ROIs). All subcortical volumes were corrected for inter-individual differences in baseline brain size

by dividing by total intracranial volume. A complete list of these regions can be found in Appendix B (B.1).

4.2.2.2 Principal Component Analysis

A principal component analysis (PCA) was used to reduce the number of individual imaging variables (regions of interest) to components consisting of brain regions with correlated cortical thickness and/or subcortical volume values. The PCA was performed using a varimax rotation, such that individual imaging variables loaded maximally onto a single component, and components are made to be orthogonal. The Kaiser criterion (eigenvalues > 1; Kaiser, 1960) was used to determine which principal components to retain for further analysis.

4.2.3 Statistical Analysis

A multiple linear regression was used to assess the relationship between anatomical brain changes and option generation, effort, and initiation deficits, as they related to apathy. To achieve this, factor scores from the significant principal components from the PCA analysis were entered as predictors into the regression model, with factors scores from the partial least squares component from chapter 3 (see section 3.3.3) as the response variable. The response variable accounted for covariance between the number of options produced in the prompted-open condition of the option generation task, and specific items from the AES, AMI, and DAS that index effort, initiation, and option generation deficits associated with apathy. Age, sex, years of education, and total score on the MOCA were included as covariates in the analysis.

4.3 Results

4.3.1 Participants & Demographics

Of the 29 participants who were included in the partial least squares analysis from Chapter 3 (see section 3.3.1.5), 22 (15 males) had acquired MRI scans at CFMM and were included in the current study. Participants ranged from 49-80 years old (mean: 69.05, sd: 7.43), and reported having 10-19 years of formal education (mean: 14.18, sd:

2.30). The average total MoCA score in the cohort was 20.14 (sd: 5.22, range: 7-29). Four participants belonged to the aMCI/AD group, 8 were in the FTD+ group, 7 belonged to the LBD/PD group, and the remaining 3 participants were HCs. Participants in the HC group had statistically significant higher MoCA total scores compared to the other three groups ($F(3,18)=6.03$, $p<0.01$).

Table 4-1 Participant Demographics for Study.

	aMCI/AD	**FTD+**	**LBD/PD**	**HC**	**Contrasts**
N	4	8	7	3	--
Sex	--	--	--	--	--
Male	1	5	7	2	--
Female	3	3	0	1	--
Age (SD; range)	68.75 (10.26; 53-75)	69.00 (9.12; 49-80)	71.43 (5.27; 66-77)	64.00 (5.00; 59-69)	F=38.83 p=0.67
Education (SD; range)	14.00 (2.29; 12-18)	14.00 (1.85; 12-17)	14.27 (2.65; 10-16)	16.67 (2.08;15-19)	F=1.55 P=0.24
MOCA (SD; range)	14.50 (4.82; 7-21)	19.25 (4.17; 13-26)	21.43 (4.78; 16-24)	27.00 (2.65; 24-29)	F=6.03 ***p*<0.01***
AES (SD; range)	43.50 (1.00; 43-45)	41.88 (15.53; 24-61)	47.42 (14.75; 29-68)	62.33 (2.08; 60-64)	F=1.92 *P*=0.16
AMI (SD; range)	34.50 (6.45; 30-44)	32.13 (12.79; 6-45)	39.00 (20.68; 1-68)	52.00 (6.93; 48-60)	F=1.39 *P*=0.28
DAS	48.50	48.00	61.00	63.33	F=2.11

(SD; range)	(9.47; 38-57)	(14.53; 26-73)	(13.38; 46-81)	(4.92; 60-69)	*p*=0.13

4.3.2 Principal Component Analysis Results

All 76 imaging variables were scaled and entered in the PCA. Using the Kaiser criterion, 15 components were retained and explained 98.127% of the variance in the dataset. Varimax rotated loadings across the 15 components determined which variables were associated most strongly with each component. Loadings of 0.30 and above were considered statistically significant (table 4.2).

Table 4-2 PCA results with 15 significant imaging components. Specific regions with loadings >0.30 and general region names are provided.

Principal Component	**Region of Interest**
PC1	Bilateral rostral middle frontal gyrus and superior frontal gyrus
PC2	Left caudate, bilateral insula
PC3	Bilateral putamen, right accumbens area
PC4	Left cuneus and precuneus, left inferior parietal gyrus
PC5	Left transverse temporal gyrus, right fusiform gyrus, right parahippocampal gyrus
PC6	Left rostral anterior cingulate gyrus, left lateral occipital gyrus, right superior temporal gyrus
PC7	Left accumbens area, bilateral inferior temporal gyri, right lateral orbital frontal gyrus,
PC8	Bilateral pallidum, left paracentral gyrus, right pericalcarine gyrus
PC9	Left pericalcarine gyrus, left pars opercularis

PC10	Left caudal anterior cingulate gyrus, bilateral lateral orbitofrontal gyrus, left pars orbitalis
PC11	Right hippocampus, right lingual gyrus, right supramarginal gyrus
PC12	Left posterior cingulate gyrus
PC13	Left entorhinal cortex
PC14	Right medial orbital frontal gyrus, left lingual gyrus
PC15	Left amygdala

4.3.3 Multiple Linear Regression

The multiple linear regression, including the 15 imaging components as predictors and the apathy factor as the response variable. The overall regression model was not statistically significant ($F(6,15)=3.00$, adjusted $R^2=0.59$, $p=0.59$) although PC6 (left rostral anterior cingulate) and PC10 (left caudal anterior cingulate) were significant predictors ($\beta= 0.52$, $p=0.006$ and $\beta=-0.42$, $p=0.037$, respectively). There was also a trend towards significance for PC9 ($\beta= -0.30$, $p=0.097$) and PC13 ($\beta=-0.47$, $p=0.052$). Please see Appendix B (B.2) for mean option generation scores for participants.

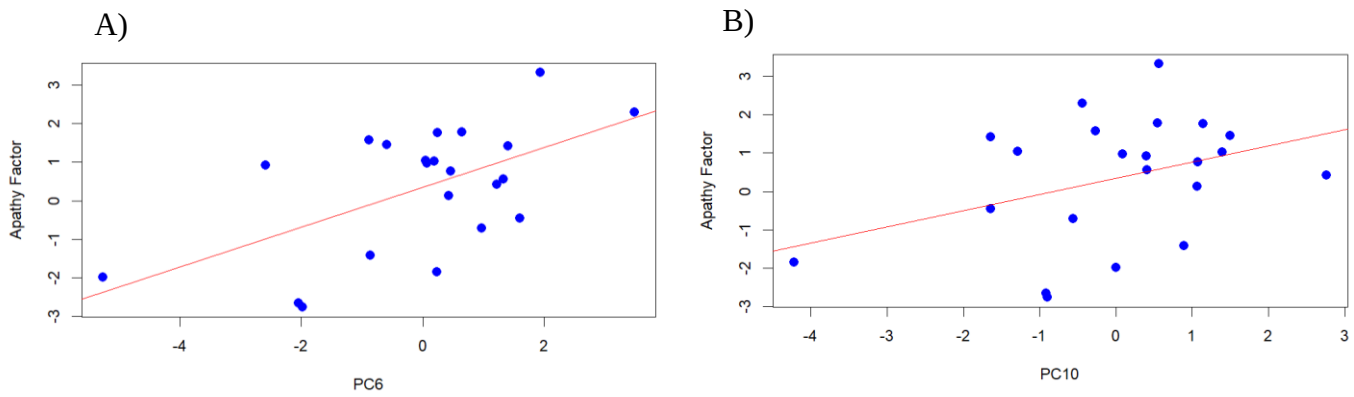

Figure 4-1 Linear regression plots for PC6 (left rostral anterior cingulate cortex) and PC10 (left caudal anterior cingulate cortex). A) A positive association between PC6 and the apathy factor is indicated. Higher scores on the apathy factor are associated with deficits in option generation, initiation, and effort (higher apathy ratings on these items and lower fluency in prompted-open scenarios) and higher scores on PC6 are associated with reduced cortical thickness predominantly in the left rostral anterior cingulate gyrus. B) A pattern of atrophy in the left caudal anterior cingulate cortex is associated with more apathy in the option generation, initiation, and effort domains and worse fluency/options generated.

4.4 Discussion

The purpose of this study was to explore the neural correlates underlying apathy in neurodegenerative dementias. Results from chapter three revealed a significant deficit in real-world behaviours related to option generation, effort, and initiation as rated by care partners that was linked to less verbal options generated in a real-world, open scenario (not goal-directed), even upon being prompted to continue generating verbal options. This result was captured in an "apathy" factor extracted from a PLS analysis. We then used this apathy factor as the response variable in a multiple linear regression model evaluating whether cortical thickness and subcortical brain volumes predicted the apathy factor scores.

The regression analysis found a trend towards an overall significant association between imaging components (PC6 and PC10) and the apathy factor. PC6 was most strongly associated with the left rostral anterior cingulate gyrus, and with the left lateral occipital

gyrus and right superior temporal gyrus to a lesser extent. . PC10 included the left caudal anterior cingulate gyrus, and the bilateral lateral orbitofrontal gyri and left pars orbitalis to a lesser extent. As expected, cortical thinning in a specific region of the ACC was related to greater apathy, as indexed by our option generation, initiation, and effort-based apathy factor. Previous research demonstrates the role of the caudal anterior cingulate cortex in conflict-monitoring, response selection, response execution, and willed control of movements (Stevens et al., 2011). The rostral anterior cingulate cortex is involved in affective processes, including emotion assessment, emotion-related learning, and autonomic regulation (Stevens et al., 2011). In the Prompted-Open condition of the option generation task, participants are asked to come up with options for behaviour in real-world situations, some of which they may have found themselves in before. An example of such a scenario is the following: "You see the lead singer of your favourite band in a bar, what could you do?" We suspect that approaching this scenario in our task may involve assessment of options from emotionally-laden past experiences. Additionally, in an "Open" scenario, there is more room for creative option generation, which may recruit response selection and from multiple generated possibilities. As predicted, there was an association between the PFC, specifically the bilateral lateral orbitofrontal gyrus loading in PC10, and our apathy factor. The orbitofrontal gyri are associated with reward-cost contingencies to inform forthcoming behaviour, and is consistently implicated in effort-based decision making models of apathy (Heron et al., 2018; Husain & Roiser, 2018). We suspect that OFC atrophy in our cohort may reflect effort discounting, as assessed by the "Effort" component of the apathy factor.

In this study, we predicted that greater atrophy in the anterior, medial, and dorsolateral PFC and dorsal ACC would be associated with more apathy and poorer fluency, potentially related to option generation deficits. Our findings were consistent with general ACC and medial PFC atrophy being associated with option generation deficits.

Limitations

Due to Covid-19 restrictions on participation in the current study, the sample size collected for the analysis was small, reducing power in our analysis. Additionally, this

work aims to assess common neural correlates of apathy across disease groups with different characteristic patterns of atrophy. As such, greater variability in brain structure may require a larger cohort with a greater number of participants per disease group than this study was able to achieve.

4.4.1 Conclusion

In conclusion, the current work is the first to explore the neural correlates of a data-driven combined apathy factor of symptoms of effort, option generation, and initiation deficits linked to poor option generation performance (fluency) across neurodegenerative dementias. Reduced cortical thickness in the left caudal and rostral anterior cingulate cortex, and the bilateral orbitofrontal cortex were significantly associated with the apathy factor, although the overall model did not reach significance.

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5 Chapter 5: General Discussion

5.1 Introduction

Apathy refers to an observable reduction in goal-directed behaviour (i.e., behaviour executed to achieve an outcome, in which the value of the outcome and cost of action are accounted for; Nobis & Husain, 2018; Husain & Roiser, 2018). It often presents as reduced engagement in previously valued activities, including hobbies, work, social interactions, and/or personal hygiene (Nyatsanza et al., 2003). Apathy is one of the most prevalent and salient neuropsychiatric symptoms of neurodegenerative dementias, such as frontotemporal dementia (FTD), Alzheimer's disease (AD), and Lewy body dementia (LBD; Nobis & Husain, 2018; Husain & Roiser, 2018). Patients with apathy experience symptoms of apathy that severely impact the quality of life of both patient and caregiver (Tavares et al., 2020; Nyatsanza et al., 2003). Yet, clinical tools for managing symptoms of apathy remain widely unavailable (Husain & Roiser, 2018). Investigating genetic variants in neurotransmitter pathways associated with the neurocognitive mechanisms of apathy is crucial to informing future clinical interventions (Ruthirakuhan et al., 2018; Mitaki et al., 2013). However, neurocognitive mechanisms that give rise to apathy are currently not well understood.

While apathy is a distinct diagnosis, it is often comorbid with other syndromes, including depression, anhedonia and fatigue (Ang et al., 2017). In order to better understand how apathy is phenotypically different from these overlapping symptoms, past research has focused on characterizing apathy as an amotivation syndrome (Marin, 1991; Costello et al., 2023). The term motivation encapsulates several mechanisms and facets of human behaviour. For instance, according to Geen (1995), motivation refers to the initiation, direction, intensity, and persistence of human behavior. Others define it as recruiting and directing behavior, selecting which of many possible actions the organism will perform (Fuchs, 2008). Furthermore, a motive can be understood as a behavior instigated by emotion or with the purpose of reaching a specific goal (Kehr, 2004). As such, a lack of motivation can seemingly occur from several different mechanistic impairments,

including impairments in initiation, planning for behaviour, selecting behaviour, or a lack of capacity to regulate emotions relevant to goal-directed behaviour. Accordingly, researchers recently have addressed the utility of assessing apathy within the content of effort-based decision-making (EBDM) for goal directed behaviours (GDB; Husain & Roiser, 2018, Ang et al., 2017).

In typical effort-based decision-making models, an individual chooses to behave in a manner to maximize the likelihood of reaching a goal (often to obtain a reward), when effort costs do not outweigh the benefits or subjective value of the reward. Deficits in effort sensitivity or reward valuation are thought to underlie amotivational states (Husain & Roiser, 2018). However, over a decade of research relating deficits in effort and reward processing to apathy in patients have not been able to produce conclusive findings regarding mechanisms underlying apathy (Husain & Roiser, 2018). In accordance with a recent review of apathy in neurodegenerative disorders by Husain & Roiser (2018), current EBDM models for understanding apathy are incomplete; they often overlook mechanisms involved in producing the capacity to engage in goal-directed behaviour, such as the ability to generate options for behaviour, termed as option generation. They also do not often consider mechanisms involved in subsequent engagement with the decision to carry out the goal-directed behaviour, such as the feeling of control of over one's own actions and their effects, termed volition.

The current thesis puts forth a novel effort-based decision-making model for investigating the neurocognitive mechanisms of apathy, to include pre- and post-decision-making components. As such, we propose that option generation, motivation and volition are three core components of goal-directed behaviour implicated in symptoms of apathy. Determining which of these components is/are impaired in apathetic patients provides a promising avenue for determining more precise behavioural approaches and neurotransmitter targets for pharmacological treatment of apathy. Accordingly, the overall objective of this thesis was to elucidate the neurocognitive mechanisms and genetic variants that underlie apathy in neurodegenerative dementias. The central hypothesis of this thesis was that impairments in option generation, motivation, and/or volition give rise to symptoms of apathy in neurodegenerative

dementias. Genetic variants in the dopaminergic system and atrophy in fronto-striatal regions of the brain were expected to be correlated with apathy in our cohort of patients with neurodegenerative dementias.

Three studies were conducted to explore neurocognitive mechanisms and genetic variants related to apathy. In Study 1, a large cohort of patients with mild cognitive impairments (MCI) and AD, and cognitively healthy controls were recruited from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. A partial least squares correspondence analysis was leveraged to examine associations between candidate single nucleotide polymorphisms (SNPs), structural brain atrophy patterns, and apathy in the sample population. In Study 2, a diverse group of patients with neurodegenerative dementias, including frontotemporal dementia (FTD), Lewy body dementia (LBD), Parkinson's disease (PD), and AD, as well as healthy controls, were recruited. A series of computer tasks were used to assess option generation, motivation, and volition in these patients and to examine how deficits in these components may relate to informant-based ratings of apathy. In Study 3, a multiple linear regression model was used to assess patterns of brain atrophy, obtained using 3T MRI, associated with the significant apathy factor discovered in Study 2.

5.2 Genetic Variants of Apathy

Previous studies have shown that SNPs related to dopaminergic function, such as polymorphisms in the *COMT* gene, may confer greater risk of apathy in a healthy population (Mitaki et al., 2012, 2013). However, there are no established associations between genes and genetic predisposition to apathy in neurodegenerative disease. One study has shown an association between the *BDNF* gene and apathy in patients with PD (Gorzkowska et al., 2021). To the best of our knowledge, in genetic cases of FTD and AD, there have been no established links between disease-causing genes and the presence of apathy in these patient groups. The *APOE* e4 allele is known to confer greater risk of developing AD in later life, and one study has shown an association between carrying the e4 allele and presence of apathy in prodromal forms of AD (Monastero et al., 2005). Study 1 of this thesis bolstered and adds to this finding from Monastero and colleagues. Our findings suggest that apathetic individuals with MCI and AD who have exactly one

APOE e4 allele and who are minor homozygotes for the *DAT1* gene demonstrate significantly greater atrophy in frontal, temporal, parietal, insular, and subcortical regions of the brain. Although the exact mechanism of the interaction is unknown, we can speculate that the genetic variant in *DAT1* may be associated with dysfunction of dopamine transporters in the brain, leading to disruptions in cortical dopamine synaptic clearance. This, in combination with reduced clearance of debris (Flowers & Rebeck, 2020) associated with the e4 allele, may contribute to neuronal cell loss. Our study is the first to establish a link between a dopaminergic genetic variant and apathy in AD.

5.3 Neurocognitive Mechanisms Underlying Apathy

Determining the cognitive mechanisms that underlie apathy has the potential to help pinpoint areas of the brain and/or neurotransmitter systems for behavioural or pharmacological interventions. Currently, clinical trials for apathy target dopaminergic pathways in the brain. For example, trials of methylphenidate, a dopamine agonist, have aimed to increase dopaminergic neurotransmission by increasing extracellular availability of dopamine via dopamine transporter inhibition (Gottlieb, 2001; Mintzer et al., 2021). However, these trials have mainly been patients with AD, are not necessarily generalizable to non-AD forms of dementia, and the effects are small and relatively short-lived (lasting up to 6 months; Mintzer et al., 2021). This may in part result from heterogeneous cognitive deficits leading to apathy even within a diagnostic group, such that some patients are responders to dopaminergic therapy, while others are not. As such, there is a marked need for synthesizing a framework of cognitive impairments associated with apathy within and across neurodegenerative dementias, and tracing these mechanisms to their biological substrates and circuits in the brain, to help enrich and optimize the design of future clinical trials.

Our model of apathy included option generation, motivation, and volition as key neurocognitive components of apathy. Evidence demonstrates that all three of these processes are modulated by dopaminergic neurotransmission (Ang et al., 2018; Moore et al., 2010; Husain & Roiser, 2018). Since these mechanisms are differentiated by the involvement of different fronto-striatal structures in the brain, elucidating whether one or more of them underlie apathy may aid in informing more targeted dopaminergic therapies

(e.g., targeting specific dopamine receptor subtypes). As such, study 2 leveraged 4 different computer-based tasks to investigated fluency (index of option generation), cognitive EBDM, motor EBDM, and intentional binding (index of volition) in patients with FTD, LBD/PD, AD, and in healthy controls. Our findings point to a subtype of apathy in this heterogenous population that is characterized by deficits in option generation, initiation, and effort sensitivity. Additionally, fluency, in the promoted-open scenario condition of option generation task, was a significant predictor of the apathy subtype or factor.

The findings of Study 2 were aligned with our hypothesis that at least one the three components (option generation, motivation, or volition) would be impaired in these dementias and that our task measures would be sensitive to these alterations. Given how involved the prompted-open condition is, it was not surprising that three of the response variables covaried with fluency. The demands of this condition likely involved the recruitment of several brain functions, including retrieval of episodic memories, working memory, planning, choice generation and option selection. As such, the task was cognitively effortful and required fluent and creative problem-solving. Additionally, given that the participants were prompted to keep coming up with options, self-initiation of thought and effort likely played a key role in task performance.

5.4 Neuroanatomical Correlates of Apathy

Past research has implicated widespread areas and circuits of the brain in giving rise to apathy in neurodegenerative, neurological, and psychiatric disorders (Godfrey et al., 2022; Sheelakumari et al., 2020; Jenkins et al., 2022). Narrowing down specific regions of the brain, and associated circuitry, in the manifestation of apathy in dementias is a crucial next step to optimizing identification of effective treatment. In Study 2, we discovered a largely cognitive and behavioural apathy factor that encapsulates issues surrounding effort sensitivity, initiation, and option generation. In Study 3, we aimed to identify brain regions associated with these apathy components. To do this, we conducted a multiple linear regression with the apathy factor as the response variable and 12 orthogonal imaging variable components as predictors. Our results showed that the left caudal and rostral anterior cingulate gyrui were most strongly correlated with our apathy

factor. These findings were as expected. Previous studies have shown a strong link between the anterior cingulate cortex and initiation, option generation and effort information processing (Kaiser et al., 2013; Bonnelle et al., 2016; Orrin et al., 1995). As such, we suspect that disruptions in the ACC may be a common neuroanatomical feature of apathy across neurodegenerative dementias. Indeed, the ACC is known to have dopaminergic inputs from the ventral tegmental area and projections to widespread areas of the brain including motor areas, parietal areas, and limbic structures, to affect cognitive, motor, and emotional processing (Wang et al., 2017; Lee et al., 2021).

5.5 Limitations & Future Directions

Several limitations exist in the studies described in this thesis. In study a heterogenous population of individuals with distinct disease pathologies, it is difficult to discern specific effects of disease pathology on the construct in question. For instance, very recent work by Mehak and colleagues (2023) suggests that apathy in AD is driven by AD pathology. As such, it could be the case that disease-specific genetic variants and/or pathological features differentially give rise to similar apathy phenotypes. Because of this, it is difficult to propose a transdiagnostic model of apathy that is independent of disease pathology. Future studies in the field can overcome this hurdle by including pathological and/or genetic predictors in their model, such as existing amyloid-beta and tau PET imaging biomarkers for AD. In study 2, a large barrier to data collection was ensuring that patients understood and retained the computer task instructions and were able to remain attentive throughout the duration of testing. In order to try to mitigate these issues, patients were asked to explain task instructions back to the experimenter and task instruction prompts were provided in the hardest task (visual search task) in each trial. Participants were also offered frequent breaks and given time for lunch and refreshments.

Future studies investigating the neurocognitive mechanisms of apathy could benefit from adapting our tasks to fMRI studies. In doing so, more precise, temporally aligned mechanistic signals can be detected as they related to critical events in the effort-based decision-making process. For example, a task that begins with generated options for action, then selecting an option, followed by a cost-benefit computation of reward versus

effort and a rating of agency following task completion would provide a single paradigm for examining EBDM, as well as the pre- and post-decisional processes involved. Additionally, the role of the ACC in our apathy factor should be further explored. Given the plethora of functions that the ACC serves in cognition, determining which ACC network(s) is associated with apathy will be a crucial next step for findings more targeted treatments for apathy. Given the novelty of our finding of the *DAT1* genetic variant combination with the possession of an APOE e4 allele in patients with AD, future studies should aim to investigate whether this genetic combination is associated with apathy across neurodegenerative dementias. Finally, while the PLS analysis identified only one apathy factor, we hypothesized that different patients within and across different neurodegenerative diseases may have different underlying cognitive deficits leading to symptoms of apathy. Further enrichment of the cohort may increase power to detect less common factors connecting cognitive domains and apathy symptoms in these patients.

5.6 Conclusions

Apathy is a debilitating neuropsychiatric syndrome associated with neurodegenerative dementias. The results of this thesis advance our understanding of impairments in effort-based decision-making for goal directed behaviours that underlie apathy across neurodegenerative dementias. We identified a genotypic combination in MCI and AD that is strongly associated with apathy and structural alterations in widespread regions of the brain. In particular, the combination of possessing one *APOE* e4 allele and the minor homozygote genotype of the *DAT1* gene are associated with cortical thinning in frontal, temporal, parietal, and insular regions and reduced subcortical volumes in individuals with apathy. In addition to pointing a potentially novel risk factor for apathy, this study helped bolster previous work detailing the involvement of the dopaminergic system in giving rise to apathy. This thesis also highlights the role that option generation, initiation, and effort play in apathy across neurodegenerative dementias. The significance of our finding lies in the discovery of an option generation scenario that is sensitive to potentially detecting apathy across neurodegenerative dementias. In terms of the neuroanatomical correlates of apathy, our findings align with previous work implicating the role of the ACC in apathy, due to its involvement in complex processes encompassing

planning, initiation, and effort-based decision making. Overall, the finding of this thesis provide novel insight into the way in which apathy may arise in neurodegenerative dementias. This thesis lays a strong foundation for future research endeavours seeking to understand associations between genes, neural circuitry, and cognitive deficits leading to apathy across brain disorders.

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Appendices

Appendix A: Supplementary Materials for Chapter 3

A.1) Effort-Based Decision-Making Task Stimuli

Low Social Reward	High Social Reward
REWARD  **Comment** from Mike	**REWARD**  **Compliment** from Sarah

Example Social Rewards for EBDM Tasks

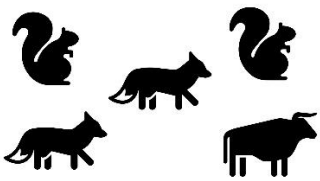
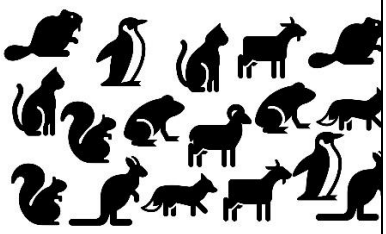
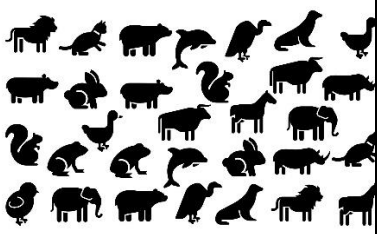
Low Monetary Reward	High Monetary Reward

Reward 	Reward 

Example Monetary Rewards for EBDM Tasks

LOW CANDY REWARD	HIGH CANDY REWARD
Reward 	Reward 

Example Candy Rewards for EBDM Tasks

EASY EFFORT LEVEL	MEDIUM EFFORT LEVEL	HARD EFFORT LEVEL
		

Example Visual Search Stimuli for Cognitive EBDM Task

A.2) Apathy Evaluation Scale (AES), Apathy Motivation Index (AMI), and Dimensional Anhedonia Scale (DAS) items Grouped into Six Apathy Model Components: effort, social reward, food reward, other reward, initiation, and option generation.

Apathy Component 1: Effort

Item	Question
AES2	S/he gets things done during the day.
AES6	S/he puts little effort into anything.
AES8	Seeing a job through to the end is important to her/him.
AES16	Getting things done during the day is important to her/him.
AMI9	When s/he decide to do something, s/he is able to make an effort easily.
AMI12	When s/he decide to do something, s/he is motivated to see it through to the end.

Apathy Component 2: Social Reward

Item	Question
AES13	Getting together with friends is important to her/him.
AMI3	S/he enjoys doing things with people s/he has just met
CA9	Social: Spending time doing these things would make him/her happy.
CA10	Social: S/he would be interested in doing things that involve other people.
CA12	S/he would actively participate in these social activities.

Apathy Component 3: Food Reward

Item	Question
BA6	S/he would enjoy these foods/drinks.
BA7	S/he wants to have these foods/drinks.
BA8	S/he would eat as much of these foods as he/she could.

Apathy Component 4: Other Reward

Item	Question
AA1	Past-time/Hobby: S/he would enjoy these activities.
AA2	Past-time/Hobby: S/he would spend time doing these activities.
AA3	Past-time/Hobby: S/he wants to do these activities.
DA14	Sensory experience: S/he would get excited thinking about these experiences.
DA15	Sensory experience: If s/he were to have these experiences s/he would savour every moment.
DA16	Sensory experience: S/he wants to have these experiences.

Apathy Component 5: Initiation

Item	Question
AES3	Getting things started on his/her own is important to her/him.
AES17	S/he has initiative.

AMI2	S/he starts conversations with random people.
AMI11	S/he gets things done when they need to be done, without requiring reminders from others
AMI14	S/he starts conversations without being prompted.

Apathy Component 6: Option Generation

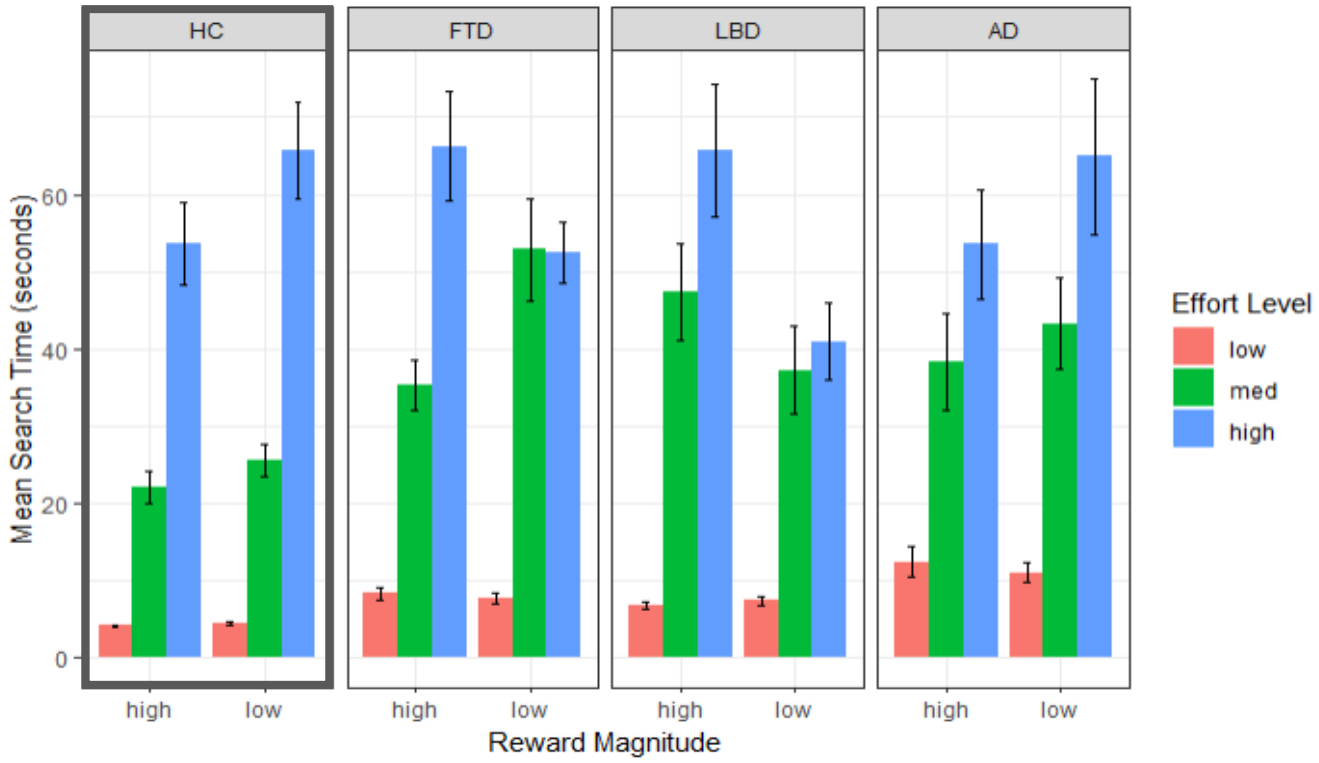
Item	Question
AES10	Someone has to tell her/him what to do each day
AMI4	S/he suggests activities for her/him and her/his friends to do.
CA11	Social: S/he would be the one to plan these activities.

A.3) Mean search times (STs) for each disease group (aMCI/AD, FTD+, LBD/PD, HC) across the different reward type x reward magnitude x effort level combinations in the cognitive effort-based decision making task

		REWARD LEVEL			
		HIGH	LOW		
REWARD TYPE	MONEY	AD: 16.84 FTD: 9.87 LBD: 7.17 HC: 15.56	AD: 11.76 FTD: 7.01 LBD: 7.00 HC: 6.42	LOW	EFFORT LEVEL
		AD: 47.83 FTD: 42.60 LBD: 39.83 HC: 52.617	AD: 44.44 FTD: 52.92 LBD: 34.88 HC: 40.20	MED	

		AD: 57.96 FTD: 64.69 LBD: 74.00 HC: 44.31	AD: 63.45 FTD: 69.80 LBD: 63.33 HC: 63.64	HIGH
	CANDY	AD: 14.60 FTD: 34.85 LBD: 7.01 HC: 4.72	AD: 9.96 FTD: 11.96 LBD: 8.44 HC: 8.46	LOW
		AD: 37.65 FTD: 49.66 LBD: 52.26 HC: 40.53	AD: 43.23 FTD: 82.85 LBD: 69.64 HC: 32.31	MED
		AD: 39.20 FTD: 75.60 LBD: 57.41 HC: 45.99	AD: 65.75 FTD:62.05 LBD: 49.97 HC: 76.99	HIGH
	SOCIAL	AD: 11.74 FTD: 10.16 LBD: 9.07 HC: 6.53	AD: 15.48 FTD: 13.40 LBD: 6.84 HC: 13.42	LOW
		AD: 44.64 FTD: 33.42 LBD: 59.27 HC: 53.90	AD: 41.95 FTD: 47.09 LBD: 65.23 HC: 52.37	MED
		AD: 60.45 FTD: 58.55 LBD: 65.41 HC: 40.55	AD: 65.51 FTD: 47.06 LBD: 38.20 HC: 55.03	HIGH

A.4) Non-significant interaction between disease group, reward magnitude and effort level for cognitive effort-based decision making task.



A.5) Mean maximum applied force (MAF) for each disease group (aMCI/AD, FTD+, LBD/PD, HC) across the different reward type x reward magnitude x effort level combinations in the motor effort-based decision making task

		REWARD LEVEL			
		HIGH	LOW		
REWARD TYPE	MONEY	AD: 0.37 FTD: 0.35 LBD: 0.40 HC: 0.54	AD: 0.47 FTD:0.34 LBD:0.38 HC: 0.50	LOW	EFFORT LEVEL

		AD: 0.73 FTD: 0.70 LBD: 0.71 HC: 0.72	AD:0.73 FTD: 0.69 LBD: 0.71 HC: 0.76	MED
		AD: 0.92 FTD: 0.94 LBD: 0.98 HC:0.94	AD: 0.93 FTD: 0.93 LBD: 0.97 HC:0.93	HIGH
	CANDY	AD: 0.35 FTD: 0.35 LBD:0.43 HC:0.43	AD:0.35 FTD: 0.33 LBD: 0.37 HC: 0.38	LOW
	CANDY	AD:0.76 FTD: 0.70 LBD: 0.72 HC: 0.74	AD: 0.74 FTD: 0.70 LBD: 0.69 HC: 0.74	MED
	CANDY	AD: 0.89 FTD: 0.92 LBD: 0.98 HC: 0.92	AD: 0.91 FTD:0.89 LBD: 0.98 HC: 0.91	HIGH
	SOCIAL	AD:0.36 FTD: 0.33 LBD:0.38 HC: 0.39	AD: 0.41 FTD: 0.37 LBD: 0.34 HC: 0.39	LOW
	SOCIAL	AD: 0.79 FTD: 0.69 LBD:0.71 HC: 0.73	AD: 0.72 FTD: 0.69 LBD: 0.68 HC: 0.71	MED
	SOCIAL	AD: 0.89 FTD: 0.92 LBD: 1.01 HC:0.95	AD: 0.90 FTD: 0.95 LBD: 0.99 HC: 0.87	HIGH

A.6) List of 20 predictor variables entered in the partial least squares analysis

mean search time for candy rewards in low effort trials
mean search time for candy rewards in medium effort trials
mean search time for candy rewards in high effort trials
mean max force applied for candy rewards in low effort trials
mean max force applied for candy rewards in medium effort trials
mean max force applied for candy rewards in high effort trials
mean search time for social rewards in low effort trials
mean search time for social rewards in medium effort trials
mean search time for social rewards in high effort trials
mean max force applied for social rewards in low effort trials
mean max force applied for social rewards in medium effort trials
mean max force applied for social rewards in high effort trials
fluency in eight seconds-goal direct scenarios
fluency in prompted-open scenarios
mean action binding
mean tone binding
MoCa total score
Age

Sex
Level of education

A.7) Mean time (in seconds) for option generation task conditions across the disease groups

Disease Group	**Eight seconds, Goal directed**	**Eight seconds, Open**	**Unlimited, Goal directed**	**Unlimited, Open**	**Prompted, Goal directed**	**Prompted, Open**
aMCI/AD	8	8	22	29.43333	31.45	36.45
FTD+	8	8	24.68889	31.62222	35.42222	35.6
LBD/PD	8	8	46.90278	52.47222	61.25	68.47222
HC	8	8	48.53333	62.06667	61	76.5

Appendix B: Supplementary Materials for Chapter 4

B.1) List of 76 ROIs Entered into Principal Component Analysis

Region of Interest	
Left-Thalamus	Right-Thalamus
Left-Caudate	Right-Caudate
Left-Putamen	Right-Putamen
Left-Pallidum	Right-Pallidum
Left-Hippocampus	Right-Hippocampus

Left-Amygdala	Right-Amygdala
Left-Accumbens-area	Right-Accumbens-area
lh_caudalanteriorcingulate	caudalanteriorcingulate
lh_caudalmiddlefrontal	caudalmiddlefrontal
lh_cuneus	cuneus
lh_entorhinal	entorhinal
lh_fusiform	fusiform
lh_inferiorparietal	inferiorparietal
lh_inferiortemporal	inferiortemporal
lh_isthmuscingulate	isthmuscingulate
lh_lateraloccipital	lateraloccipital
lh_lateralorbitofrontal	lateralorbitofrontal
lh_lingual	lingual
lh_medialorbitofrontal	medialorbitofrontal
lh_middletemporal	middletemporal
lh_parahippocampal	parahippocampal
lh_paracentral	paracentral
lh_parsopercularis	parsopercularis
lh_parsorbitalis	parsorbitalis

lh_parstriangularis	parstriangularis
lh_pericalcarine	pericalcarine
lh_postcentral	postcentral
lh_posteriorcingulate	posteriorcingulate
lh_precentral	precentral
lh_precuneus	precuneus
lh_rostralanteriorcingulate	rostralanteriorcingulate
lh_rostralmiddlefrontal	rostralmiddlefrontal
lh_superiorfrontal	superiorfrontal
lh_superiorparietal	superiorparietal
lh_superiortemporal	superiortemporal
lh_supramarginal	supramarginal
lh_transversetemporal	transversetemporal
lh_insula	insula

B.2) Mean Number of Options Generated in Study Sample (N=22) for Eight-second Goal Directed and Prompted Open Conditions

Disease Group	**Eight-Second Goal Directed Condition**	**Prompted Open Condition**
aMCI/AD	1.33	3.21
FTD+	1.83	6.00
LBD/PD	1.62	7.10

HC	2.44	6.92

Curriculum Vitae: Rubina Malik

EDUCATION

Western University (2019–Present)

Schulich School of Medicine & Dentistry
PhD in cognitive neurology
Supervisor: Dr. Elizabeth Finger
Committee members: Dr. Rob Hegele, Dr. Lena Palaniyappan, Dr. Sean Cregan

McMaster University (2017–2019)
Department of Psychology, Neuroscience and Behaviour
MSc. in Experimental Psychology (Cognitive Neuroscience)
Supervisor: Sukhvinder S. Obhi
Committee members: Dr. Sigal Balshine, Dr. Ranil Sonnadara

McMaster University (2012–2017)
Honours B. Art Sc. (with distinction)
Major: Arts & Science Program & Origins Research Specialization
Minor: Religious Studies

PUBLICATIONS

Restrepo-Martinez, M., Ramirez-Bermudez, J., Chacon-Gonzalez, J., Ruiz-Garcia, R., **Malik, R**., Finger, E. (2023). Defining repetitive behaviors in frontotemporal dementia. *Brain* (accepted).

Malik, R., Jenkins, M., and Obhi, S. (2023). What does rejection do to us? A review of the social exclusion literature (in prep).

Finger, E., **Malik, R**.…Rohrer, J. (2022). Neurodevelopmental effects of genetic frontotemporal dementia in young adult mutation carriers. *Brain,* awac446. https://doi.org/10.1093/brain/awac446

Malik, R., Galang, M., and Finger, E. (2022). The sense of agency for brain disorders: a comprehensive review and proposed framework. *Neuroscience & BioBehavioral Reviews, 139*(104759).

Galang, M., **Malik R.**, Kinley, I., and Obhi, S. (2021). Studying Sense of Agency Online: Can intentional binding be observed in uncontrolled online settings? *Consciousness & Cognition*, *95*, 1–7.

Malik, R. (2021). Cranial connections: what they are and how they are affected in very preterm born infants. *The Dorsal Column, 2*(1). https://songsuwo.ca/volume2issue.

Engle, C., Chin, A., **Malik, R**., and Stone, J. (2020). Fomites with your coffee: Bacteria abundance and transmission on paper cup rims. *The Canadian Journal of Biomedical Research and Technology, 3*(1), 1–7.

Malik, R. (2020). Down low, too slow: How you brain learns optimal hand control. *The Dorsal Column, 1*(3). https://songsuwo.ca/vol1-issue3.

Malik, R., and Obhi, S. (2019). Activating memories of social exclusion reduces the sense of agency: a study using intentional binding. *Consciousness & Cognition, 71*, 30–38.

SCHOLARSHIPS & AWARDS

WESTERN UNIVERSITY ($ in CAD)

Parkwood Institute Research Student Endowment for Mental Health Research (2022)
Value: $10,000

Schulich Medicine & Dentistry Harold Brett Memorial Fellowship in Neuroscience (2021)
Value: $1,200

Parkwood Institute Research Student Endowment for Mental Health Research (2020)
Value: $10,000

Jonathan & Joshua Memorial Graduate Travel Scholarship (2020)
Value: $1,400

CIHR Frederick Banting & Charles Best Doctoral Award (2020–2023)
Value: $105,000 ($35,000/year)

Ontario Graduate Scholarship (OGS; 2020–2021) – Declined for CIHR
Value: $15,000

Neuroscience Art Award (2020)
Value: $100

MCMASTER UNIVERSITY ($ in CAD)

SSHRC Canadian Graduate Scholarship—Master's (2018–2019)
Value: $17,500
e-Campus Ontario Digital Inclusion Research Grant (2017–2018)
Value: $20,000
McMaster Entrance Honour Award III (2012–2013)
Value: $1,000

PRESENTATIONS

Malik, R., Finger, E.…Rohrer, J. (2022). Neurodevelopmental effects of genetic frontotemporal dementia in young adult mutation carriers. Poster given at International Society for Frontotemporal Dementias Conference. Lille, France.

Malik, R., Restrepo, M., Kinley, I., Coleman, K., Jesso, S., Hegele, R., Mitchell, D., Pasternak, S., Garcia, R., Berih, M., Finger, E. (2022). A neurocognitive model for apathy in neurodegenerative dementias: preliminary findings in FTD, LBD, and AD. Poster given at International Society for Frontotemporal Dementias Conference. Lille, France.

Malik, R., Finger, E.…Rohrer, J. (2022). Neurodevelopmental effects of genetic frontotemporal dementia in young adult mutation carriers. Poster given at International Behavioral Neurosciences Society Conference. Glasgow, UK.

Malik, R., Finger, E. (2022) Apathy-APOE genotype interactions predict disease progression in cognitively normal and mild cognitive impairment participants. Talk given at Clinical Neurological Sciences Research Day. London, ON, Canada.

Malik, R., Beaton, D., Ahmed, J., Saykin, A., Nho, K., & Finger, E. (2021). *Neural substrates and genetic variants underlying apathy in Alzheimer's disease*. Talk given at Retiring with Strong Minds. London, ON, Canada.

Malik, R., Beaton, D., Ahmed, J., Saykin, A., Nho, K., & Finger, E. (2021). *Neural substrates and genetic variants underlying apathy in Alzheimer's disease*. Poster presented at London Health Research Day. London, ON, Canada.

Malik, R., Beaton, D., Ahmed, J., Saykin, A., Nho, K., & Finger, E. (2021). *Neural substrates and genetic variants underlying apathy in Alzheimer's disease*. Poster presented at Parkwood Institute Research Day. London, ON, Canada.

Malik, R., Beaton, D., Ahmed, J., Saykin, A., Nho, K., & Finger, E. (2021). *Neural substrates and genetic variants underlying apathy in Alzheimer's disease*. Poster presented at Clinical Neurological Science Research Day. London, ON, Canada.

Malik, R., & Obhi, S. (2019). *Activating memories of social exclusion reduces the sense of agency: A study using intentional binding*. Poster presented at the Canadian Society for Brain, Behaviour, & Cognitive Science Conference. Waterloo, ON, Canada.

Malik, R., & Obhi, S. (2019). *Activating memories of social exclusion reduces the sense of agency: A study using intentional binding*. Talk presented at the Current Research in Engineering, Science & Technology Conference. Hamilton, ON, Canada.

Malik, R., & Obhi, S. (2018). *Activating memories of social exclusion reduces the sense of agency: A study using intentional binding*. Poster presented at the PNB Graduate Research Conference. Hamilton, ON, Canada.

Malik, R., & Stone, J. (2017). *Gamma radiation tolerance in cryobiotic versus hydrated tardigrades*. Presented at the Origins Undergraduate Research Colloquium. Hamilton, ON, Canada.

TEACHING EXPERIENCE

GRADUATE

Western University

Ethical Research Practices (MEDSCIEN 9504): September 2021–April 2022
Selected Topics in Medical Sciences (MEDSCIEN 4930Z): September 2020–April 2021
Integrative Neuroscience (ACB 4451F): September 2019–December 2019

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Integrative PNB Through Scientific Writing (PNB 2XD3): January 2019–April 2019

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The Indian Religious Tradition (ARTSSCI 3L03): September 2016–December 2016