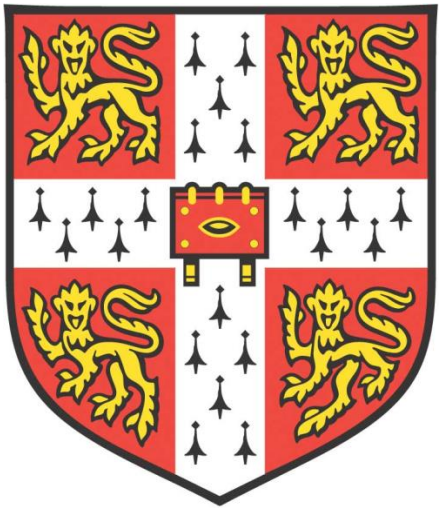
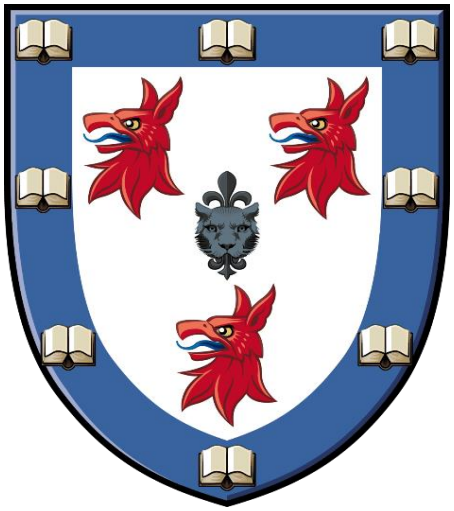
DECISION-MAKING IN HUNTINGTON'S DISEASE





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I began to realise how important it was to be an enthusiast in life. If you are interested in something, no matter what it is, go at it full speed. Embrace it with both arms, hug it, love it and above all become passionate about it. Lukewarm is no good. Hot is no good either. White hot and passionate is the only thing to be

- *Roald Dahl*

DECLARATION

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared below and specified in the text. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my thesis has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the relevant Degree Committee

The research conducted in **Chapter 2** was a joint project with Sam Hewitt, a research assistant in Professor Barker's group. We share first authorship for a paper that has been submitted for peer review; for accuracy I use 'we' instead of 'I' in this Chapter. I wrote the study protocol and ethics application. Sam recruited and tested the first third of participants and I recruited and tested the second two-thirds. I produced Figures 5 and 6, and table 2. Sam ran the final models and produced the final figures for 7, 8 and 9. I ran the earlier models and produced preliminary figures. We both wrote the manuscript on a shared document; I adapted it for this thesis.

Chapter 7 describes an app for which the back end code was written by Taketomo Isazawa. He also produced the low-level data block diagram in Figure 52. Taketomo also contributed to the logo design, the in-app text and to the discussion about ideas for new features.

ABSTRACT

Huntington's disease (HD) is a neurodegenerative disorder caused by an expansion mutation in the huntingtin gene. Gene carriers are currently diagnosed with manifest HD when a movement disorder becomes apparent although such problems are often preceded by cognitive and psychiatric features which can impair decision-making (DM). Given the nature of living with a progressive, genetic disease, the consequences of decisions made by HD gene carriers can be particularly impactful at all stages of the condition.

A decision requires individuals to perceive and process information, estimate likelihoods, to evaluate options, reflect on past choices and select actions. Decision science spans many disciplines, from psychology to neuroscience and economics, which has generated a contemporary theory to explain DM as a rational-intuitive dual-process. People have an extraordinary ability to use logic and rationality to make complex choices as well as an efficient intuitive strategy to make decisions when cognitive costs are high and time is limited. To date, the rational-intuitive metaphor has not been applied to understand decision making problems in HD, neither in theory nor in practice.

This thesis presents a number of clinical studies in which some aspects of the rational-intuitive theory of DM is investigated in HD, followed by two studies where interventions based on this theory are tested.

I first explored the wider literature to learn about the neuroscience of DM, its neurobiological overlap with HD, how it has been studied previously and what conclusions have been made in HD. This highlighted gaps in our knowledge, particularly on the low-level perceptual and high-level reflective processes that are involved in DM in HD patients. I have shown that perceptual DM is impaired in premanifest individuals, and this gets worse in manifest patients (compared to controls) but there are no differences in metacognition.

I next sought to dissect DM from a rational-intuitive perspective. There was no suitable task to do this across patient and control populations so I built and tested a new cognitive task that could be carefully controlled in an experimental setup. I went on to test this in a larger cohort to characterise choice deliberation and consistency across the adult lifespan. I show that the use of choice attributes declines gradually with age, choice

consistency is maintained and possibly enhanced with age, and intuitive processing, while unpredictable and inconsistent, is also maintained across the lifespan.

I show in a subsequent study that patients with HD and Parkinson's disease do not display differences to controls in DM in my task, and instead it is again increasing age, not disease status, that confers a gradual decline in the use of choice attributes, while intuitive processing is unaffected by both age and disease.

Finally, I investigated two mechanisms to support rational DM in HD patients and older adults. First, a pharmacological study of acute dopaminergic and noradrenergic medication effects on rational processing. Second, I designed and co-built a smartphone application called Triage to help users recognise important emails and letters, and to highlight key terms requiring decisions in the text.

In summary, these investigations suggest that there are perceptual DM impairments in HD but not in metacognition or aspects of rational processing. Instead, increasing age alone is associated with reduced rational DM. Using these findings as a platform, it is possible to build interventions to support continued cognitive function and autonomy in patients with HD and healthy older adults with applications to other chronic neurodegenerative disorders.

ACKNOWLEDGEMENTS

I have found a profound sense of community and vibrancy in Cambridge which has made these years lively and enjoyable. I feel lucky to have been supervised by Professor Roger Barker, who has shown me what kind and inspiring leadership looks like, and given me the independence to indulge in research tangential to his own. My advisors, Drs Sarah Mason and Fabian Grabenhorst were immensely grounding, giving their expertise to connect ideas across disciplines…and kindly alerting me when my ideas ran away from fact.

The Barker research group, all 40-odd members, was such an enriching team to be a part of. They taught me how satisfying it can be to be disagreed with. They rode the PhD rollercoaster in my carriage every day; they provided cake for breakfast, listened to my 3pm woes and joined Clinic dance parties with gusto. Marta Camacho, Kate Harris, Sam Hewitt, Katie Andresen, Elise Laperrousaz, Shaline Fazal, Molly O'Reilly, Laura Sherlock, Miriam Schaepers, Maha Afaldi, Zanna Voysey and Kelli Torsney, you each made bad moments manageable and good ones great.

The Cambridge University Boat Club brought me to Cambridge and drove me through it. The men and women of this club gave me two priceless things, confidence and resilience, and there is nothing I wouldn't do for them. The 2017 Blue Boat affirmed that a good crew is to be cherished above all, and the 2018 crew enforced that. Sally O'Brien, Hannah Forde and Tricia Smith, you were a constant source of support. Myriam Goudet-Boukhatmi and Daphne Martschenko, you were the role models I didn't know I needed.

To the Sunday Roast Club, Athena's Swaggy Swans, Antipodean Brunch Club, New Square and DeFreville squads, Homerton College and CamBRAIN Society: you were my family on this side of the world.

I would also like to thank the participants who took part in my research at the HD and PD Clinics at the Centre for Brain Repair. It's been incredible to learn from you all. I am grateful to Donald Shepherd and the Parasol Foundation Trust who funded me and this research.

And lastly, to my mum and dad. Thanks for instilling in me the confidence to move across the world and be unashamedly enthusiastic.

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List of Abbreviations and Acronyms

ACE-R	Addenbrooke's cognitive exam – revised
AIC	Akaike information criterion
ANOVA	Analysis of variance
BPIC	Bayesian predictive information criterion
CAG	Cytosine-Adenine-Guanine
CPREC	Cambridge Psychology Research Ethics Committee
CRT	Cognitive reflection test
CRUNCH	Compensation-related utilisation of neural circuits
DA	Dopamine
DIC	Deviance information criterion
DLPFC	Dorsolateral prefrontal cortex
DM	Decision-making
EEG	Electroencephalography
FI	Faith in intuitive questionnaire
GDMS	General decision-making style
GDPR	General data protection regulation
GLM	Generalised linear model
HADS	Hospital anxiety and depression scale
HD	Huntington's disease
(H)DDM	(Hierarchical) drift diffusion model
HDI	High density interval
MANOVA	Multivariate analysis of variance
MMSE	Mini mental state examination
NART	National adult reading test
NFC	Need for cognition questionnaire
OCR	Optical character recognition
OFC	Orbitofrontal cortex
PD	Parkinson's disease
PFC	Prefrontal cortex
PID	Person-identifiable data
RAM	Random access memory
RT	Response time
SDHS	Secure data hosting server

SE-ADL	Schwab and England independence scale
SNP	Single nucleotide polymorphism
SNPC	Substantia nigra pars compacta
SST	Stop signal task
STN	Subthalamic nucleus
UHDRS TFC	Unified Huntington’s disease rating scale total functional capacity
UHDRS TMS	Unified Huntington’s disease rating scale total motor score
UI	User interface
UPDRS	Unified Parkinson’s disease rating scale
VIQ	Verbal IQ
VMPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area

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1 INTRODUCTION TO DECISION-MAKING IN HUNTINGTON'S DISEASE

Decision-making (DM) relies on a broad range of interdependent cognitive processes. A value-based decision requires individuals to process information and estimate probabilities, to evaluate options and select actions – to guide the selection of an option amongst alternatives with different outcomes (Groman et al., 2020; Sanfey et al., 2006). Key brain regions in DM processes are also affected by early and progressive pathology in Huntington's disease (HD), a genetic neurodegenerative disorder. Cognitive decline is a well-reported feature of HD, although impairments are not uniform across gene carriers, with some individuals remaining cognitively healthy much longer than others (Begeti et al., 2013; Walker et al., 2017). Conversely, cognitive impairments in HD gene carriers can also emerge before overt motor features (Baake et al., 2017) and 40% of premanifest individuals also meet criteria for mild cognitive impairment (Duff et al., 2010). This identifies a window where poor DM may go undetected.

Given the nature of living with a progressive, genetic neurodegenerative disease, the consequences of decisions made by HD gene carriers can be particularly impactful. This includes whether to have a genetic test, to have children, to continue to work and drive, and to participate in clinical research (Etchegary, 2006; Hamilton et al., 2003; Jacobs et al., 2018; Klitzman et al., 2007; Mason et al., 2017; Watkins et al., 2018). It is

therefore important to understand how the ability to make decisions is affected at an individual level in HD gene carriers, however, studies looking at this are scarce.

This Chapter will summarize the literature on DM and how it has been measured in HD. This will then lead onto to the research projects within my thesis which attempt to give a more thorough understanding of the impact of HD-specific cognitive changes on DM. Linked to this is work on DM in healthy populations, given this is relatively more advanced.

The academic search engine PubMed was used with the following search terms: HD OR Huntington OR Huntington's AND Decision-making OR decision OR choice OR risk. Articles irrelevant to the topic were excluded and all other results from January 2000 to December 2020 were included. Irrelevant articles concerned non-experimental DM, individuals without a confirmed genetic test, or articles about clinician (instead of patient) DM. Finally, a manual review of the bibliographies was conducted to find additional articles.

1.1 The neurobiology of decision-making

The complexity of DM can easily be realised by the fact that numerous brain regions have been implicated in DM by studies using functional neuroimaging in humans and electrophysiological recordings or lesion approaches in animals. A demarcated frontostriatal network connects the prefrontal cortex with the striatum and is regularly implicated in value-based processing of decisions. Previous reviews have further split the frontostriatal networks into those used in habitual and goal-directed behaviours, and below are the key brain regions implicated in these (Balleine & O'Doherty, 2010; Cohen et al., 2005; Crittenden & Graybiel, 2011; Gleichgerrcht et al., 2010; Kable & Glimcher, 2009; Rangel et al., 2008; In particular see (Haber, 2016) Figure 6). Figure 1 is a schematic of these regions in the human brain, while Table 1 lists and briefly summarises the regions and their roles. It is important to note that these regions are not always discrete and lack clear, uniformly applied borders, but they are useful to decompose DM behaviours into testable processes. Converging evidence supports these regions and their roles in habitual and goal-directed DM, but this is not a comprehensive collection of all regions involved in these processes. Critically, some of these regions are also those with the earliest detectable changes in HD gene carriers (Nair et al., 2021; Scahill et al., 2020) and subsequently, the progressive neurodegeneration in HD maps on to other regions that are required for DM (Wijeratne et al., 2018).

The goal-directed regions include the orbital prefrontal cortex (OFC; Hare et al., 2008), frontal polar cortex (Boorman et al., 2009), ventromedial prefrontal cortex (VMPFC; De Martino et al., 2013; Shapiro & Grafton, 2020), dorsolateral prefrontal cortex (DLPFC; Rangel et al., 2008) and the dorsomedial striatum (Kable & Glimcher, 2007; Yin et al., 2005). This network encodes the relationship between actions and outcomes with choice behaviour dependant on past and hypothetical outcomes (Balleine & O'Doherty, 2010; Rangel et al., 2008) and these regions exhibit functional connectivity at rest (Di Martino et al., 2008). Habits are stimulus-response associations: behaviour which depends on the stimulus rather than the outcome (as in goal-directed DM; Balleine & O'Doherty, 2010). Habitual DM is mediated by the dorsolateral striatum (Rangel et al., 2008; Yin & Knowlton, 2006) and specific ablation of dorsolateral striatal patches (also known as striosomes, described below; Prager & Plotkin, 2019) in mice impairs habitual responding (Nadel et al., 2020).

The striatum plays a role in both goal-directed and habitual DM and is itself a complex brain region. It is the largest subcortical structure in the human brain and is heavily connected, receiving diverse topographical projections from the cerebral cortex and thalamus and projecting to nuclei throughout the basal ganglia, and receives further re-entry loops from these regions (Choi et al., 2017; Lanciego et al., 2012; Liu et al., 2020). The striatum has been described as "where skills and habits meet" and a region critical for choosing optimal behaviours (Graybiel & Grafton, 2015). The striatum also plays a central role in action-selection and movement. Moving topographically from the ventral-medial to dorsal-lateral striatum, value encoding activity shifts to the associative and motor aspects of DM (Burton et al., 2015).

Striatal neurons can be described in three ways. First, spatially, the dorsal striatum (caudate and dorsal putamen) and ventral striatum (nucleus accumbens and olfactory tubercle). Second, pharmacologically, striatal cells differentially express D1-type or D2-type dopamine receptors and these comprise the majority of direct and indirect motor pathways, respectively. Third, histologically, as the striatum is composed of a striosome and matrix cellular mosaic (Crittenden & Graybiel, 2011). Striosomes receive inputs from the prelimbic cortex and output to the substantia nigra pars compacta (SNpc). Matrix neurons are functionally distinct and receive afferents from the sensorimotor cortex and project to basal ganglia output nuclei. Striosomes preferentially target dopaminergic neurons in the ventral tegmental area (VTA) and SNpc, connecting them with the ventral and dorsal striatum, respectively (Lebouc et al., 2020). Importantly, loss

of striatal neurons is thought to cause chorea in HD (discussed below) and, given the prominent role of these neurons in DM it follows that this pathology may also affect DM. However, the complex structure and functions of striatal neurons makes studying this difficult.

Conflict between goal-directed and habitual processes can lead to poor DM, but the two processes can also work in synchrony (Rangel et al., 2008). For example, both the habitual and goal-directed systems place high value on food at meal times, however, an alcoholic at a bar has an habitually high value for a drink but a goal-directed low value to avoid it. There are additional regions which add nuance to the goal-directed and habitual DM processes. For example, processes that involve valuing morals as well as social and cultural norms. There also needs to be integration of risk and uncertainty into DM. These additional regions are briefly described below, moving from the basal ganglia outward to cortical regions.

Amygdala neurons hold diverse yet distinctive roles. In "value" neurons, increased firing indicates a high value of objects based on a monkey's own experiences and observations. In "social" neurons, increased firing indicates the acknowledgement of others' choices. In "simulation" neurons, firing levels predict the choices of others. Importantly, these changes in firing rate appear to be spontaneous, that is, with no corresponding afferent input (Grabenhorst et al., 2019). In another study, unique "location" neurons in the amygdala had firing rates dependent on the location of rewarding stimuli (Peck & Salzman, 2014). Furthermore, amygdala neurons demonstrate firing that gradually increases over choice sequences to serve as intrinsic progress evaluators (Grabenhorst et al., 2016). The VTA drives plasticity in the amygdala through a dopaminergic input from the VTA, which is activated during reflexive choice behaviour, including during fear learning protocols (Tang et al., 2020).

Subthalamic nucleus neurons encode thresholds between fast and accurate decisions – low frequency oscillations are associated with the threshold as it relates to accuracy, and the introduction of STN beta frequencies decreases decision thresholds irrespective of instructions (Herz et al., 2017). Globus pallidus neurons projecting to the habenula in mice encode whether an outcome was better or worse than expected through altered firing rates. These neurons sit within a larger evaluation network, innervated by striatal and subthalamic nucleus neurons in mice (Stephenson-Jones et al., 2016). In humans, the habenula is a small structure and functionally connects the forebrain with the ventral midbrain (Boulos et al., 2017).

The cingulate cortex is regularly implicated in DM. Rostral and anterior activity is consistent with reward-action association behaviour and the initiation of behavioural change in response to errors (Rushworth et al., 2011). The posterior cingulate tracks subjective value of reward (Kable & Glimcher, 2007). The parietal cortex is similarly engaged during some goal-directed DM. It is active during information gathering, and in conjunction with the anterior pole of the frontal cortex, in flexible choice behaviours it appears to facilitate the switch to an alternative option. Decreased tolerance for risk (variance among alternatives) is associated with decreased volume in the parietal cortex (Boorman et al., 2009; Furl & Averbeck, 2011; Grubb et al., 2016). A white matter pathway connects the anterior insula cortex with the prefrontal cortex, striatum and nucleus accumbens (Kohno et al., 2017). Activity in the anterior insula cortex is also consistent with risk evaluation (Rangel et al., 2008) and with a retrospective evaluation of experiences with regard to expected versus actual reward (Furl & Averbeck, 2011). Finally, these regions and networks are critically dependent on midbrain dopamine levels to encode utility throughout the DM process. The ventral tegmental area supplies much of this dopamine, via the nucleus accumbens, to signal to the striatum and frontal cortex (Schultz, 2015; Verharen et al., 2018).

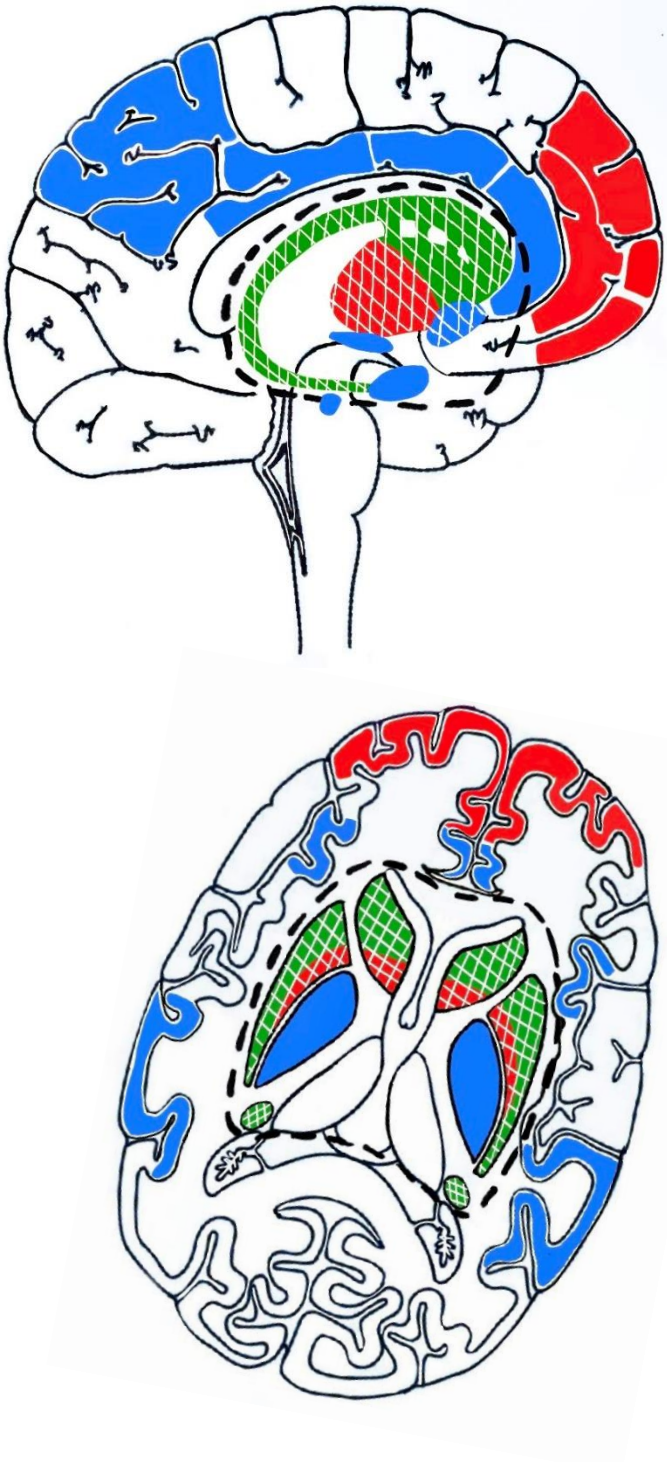


Figure 1. A stylised depiction of the brain regions required to make value-based decisions (top = mid-sagittal section, bottom = horizontal section). Hashed areas are also affected by the earliest HD pathology and neurodegeneration – namely the dorsal and ventral regions of the striatum. Black dashed lines denote the basal ganglia.

Goal-directed DM regions in red encode the relationship between actions and outcomes, by assigning value to actions and evaluating reward. The dorsomedial striatum, ventromedial, dorsolateral and orbitofrontal prefrontal cortices, and the frontopolar cortex are included.

Habitual DM in green supports stimulus-response behaviour and action selection programs. The dorsolateral striatum is primarily responsible for this.

Additional regions in blue also play substantial roles in value-based DM: the amygdala, subthalamic nucleus, nucleus accumbens, ventral tegmental area, globus pallidus, cingulate cortex, parietal cortex and anterior insula cortex are all highlighted.

Table 1. Many brain regions are involved in decision making and some of these show activity consistent with goal-directed (in red) or habitual behaviour (green). Other regions in blue have a more generalised role in decision making. Those in bold are affected by earliest HD pathology and neurodegeneration.

Decision-Making Process	Brain Region	Brief summary of roles	References
Goal-directed (red) Action-outcome associations, instrumental learning	Frontopolar cortex	Supports flexibility during goal directed behaviour by monitoring the value of alternate options	(Boorman et al., 2009; Rushworth et al., 2011)
	Orbitofrontal cortex (OFC)	Activity is associated with the computation of value-related signals, mediated by subjective goal and attribute values by visual cues with vmPFC; More specific stimulus reward relationships are computed in the lateral OFC	(Abitbol et al., 2015; De Martino et al., 2006; Hare et al., 2008; Padoa-Schioppa & Assad, 2008; Rushworth et al., 2011)
	Ventromedial PFC (VMPFC)	Reflects value assigned to choices under consideration: First to the current choice under consideration, then secondary confidence in the valuation of choice options	(Abitbol et al., 2015; De Martino et al., 2013; Kable & Glimcher, 2007; Shapiro & Grafton, 2020)
	Dorsolateral PFC (DLPFC)	Exhibits goal-value signals in monkey and rat electrophysiology and higher fMRI BOLD signal in humans for behavioural measures of goal value	(Rangel et al., 2008)
	Dorsomedial striatum	Activity in goal-directed valuation changes with age at the expense of performance; blockade of NMDA receptors or lesions (in rats) prevent action-outcome association	(Kable & Glimcher, 2007; Lau & Glimcher, 2008; Rangel et al., 2008; Yin et al., 2005)

Habit (green) Automated behaviour insensitive to outcomes (stimulus-response)	**Dorsolateral striatum**	Active during stimulus-response behaviours; Ablation of patch/striosome cells (in mice) impairs habitual responses	(Balleine & O'Doherty, 2010; Nadel et al., 2020; Rangel et al., 2008; Yin & Knowlton, 2006)
Additional regions required for DM (blue), e.g. morals, social contexts, cultural norms, temporal delay, long-term goals	Amygdala	Single-neuron-level evaluation of choice attribute value and location, acknowledging and predicting others' choices, and monitoring progress over time; Activity tracks behavioural response to reward-related cues and salient sensory events	(Cohen et al., 2005; Corbit & Balleine, 2005; Grabenhorst et al., 2016, 2019; Peck & Salzman, 2014; Tang et al., 2020)
	Nucleus accumbens (part of ventral striatum)	Receives dopaminergic projections from ventral tegmental area and projects to striatum and frontal cortices, required for DM and movement; Ventral striatal activity tracks reward prediction error	(Pagnoni et al., 2002; Schultz, 2015; Verharen et al., 2018)
	Ventral tegmental area	Dopaminergic projections to amygdala and nucleus accumbens (with subsequent projections to dorsolateral and dorsomedial striatum); Activity is recorded during flexible and reflexive behaviour in response to aversive and appetitive stimuli	(Beier et al., 2015; Tang et al., 2020)
	Subthalamic nucleus	Encodes threshold between fast and accurate decisions	(Herz et al., 2017)
	Globus pallidus	Relative value of outcomes encoded through firing rate projected to the habenula (in rodents); Innervated by subthalamic nucleus and striatum	(Boulos et al., 2017; Stephenson-Jones et al., 2016)

	Posterior cingulate cortex	Tracks subjective value of reward	(Kable & Glimcher, 2007)
	Anterior and rostral cingulate cortex	Reward-action association; Initiates change in behaviour in response to errors in reward-guided DM	(Rushworth et al., 2011)
	Anterior insula cortex	Retrospective evaluation of experience and expectation of reward; fMRI activity is consistent with risk evaluation	(Furl & Averbeck, 2011; Rangel et al., 2008; Vestergaard & Schultz, 2020)
	Parietal cortex	Greater activity during information gathering and is engaged during flexible behaviour (with frontopolar cortex) when switching to alternative choice; Decreased volume is associated with a reduced tolerance for risk	(Boorman et al., 2009; Furl & Averbeck, 2011; Grubb et al., 2016)

1.2 Huntington's disease

A pathologically expanded triplet repeat of cytosine-adenine-guanine (CAG) in the huntingtin gene underlies why a person develops HD (The Huntington's Disease Collaborative Research Group, 1993) and it affects one in 8300 people in the United Kingdom (Evans et al., 2013). The expansion gives rise to a mutant variant of the huntingtin protein which is prone to aggregate and cause widespread neuronal dysfunction, death and regional atrophy (Vonsattel & DiFiglia, 1998). The length of the expansion is inversely related to the age at which the disease presents, most typically with chorea between 40 and 50 years of age (Lee et al., 2012). Prior to this point, gene carriers are typically described as being 'premanifest'. The mutation is autosomal dominant and fully penetrant. Disrupted cognition, emotional processing and psychiatric features including apathy, irritability and perseveration are also common early features of HD but tend to vary between individuals (Bates et al., 2002).

Progressive impairments in executive functions such as forward planning, anticipation, judgment, reasoning, cognitive flexibility and working memory, as well as attention, immediate and long-term memory and reduced psychomotor speed, have been documented in patients with early HD (Ho, Sahakian, Brown, Barker, Hodges, Ane, et al., 2003). In fact, some studies have shown that in premanifest gene expansion carriers there are some deficits in these same executive functions, along with cognitive flexibility, attention, psychomotor speed, working memory and verbal fluency (Baake et al., 2017). In addition, disrupted emotional processing is present in premanifest HD and progresses with the disease course (Johnson et al., 2007; Mason et al., 2015; Tabrizi et al., 2013). Despite clinical features in some patients, the premanifest phase is highly heterogeneous and gene carriers often have no behavioural impairments. The heterogeneity also means that the prediction of cognitive changes in an individual with HD is challenging (Stout et al., 2011). Quality-of-life commonly reduces with increasing disease severity which has been linked more to cognitive than motor changes (Hawton et al., 2019; Helder et al., 2001). At motor onset, 84% of patients have mild cognitive impairment while 5% have dementia. After five years, 24% of patients have mild cognitive impairment while 69% meet criteria for dementia (significant impairments in more than one cognitive domain and significant loss of functional independence) (Julayanont et al., 2020).

Brain atrophy in HD is known to begin many years before clinical onset and there is considerable overlap with those regions involved in DM (Figure 1). The earliest

degeneration occurs in the projection neurons that make up 95% of the striatum (Wijeratne et al., 2018; Wu et al., 2017) especially in the striosome (also known as patch regions), rather than the matrix cells (Lebouc et al., 2020), with the preferential loss of the D2-type indirect pathway cells (Glass et al., 2000) and activity reduction in the ventral striatum (Enzi et al., 2012; Langley et al., 2020). Indeed recently it has been shown that gene carriers 25 years from onset (predicted) have aberrant striatal activity for the representation of value compared to well-matched healthy controls (Nair et al., 2021). There are also microstructural abnormalities in white matter as well, decades before clinical onset, that progress from central, subcortical structures to the cerebral cortex (Estevez-Fraga et al., 2020). Together, these early changes in cognition and brain structure would suggest that both habit and goal-directed processes should be affected in HD early on although this has not been studied to date.

Changes to the dopamine (DA) system in HD probably underlie some of the involuntary movements seen in this condition, specifically due to reduced inhibition in the basal ganglia motor pathway leading to excessive movements or chorea. It is thought that lost striatal type-2 DA receptors in the indirect pathway are responsible for this (Glass et al., 2000), as confirmed with PET imaging (Pavese et al., 2003), and which is first seen in premanifest gene carriers (i.e. prior to the onset of motor features). Dopamine receptor dysfunction subsequently progresses across frontal and temporal regions (Pavese et al., 2010) and correlates with the severity of motor impairment and functional capacity (Andrews et al., 1999). Dopamine antagonists reduce HD chorea (i.e. apparently decreasing DA further) but their effectiveness is thought to be due to increased striatal activity in compensation for DA receptor loss (Ariano et al., 2002). These antagonists, however, can have negative effects on cognition in manifest HD patients (Harris et al., 2020) and the adverse side effects of DA antagonists worsen over time (Louis et al., 1999).

Brain region volume loss is detectable earliest in the putamen and caudate (striatum), then the pallidum is affected, followed by insula white matter, amygdala, optic chiasm, then becomes more widespread to affect posterior insula cortex and basal forebrain with compensatory ventricular enlargement (Wijeratne et al., 2018). At the most severe stages of HD, post mortem analysis indicates that there is a 95% cell loss in the caudate nucleus and considerable atrophy of the nucleus accumbens, globus pallidus and frontal lobes. The HD brain is approximately 80% of the weight of a normal control brain at post mortem (Vonsattel et al., 1985; Vonsattel & DiFiglia, 1998).

DM deficits represent a considerable clinical burden in HD (Duff et al., 2010; Rosenblatt, 2007; L. H. Watkins et al., 2000). These deficits may be deeply consequential for HD patients, where there is anecdotal evidence of them making unwise decisions such as travelling abroad without support, driving when unsafe, undertaking dangerous jobs and spending recklessly. More widely, poor DM is at least partly responsible for the financial strain placed on patients and their families, a cause of worry and trepidation, and impacts on the patients' ability to live autonomously. These difficulties in everyday situations have not been empirically studied.

1.3 How is decision-making measured in Huntington's disease?

Three tasks are commonly used to examine DM deficits in clinical populations: the Iowa Gambling task (IGT), Cambridge Gambling Task (CGT) and the Game of Dice Task (GDT). All three tasks are complex and involve multiple cognitive processes, thus, impairment (below control performance) may have more than one cause. All tasks rely on the regions discussed above which are implicated in goal-directed DM. The tasks are less tightly controlled compared to many DM neurophysiological or neuroimaging studies that aim to dissect these component processes. However, all tasks have the advantage that they are relatively life-like and can be performed by patients.

It is important to note here that 'risk' in the context of these, and most other psychological tasks, is interpreted as the probability of loss; this usage is distinct from the one in economics, behavioural economics and neuroeconomics, where risk is commonly defined as the variance of outcomes.

The IGT, formally the Bechara Gambling Task (Bechara et al., 1994), shows participants four identical decks of cards, either physically or virtually (Figure 2). The patient is then instructed to reveal one card at a time from a deck of their choice. On the reverse of the cards are gain and loss amounts. Two decks have high gains, but even higher average losses (A and B in Figure 2). The other two decks have less appealing gains and smaller losses, but over the course of the task they provide greater net winnings (C and D in Figure 2) but participants are not told of these contingencies – they must be learned. Participants draw 100 cards but are not told this in advance. The IGT is used to measure DM in contexts of ambiguity (first part of task when the win/loss contingencies are unfamiliar and therefore ambiguous) and risk (latter parts of task when win/loss contingencies and variance between options are assumed to have been learned) (Brand et al., 2007).

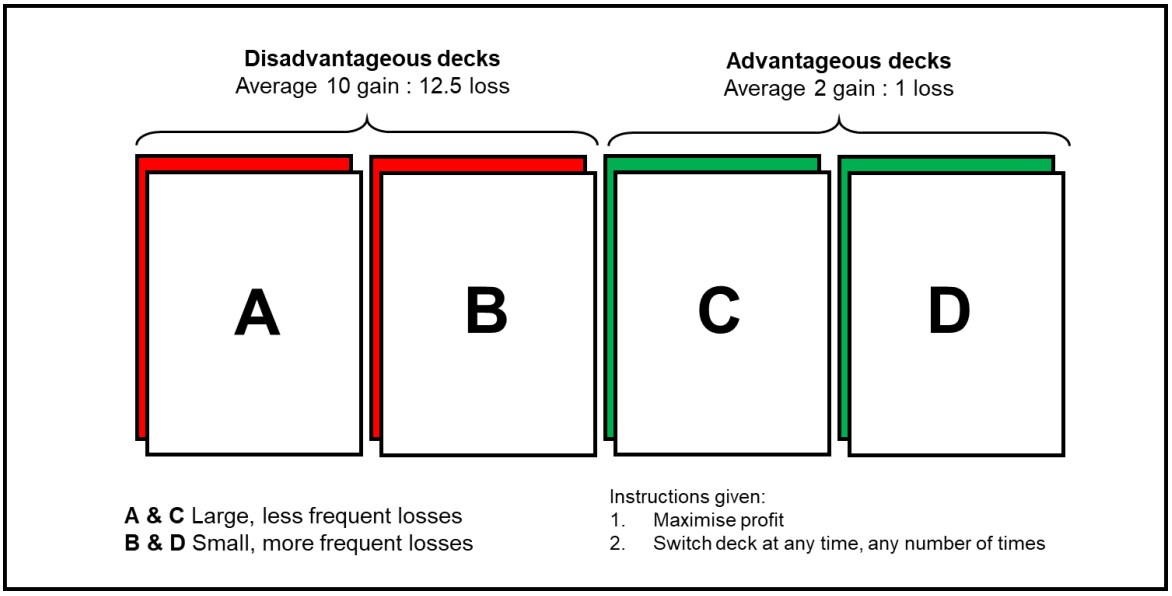


Figure 2. Schematic of the Iowa Gambling Task (IGT), formerly the Bechara Gambling Task, where participants must choose from four decks of cards to accrue maximum points. Unknown to the participant, two decks are advantageous and two are disadvantageous.

The ventromedial prefrontal cortex is predominantly activated during the IGT as players determine the value of the different decks. Patients with damage in this area have impaired performance, as do older adults: the VMPFC is one of the earliest regions to show reduced connectivity as we age (Halfmann et al., 2014). Impaired performance has also been attributed to disturbances in the OFC and the DLPFC (van den Bos et al., 2013). The IGT is undoubtedly a complex task. It is difficult to disentangle learning, motivation

and attention - especially in the later stages of the task. There is a large span of behaviours observed in the IGT in healthy people, but its ecological validity in clinical groups is supported (Jacus et al., 2018).

HD patients perform comparably to age-matched controls in the first half of the IGT when learning new rules in ambiguous circumstances. It is reported that early manifest patients make fewer advantageous choices in the second half of the task, where the task concepts must be held in working memory and risk propensity is a factor (Stout et al., 2001). However, this finding is not universal. A second study found a reduced skin conductance response (i.e. a reduction in autonomic response where anticipatory responses to losing gambles are the norm) following loss trials in HD patients compared to controls and yet the number of advantageous selections was comparable (Campbell et al., 2004). A third study found that patients made fewer advantageous choices when only the first half of the task, decisions under uncertainty, was implemented (Adjeroud et al., 2017). It is agreed, however, that premanifest patients demonstrate comparable performance to healthy controls in both phases of the IGT (Adjeroud et al., 2017; Holl et al., 2013). These contradictory results in manifest HD patients might be attributable to three separate studies deconstructing and adminstering the IGT in different ways (Adjeroud et al., 2017; Campbell et al., 2004; Stout et al., 2001). Adjeroud and colleagues shortened the test to measure DM under uncertainty, whereas Stout and colleagues used the full length test to measure DM under risk, and Campbell and colleagues used this same interpretation but in a novel computerised format. While these small differences may not be of note alone, it is likely that they sum to confound the findings in the already small and heterogeneous HD cohorts being tested where individual differences can give contradictory results, especially in the context of a complex task such as the IGT.

The CGT is a second commonly used task in decision research in HD (Rogers et al., 1999). Participants see 10 boxes on a screen, some are red and some are green (Figure 3). Behind one box is a yellow square. Participants must guess the colour of the box which hides the yellow square, either red or green. They then place a bet on their guess: if it was correct they win the number of points of their bet, if they lose they lose that number. Furthermore, the task has two conditions: an ascending and a descending bet amount, where the bet amount starts low and increases every five seconds, or starts high and decreases, respectively. The CGT is favoured because it does not rely on learning or working memory, a common confound in neurodegenerative disease populations, and

measures risk and impulsivity in DM. Performance on the task requires the VMPFC and the OFC (Bechara, 2005) as players calculate value probabilities and make choices.

No differences between premanifest patients and controls are seen in the ascending bet condition, but in the descending condition premanifest patients make higher bets by choosing an earlier amount (Galvez et al., 2017). This was interpreted as increased impulsivity in premanifest patients leading to poorer decisions, although the study did not measure impulsivity independently. Contrary to this finding, a second study with moderate stage manifest HD patients found no differences in bet size in either condition, nor in selection of the most likely outcome. The only group difference in comparison to healthy controls was an increased response time (RT) (Watkins et al., 2000). This may represent loss of the goal-directed regions, such that performance could be rescued by an increased RT. It might also be that the motor features of HD influence RT, due to either psychomotor slowing or a delayed click response.

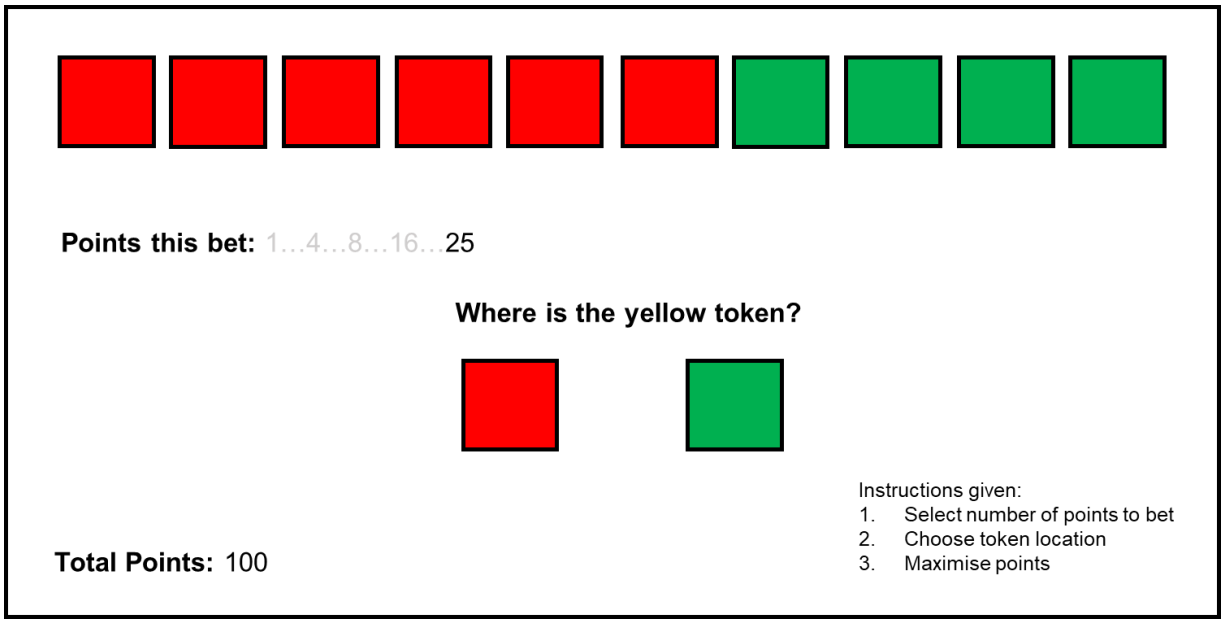


Figure 3. A schematic of the Cambridge Gambling Task (CGT) where participants must place bets on their predictions about where the yellow token is hidden, beneath a red or a green box.

The *Game of Dice task* (GDT) is the third commonly used decision task (Brand et al., 2005). Participants predict the outcome of 18 single die rolls (Figure 4). They can predict a single number outcome (e.g. roll a 2), or two, three or four number combinations (e.g. roll a 1, 2, 3, or 4). The chance their chosen number (or numbers) will be rolled increases respectively, but the amount they could win with a successful guess decreases

(£1000, £500, £200, £100, respectively). The GDT uses stable probabilities to reduce the need for learning and memory and to measure DM under explicit risk. Optimal task performance requires the DLPFC and participants with lesions here perform less well (Brand et al., 2006).

No differences in total score compared to controls was found in either manifest or premanifest patients in the GDT (Adjeroud et al., 2017). A second study confirmed no differences between premanifest and control groups' total scores. However, this study did find increased RTs in the premanifest participants compared to controls, and safer strategies to mitigate risk taking in the premanifest gene carriers (D'Aurizio et al., 2019). Similar to the CGT, this might indicate early loss of the regions required for goal-directed behaviour, but only to the extent that reduced performance can be compensated for.

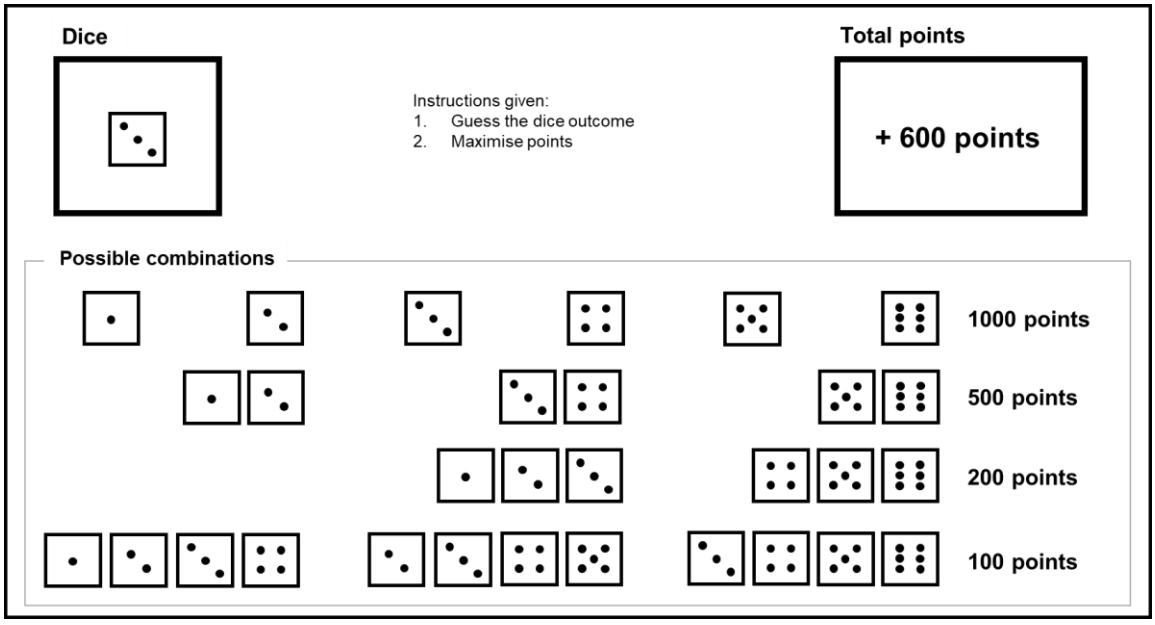


Figure 4. A schematic of the Game of Dice task (GDT) where participants must guess the outcome of a single die roll, then bet on the outcome to maximise their points.

Less universal tasks have also investigated DM in HD. For example, Heim and colleagues used the beads task to investigate information gathering in DM in premanifest, manifest HD and control participants. Information gathering relies on the goal-directed DM network (Furl & Averbeck, 2011). The authors found that HD patients gathered the least information, followed by premanifest close-to-onset, and that premanifest far-from-onset performed comparably to controls. This was interpreted as a tendency to jump to conclusions in later stage disease, although the number of incorrect decisions did not differ between groups (Heim et al., 2020). Similar to the previous tasks, this result

suggests that the goal-directed regions are compromised before overt motor onset in premanifest gene carriers.

1.4 Conclusions about general decision-making in Huntington's disease

Few studies have investigated DM in HD and those that have, have used low-level cognitive tasks with conflicting results. This does not reflect the more advanced state of research into DM, where neuroeconomics has united psychology, neuroscience and economics (Glimcher, 2011; Rangel et al., 2008; Sanfey et al., 2006), and grown to build integrated and clinically useful computational models of DM (for example, Konova et al., 2020). There appears to be impaired goal-directed DM in manifest HD patients but this is not consistently found in premanifest individuals. Habitual DM has not been measured in either group.

DM studies in HD patients over the last two decades have nevertheless provided us with several useful conclusions. First, patients have increased response time (RT) in decision tasks. Premanifest gene carriers close to estimated disease onset respond slower in reward and punishment conditions than controls, and premanifest patients far from onset respond slightly slower than controls (Enzi et al., 2012; Galvez et al., 2017; Vaportzis et al., 2015). Importantly, Watkins and colleagues found that manifest HD patients were slower in the CGT but this was accounted for by psychomotor slowing and not decision information processing per se (Watkins et al., 2000). Conversely, Enzi and colleagues incorporated "no outcome" trials which might be considered a substitute for the measurement of psychomotor slowing and motor impairment. They found no RT differences in these trials, while slower times were observed for the 'reward' and 'punishment' trials in the HD-close to-onset group, versus controls (Enzi et al., 2012). These results suggest that it is essential to consider psychomotor slowing and motor impairment when RT is an outcome of interest.

Second, HD patients make rational choices in accordance with expected value. Patients chose the most likely option just as often as controls in the CGT (Galvez et al., 2017; Watkins et al., 2000). In a novel gambling task with explicitly stated probabilities and gain or loss amounts, patients and controls displayed no difference in choice patterns: all accepted a similar proportion of positive expected value gambles and rejected negative

expected value gambles (Minati et al., 2011). This conclusion applies to both premanifest and manifest HD patient groups.

Third, patients can understand the decision tasks given to them. In the most simplistic levels of cognitive tasks, Watkins and colleagues found no comprehension impairments (Watkins et al., 2000), and in the CGT, a similar response to controls in the ascending condition suggests that patients understood the task (Galvez et al., 2017). In the control condition of a gain and loss task, no RT or performance differences were observed between patients and controls, which also suggests they understood the task (Minati et al., 2011). In a moral behaviour questionnaire, a correlation between similar items in individual HD patients and controls was observed which suggests that participants made similar interpretations (Eddy & Rickards, 2012). In spite of this, it is important to confirm understanding prior to the administration of any task, and also to be clear that understanding an experimental paradigm does not necessarily equate to understanding in real-life situations.

Furthermore, when performance impairments were present in HD groups, they were measured at easier levels compared to controls, but as difficulty increased, control performance also suffered. For example, in a task that required planning movement sequences, performance was comparable for simple one- or two-step problems. However, patient error rates were significantly higher when they processed three or four pieces of information. By the five-step problem stage, the group difference was lost as control performance declined (Watkins et al., 2000). Similarly, Vaportzis and colleagues found that HD patients were impaired in the harder levels of simple choice and digit-span forward tasks whilst controls were not. Once again, when the task got harder still (complex choice and the digit-span backwards tasks), the group differences were lost. The authors concluded that although HD patients' performance had suffered in an easier single task level, they could incorporate the most difficult task without further reductions in their accuracy (Vaportzis et al., 2015). It should be noted, however, that the observed convergence of results in difficult task levels may be due to floor effects.

Next, there is no conclusive evidence of altered patient sensitivity to rewards because previous studies present conflicting conclusions. Through measurement of skin conductance response (SCR), one study found that HD patients felt reduced impact of loss (Campbell et al., 2004). Similarly, a review proposed that HD patients are unresponsive toward rewards and losses, even more so than pathological gamblers (Kalkhoven et al., 2014). On the other hand, Van Wouwe and colleagues did not see

reduced sensitivity to losses, but rather found that patients were biased toward the high risk/high reward selections in comparison to controls (van Wouwe et al., 2016). Interestingly, when simple gambling choices were modelled, there were no differences in the value curves generated between HD patients and controls. This suggests that patients were not valuing the choices differently than controls in either the loss or gain domains (Minati et al., 2011).

Finally, it is not clear whether HD patients make more risky decisions than matched healthy controls. Past studies agree that premanifest gene carriers do not have an increased tendency to take risks (Adjeroud et al., 2017; Galvez et al., 2017; Holl et al., 2013). Two separate studies similarly found that manifest patients were no more inclined to seek risk either (Adjeroud et al., 2017; Campbell et al., 2004), however, two other studies concluded the opposite (Stout et al., 2001; van Wouwe et al., 2016). Kalkhoven and colleagues suggested a possible reconciliation of these findings: manifest HD patients do not have an increased tendency to take risks, but once risky behaviour is rewarded, they tend to respond by making more risky decisions than controls (Kalkhoven et al., 2014). This poses the question whether the impaired decision behaviour in manifest HD is in fact a reward dysfunction, despite other studies failing to find conclusive evidence for this (see paragraph above).

In conclusion, it appears that goal-directed DM is affected in HD gene carriers but it is difficult to draw useful and absolute conclusions from the existing literature, which is, at times, contradictory. It is a challenge to conduct cognitive research in HD due to its progressive nature and heterogeneity, despite its monogenic cause. It is difficult to recruit large enough cohorts to overcome this (Vaportzis et al., 2015), or to implement a strict study design to control for relevant variables (for example, the effects of psychomotor slowing or motor impairment) and draw clear conclusions. Furthermore, clinical groups are susceptible to selection biases, for example, where individuals might be more motivated to perform well or only the most able individuals participate (Hernán et al., 2004).

1.5 Advancing decision-making research in Huntington's disease with dual-process models

In this thesis, I approached DM from a perspective not considered previously. Early neurodegeneration in HD occurs in regions that are required to make goal-directed and habitual decisions and these processes have previously been likened to the rational and intuitive processing of decision variables, respectively. Dual-process models such as these have not been investigated in HD, but have their roots and applications across psychology, neuroscience and economics. They generally recognise two types of cognitive processes, reflective and impulsive, as separate yet interdependent drivers of DM (Bechara, 2005; Damasio, 1994; De Martino et al., 2006; Strack & Deutsch, 2004). The Chapters that follow begin to quantify rational and intuitive processing behaviour across the lifespan and in HD gene carriers to understand whether impairments in either process are responsible for the anecdotal and empirical DM problems reported in HD.

1.6 Rational-intuitive decision-making

An optimal decision is one which produces the outcome with the greatest utility. However, humans do not make consistently optimal decisions. Limited by processing speed and faced with complex decision environments, human cognition is influenced by biases and intuitions that streamline the many decisions we make daily, but this can sometimes serve to undermine our DM capabilities (Kahneman & Tversky, 1982). Imperfect information and time constraints can further reduce our capacity to make optimal decisions. For example, we can quickly dispose of junk mail and retain bills without carefully studying our post, to our obvious benefit. However, when faced with other, apparently simple decisions, we can arrive at the wrong answer, for example, clicking on an email link to fall victim to a scam. A common method to test these flaws of intuition is called the Cognitive Reflection Test (CRT), for example: "A bat and a ball cost £1.10. The bat costs £1.00 more than the ball. How much does the ball cost?" (Frederick, 2005). The intuitive response is to answer, "10p" when in fact the answer is 5p. The correct answer can be calculated after some deliberation. It is deliberation, or rationalisation of choice variables and outcomes that can lead to optimal DM, although the contextual cues which drive intuitive processing also confer an advantage in real-life DM.

Intuitive decisions are autonomous and habitual; driven by stimulus-action associations, they tend to be fast with a light load on central processing but also error-prone (Evans & Stanovich, 2013). Incorrect information processed intuitively can lead to "reverse cascades", or impaired early decisions down the wrong path (Sgroi, 2003), but intuitive heuristics also provide a more realistic application of mental resources in the real world and regularly perform comparably to complex rational processing (Todd & Gigerenzer, 2000).

Rational decisions involve serial processing and deliberation of alternatives, and thus are slower and require more cognitive effort than intuitive processes. A rational DM process can result in consistent choices in noisy environments. Cognitive ability is required to some extent, but so is a disposition to be open-minded and diligent during DM (Stanovich, 2011). It is not clear whether these are two entirely separate processing systems, or, more likely, there exists quasi-rational processing in between (Dhami & Thomson, 2012).

These descriptions are still useful however, as understanding how individuals and groups use intuitive and rational processes has led to more accurate predictions of choice and response time (Trueblood, 2013) and to interventions (or 'nudges') that support optimal and autonomous DM (Service et al., 2014). For example, by implementing opt-out rather than opt-in pension schemes, the cognitive effort to save for a pension was lessened which resulted in a participation rate increase from 61% to 83% in a UK study. Nudges are interventions which alter behaviour in a predictable way to reduce irrational DM, without mandating or forbidding any options, and they have been implemented across many contexts (Hausman & Welch, 2009; Thaler & Sunstein, 2008). Applied to HD, it might be possible to characterise decision behaviour by understanding if and how rational and intuitive DM are different in gene carriers. Furthermore, interventions based on the rational-intuitive paradigm might benefit gene-carriers' DM.

1.7 Present research

In this thesis, tasks which distinguish component DM processes were employed: evidence accumulation, metacognitive efficiency, integration of decision attributes, and choice mechanisms. The rational-intuitive paradigm was then applied to interpret the latent processes. To date no tasks in the HD DM literature have investigated this, nor are any sufficiently life-like while also retaining a high degree of experimental control and

being appropriate for both patients and controls. To this end, a new task was developed to investigate some aspects of deliberation and consistency using single and multi-attribute choices. To validate this task and ensure the component processes were well-understood, a carefully selected group of auxiliary tasks were used in conjunction. Finally, and based on the findings of four clinical studies, two interventions were designed and tested to address DM impairments, one pharmacological and one app-based.

1.8 Objectives

The purpose of this research project is to contribute a better understanding of DM in HD by building from known neurobiology which overlaps with HD pathology, from the conclusions and gaps in prior HD DM research, and by integrating advances in DM research from other fields. In doing so, this research also aims to explore the effects of subtle cognitive decline on DM and ways to improve DM in affected individuals.

2 IMPAIRED PERCEPTUAL DECISION-MAKING PRECEDES THE CLINICAL DIAGNOSIS OF MANIFEST HUNTINGTON'S DISEASE

2.1 Summary

To perform well in cognitive tasks, we must integrate perceptual evidence and reflect accurately on our performance. HD is associated with heterogeneous impairments in a range of cognitive tasks. However, the cognitive mechanisms which underlie these are poorly understood. In this study, perceptual DM and metacognitive insight were separately tested in patients with pre- and early-manifest HD, and age- and sex-matched controls. Behavioural data were analysed with a hierarchical drift diffusion model and a Bayesian model of participants' trial-by-trial confidence ratings as insight into their perceptual performance.

To achieve equivalent perceptual performance to controls, pre- and early-manifest gene carriers required significantly increased stimulus strength. Models revealed that in response to increasing stimulus strength, when evidence should be accumulated more quickly, pre- and early-manifest individuals had reduced evidence accumulation rates compared to the control group. Premanifest individuals also had significantly narrower decision thresholds than controls, which were narrower still in manifest HD. Hierarchical Bayesian estimation of metacognitive efficiency showed that despite marked perceptual differences, HD gene carriers retained metacognitive insight into their performance comparably to controls. This suggests that perceptual DM deficits appear early in the disease course (prior to clinical diagnosis) but are separate to unimpaired metacognitive insight. This may explain some of the earliest problems reported by patients, could be used to predict disease onset, and intact metacognitive insight could be

exploited as a therapeutic tool to improve quality of life following a genetic diagnosis of HD.

2.2 Introduction

Premanifest HD gene-carriers can experience a range of cognitive and psychiatric issues which become more apparent with manifest disease, including impairments in executive cognition (planning, reasoning, working memory and attention; Ho, Sahakian, Brown, Barker, Hodges, Ané, et al., 2003), psychomotor processing speed, visuospatial function and emotion recognition (McColgan & Tabrizi, 2018). These abilities are measured with cognitive tasks which, at their simplest, require participants to perceive a stimulus and execute a decision. Repeated trials often require participants to reflect on the accuracy of their previous decisions, an ability also called metacognitive insight. Despite the roles of perception and metacognitive insight in many of the cognitive domains we use to define disease stage, they have not been explicitly tested in HD.

2.2.1 Perceptual decision-making and metacognition in Huntington's disease to date

Perceptual DM refers to making decisions about a percept (from a limited set of possible options). For example, deciding if a piece of fruit is ripe or not. This requires evaluating the available sensory evidence and executing a decision. This is a fundamental requirement of many daily activities and is captured by various neuropsychological tests (Coppen et al., 2019), because these often involve the interpretation of a percept and then some response. As such, any problems in perceptual DM could underlie several of the cognitive impairments reported in HD (Ding & Gold, 2013; O'Callaghan et al., 2017).

A second essential aspect of effective DM is the ability to accurately reflect on decisions we have already made. This is referred to as metacognitive insight. Since all humans are challenged by imperfect perception and recollection, we use confidence to determine the credit to weight an information source and regulate perceptual evidence accumulation (Balsdon et al., 2020). In HD, poor awareness of deficits is evidenced by a divergence between the reports of patients and carers (Bertrand et al., 2016) and patients typically underestimate their impairments when asked to explicitly reflect on them (Ho et al., 2006). However, studies such as these which rely on self-reports are subject to confounding influences such as response bias (e.g. optimism), personality traits (e.g. anxiety) and temporary psychological states (e.g. stress). Metacognitive insight can be

quantified experimentally by measuring the calibration of confidence judgements to objective perceptual performance. This local trial-by-trial insight is different to the global metacognitive insight assessed previously in HD and less affected by confounders.

Local metacognitive insight in the healthy population is associated with brain regions affected in HD gene-carriers. During metacognition, there is increased anterior and medial prefrontal cortex activity (David et al., 2012; Fleming et al., 2014; Yuki et al., 2019) and myelination alterations in the hippocampus and prefrontal cortex are related to metacognitive ability (Allen et al., 2017). Beginning in the premanifest stage of HD, there is grey matter loss in the prefrontal cortex (Lambrecq et al., 2013) and hippocampal dysfunction is reported with late premanifest and manifest disease (Begeti et al., 2016).

2.2.2 The present study

We sought to investigate perceptual decision making and metacognitive insight in HD. Perceptual DM performance and metacognitive insight into that performance are inextricably linked in typical testing settings. In this study, we used an established paradigm to separately test these functions in premanifest and early-manifest HD, and in age- and sex-matched healthy controls. Perceptual DM performance across participants was matched with a procedure that adjusted the stimulus strength (evidence in favour of the correct choice) on each trial. We hypothesised that HD gene carriers would show impairments in perceptual DM, characterised by a decoupling of evidence accumulation rate with the clarity of evidence presented. In addition, we predicted that this would be compounded by reduced metacognitive efficiency and that both of these impairments would be significantly greater in those with early-manifest disease.

2.3 Methods

2.3.1 Participants

Sixty-three participants completed this study (14 patients with early-manifest HD, 20 premanifest gene carriers and 29 healthy controls). All HD gene carriers had a genetically confirmed diagnosis (CAG $\geq$ 36). Patients were defined as having early-manifest disease when they had a Unified Huntington's Disease Rating Scale total motor

score (UHDRS TMS) > 5 (Huntington Study Group, 1996). The groups were matched for age and sex. Inclusion criteria were Mini Mental State Examination (MMSE) score > 26 (normal range) and UHDRS initiation and saccade velocity total scores less than or equal to 1 (indicating minimal impairment in one domain only, maximum possible score is 16). Therefore, all included participants with gene-positive HD had no global cognitive or saccadic impairments as detected during examination by an experienced Consultant Neurologist, Dr Roger Barker. Exclusion criteria were any significant comorbid psychiatric or neurological diagnoses. Participants with HD were recruited from the HD Clinic at the University of Cambridge and Cambridge Universities Hospitals NHS Trust. Controls were recruited from the local community. All participants gave prior written informed consent. This study was approved by the Oxford South Central-C Research Ethics Committee (19/SC/0153) and the Medical Health Research Authority in the United Kingdom.

2.3.2 Stimuli and Procedure

We employed a task previously used to separately assess perceptual DM and metacognition in clinical groups (Fleming et al., 2014), implemented in MATLAB (Mathworks) and Psychtoolbox (Brainard, 1997). The code used to run the task, 'Metadots', is available online (https://github.com/metacoglab/meta_dots, last accessed 21/03/2021). Participants were required to make an alternative forced choice judgement about which of two briefly presented (0.7s) circles contained more dots, for which there was no RT limit. One of the two circles contained 50 dots while the other circle contained a number of dots bounded between 1 and 100. On each trial, this was immediately followed by a confidence rating which had to be made within 4s of the confidence scale being shown. All stimuli were high contrast (white on black, Figure 5). A one-up two-down staircase procedure equated performance across participants based on response accuracy by manipulating the stimulus strength (specifically, the absolute difference in the number of dots between the two circles: Δ dots) such that performance was constant at around 71% accuracy (Figure 7A). The staircase procedure was initiated during a practice phase which provided feedback on decision accuracy. Feedback to the participant was not given after the practice. Importantly, equating performance in this way could limit the range of dot differences (stimuli strength) seen by each participant which might subsequently alter the parameter values computed by our computational model. To normalise the ranges of dot differences, Z-scores were calculated in a within-subject manner to represent the distributions of stimulus strength that each participant saw across

200 trials. All participants completed the MMSE and the National Adult Reading Test (NART), which was used to calculate predicted verbal IQ (VIQ).

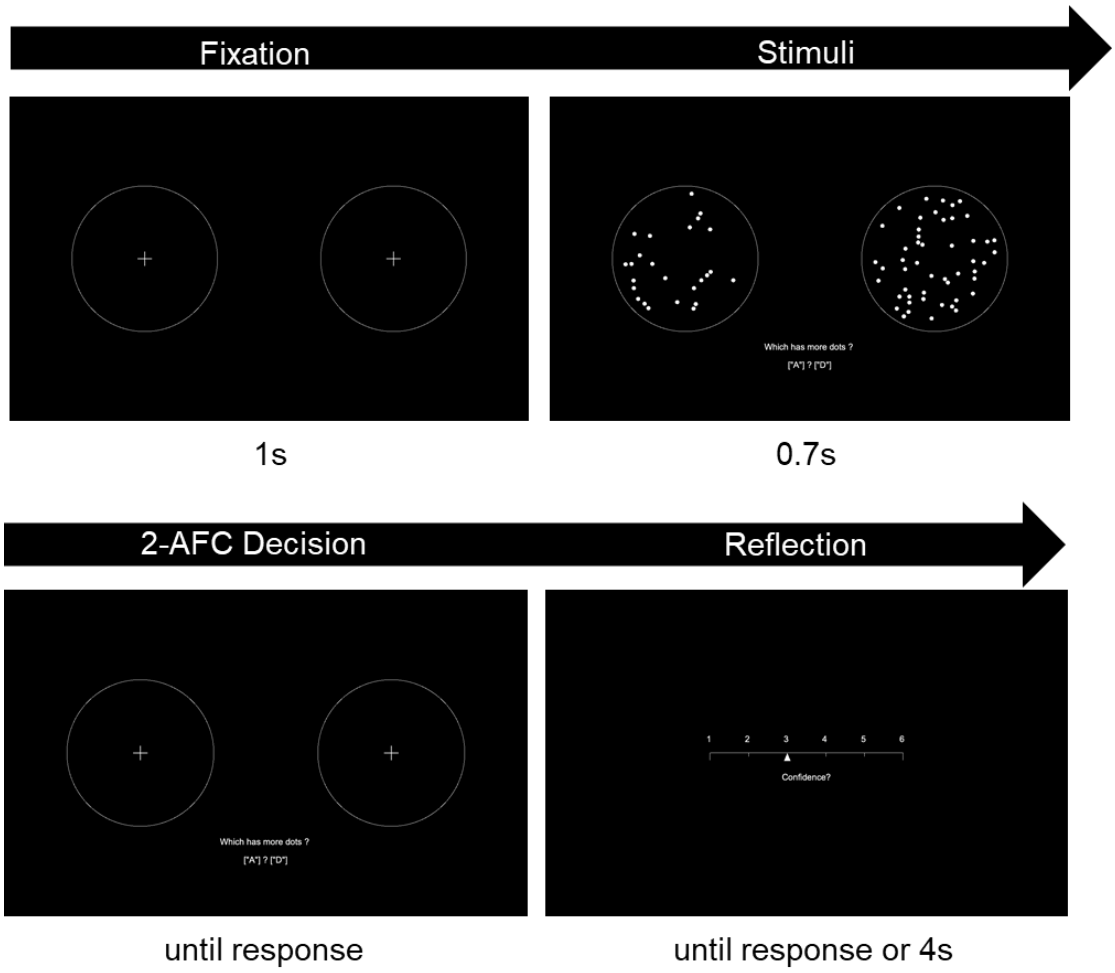


Figure 5. Meta-dots task. Participants are required to make an alternative forced choice judgement about which of the two stimuli (circles) contain more dots. The stimuli are presented for 0.7 seconds. This is immediately followed by a confidence rating to which participants have 4 seconds to respond. Figure adapted from Fleming et al., 2014.

2.3.3 Computation modelling of perceptual decision-making

The hierarchical Bayesian drift diffusion model (HDDM) (Wiecki et al., 2013) was used to understand how differences in behaviour might arise by estimating independent latent components of the DM processes (Figure 6). The model simulates two-alternative forced choices as a noisy process of evidence accumulation through time, where sensory information is presented and the participant determines whether this information provides evidence for either choice (Frank et al., 2015). Group-level

parameters are estimated on the basis of behavioural data (RT and choice accuracy), under the assumption that participants within a group are similar, but not identical, to each other. Parameter estimates are therefore constrained by group-level distributions. The rate of evidence accumulation is determined by the drift rate (v) parameter. Higher drift rates are related to faster and more accurate choices. A choice is made once the evidence reaches a decision boundary (a), which indicates the information threshold required to commit to a decision and is related to response caution, with higher threshold indicating slower, more accurate choices. A third parameter, bias (z) indicates a starting point likelihood towards one boundary. The final parameter estimated was non-decision time (t), which captures decision-independent processing time.

HDDM is particularly well suited for clinical research studies because it is able to capture sources of uncertainty in the data (e.g., small group size and heterogeneous group features) in the form of posterior probability distributions of the parameter estimates. This analysis was implemented in the openly available HDDM python toolbox (v0.8.0).

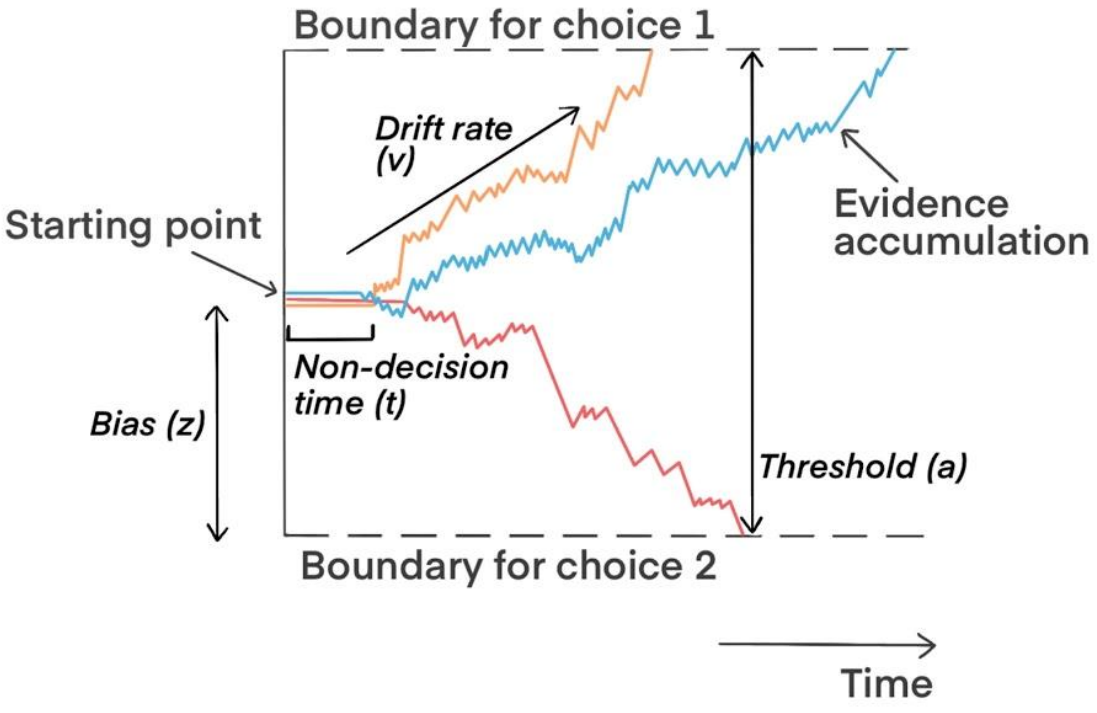


Figure 6. The drift diffusion model was used to understand a decision between two choices as a noisy process of evidence accumulation through time. This schematic shows representative examples and not real data. Figure adapted from Wiecki, Sofer and Frank (2013).

2.3.4 Computational modelling of metacognition

We used metacognitive efficiency (M-ratio) to compare metacognition across premanifest HD, early manifest-HD and healthy controls. M-ratio is an established marker of metacognition based on signal detection theory (Fleming, 2017; Fleming & Lau, 2014). Signal detection theory recognises that human DM occurs with a background of uncertainty and therefore measures a person's sensitivity to signal versus noise by comparing their response to the objective stimulus. Intuitively, it measures how likely a person is to detect a pattern in noise. It is a unitless measure that is not affected by bias (individuals favouring a particular response) and can be compared across different people and situations.

M-ratio describes how much of the available signal (a participant's perceptual sensitivity, d') is captured by their confidence ratings. Specifically, M-ratio is the ratio between metacognitive sensitivity (meta-d') and perceptual sensitivity (d'), where perfect sensitivity to perceptual performance would generate an M-ratio of 1. As such, this method controls for differences in perceptual ability as well as response biases (e.g. repeated responses at particular points on the confidence scale), and for this reason is best suited to compare metacognition across clinical groups. A M-ratio <1 indicates that some degree of noise or imprecision has influenced an individual's confidence rating such that the individual does not exploit all the available perceptual signal for their metacognitive judgement. A M-ratio >1 implies that the individual is able to draw on additional information about themselves or the task (beyond the available perceptual signal) when reporting confidence (Fleming & Daw, 2017).

M-ratio was estimated with a hierarchical modelling approach implemented in an openly available MATLAB toolbox (HMeta-d, (Fleming, 2017)). This toolbox is a Bayesian extension of the original metacognitive efficiency model (Maniscalco & Lau, 2012). Similar to the HDDM, it provides robust parameter estimates in the face of uncertainty inherent in clinical groups of small sample size and relative heterogeneity. This method also provides information about the uncertainty of the M-ratio estimates both within individuals and in the form of posterior distributions at the group level (Fleming, 2017).

2.3.5 Data management

Clinical data were collected and managed using REDCap electronic data capture tools (Harris et al., 2009, 2019) and person-identifiable information (PID) was held on the secure data hosting service (SDHS), both hosted at The University of Cambridge.

2.3.6 Statistical power

Our hypotheses addressed both differences in perception and metacognition between three independent groups. This study was powered *a priori* to detect a difference in perception based on O'Donnell and colleagues who found deficits on a similar two alternative forced choice task in a small sample of HD gene carriers. Since effect size was not reported, G*Power software 3.1.9 (Faul et al., 2007) was used to estimate the effect size (Cohen's $f = 0.44$, $\alpha = 0.05$, two-tailed) based on reported means (O'Donnell et al., 2003). This showed that a total sample size of 54 was required to achieve power of 0.8.

There are no published findings on metacognitive efficiency in HD. We confirmed *a priori* that the above sample size estimate was also sufficient to detect a difference in metacognition based on the effect size obtained by Fleming and colleagues (2014). This study detected differences in metacognitive efficiency across two clinical groups and controls using the same Metadots task. We estimated the effect size (Cohen's $f = 0.53$, $\alpha = 0.05$, two-tailed) based on reported means. This revealed that a total sample size of 39 was required to achieve power of 0.8.

2.4 Results

2.4.1 Participant demographics

Five participants were excluded prior to the analysis; four early-manifest HD patients due to saccadic impairment and one individual with premanifest HD was excluded due to a technical error while they completed the task. Included participants (N=58) were well-matched for age and sex across the groups (Table 2). All participants had MMSE scores in the normal range, but the early-manifest HD group had lower scores ($H(2)=10.5$, $p=0.005$). Premorbid VIQ was also significantly different between the groups ($F(2, 54)=5.2$, $p=0.009$). However, since all patients fell within the normal ranges, differences in VIQ or MMSE were not considered to be of clinical significance. The

premanifest group had lower UHDRS TMS and TFC scores than early-manifest HD patients, as expected. Three of the early manifest patients and one premanifest gene carrier were taking low-dose dopamine antagonists (all Olanzapine, 2.5-5mg/day).

Table 2. Participant demographics. Groups were matched for age and sex. Groups had clinically normal, yet statistically different general cognitive and verbal IQ scores. The premanifest and early-manifest patients were different in their UHDRS motor scores and functional capacity, as expected. Abbreviations: MMSE = Mini-Mental State Examination; UHDRS = Unified Huntington's Disease Rating Scale; TFC = Total Functional Capacity. *One premanifest individual had an unusually high motor score (12) due to an unrelated hand injury; all other premanifest gene-carriers had scores <5. **One premanifest individual did not complete the National Adult Reading Test for verbal IQ.

	Premanifest HD (N=19)	**Early-manifest HD (N=10)**	**Control (N=29)**	**Test Statistic**	**p-value**
Age				1.5	**0.226 (1)**
- Mean	47.8	55.9	51.6		
- Range	28.7 - 75.4	37.2 - 67.0	29.3 - 73.4		
Sex, Female	11 (57.9%)	7 (70.0%)	12 (41.4%)	2.9	**0.238 (2)**
MMSE				10.5	**0.005 (3)**
- Mean	29.7	28.6	29.7		
- Range	28.0 - 30.0	26.0 - 30.0	28.0 - 30.0		
Premorbid Verbal IQ				5.2	**0.009 (1)**
- Mean	113.5**	111.6	118.1		
- Range	100.0 - 127.0	104.0 - 124.0	107.0 - 127.0		
UHDRS Motor				4	**<0.001(4)**
- Mean	2.3	14.7	-		
- Range	0.0 - 12.0*	6.0 - 26.0	-		
TFC				164	**<0.001(4)**
- Mean	12.8	11.4	-		
- Range	**11.0 - 13.0**	**10.0 - 13.0**	**-**		

1. Linear Model ANOVA
2. Pearson's Chi-squared test
3. Kruskal-Wallis one way ANOVA
4. Mann-Whitney U Rank Sum test

2.4.2 Behavioural analysis

To assess behavioural performance, we compared mean accuracy (% correct), stimulus strength (Δ dots), RT and confidence ratings using one-way ANOVA or Kruskal-Wallis test as non-parametric equivalent. The staircase procedure successfully matched accuracy (% correct) across the groups *(H(*2, 55)=1.91, *p*=0.38, η^2_p=0.03; Figure 7A). The mean stimulus strength to achieve that performance however, differed significantly between the groups (*F*(2, 55)=13.85, *p*<0.001, η^2_p=0.33). Pairwise comparison showed that patients with early-manifest HD (mean=7.13± SEM=0.4, Bonferroni correction applied) completed the task with significantly greater stimulus strength (i.e. reduced difficulty level) compared with healthy controls (mean=5.68 ± SEM =0.29; 95% CIs of mean difference=1.25-3.53, adjusted *p*<0.001), and compared with the premanifest group (mean=4.74± SEM=0.23; 95% CIs of mean difference=0.24-2.67, adjusted *p*=0.014). Further, the premanifest group performed with a significantly greater stimulus strength than the control group (95% CIs of mean difference=0.02-1.86, adjusted *p*=0.043; Figure 7B). This showed that individuals with premanifest and early-manifest HD were impaired in making perceptual decisions compared to healthy controls. There were no significant differences in mean RT (*F*(2, 55)=2.03, p=0.14, η^2_p=0.07; Figure 7C) or confidence level across the groups (*F*(2, 55)=0.34, *p*=0.71, η^2_p=0.01; Figure 7D). This confirms that all participants were able to make the forced choice decision and use the confidence scale as instructed. Further, task accuracy was also matched across the groups throughout the entire experiment (data not shown). Specifically, there were no differences in accuracy across task blocks (*F*(7, 440)=0.59, *p*=0.77, η^2_p=0.01), and no interaction effect of group by block (*F*(14, 440)=1.02, *p*=0.43, η^2_p=0.03).

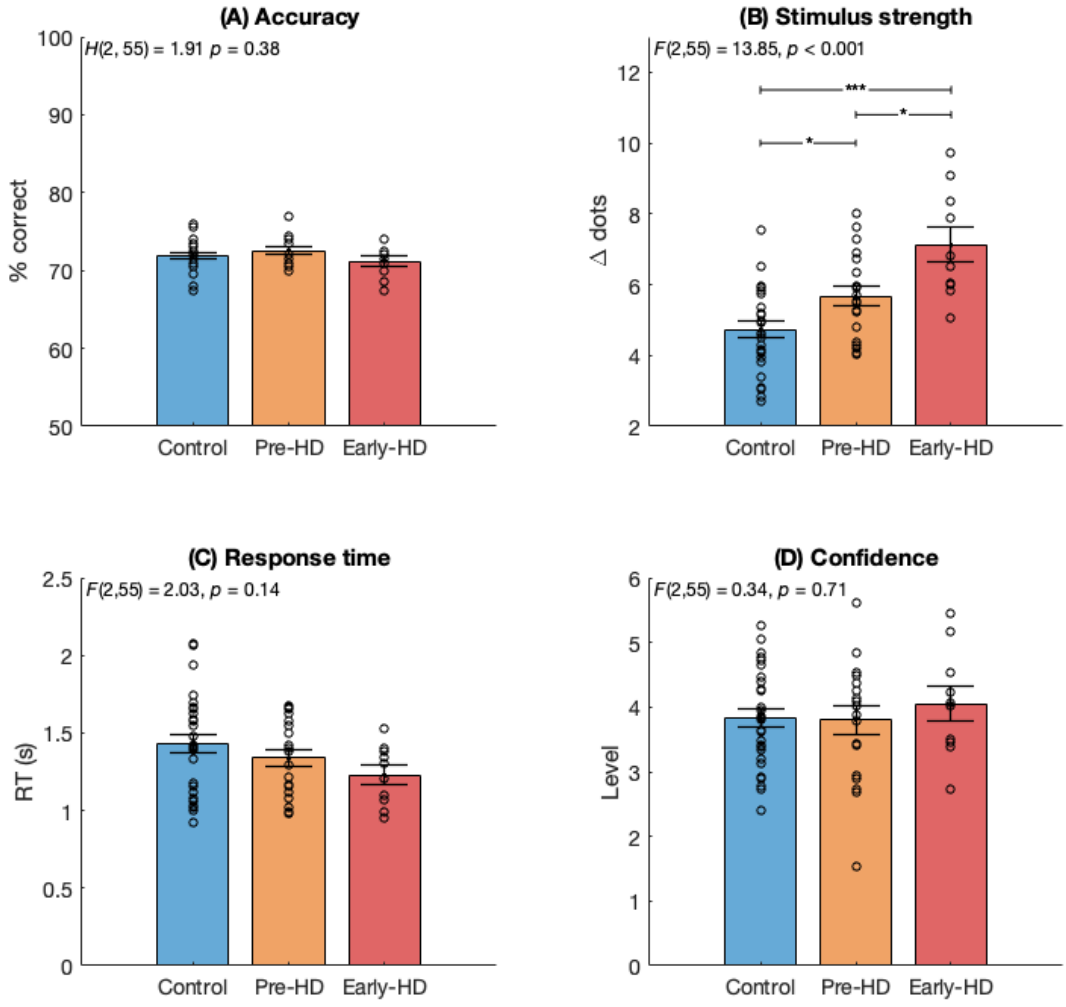


Figure 7. Accuracy was controlled across the groups by the staircase procedure such that all participants made the correct choice approximately 71% of the time (A). Stimulus strength (Δ dots) was significantly increased in the early-manifest group, compared with both groups, and also in the premanifest group compared to the control group (B). No significant difference in mean response time across the three groups (C). The trend of reduced reaction times in gene carriers is further explored using the HDDM. No significant difference in mean confidence level (D). Bar =mean ± SEM (errors). Circles = subject mean values. *Bonferroni corrected p value<0.05. ***Bonferroni corrected p value<0.001. Abbreviations: pre-HD=premanifest HD, early-HD=early-manifest HD.

2.4.3 Perceptual decision-making model-based analysis

To further investigate this behavioural impairment in HD patients, we used a hierarchical drift diffusion model (HDDM). Prior to entering the data into HDDM, trials with exceptionally early (<0.1s) or late (median+3 median absolute deviation) RTs were

excluded (n=686, 5.91%) according to best practice for RT data and HDDM parameter estimation (Hauser et al., 2017; Leys et al., 2013). Across the groups, there was no difference in the proportion of trials excluded and the proportion that would be expected given the relative sizes of the groups (Chi-square=0.04, p=0.98).

To determine the best-fitting model to our data, a number of regression models were implemented within HDDM, in which responses were coded as correct and incorrect choices, and drift rate was modulated by stimulus strength on every trial. This is because we explicitly manipulated trial-by-trial stimulus strength, and it is well established that this directly influences accumulation of evidence (Gold & Shadlen, 2007; Hauser et al., 2017; Ratcliff & McKoon, 2008). In order to test our hypothesis that patients with HD would show a decoupling between evidence accumulation rate and the evidence presented to them, Z-scores of stimulus strength within subjects were calculated, such that each participant had their own Z-score, reflecting the distribution of stimulus strength they were presented with. This allowed us to determine the relationship between drift rate in individuals carrying the HD gene, without the confounding influence of absolute differences in stimulus strength (Δ dots; Figure 7B). We did not estimate response bias because we explicitly controlled accuracy across participants, and there is no theoretical basis to expect bias toward a correct choice in this task (each trial is independent and the correct answer on a given trial is equally likely to be either option).

To address potential collinearity among parameters we fitted each model by estimating only group level posteriors for each regression coefficient, rather than for individual participants. Each regression model was sampled with 20,000 chains, and the first 1000 chains discarded to estimate each parameter distribution. The best fitting model was determined by comparing Deviance Information Criterion (DIC) and Bayesian Predictive Information Criterion (BPIC) for each model (lowest value indicated best fit). To assess group differences, all groups were entered into the same hierarchical model and group membership was used to predict differences in the parameters, as implemented in the regression. We assessed five regression models of increasing complexity in which:

1. Stimulus strength influenced drift rate directly
2. Group and stimulus strength influenced drift rate directly
3. Group and stimulus strength influenced drift rate directly, and their effect on drift rate interacted (i.e., group predicted how strongly stimulus strength influenced drift rate)

4. Group and stimulus strength had independent effects on drift rate (v) and their effects on drift rate interacted. Group also had a separate effect on decision threshold (a)
5. Group and stimulus strength effect on drift rate interacted and group had separate, direct effects on decision threshold and non-decision time

Both DIC and BPIC were lowest for model number 4. This model was characterised by a regression in which drift rate was modulated by group and stimulus strength, their interaction, and decision threshold was modulated by group:

$$v \sim Z_{\text{stimulus strength}} + \text{group} + (Z_{\text{stimulus strength}} * \text{group})$$

$$\alpha \sim \text{group}$$

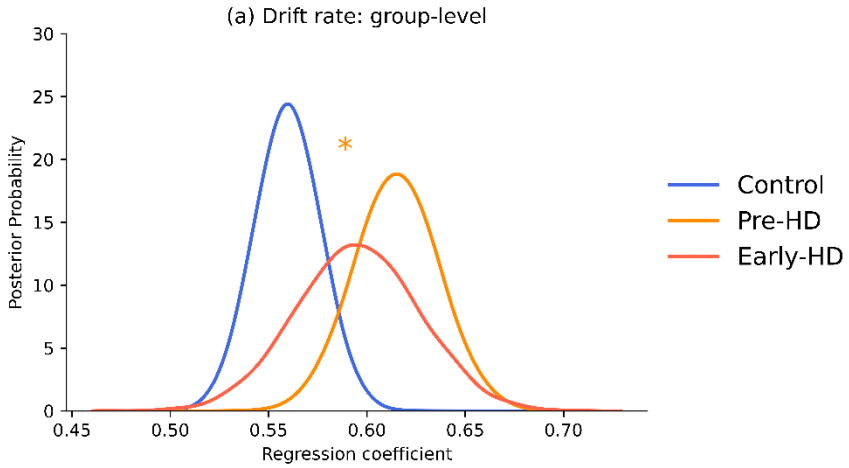
Prior to analysing the posterior distributions of this model, we confirmed its reproducibility by running four, independent models in parallel and computing the Rhat statistics on the resulting parameters. Rhat (or Gelman-Rubin) statistic is the ratio of the variance of each parameter when pooled together across the four models, to the within model variance. Therefore, Rhat quantifies the extent to which separate models reach different conclusions (Gelman et al., 2013). Model parameters demonstrated excellent convergence for all estimated parameters (mean=1.00003, range=0.99998-1.00015). Satisfied with this, we combined the chains of the four models and analysed the posterior distributions of the combined best-fitting model, which significantly increased the sample size for the parameter estimates (80,000 chains, initial 4000 discarded).

Next, Bayesian estimation was used to assess if meaningful differences existed in the parameter estimates of the combined model for pairwise group comparisons (Kruschke, 2013). The posterior distributions of each group were directly compared and the probability that the difference between the group distributions was in the opposite direction (to that indicated by the mean) was calculated. This is similar to a one-tailed t-test (the probability that the greater of two distributions was in fact smaller), where probability (P)<0.025 (one-tailed) was considered statistically significant.

At the group level (considering all trials equally), there was a significant increase in the drift rate parameter in the premanifest group (M=0.614, SD=0.021) compared with the control group (M=0.561, SD=0.016; P=0.022). Drift rate in the early-manifest group was not significantly reduced compared with the control group (M=0.595, SD=0.03, P=0.16) or the premanifest gene carriers (P=0.31; Figure 8A).

However, the group-level drift rate does not take into account differences in stimulus strength between the groups (Figure 7B). Consistent with our hypothesis, the interaction of group*$Z_{stimulus\ strength}$ revealed significant differences between both HD groups and the healthy controls. In controls (M=0.243, SD=0.016), the effect of increasing $Z_{stimulus\ strength}$ on drift rate was significantly greater than in the premanifest group (M=-0.015, SD=0.026; P<0.001), and the early-manifest group (M=0, SD=0.034; P<0.001). In other words, compared with both HD groups, healthy controls responded to relatively stronger evidence in favour of the correct decision by accumulating evidence toward that decision threshold more quickly. There was no significant difference between the premanifest and the early-manifest groups (P=0.34; Figure 8B), implying that this deficit emerges early and was stable between disease stages.

Comparing the decision threshold parameter, further significant differences between the groups were found. Patients with early-manifest HD adopted the lowest threshold (M=1.69, SD=0.018), which was significantly reduced compared to the premanifest gene carriers (M=1.89, SD=0.016, P<0.001) and the control group (M=1.99, SD=0.014, P<0.001). The threshold adopted by the premanifest group was also significantly reduced compared to the control group (P<0.001; Figure 8C). This meant that decision thresholds were consistently narrowed with increased disease status.



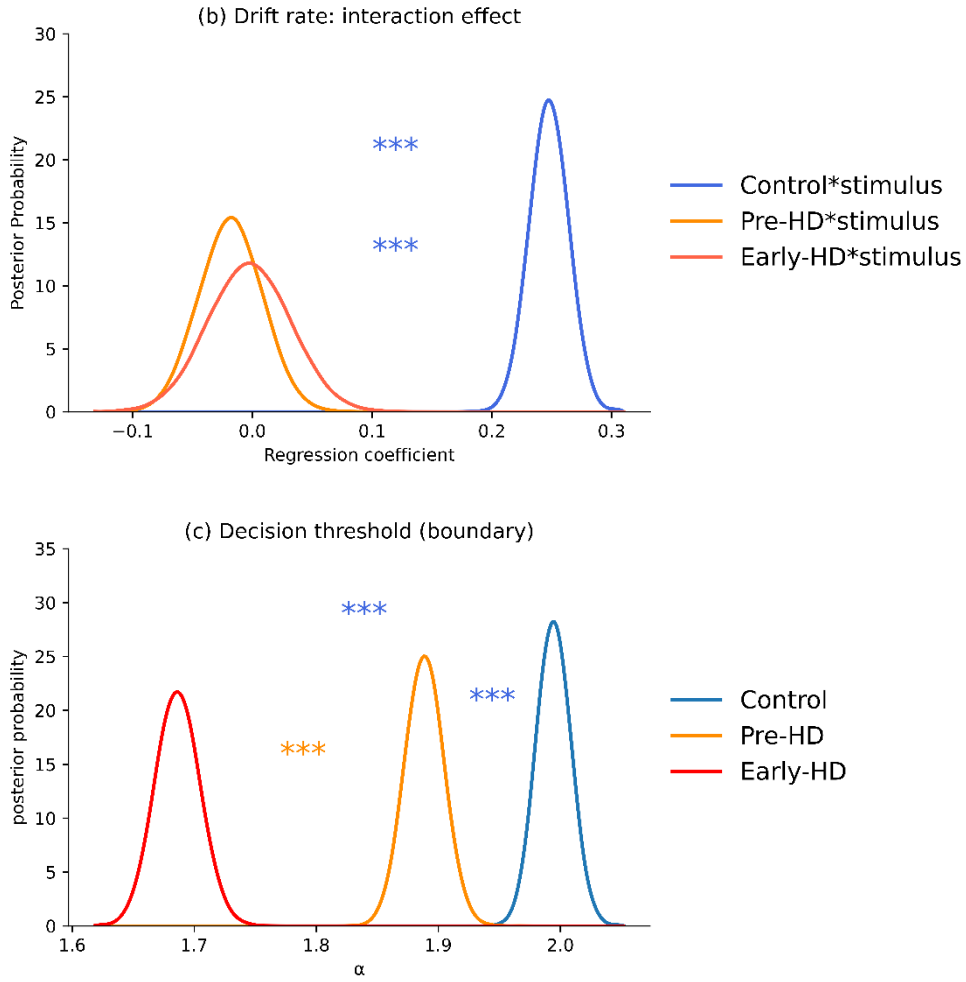


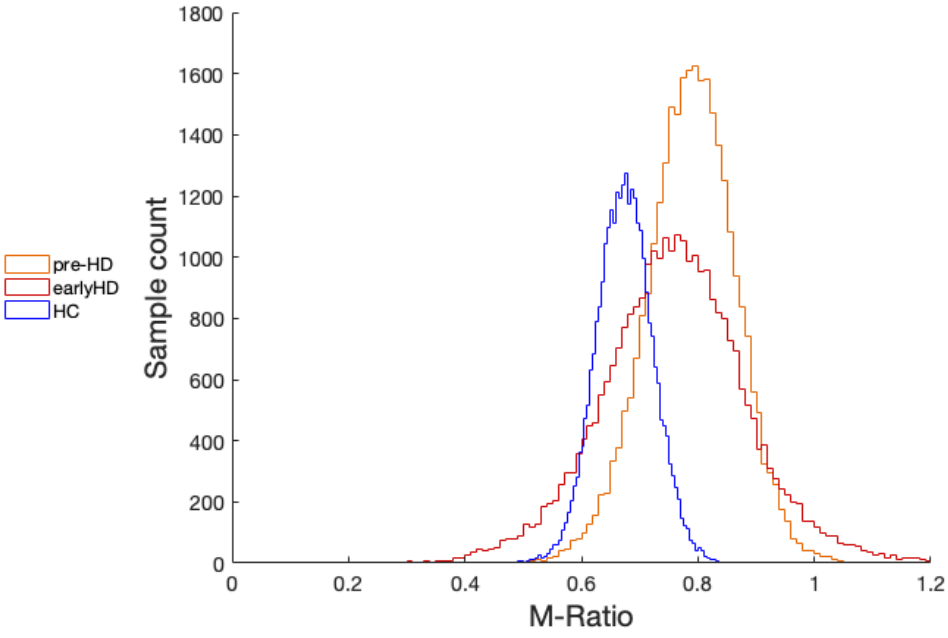
Figure 8. Posterior probability distributions from the HDDM regression model. Group level drift rates (A). Significant interaction between drift rate and stimulus strength (B): the effect of increasing $Z_{\text{stimulus strength}}$ on drift rate in both premanifest HD and early-manifest HD was significantly reduced compared with the control group. Significant reductions in decision boundary in with greater disease status (C). ****P*(one-tailed)<0.025. ******P*(one-tailed)<0.001. Further statistical values are reported in text. Asterisk colours indicate the significantly greater posterior distribution in pairwise comparisons.

2.4.4 Metacognition model-based analysis

To estimate metacognitive efficiency, we included all trials in which the participant provided a confidence rating within 4s (mean number of trials=196.45, mode=200). The mean trials with confidence ratings provided by each group did not significantly differ ($H(2, 55)=4.79$, $p=0.09$). The M-Ratio for each group was estimated separately and then the resulting posterior group distributions were compared. Ten thousand chains were sampled for each group posterior M-Ratio distribution. To assess significance in pairwise comparisons, the group comparison approach by Fleming (2014)

was followed. This is slightly different to that employed in the perceptual DM model. It involved calculating the difference between two distributions and comparing the overlap of the resulting difference distribution with 0, as well its 95% high density interval (HDI). Probability <0.05 (two-tailed) was considered statistically significant. This approach is similar to a frequentist statistical test; it assesses the probability that the difference between the groups is 0, and the 95% HDI are similar to confidence intervals.

There was no significant difference in M-Ratio between healthy controls (M=0.68) and premanifest HD gene carriers (M=0.82; *P*=0.1, 95% HDIs=-0.095-0.388). There was also no significant difference between the early-manifest HD gene carriers (M=0.79) and the control group (*P*=0.25, 95% HDIs=-0.282-0.475). Metacognitive efficiency (M-Ratio) was also not reduced with greater disease burden since early-manifest HD gene carriers did not significantly differ from premanifest group (*P*=0.59, 95% HDIs=-0.458-0.34; Figure 9). Similarities in metacognitive efficiency between the groups were not due to any differences in perceptual sensitivity as this was matched (*H*(2, 55)=0.86, *p*=0.65; Figure 7A).



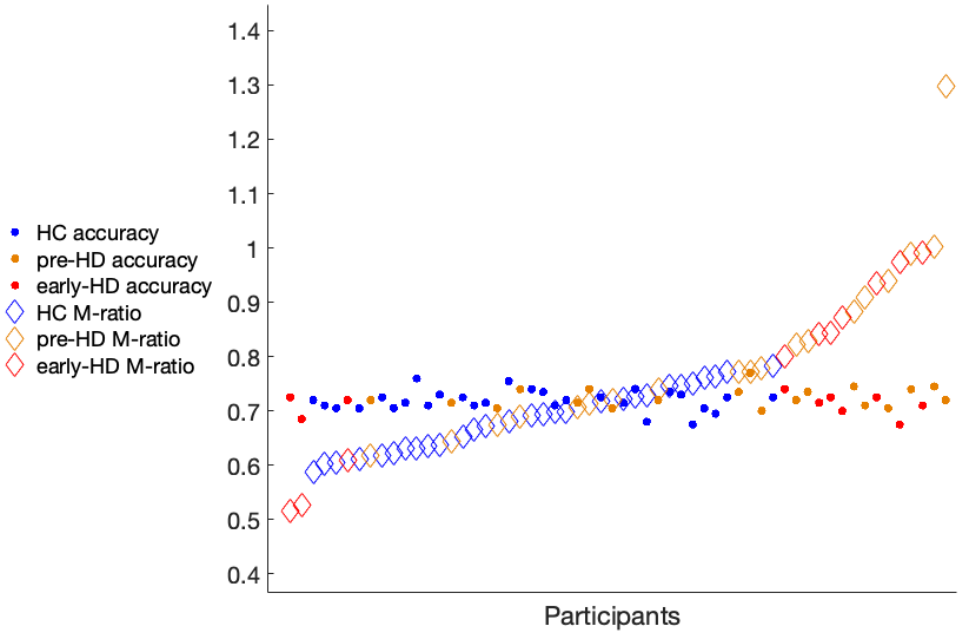


Figure 9. Despite marked perceptual accuracy differences there is significant overlap in the group M-Ratio distributions, indicating that gene carriers typically showed similar metacognitive performance to controls (top). Mean M-ratio and accuracy (proportion correct) of individual participants (bottom). These individual values are derived from a hierarchical model so they cannot be compared individually (they are not statistically independent). The inclusion of the outlier premanifest patient (with a particularly high M-Ratio) did not qualitatively or statistically affect the group posterior distribution for the premanifest group.

2.5 Discussion

We report for the first time that there is a deficit in perceptual DM in premanifest HD. This was increased in a group that had progressed to manifest disease, indicating it is a product of the disease process rather than a static genotype effect. After controlling for perceptual DM, we found that HD gene carriers (regardless of disease stage) had intact metacognitive insight; they were able to reflect on their perceptual performance with similar accuracy as healthy controls.

2.5.1 Perceptual decision-making

Perceptual DM in this task was independent of learning or memory because each trial was independent and responses were provided immediately. HD gene carriers needed

the task to be significantly easier to perform as well as controls. A computational approach identified two independent mechanisms behind this impairment.

1) Gene carriers were impaired in accumulating perceptual evidence

We explicitly manipulated the evidence (stimulus strength/task difficulty) on each trial in a within subject manner to match perceptual decision accuracy across participants. Previous studies have found that speed of evidence accumulation is tightly coupled to stimulus strength (Gold & Shadlen, 2007). We replicated this effect in our control group, in which increasing stimulus strength served to increase drift rate. However, the effect of increasing stimulus strength on drift rate in the premanifest and early-manifest groups was significantly reduced compared with the control group (Figure 8). This was not due to any differences in absolute stimulus strength across the groups which was accounted for by Z-scoring stimulus strength within each participant. In other words, as the objective evidence in favour of the correct choice became stronger (relative to each individual's mean), the evidence accumulation rate in premanifest and early-manifest HD gene carriers did not increase as it did in controls. One limitation of this conclusion is that by controlling task performance at 71% with a staircase procedure, we also limited the range of stimuli strengths seen by each participant. The calculation of within-subjects Z-scores goes some way to account for this contrived method, but there may still be a circularity such that those who saw a reduced range of dot differences also had a reduced range of drift rates across the 200 trials.

2) Gene carriers used a reduced threshold, requiring less evidence before deciding

Premanifest gene carriers adopted significantly narrower decision thresholds compared to the control group, which were further significantly reduced in early-manifest patients. The wider decision threshold adopted by our control group reflects a more cautious DM approach (Ratcliff & McKoon, 2008). We can infer that this was a superior strategy in the task because it was associated with performance at a significantly increased difficulty level.

Deficits in accumulating perceptual evidence which appear early in the disease course may interfere with performance on a range of higher order cognitive tasks (Ding & Gold, 2013). For example, the identification of ambiguous shapes and objects is affected in early-manifest patients (Coppen et al., 2019) and both premanifest and manifest gene carriers show impairments in the recognition of faces and emotions (Johnson et al., 2007; Kempnich et al., 2018; Martínez-Horta et al., 2020). Low-level

perceptual DM impairments may also contribute to behavioural DM deficits in gene carriers that are present prior to the onset of overt motor features (Duff et al., 2010), although this is speculative and should be investigated further.

Impulsive responses are commonly reported in HD gene carriers (Johnson et al., 2017). For example, response inhibition is impaired due to increased latency and variability of eye-movement saccades (Júlio et al., 2019; Lasker & Zee, 1997). One consideration is that impulsivity accounts for impaired perceptual DM by reducing decision thresholds and evidence accumulation rates. However, if this was sufficient to explain our data, we would also expect gene carriers to show significant reductions in RT, and impaired metacognition (impulsive confidence reports would be more stochastic and weakly exploit the available perceptual signal). By excluding gene carriers with saccadic delays and dissociating perceptual from metacognitive decisions, we show that perceptual DM deficits are likely independent of saccadic impairments and associated response impulsivity. However, it remains possible that gene carriers' impulsivity underlined their perceptual decisions, but they retained metacognitive awareness of this. Future studies should consider the compounding effects of saccadic, impulsivity and perceptual DM impairments as drivers of clinical impairments in gene carriers.

2.5.2 Metacognition

We hypothesised that metacognitive efficiency would be reduced in HD gene carriers but found no evidence to support this using our hierarchical modelling approach. This cannot be explained by differences in perception because we accounted for this by comparing the ratio between perceptual and metacognitive sensitivity (M-Ratio). The task design also matched perceptual DM performance across the groups in terms of choice accuracy (% correct) and perceptual sensitivity. Since M-Ratio quantifies metacognition in units of perceptual sensitivity it is meaningful to compare this to the optimal value of 1 and values obtained in comparable studies. Based on group means, the premanifest and early-manifest gene carriers utilised approximately 79% and 82% of the available perceptual signal for their metacognitive judgements respectively. This is similar to that achieved by a large online sample of healthy volunteers in the same task (84%; Rouault et al., 2018). However, we note that there was increased uncertainty in the M-Ratio for the early-manifest HD group; the posterior distribution is wider, with longer tails (Figure 9). This is likely due to the smaller sample size and heterogeneity of this group.

This finding of intact metacognitive efficiency contrasts with reports of anosognosia (loss of insight in a clinical population; Bertrand et al., 2016; Souchay, 2007) in some manifest patients with HD (Duff et al., 2010; Isaacs et al., 2020). However, studies which use self-report or questionnaires to estimate metacognition are vulnerable to biases in memory (e.g. recency effects), personality (e.g. openness) or response (e.g. often reporting low confidence), and any confounding cognitive (e.g. episodic memory) or psychiatric impairments (e.g. low mood). In this study, we excluded patients with marked functional or cognitive impairments. Therefore, metacognitive impairment may well develop as the condition evolves in patients with overt HD.

We quantified metacognition as insight into *perceptual* performance. Therefore, it is possible that changes to metacognition occur early in the disease course in other domains or in ways that we did not capture. For example, research into metamemory in Alzheimer's dementia has differentiated between local and global confidence, showing that local (i.e., trial-by-trial) metacognitive estimates are intact but global self-estimates such as self-efficacy and self-esteem are altered (Gallo et al., 2012).

HD gene carriers in this study may have achieved good metacognitive efficiency because they were vigilant to their DM performance, due to knowledge of their genetic status. In the clinic gene carriers and their families often report 'symptom hunting' (i.e. paying extra attention to detect functional changes), because they are anxious about the emergence and impact of symptoms. The selection bias in clinical studies where only the most able and motivated individuals participate may have further contributed to this (Hernán et al., 2004). Recent work has also shown that increasing CAG repeat lengths can be associated with advantageous brain structure (Lee et al., 2017), and improvements in cognitive performance, even in low pathological ranges for HD (Schultz et al., 2021).

2.5.3 General discussion

The combination of impaired first-order cognition (perception) but intact second-order cognition (metacognition) raises interesting questions for future studies. For example, in the general population, confidence and metacognition have been associated with reports of anxiety, depression, compulsive behaviour and intrusive thoughts (Rouault et al., 2018). An intuitive hypothesis is that metacognitive awareness of first-order cognitive deficits in premanifest HD may contribute to (and/or be driven by) the high levels of anxiety and depression in some patients (Epping et al., 2016; Julien et al., 2007). A recent feasibility study has shown that mindfulness-based cognitive therapy can

be beneficial to individuals with premanifest HD (Eccles et al., 2021). This suggests that exploiting intact metacognition might be a therapeutic tool to improve quality of life.

We did not include medication effects in our analyses. Dopamine is well-known to affect cognition (Cools & D'Esposito, 2011) and manifest HD patients are often prescribed dopamine antagonists to help with many of their disease features, but these can increase the rate of cognitive decline (Harris et al., 2020). No study has investigated the relationship between perceptual DM and long-term anti-dopaminergic medication in HD. However, only 4 of 29 gene carriers in this study were taking anti-dopaminergic medication, and all at low dose, so the pattern of deficits cannot be explained by this.

2.6 Conclusions

By dissociating perception and metacognition in HD, we show that perceptual DM impairments exist in patients without any other obvious symptoms or signs, but that metacognitive insight into DM remains intact, even in those who have progressed to manifest disease. Since perceptual DM is a cognitively demanding process, identifying important information and simplifying it - prior to perception - might benefit HD gene carriers.

Low-level perceptual issues may drive higher-order cognitive deficits that are widely described in the HD literature, and studies should take care to consider perceptual DM before ascribing impaired performance to higher-level cognitive processes. Clinical trials of disease modifying therapies in HD are increasingly targeting premanifest patients. The perceptual deficits shown in this group could be considered as potential behavioural biomarker in such trials, and provide insight into possible interventions to support declining cognition in HD.

3 Development and Testing of a New Cognitive Task to Measure Rational and Intuitive Processing

3.1 Summary

This Chapter describes the construction of a new cognitive task that measures aspects of rational and intuitive DM. Dual-process theory supports this account of DM, coined in the 1970s by psychologists Daniel Kahneman and Amos Tversky. Since then, this theory has been used to explain the poor choices people sometimes make, and support more optimal DM at an individual level. This paradigm has never been applied specifically to clinical groups of patients. A review of the literature made clear that the tests commonly used to understand when and how individuals make rational or intuitive decisions were not suitable for patients with cognitive or motor impairments, and to a lesser extent, to people of different ages, cultures and education levels. This Chapter covers the development of and motivation for the new task and iterative pilot testing. The final task uses a food choice context to measure how participants use choice attributes in their decisions, their choice consistency across repeated trials and decisions under time limitations. Subsequent Chapters go on to show that this task introduces formal choice-modelling in an ecologically valid context that is feasible for neurological patients. This is of major relevance, where interventions might be applied specifically in mild cognitive impairment or dementia, to support prolonged autonomy and independence, relieving the burden of care from family members, carers and the social care system.

3.2 Introduction

3.2.1 Rational-intuitive processing in decision-making

Rational-intuitive processing implies that we have two methods for making decisions: a conscious and deliberative one which requires thought and effort, and an intuitive method whereby decisions can be made quickly. The former method is more reliable but at the cost of time and effort to consider all potential consequences, it cannot be employed for every decision. The latter method allows us to move through a busy and engaging world based on past experiences and heuristics – rules of thumb – rather than a consequentialist analysis. The two processes interact and often run in parallel to create a quasi-rationality (Dhami & Thomson, 2012). At an individual level, a rational process might be employed to maintain a diet. An intuitive process might be used to buy coffee, and accompanied by the rational process of diet maintenance, you may be deterred from buying a slice of cake as well (Rangel et al., 2008).

Across populations there is a need to understand when and how people default to rational or intuitive processing in their DM. The following example was adapted from an article in *The Spectator* by Rory Sutherland (Sutherland, 2020). The coronavirus pandemic bought into contention the reliability of scientific evidence, a rational process that takes time. Thrust into unknowns, this deliberative process could not respond aptly. One example of this is the uptake of face masks in the West (where it was not previously a rule of thumb to wear one). The scientific method could not explicitly resolve the extent to which masks limit transmission. Some people deployed their intuitive judgement to assert their rights *not* to wear a mask, where others asserted the opposite. Sutherland concluded "An insistence on the scientific method has costs as well as benefits – it is slow and may reduce the solution to those actions you can easily quantify or justify in advance. There is, after all, good reason why humans have evolved decidedly unscientific instincts for decision-making: in the messy world we inhabit, the facts that are available are usually not important, and the facts that are important are usually not available." Both rational and intuitive processing are important but this example makes clear that each process must be applied in the right circumstance. A better understanding of how individuals and groups use rationality and intuition in their decisions is important to predict and support behaviour.

3.2.2 Theoretical need for a new cognitive task

A rational-intuitive DM paradigm could explain cognitive (and subsequent behavioural) impairments in HD patients. To the best of my knowledge, this has not been applied to understand or better treat the cognitive features seen in any neurodegenerative disease previously. Prior research into DM in HD has been not been done in depth and not focussed on gaining mechanistic understanding of choice, whereas DM research in the healthy population is relatively advanced (see Chapter 1). Anecdotal evidence from patients at the Cambridge HD Clinic suggests that patients struggle with intuitive choices. Simple and inconsequential decisions take much longer than they should. One patient, who had a job with responsibilities that required important consequential decisions to be made on a daily basis, reported that she spent a long time in the supermarket trying to choose between different types of biscuits. She recognised that it was silly and was frustrated by the time she had to spend deciding but couldn't help herself. What's more, there is also evidence to support rational processing impairments. Patients are susceptible to making rash decisions about large sums of money. For example, in the clinic I have met patients that have ordered 13 high-end watches online, bought aquariums from Amazon (but have no fish), transferred large sums of money to a fraudulent individual, and purchased a new car despite not having a driver's license. These events often place huge financial strain on patients and their families, are a cause of worry and trepidation and impact on patients' ability to live autonomously.

3.3 Objective

The objective of this Chapter was to create and pilot a new cognitive task that could be used to measure some aspects of rational and intuitive processing in controls and patients with HD. The task would be a starting point to better understand DM in neurological populations. Furthermore, the task could have potential for use in longitudinal studies to study how this changes over disease progression as well as to quantify the efficacy of any DM interventions.

3.4 Methods

This heavily methods-focused Chapter is divided into four interspersed methods and results sections, one for each pilot version of the DM task battery.

3.4.1 Development of a new cognitive task to test aspects of rational-intuitive processing in decision-making

An extensive search to find appropriate cognitive tasks to measure aspects of rational and intuitive processing was carried out (Appendix 1). From the 104 tasks reviewed, none were sufficient to measure these cognitive processes according to the following criteria:

1. The task is not so complex that it may not be understood by anyone with mild cognitive impairment.
    a. The task places little or no emphasis on learning or working memory requirements.
2. The task is not confounded by participants with motor impairments who might be slower to respond.
3. The task is relatively life-like, i.e. it has ecological validity such that different salience or motivation between groups would be unlikely to confound results.
4. The task results can be analysed, and have meaning, at both a group and individual level.
5. The task is short enough that participants can complete it in one sitting, without becoming bored or distracted.
6. The task is not susceptible to practice effects.

A new task called the Party Food task was created using PsychoPy open-source software (Peirce, 2007). No gold standard measure existed to validate and compare with this task. Instead, a three-way convergent validation method was employed to validate the three revisions of the new task (Figure 10). This method was maintained throughout task development and validation but individual tasks within it were altered or excluded, or their purpose redefined. An aggregate score was calculated for each task set below. The tasks in the central red column would eventually comprise the whole test battery and the tasks in the outer blue columns would be excluded. In order to do this, the aggregate score from each column must correlate significantly based on either a Pearson's or Spearman's test.

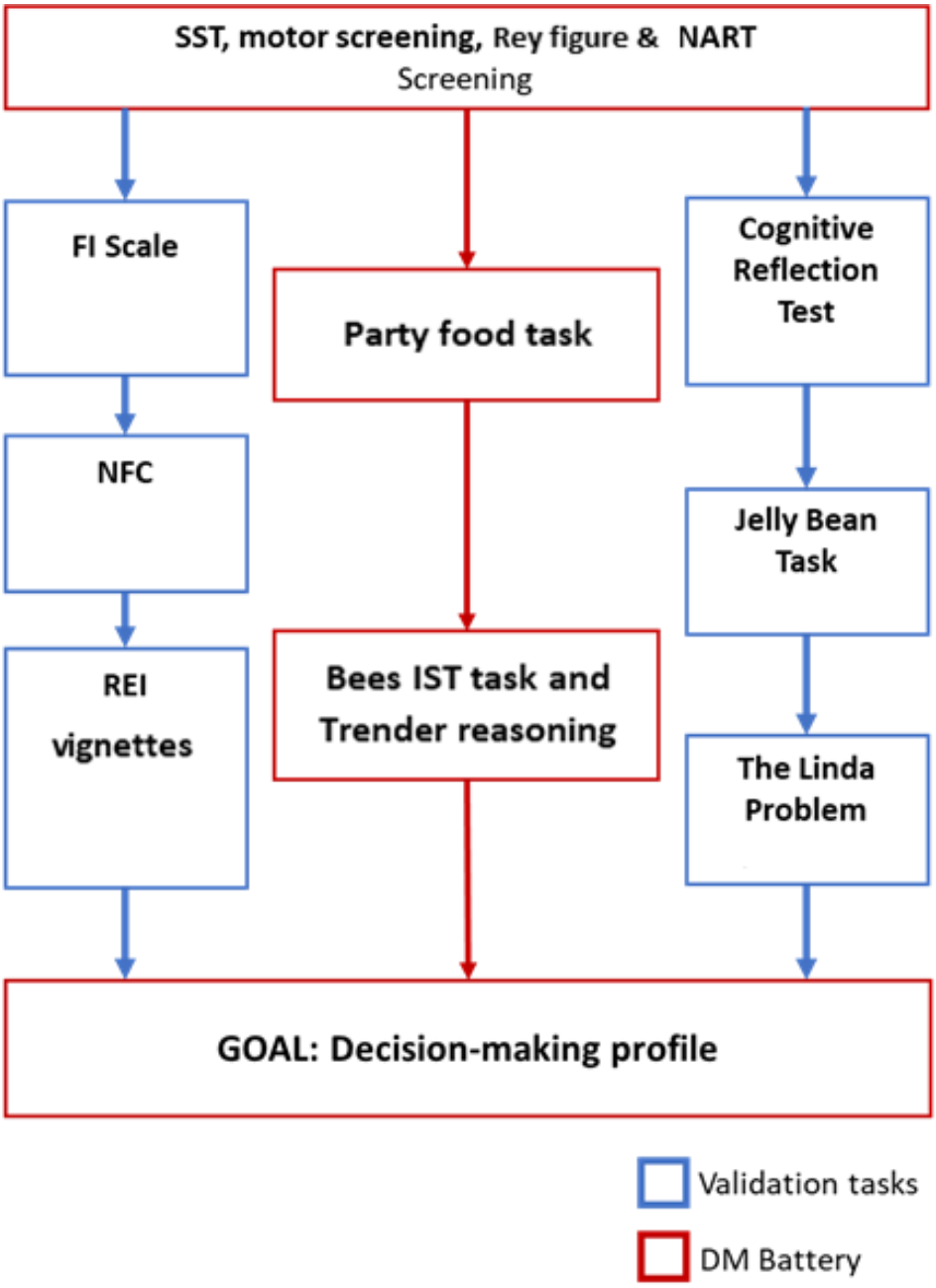


Figure 10. To validate the new decision making task (two-choice discrimination, Party Food), a convergent validation method was used. Each vertical section of this flow chart represents a separate set of tests that should converge on the same decision making profile in a single participant. In red are the core tasks, which once validated, would comprise the entire test. In blue are the validation measures which would be excluded following validation. Abbreviations: SST = stop signal task; NART = national adult reading test FI = faith in intuition; NFC = need for cognition; REI = rational-experiential index; IST = information sampling task.

3.4.2 Version 1

3.4.2.1 Rationale and set-up, October 2018

The primary aim at this stage was to create a task that could quantify aspects of intuitive information processing as there were sufficient tasks already available to measure rational processes. Version 1 of the Party Food task was created using PsychoPy software V1.85 and Prashanth Ciryam (PhD student, Department of Chemistry, University of Cambridge) was instrumental in overcoming several code problems in this version. Each decision was between two food items, under the premise that the participant is throwing a party and must buy items for themselves and their guests. In this way the task is ecologically valid: both patients and controls frequently make decisions in a supermarket about what to purchase. The third person narrative was included for those patients with a percutaneous endoscopic gastronomy tube, for whom consuming food from a supermarket is not possible, but the premise of buying food for others still remains.

Ten common Party Foods and items were selected for version 1. For each item, open-source photos of expensive and cheap options of that food item were downloaded from the internet. The prices were taken from online UK supermarkets such as Tesco and Waitrose. The images were matched for quality and contents as best as possible. For example, both cheap and expensive cupcake images were the same size and contained a similar number of cupcakes (Figure 11).

Figure 11. An example of two stimulus images from the Party Food task version 1. Two versions were created, with the images on opposite sides of the screen, a crude way to randomise left/right placement.

Each pair of images and the attached text is referred to as a stimulus image. For each item (e.g. cupcakes), three stimulus images were prepared which contained two photos, two titles and two prices (Figure 11 and 12). The side of screen was counterbalanced by creating three more stimulus images per item and reversing the text and image placement.

The prices and images were interchanged to alter the complexity of the decision. When presented with fewer choice attributes the decision should be faster and more intuitive, and because of this, RT could be used to infer the type of decision processing. It is important to note that this method of inference is not unanimously supported and one study found that when discriminability is controlled for in value-based choice tasks, there is no evidence that one type of choice is faster than the other (Krajbich et al., 2015). A published response to this criticism agreed that the inference of mental processing from RT is valid in the particular case of value-based choice tasks, but the article by Krajbich and colleagues is limited in its wider application to rational-intuitive DM (Pennycook et al., 2016). The use of RTs has been conceptually replicated using multiple measures: conflict/no-conflict problems, syllogisms, ratio bias tasks, conjunction fallacy tasks, memory recall tests, galvanic skin response, fMRI and event-related potential (De Neys, 2012, 2014). This supports the idea that a slower RT is caused by detection of conflict between initial responses to cause rational processing (Pennycook et al., 2015). However, the influence of individual preference in value-based tasks is still a confound in rational-intuitive tasks and should be eliminated in task construction, or at least accounted for in any analysis.

In response, this task therefore pooled RTs across each level of complexity to minimise the effect of single-choice preference differences between participants. Participants saw three levels of complexity in their choice attributes: Level 1) same price/same image, level 2) same price/different image, and level 3) different price/different image, thus causing conflict between the options and engaging rational processing. In level 3 choices, where both price and image differed (Figure 12), participants would deliberate more and this would be reflected in the increased RT compared to the level 1 choices. The level 2 choices would fall into the quasi-rational domain between rational and intuitive processes and produce a medium RT. In this way, individual propensity to deliberate could be extracted based on relative individual differences in RT across the levels.

Figure 12. Four stimulus images. On the left, the level 2 choices, and on the right, the level 1 choices in which no attributes differed between the two options.

In total, participants saw 60 choice screens (10 items x 6 stimulus images). The ten items were: beer, biscuits, carrot cake, champagne, cola, cupcakes, doughnuts, ice cream, pizza and sausage rolls. The decision screens were preceded by the following instructions:

"You're throwing a party and need to buy some food for your guests.

You will need to choose between two items, then use the left and right arrow keys to choose which item you will put into your basket.

Ready?

Press space to continue."

In the flow diagram below, the instructions are represented by the red "readyMessage", and each trial by the red "trial" (Figure 13). The stimulus images were listed in a spreadsheet and presented in a random order according to the white "trials" loop, until all 60 choice screens had been presented.

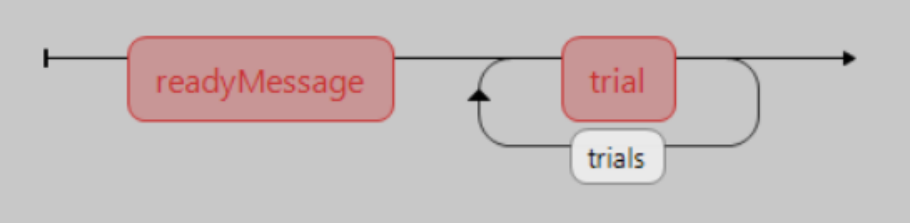


Figure 13. Flow diagram for the Party Food task version 1.

The task took approximately 2.5 minutes to complete. This version of the task was piloted in ten healthy young-adult participants and approved by the Cambridge Psychology Research Ethics Committee (CPREC; PRE.2018.090) and then incorporated into a larger decision battery with additional tasks for convergent validation (Table 3). The components of the study and time to complete each component is included in the Table below. Detailed explanations of the tasks are included in Appendix 2 and an example participant information sheet and consent form are included in Appendix 3.

Table 3. Decision making task battery, version 1. Includes Party Food task version 1. Abbreviations: HADS = Hospital anxiety and depression scale; NART = National adult reading test; SST = Stop signal task; DM = decision making; FI = Faith in intuition scale; NFC = Need for cognition scale; CRT = Cognitive reflection test.

Assessments	Time to complete (mins)
Informed Consent	5
HADS	5
NART	5
Response inhibition: SST	15
DM Questionnaires: FI, NFC, Vignettes	15
DM Tasks: Party Food, Bees IST, Trender reasoning, Jelly bean task, Linda problem, CRT	40
Complex Rey Figure drawing	10
TOTAL TIME TO COMPLETE [plus breaks]	**1h35**

3.4.2.2 Results and Conclusions

Ten healthy controls were participants in the pilot testing for the Party Food task version 1 (Table 4). No measures of global cognitive and motor impairment were included in this pilot test phase of the task battery as it was assumed the controls were normal given they were either university undergraduates or holding down full time jobs.

Table 4. Demographics for control participants for the Party Food task version 1 pilot testing. Abbreviations: HADS = Hospital anxiety and depression scale; NART = National adult reading test.

Controls N=10	Mean (range)
Age	27.3 (22-41)
Gender, % male	10
NART (premorbid IQ score out of 50)	31.6 (22-37)
HADS (>10 is minimum clinical cut off)	6.5 (1-15)
Rey Figure drawing (out of 36)	36

The relationship between RT and stimulus image type was as predicted: RT increased as the number of different attributes between the two choices increased (Figure 14). This positive slope was interpreted to indicate increased deliberation over the

decision. The pattern also existed at an individual level. In most participants, the level 3 choices had a significantly increased RT. However, it could not be concluded that the level 1 choices (where options were identical) were representative of intuitive decisions, after all, there was no decision to be made. The task merely confirmed what is already known: people take more time to process more pieces of information, primarily due to the increased time to attend and encode extra information.

However, further interpretation of these results suggested that the premise and overall task setup were successful in part. Firstly, the control participants were not making random choices. Choice consistency was high, with participants selecting the same option in 93.5% of repeat trials, despite counterbalancing and order randomisation. Secondly, the Party Food task version 1 captured aspects of the dual-process paradigm wherein we make most decisions automatically while few are deliberated upon –the positive slope for RT against complexity, where it takes longer to process more information, suggests that the task set up allows participants to deliberate their choices. Finally, the distribution of RTs for each column of the graph is left skewed. Participants are making most decisions very quickly, or intuitively, regardless of the amount of information that is presented, in keeping with previous research into choice reaction times (Kahneman & Tversky, 1982; Ratcliff & McKoon, 2008).

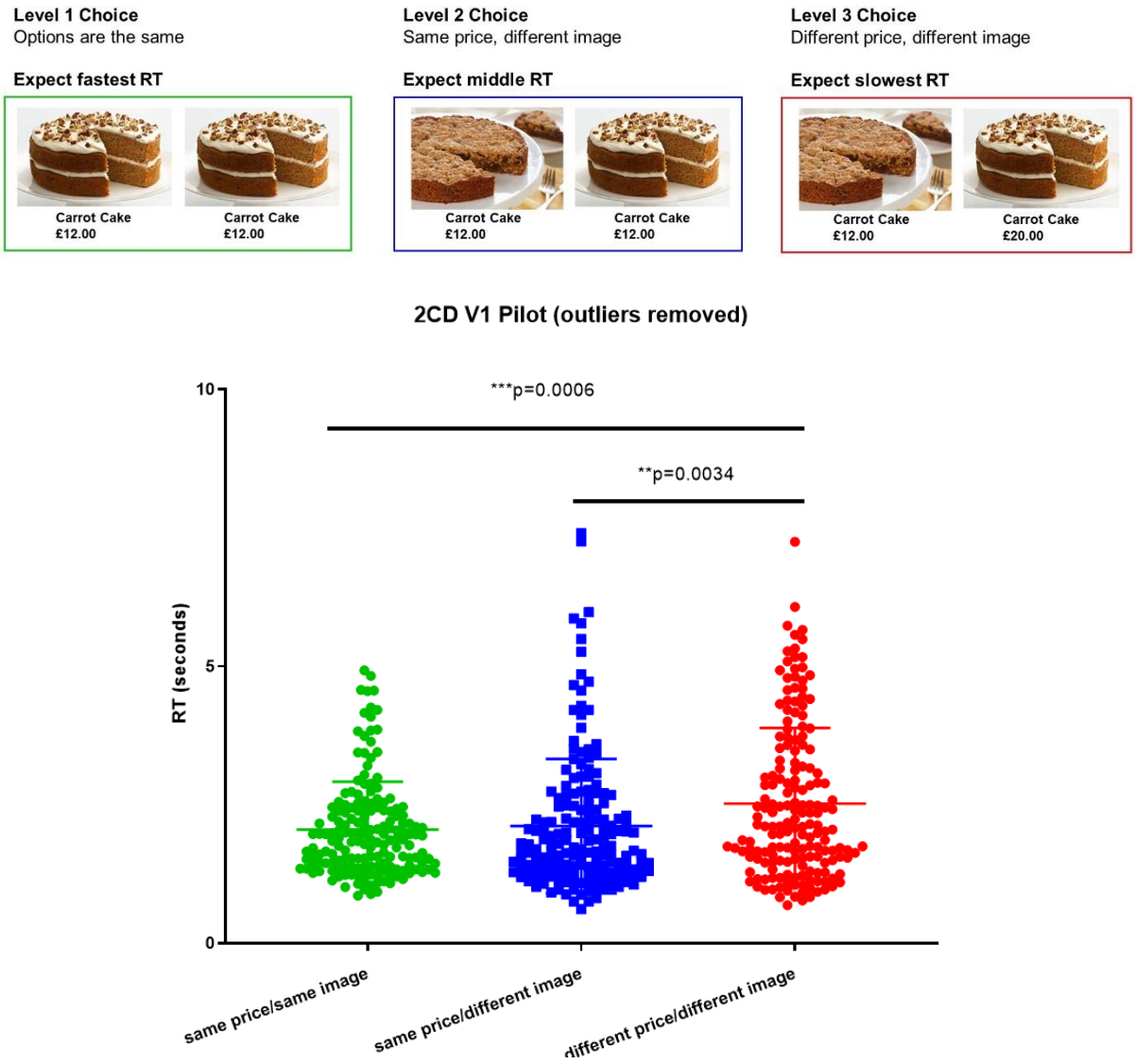


Figure 14. Party Food task version 1 pilot results. Response times (RT) for all participants are plotted against the type of stimulus image. Outliers removed were defined as data points ± 1.5×IQR. Error bars indicate mean ± SD. Level 1 choices are in green (same image, same price), level 2 choices are in blue (difference image, same price), and level 3 choices are red (different image, different price).

3.4.2.3 Convergent validation analysis

Aggregate scores for each of the three convergent streams were calculated in order to plot correlations and validate the new task (Figure 10). A higher aggregate score suggested increased deliberation. Three validation questionnaires were completed by the participants (need for cognition (NFC), faith in intuition (FI) and rational/experiential vignettes). Past literature was not unanimous nor clear about how to score the vignettes so only the NFC and FI scores were used (Epstein et al., 1996). The aggregate was

calculated by summing the NFC score and the negative FI score to give a self-reported quantification for rational processing. The lowest possible score was -72 and the highest was +82. Scores in the pilot group ranged between -35 and 23.

Three short tasks put participant's intuitive and rational processing in conflict. The CRT, jelly bean task, and the Linda problem are constructed such that the answer given indicates whether someone deliberated or answered intuitively. The aggregate score was calculated as follows: (number correct in CRT) + (most probable option in jelly bean task) + (correct answer to Linda problem). The lowest possible score was 0 and the highest was 10. Scores ranged between 3 and 7.

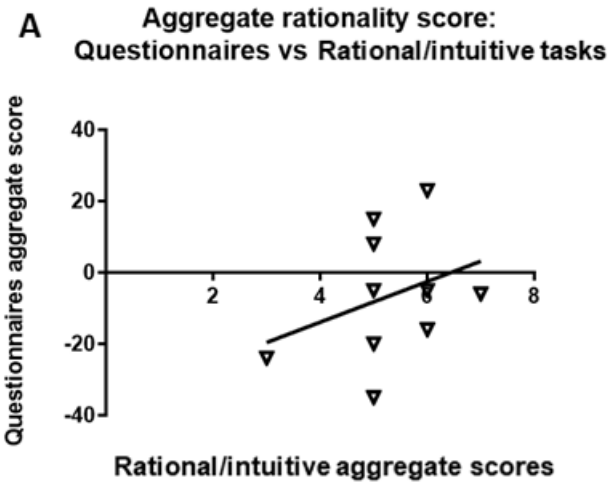
The third aggregate score was composed of the core tasks: the Party Food task V1, the bees task and the Trender reasoning task. The Trender task measures complex pattern recognition, where ability to deliberate on possible patterns gives a higher score. Participants score one point for each pattern they could identify. The highest possible score was 12, and participants ranged from 7 to 11. The bees task asks participants to hypothesize an outcome based on limited information. Very briefly, participants see 37 'bees', hidden beneath honeycombs in a hive. Bees are one of two colours. Participants are instructed to reveal as few bees as possible but estimate the majority colour correctly. The average number of samples taken plus the average difference between colours at decision were used to quantify propensity for rationality. The highest score possible was 72 and the lowest was 1, though in reality scores ranged between 7.6 and 43.5. Finally, the new task was quantified by calculating the ratio between level 3 and level 1 RTs, averaged for each participant. This value was weighted using z-scores to be comparable to scores from the Trender and bees tasks.

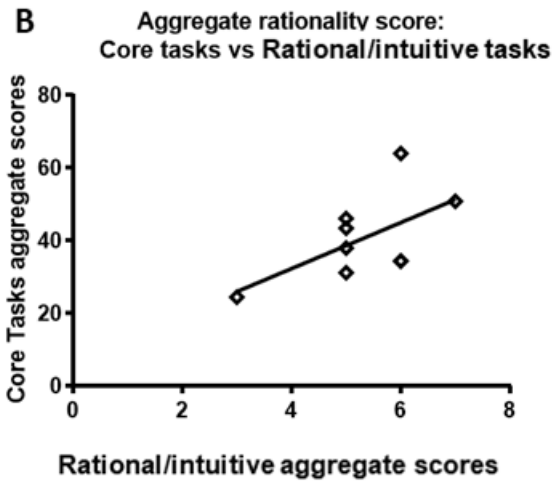
The aggregate score was calculated as follows:

(**Party food task V1** [(RT different price-different image) ÷ (RT same price/same image)] x 10)	+	(**Trender reasoning** number correct)	+	(**Bees task** [average number of samples + average difference between colours at time of decision])

These three aggregate scores were correlated against one another to validate the new task. The Shapiro-Wilk test for normality was used for each set of aggregates and each passed, with accompanying QQ plots concluded to be normal, although with few

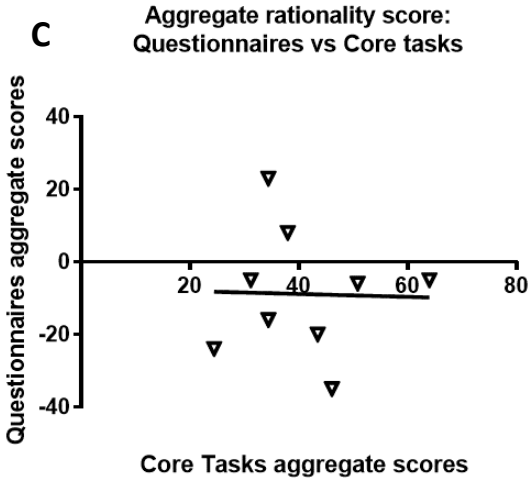
data points (results not shown), and the Pearson correlation was applied between the aggregate scores (Figure 15).





Pearson r	
r	0.3338
95% confidence interval	-0.3746 to 0.7961
R squared	0.1114
P value	
P (two-tailed)	0.3459
P value summary	ns
Significant? (alpha = 0.05)	No

Pearson r	
r	0.5972
95% confidence interval	-0.1109 to 0.9031
R squared	0.3567
P value	
P (two-tailed)	0.0895
P value summary	ns
Significant? (alpha = 0.05)	No



Pearson r	
r	-0.02702
95% confidence interval	-0.6790 to 0.6487
R squared	0.0007302
P value	
P (two-tailed)	0.9450
P value summary	ns
Significant? (alpha = 0.05)	No

Figure 15. To validate the new decision making test battery Pearson correlations were calculated between aggregate scores from three sets of convergent tasks. Graphs and values for the correlations are presented. A) Questionnaires correlated with intuitive/rational conflict tasks. B) Core tasks correlated with intuitive/rational conflict tasks. C) Core tasks did not correlate with questionnaires. Note that only 9 scores were available for the core tasks because one task crashed and could not be reset during the session (B and C). In Figure (B) there are two points at (6, 34).

The three sets of tests correlated numerically in two of three instances, but the distribution of scores and apparent weight given to outlying scores, in addition to the small pilot sample size, was not convincing. For example, five participants had an aggregate score of 5 in the intuitive/rational conflict tasks. This problem may be attributed to the task code: for most participants the intuitive/rational tasks crashed part way through. This may have provided an unintentional opportunity for participants to deliberate on their approach and/or answers. In conjunction with the conclusion to tweak the Party Food task, it was decided that the score aggregation should be more sensitive to individual propensity to rationalise their decisions.

3.4.3 Version 2

3.4.3.1 Rationale and set-up, December 2018

The primary aim for version 2 of the Party Food task and the DM battery was to improve the quantification of intuitive decisions and capture more spread in the quantification of deliberation during the decision process. To achieve the first aim the Party Food task was split into two parts: part 1 measured rational DM relative to part 2, which forced participants to make intuitive decisions by introducing a time limit to the decisions (Phillips et al., 2016). To facilitate this change, the stimulus images from version 1 were discarded. Instead, each choice seen by participants corresponded with a spreadsheet row which contained values for the different attributes presented on screen and was implemented by the PsychoPy software.

Part 1 of version 2 was similar to version 1. Participants were presented with three types of choices in which the number of decision attributes varied. As shown in Figure 16, in the green box (level 1 choices), only price and image were presented. The 'no choice' level from version 1 where options were identical, was removed in version 2 as these had caused participants' confusion as they tried to 'spot the difference'. In the red box (level 3 choices) each option has an image, price, quantity, cost per unit and an eco-friendliness rating. The blue box (level 2 choices) falls in the middle, with attributes for image, price, quantity and cost per unit. The new attributes were again taken from online supermarket information except for the eco-friendliness values which were randomly generated ratings between 1 and 10 out of 10. By increasing the range of attributes per decision, version 2 aimed to increase RT range, ultimately to better distinguish patient and control groups. To the same end, the number of trials was increased. Thirteen

different items were used. Each choice was presented four times and counterbalanced for side of screen. Thus each level (green, blue and red) had 52 choices, for 156 total choices.

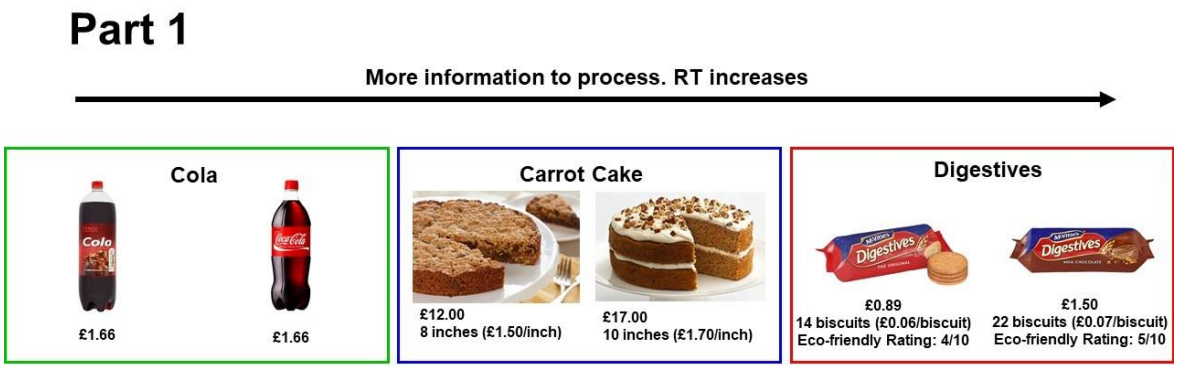


Figure 16. Party Food task version 2, Part 1. Three types of choices were presented which varied in the amount of information given to make the decision. On the left hand side in the green box, only image and price attributes are given to make the decision. In the red box on the right hand side, there are images, prices, quantities, cost per unit and an eco-friendliness rating. As found in the previous version of the Party Food, increased information leads to increased response time (RT) and it is assumed that participants deliberated more during this time.

Part 2 of the Party Food task version 2 introduced a time limit to each decision (Figure 17). It has been reported that time pressures decrease the relationship between rational DM and performance, while not affecting the relationship between intuitive DM and performance (Phillips et al., 2016). Thus, part 2 of the Party Food task version 2 should allow participants to make only intuitive choices whereas part 1 allows both rational and intuitive choices to be made.

Each time limit was calculated relative to the individual: initially, the average RT (per level) in part 1 was introduced as the stop duration for part 2. Immediately it became clear that control participants did not struggle to answer within this time limit as they did not miss any trials, nor appear to be under much pressure to make a choice. The time limit was reduced to 75% of the average time (per level) from part 1. Any missed trials were excluded from the RT distribution (because no time was generated), but any participant who missed more than 20% of trials was excluded from analyses (3 participants missed >20% of level 1 trials). Aside from the time limit, part 2 was identical to part 1 with 13 novel food items for 156 total choices.

The additional choices (60 in V1 and 2x156 in V2) necessitated the addition of breaks. A break screen of unlimited duration was introduced after every 39 choices.

Between parts 1 and 2, participants completed the two DM questionnaires for approximately 10 minutes (Luke et al., 2012; Scott & Bruce, 1995).

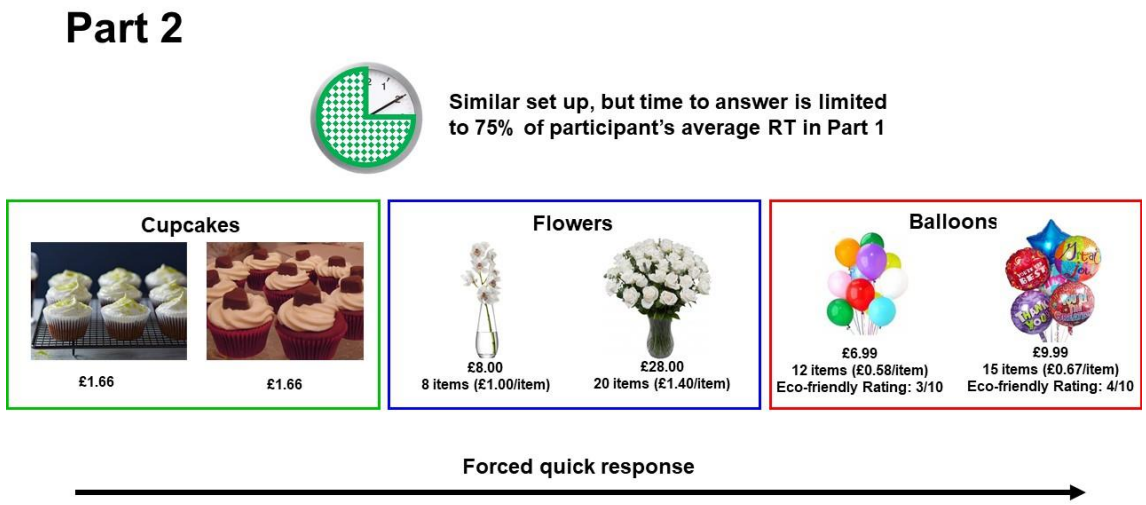


Figure 17. Party Food task version 2, part 2. The three levels of choices remain as per part 1 but a time limit is imposed on participants to make a decision. The time limit is 75% of the average response time (RT) (per level) in part 1.

As in the version 1 flow diagram, the instructions are represented by the red "readyMessage", and each trial by the red "trial" (Figure 18). Trial breaks are included with some short code under "Trial_Break" and these two elements are repeated according to the conditions in the white "trials" loop, which was linked to the spreadsheet with text and image attributes. The trials were presented in a random order.

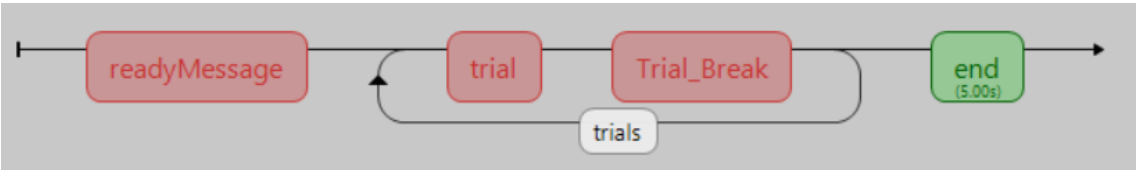


Figure 18. Flow diagram for Party Food task version 2, part 1.

The updated task was part of an updated and better informed test battery (Table 5). Specifically, the motor screening task was removed because the relative time limit imposed in part 2 now normalises any motor delays relative to each individual. The rational-experiential vignettes were also removed because they lacked an objective scoring method. Time to complete was revised based on the previous pilot study.

Table 5. Decision making test battery, version 1. Includes the Party Food version 2.

Assessments	Time to complete (mins)
Informed Consent	5
HADS	5
NART	5
Impulsivity: SST	5
DM Questionnaires: FI, NFC, decision making experience, GDMS	20
DM Tasks: Party Food task, Bees IST, Trender reasoning, Jelly bean task, Linda problem, CRT	25
Complex Rey Figure drawing	2
PLUS BREAKS	**TOTAL 1hr 17**

3.4.3.2 Results and Conclusions

Thirteen healthy, young-adult controls participated in the pilot of the Party Food V2 (Table 6) and the new study was approved by the CPREC (PRE.2018.121) as the task changes constituted a new application, rather than an amendment. The SDMT, Stroop test, and Trail making A and B were not given to the participants as they were all students at the University of Cambridge and therefore presumed unimpaired on these global cognitive tests.

Table 6. Demographics for control participants for Party Food V2 pilot test.

Controls n=13	**Mean (range)**
Age	26.4 (22-31)
Gender (% male)	33.3
NART (premorbid IQ score out of 50)	35.1 (24-45)
HADS (>10 is minimum clinical cut off)	6.9 (2-11)
Rey Figure drawing (out of 36)	35.9 (34-36)

The Party Food version 2 was more sensitive to participant deliberation in part 1. Increased range of attributes and number of choices distinguished RTs across the three level more significantly compared to the previous version (p=0.0006 in V1 vs. p<0.0001 in V2) (Figure 19). In these calculations, RT outliers were removed as they represented times when the participant was distracted during the task and were not representative of the individual's decision processing. The increasing RT across the three levels persisted at a group and individual level in version 2 to suggest that participants were using a rational decision process as more attributes were shown. Choices were not random: participants made the same decisions upon repeat presentations of the same choice 96.4% of the time.

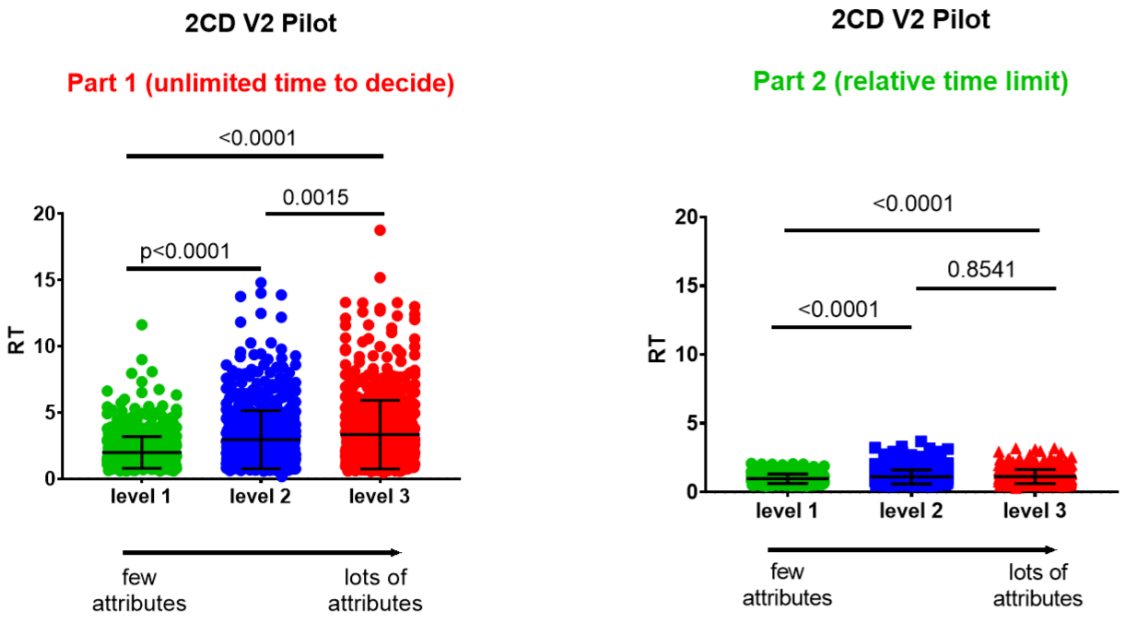


Figure 19. Party Food task V2 pilot test results. Response times (RT) for all participants are plotted against the number of decision attributes that were present. Outliers removed were defined as data points ± 1.5×IQR. Error bars indicate mean ± SD.

Part 2 of the Party Food task version 2 measures intuitive decision processing. A stringent time limit imposed on the decision process prevented participants from deliberating and it was assumed that they were using intuitive processing based on past experiences, heuristics and biases (Tversky & Kahneman, 1974). If participants took too long to respond (evidence of deliberation), the trial ended and no response was recorded. Any participant with more than 20% of these 'non-trials' was not included in analyses, and in the Party Food task version 2, three participants' level 1 trials were excluded, but no level

2 or 3 trials. This was evidence to support that a 25% reduction in time to respond based on the first part of the task was realistic and achievable for participants. The range of RTs is clearly lower than in part 1 (Figure 19). Zooming into the Y-axis allows the decision pattern to be interrogated further (Figure 20) and this shows that the positive slope is still evident. This suggests that participants were not aimlessly choosing and were still attending to and encoding the information: RT was still higher when participants were presented with more choice attributes. The most basic level one choices with only an image attribute were driving this effect in a one-way ANOVA. These two observations confirmed that participants were still engaging in decision behaviour, but using a different process(es). Choice consistency was lower in the part 2, only 90.3% compared to 96.4% in part 1, which also attests to the use of a different decision process, where intuitive processes are more error prone.

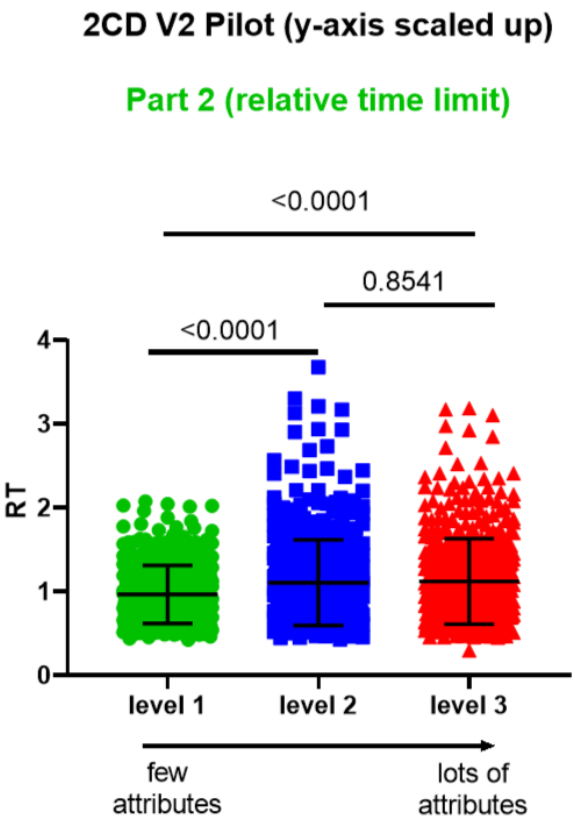


Figure 20. Results from the Party Food V2 part 2 pilot study. Response time (RT) is plotted against the number of choice attributes and the y axis is scaled up in comparison to the previous figure. Error bars indicate mean ± SD.

One final quality check for version 2 required confirmation that the RT distributions were in keeping with classic choice RT tasks. Simple two-choice decisions are positively skewed (Ratcliff & McKoon, 2008). Visually, the RTs in part 1 appeared to follow this pattern whereas the distributions in part 2 were shifted to a more uniform distribution (Figure 21). This shift may suggest the use of different decision processes but it is impossible to ascertain this by visual inspection or by simple statistical comparison. In the future, the distributions could be analysed with a computational drift diffusion model (e.g. Ratcliff & Rouder, 1998). These differences between parts one and two of version 2 of the task were sufficient to conclude that it measured rational and intuitve decision processes.

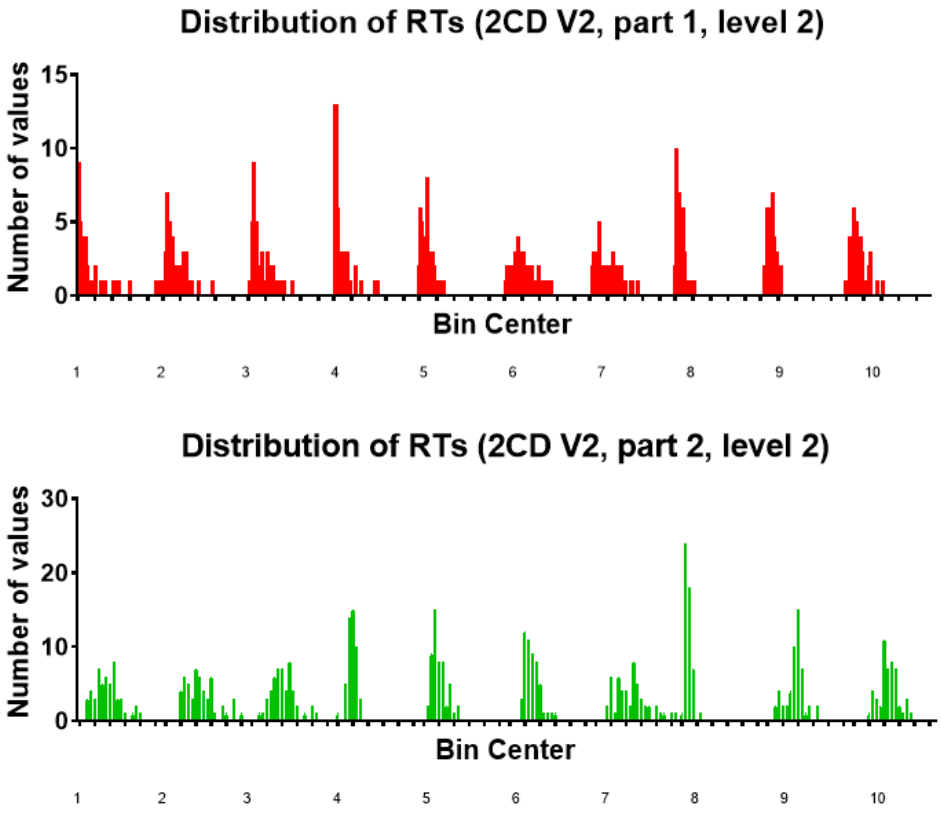


Figure 21. Response time (RT) distributions from the Party Food task version 2 pilot participants. The general observation is that distributions shift from the traditional positively skewed shape to more normal or uniform distributions. This shift is investigated in version 3 of the task to understand how decision processes are changing.

3.4.3.3 Convergent validation analysis

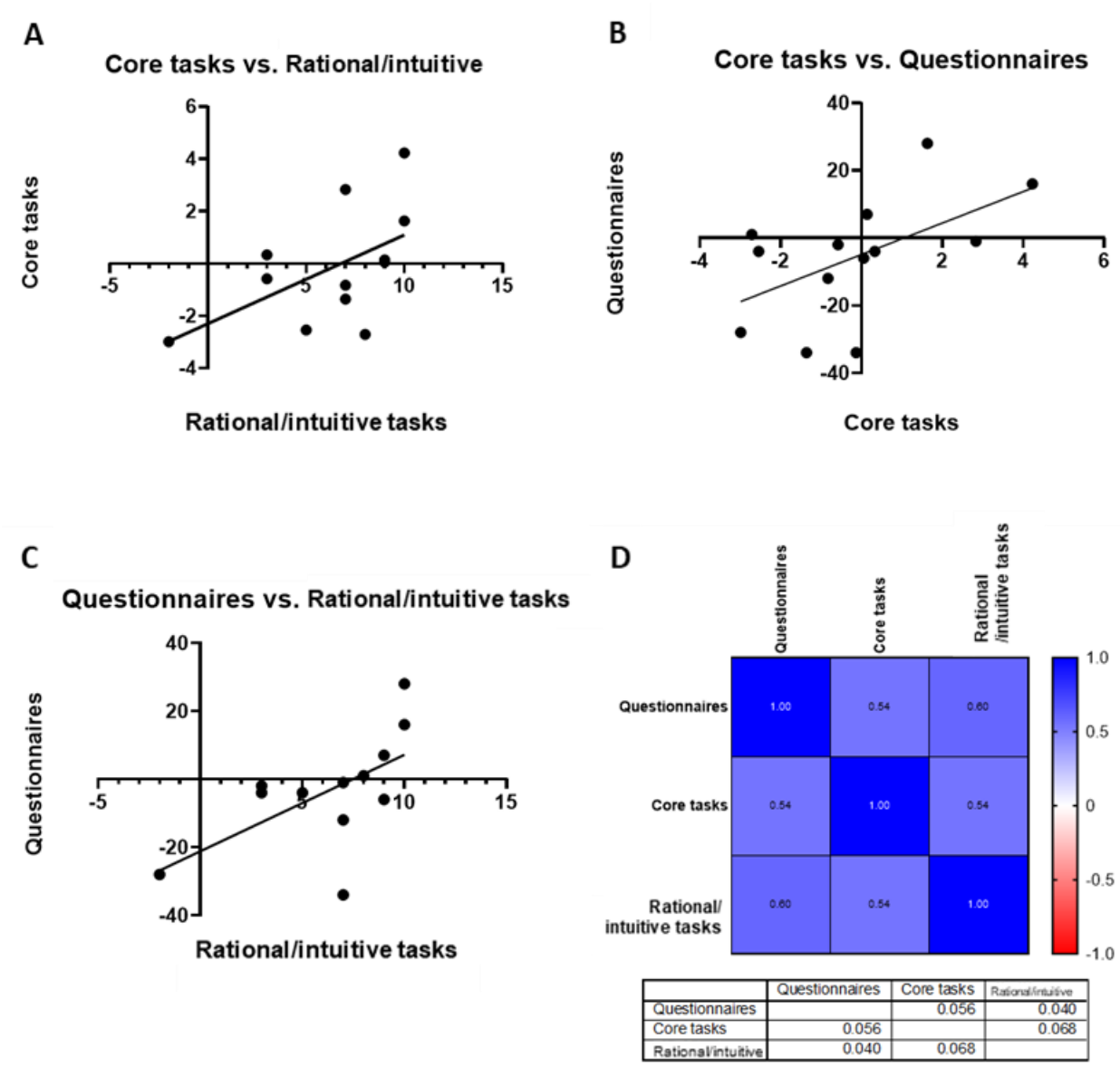
As in the previous version of the DM battery, an aggregate score was calculated for each of the three streams: new task, questionnaires, old tasks. A higher score suggested increased deliberation and reduced intuitive processing. In version two, the aggregate calculation was updated in three ways:

1) The aggregate score for the questionnaires was updated to include an additional measure. The general DM style (GDMS) breaks down decision style into five types: rational, intuitive, dependent, avoidant and spontaneous. Participants answered 25 questions and were given a score for each of these five types (Scott & Bruce, 1995). The rational sub score was added to the negative intuitive sub score, which was included in the questionnaires score aggregate [**NFC** + (-**FI**) + **GDMS** rational + (-GDMS intuitive)]. This provided a more robust self-report measure of the same variables in an attempt to regulate the wide range of scores from the version 1 validation. The lowest possible score was -92 and the highest possible score was +112. Scores in the pilot group ranged between -34 and 28.
2) The rational-intuitive conflict tasks were not changed, but the aggregate score was updated to increase the range of scores. The number of points from rational thought processes was summed and the number of points lost due to intuitive processing errors was subtracted. The new aggregate score was calculated as follows:
   *(number correct in **CRT**) + (number correct in **jelly bean task** [participant chose higher probability outcome]) + (correct answer to **Linda problem**) - (number incorrect in jelly bean task [participant chose lower probability outcome]) + (number of intuitive answers in CRT)*
   The lowest possible score was -9 and the highest was 10. Scores ranged between -7 and 10.
3) Z-scores were used to equally weight the three tasks: Party Food, Trender and bees. Each participant's score was converted to a Z-score with the mean and standard deviation calculated from all scores in the version two pilot. The part 2 scores were not included because they were a measure of intuitive processing and the above results suggested a fundamental change in the decision processes used in the task.

Party Food task V2 Part 1 [z-score for slope between RT level 1-2-3]	+	**Trender reasoning** [z-score for number correct/total possible]	+	**Bees task** [z-score for (number of samples taken + average difference between colours at time of decision ÷ total possible]

The three aggregate scores were correlated against one another to validate the Party Food V1. The Shapiro Wilk test for normality was used for each set of aggregates and each passed, with accompanying QQ plots concluded to be normal (results not shown), and the Pearson correlation was applied between the aggregate scores (Figure 22). It was expected that these correlations would be positive. This means that the new task measures rational processing comparably to the validation measures.

The correlation plots for the decision battery were more convincing for convergent validation of version 2 than the previous version, especially given the low sample sizes. Pearson r values range between 0.54 and 0.60 with p-values between 0.04 and 0.06. The spread of the scores in each aggregate was also improved. Each of the regression lines appears to be driven by one or two distal data points, so for this correlation to be more convincing still, the sample size should be increased. However, the convergent validation was convincing enough to warrant the investigation of new downstream analyses of the task in the next version.



	Questionnaires	Core tasks	Rational/intuitive
Questionnaires		0.056	0.040
Core tasks	0.056		0.068
Rational/intuitive	0.040	0.068	

Figure 22. To validate the Party Food V2 Pearson correlations were calculated between aggregate scores from three sets of tasks. Graphs and statistics for the correlations are presented. A) Core tasks correlated against intuitive/rational conflict tasks. B) Core tasks correlated against questionnaires. C) Intuitive/rational conflict tasks correlated against questionnaires. D) Correlation matrix displaying Pearson r values and P values (below).

3.4.4 Version 3

3.4.4.1 Rationale and set-up, February 2019

The primary aim for version 3 of the Party Food task and the DM battery was to permit more sophisticated downstream methods of analysis while maintaining or improving the convergent validation r values. As mentioned in the previous section, the distribution of RTs should be investigated with drift diffusion models. However, to

achieve this, the models require a binary correct/incorrect answer in addition to the RT distributions. There is no correct choice in the Party Food: preferences are subjective based on the attributes presented. To this end, it was necessary to quantify the choice attributes, image, cost, quantity, value, and eco-friendliness per participant. Logistic regression was used to create psychometric curves for each attribute by calculating the left-right difference in attribute value the corresponding left-right choice probability. For the image (non-numerical), it was necessary to update version 3 to include image-only choices where preference for image could be obtained independently of other attributes. Thus, the following three levels of choice were presented (Figure 23). Aside from this change, the task remained identical to the previous version and took the same amount of time to complete.

Outliers from individuals' RT distributions after part 1 of the Party Food task version 3 were removed before the time limit was set for part 2 instead of during analyses only.

Figure 23. An example of the three levels presented to participants in the Party Food task version 3. Level one contains only image attributes, while level two contains image and cost attributes, and level three remains the same as in version 2.

Outliers were defined as ± 1.5 × IQR. This change was made to improve the accuracy of part 2 time limits. Finally, version 3 was improved aesthetically to be more user friendly and to look more professional.

3.4.4.2 Results and conclusions

Eleven healthy, young-adult, control participants completed the pilot testing for the Party Food task version 3 (Table 7) under the same ethical approval as the previous version (PRE.2018.121). Participants were well matched ($p>0.1$, student's t-tests) to the control participants who completed the previous version of the Party Food task.

Table 7. Participant demographics for pilot testing for version 3 of the Party Food task

Controls n=11	**Mean (range)**
Age	25.6 (18-30)
Gender (% male)	27.3
NART (premorbid IQ score out of 50)	35.1 (17-48)
HADS (>10 is minimum clinical cut off)	9.1 (2-15)
Rey figure drawing (out of 36)	35.9 (35-36)

The RT for each level in part 1 of the task were distinguishable to the same extent as in version 2 of the task ($p<0.0001$) (Figure 24). Again, the positive slope across the three levels persisted at a group and individual level to suggest that participants were using a rational decision process, deliberating more when faced with more choice attributes. Choices were not random: participants made the same decisions upon repeat presentations of the same choice, 96.3% of the time. Part 2 of the task was analysed in the same way as the previous version. Four participants' level one trials were excluded as they failed to make a choice within the time limit for more than 20% of decisions, in addition two participants' level two trials and one participant's level 3 trials were also excluded. This proportionately high number of excluded trials warranted investigation in version 4 of the task.

As shown in Figure 24 (part 2), the range of RTs is reduced compared to those in part 1, confirming again that participants were probably not deliberating during the decision process. In contrast to version 2, zooming in on the y-axis shows the positive slope across the three levels is no longer present. Assuming participants' were processing their decisions intuitively, it is most likely that they did not encode all of the attributes on screen and instead made an intuitive decision based on a single preselected attribute (Figure 25). The average RT in part 2 supports this; across participants, RT was faster, 0.8 seconds in version 3 versus 1.0 second in version 2, and the range was reduced in version 3. Further, the choice consistency in part 2 was 80.6%, much lower than in part 1, and also 10% lower than in the version 2 – this roughly accounts for the decreased RT.

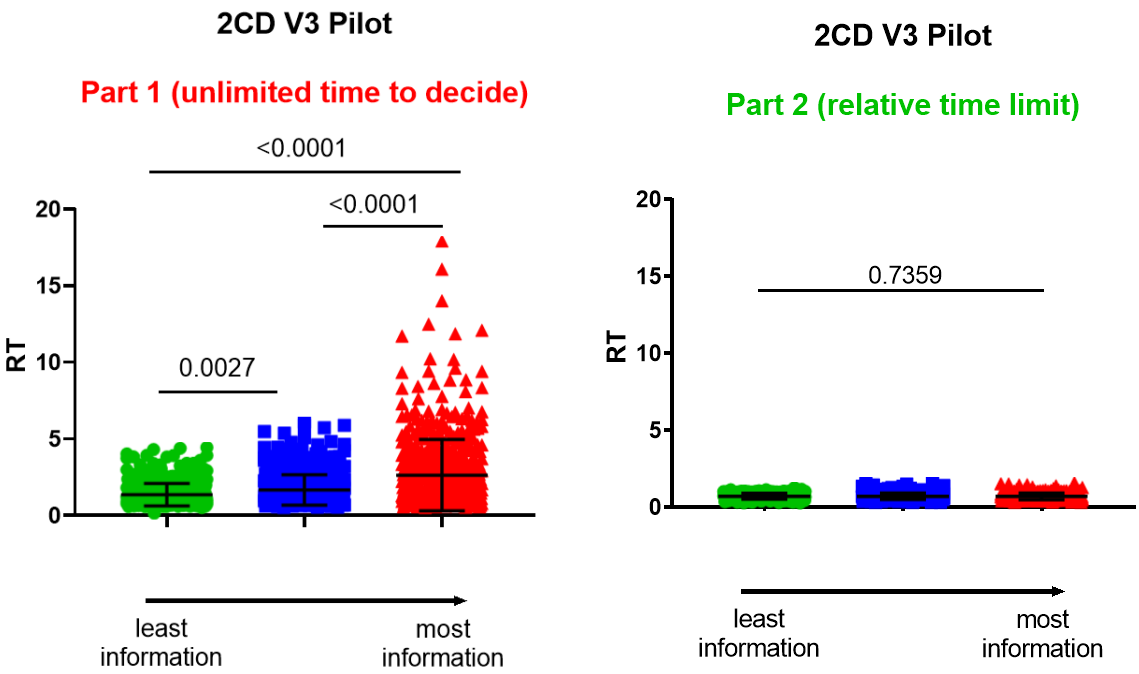


Figure 24. Party Food task version 3 pilot test results. Response times (RT) for all participants are plotted against the number of decision attributes that were present. Outliers removed were defined as data points ± 1.5×IQR. Error bars indicate mean ± SD. Note that the task was named "2CD" at this point (two-choice discrimination).

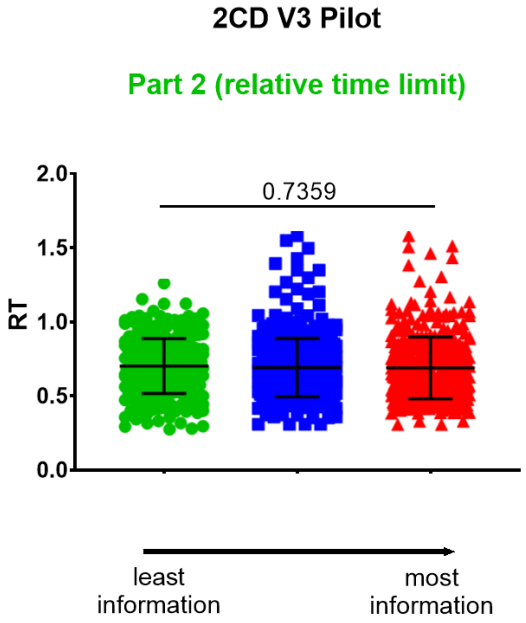
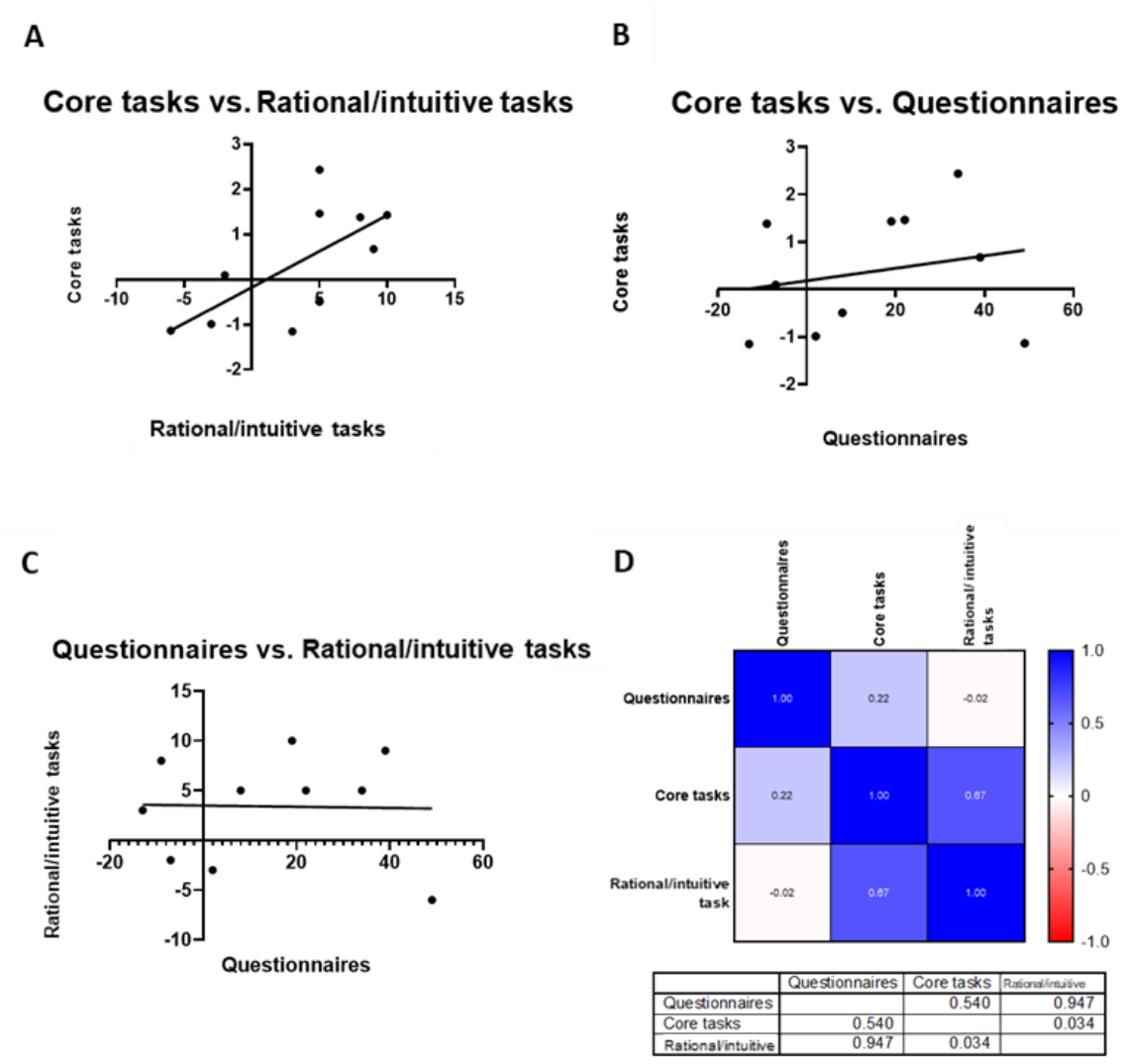


Figure 25. Results from the Party Food task version3 part 2 pilot study. Response time (RT) is plotted against the number of choice attributes and the y axis is enhanced in comparison to the previous figure. Error bars indicate mean ± SD. Note that the task was named "2CD" at this point (two-choice discrimination).

3.4.4.3 Convergent validation analysis

The same methods as the previous version were used to validate version 3. The aggregate score was calculated for the questionnaires, the intuitive/rational conflict tasks, and the core tasks. Each set of aggregate scores was normally distributed to warrant use of the Pearson correlation. Unlike version 2, however, the r values for any correlation with the questionnaires were remarkably low (r(questionnaires vs core tasks)=0.22 and r(questionnaires vs intuitive/rational conflict tasks)=-0.02) (Figure 26). This was because the average aggregate score for the questionnaires was significantly different between versions two and three, -5.6 and 14.91, respectively (Welch's t-test p=0.0167), whereas all other demographics and scores were matched (p>0.1). The correlation between the core tasks and the intuitive/rational conflict tasks was marginally improved (r=0.67) compared to the previous version (r=0.54). It was concluded that the self-report questionnaires were not sufficiently reliable to measure intuitive and deliberative decision processes and they were excluded from the task battery. Theoretically this makes sense: intuitive decisions comprise more than 90% of our daily choices and are subconscious and autonomous, processes which a conscious self-report measure would not capture (Evans & Stanovich, 2013). The improved correlation between the core tasks and the intuitive/rational conflict tasks was attributed to the alteration in level one of version 3, which subsequently altered the RT slope across levels 1-3. At this point the Party Food task version 3 was considered to have met the requirements of convergent validation.



	Questionnaires	Core tasks	Rational/intuitive
Questionnaires		0.540	0.947
Core tasks	0.540		0.034
Rational/intuitive	0.947	0.034	

Figure 26. To validate the Party Food task version 3 Pearson correlations were calculated between aggregate scores from three sets of tasks. Graphs and statistics for the correlations are presented. A) Core tasks plotted against intuitive/rational conflict tasks. B) Core tasks plotted against questionnaires. C) Intuitive/rational conflict tasks plotted against questionnaires. D) Correlation matrix displaying Pearson r values and P values (below).

3.4.4.4 Other considerations for the decision battery

All validation was performed in non-generalisable samples at Cambridge University. Undergraduates, graduates and employees of the University were participants in pilot testing. The participants were probably more driven towards academic success, more intelligent and more uniform that a truly random sample from the UK population and this may need to be considered in future analysis. No participants completed all three development versions of the task, but the three separate groups were matched for the aforementioned demographic characteristics.

Secondly, the intuitive/rational conflict validation tasks were familiar to about 10% of the participants when asked after completing the battery. However, familiarity with the questions did not indicate whether they would answer correctly; in fact, most did not. This highlights the need for the new task to measure rationality and intuition, which does not require learning or memory and is therefore less likely to have practice effects.

A third consideration is the assessment of metacognition in decision behaviour as a covariate in deliberative decision processing. The addition of a confidence scale after a subset of choices in the task could assess this and it could be added to future developments of the task.

Another consideration is informational sampling bias that directs decisions rather than decision processing itself. Analysis of information sampling in over 32,000 people during a gambling task showed three systematic misattributions for decision behaviour: 1) Positive evidence approach: the option from which more information is collected is the final choice; 2) Sampling the favourite, where information is only gathered from preferred options; 3) Rejecting unsampled options, where an interaction between information sampling and subsequent choice plays a role (Hunt et al., 2016). The tendency to succumb to one of these biases varies across individuals but is stable across task repeats although is related to age and educational attainment. Because this information sampling bias is stable for individuals it was not quantified for this task, but in future iterations it may be important to add eye tracking to the task battery to calculate the 'Pavlovian approach-avoid parameter' discussed by Hunt and colleagues.

3.4.5 Version 4

3.4.5.1 Rationale and set-up, April 2019

The primary aim of version 4 was to alter the task so that psychometric analysis could be applied at an individual level, as opposed to the group-level analysis conducted so far. This also provides an alternative output variable to inferences based on RT. Left-right choice and attribute values were used to fit a logistic regression model to each individual's choices. Psychometric curves then allowed me to understand individuals' preference weighting of each choice attribute by assigning coefficients to each attribute. The Party Food task version 3 was updated for valid regression models to be calculated:

1. Reduce multicollinearity of the three decision attributes
2. Increase the predictive power of the logistic model for individual choice behaviour.

This work was carried out in collaboration with Dr Fabian Grabenhorst from the Department of Physiology, Development and Neuroscience at the University of Cambridge.

Multicollinearity is a problem in multi-attribute decision tasks and occurs when one attribute can be linearly predicted from another with a substantial degree of accuracy. In this task, the level three trials contained information about cost, quantity and eco-friendliness. Practically, it means that a strong correlation between the decision attributes would make it impossible to distinguish the attribute(s) on which an individual based their decisions. The attributes in version 3 of this task were significantly collinear, so the price, quantity and eco-friendliness values were manipulated to avoid this. The number of multi-attribute trials was tripled from 52 to 156. In half of the new trials, the attribute values were reversed, i.e. the cost associated with image_left was swapped to image_right. For the remaining trials the attribute values were randomly, yet realistically, modified. The increased number of trials and variation in attribute values reduced the multicollinearity (Table 8), but further manipulations were required to ensure the r values were not significant.

Table 8. Pairwise correlation coefficients for multi-attribute trials in versions 3 and 4 of the Party Food task

Pairwise correlation coefficients	**Cost vs Quantity**	**Cost vs Eco-friendliness**	**Quantity vs Eco-friendliness**
Version 4	-0.2643	0.4901	-0.0981
Version 3	-0.5789	0.4455	0.6498

3.4.5.2 Improving model fit

Increasing the number of choices improved the regression model to better fit participants' actual choices. Version 4 increased from 312 total trials (including parts 1 and 2), to 520 total trials. Part 1 accounted for this increase, from 156 to 364 trials, while part 2 remained unchanged. The time taken to complete part 1 increased from approximately five minutes to ten minutes per participant. This was deemed acceptable for the participants in this study as many tests run for 15-20 minutes, for example, the Cambridge Gambling Task and the One Touch Stockings Tower of London task (Cambridge Cognition, 2006). Breaks were incorporated approximately every 40 trials and participants instructed that they could get up, get a drink or go to the bathroom.

Distributions of the choice attributes to confirmed that no unreasonable or erroneous values were included (Figure 27). It was subsequently necessary to normalise the values of the difference choice attributes given the differences in values (see x-axes, Figure 27) by calculating each value as a proportion of the maximum for each attribute.

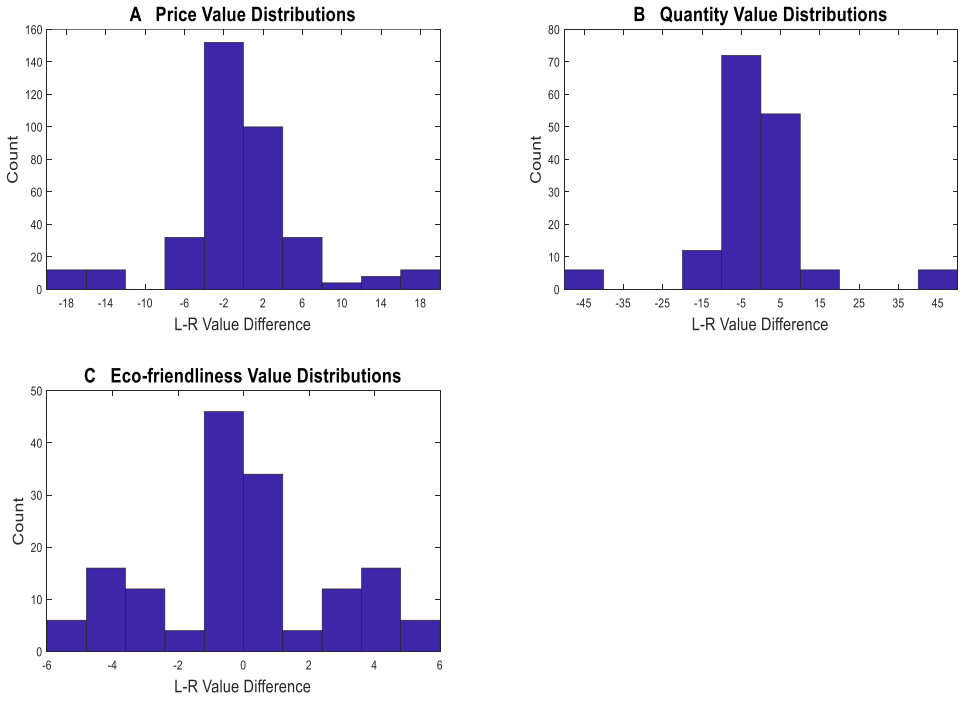


Figure 27. Value distributions for choice attributes quantified from the Party Food task (Part 1): A = Price attribute value distribution; B = Quantity attribute value distribution; C = Eco-friendliness attribute value distribution.

Normalisation of difference values between attributes for left-right choices also improved model fit. Initially, the absolute values for the attributes were varied because they were calculated in difference units, for example, 700-750 = -50mL, whereas 8-10£ = -2£. The large differences were skewing the difference values. To normalise data the difference between two x values (i.e. the price on the left minus the price on the right for one trial) was divided by the sum of the difference between the left and right choices (i.e. the price on the left minus the price on the right for all trials). This outputs a list of new values, normalised to the data set. It was promising to see that normalising the values and increasing the number of trials improved the model fit (Table 9) and also improved multicollinearity (Figure 28).

Table 9. Logistic regression model values for a test participant. Increasing the number of trials and normalising the left-right attribute difference values improved the fit of the logistic regression model used for psychometric modelling of the participants' choices. Only cost was presented in the single attribute trials, whereas cost, quantity and eco-friendliness was presented in the multi-attribute trials. Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion.

	Variance explained	**% correctly predicted choice**	**AIC model quality (lower is better)**	**BIC model quality (lower is better)**
Single attribute trials **non-normalised, fewer trials**	0.2550	88.4615	165.1240	171.2237
Single attribute trials **normalised, more trials**	0.4255	88.4615	128.2392	134.3389
Multi-attribute trials **non-normalised, fewer trials**	0.2372	83.9744	172.9707	185.1701
Multi-attribute trials **normalised, more trials**	0.3832	86.5385	141.3818	153.5812

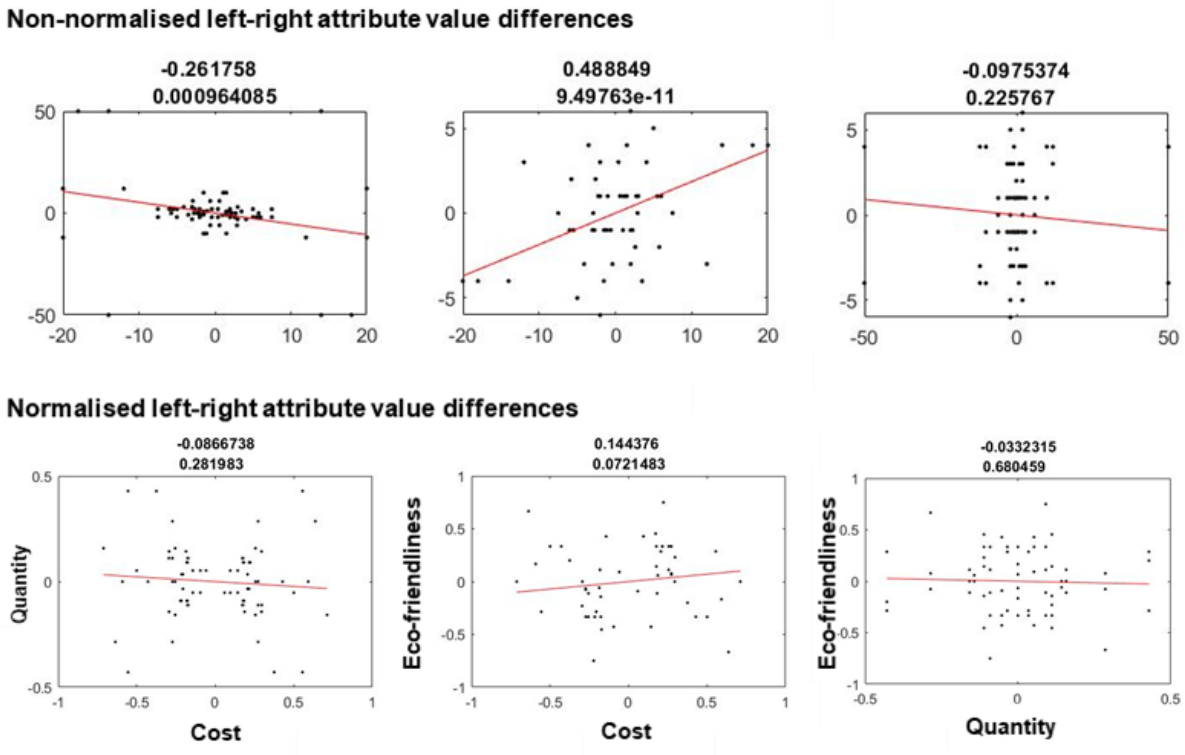


Figure 28. Non-normalised (top) and normalised correlation plots between each of the pairs of attributes (on each plot: top number is pairwise correlation r value, bottom number is p-value; left plots are cost-quantity, middle plots are cost-eco-friendliness, right plots are quantity-eco-friendliness). Shared variance for version 4 choice attributes, left to right R^2= 0.007, 0.019, 0.001.

These pairwise regression plots show outliers in the difference values for each attribute. Normalisation reduced the severity of any outliers. Shared variance between the attributes was low (R^2 in Figure 28 caption) which meant variance in a participant's choice could be explained by the different attributes. Thus, the fourth version of the Party Food task gives the most refined analysis of participant DM based on attributes to date.

3.4.5.3 Example participant

These data were produced to test the analysis above. Ninety percent of choices were for the cheapest item, that is, 37/364 were for the more expensive item, and all other attributes were ignored. Figure 29 below shows the regression coefficients for each of these three attributes and the y-intercept, the p-values for the correlation coefficients (i.e. are they are significantly different from zero?), and the standard errors.

	Beta, regression coefficients =	P value	Standard error
Y intercept	-0.0476	0.8273	0.2183
Cost +	6.3303	0.0000	1.0279
Quant +	0.7138	0.6773	1.7154
Eco +	0.4608	0.5466	0.7644

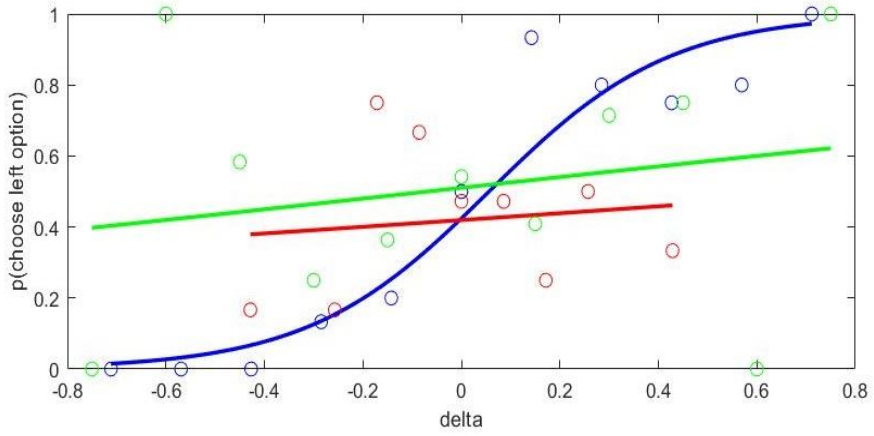


Figure 29. Regression coefficients, p-values and standard errors (in Table) and plotted logistic curves to demonstrate the strength of each attribute to predict left choice (blue = cost, red = quantity, green = eco-friendliness).

A larger absolute coefficient suggests the attribute better explains the participant's choices. First, if the y-intercept is significantly non-zero, it suggests that there is an implicit left/right choice bias in the data set, and left-right counterbalancing is needed in the task to minimise this bias. This counterbalancing is capitalised upon to measure choice consistency. Each choice is presented to participants four times and the variance across these choices is calculated as a proxy for consistency (used in subsequent Chapters).

The graph includes the psychometric curves for each of the decision attributes: cost in blue, quantity in red, and eco-friendliness in green. The line with the tightest sigmoid curve is the attribute which best discriminates the left-right choice behaviour of the participant, and the coefficients can be combined to explain more of the variance in choice behaviour (integrated decision variable; used in subsequent Chapters). The dots are not data points, rather they are a probabilistic representation of this simulated choice behaviour. For each left-right difference (delta), each participant exhibits a probability that they will choose the left option. This can be visualised with a histogram of the deltas.

Below are the number of left minus right choices that fall into each bin of the histogram (11 bins in this case, between delta = -0.8 and 0.8).

N = 2 8 6 24 36 4 36 26 4 8 2

Each bin of the histogram has a probability of being selected, based on the left-right choice of the participant. N1 below is the number of times left was chosen and the bin it corresponds with. We can see this (simulated) participant rarely chose left when the item cost a lot more than the item on the right hand side.

N1 = 0 0 0 4 6 2 34 19 4 6 2

From this and the estimated coefficients (from the logistic regression), a line through these points is computed. This is the blue, red or green line in the above graph (Figure 29).

3.5 Conclusions

The Party Food task iterations and analyses provide a strong starting point from which to test a larger group of controls with a wider demographic range (Chapter 4) and later, to test patients with Huntington's and Parkinson's diseases (Chapter 5). Finally, more versions of the Party Food task were built to use for testing in a longitudinal intervention study (Chapter 6).

In summary, the task provides a novel way to test some aspects of rational and intuitive processing, namely the use of choice attributes and consistency across ecological choice contexts. It is simple to understand and complete, and differences in the motor abilities of participants can be controlled for. The shopping context captures a paradigm that is comparable across a wide demographic range and has minimal cultural biases nor learning and memory requirements. In its most recent version, the decisions made by participants can be analysed carefully at an individual level, and this is further expanded upon in Chapters 4 and 5. A downside to the task is that it is completed on a computer, and those unfamiliar with using a screen and mouse may be disadvantaged. Furthermore, is does not measure rational and intuitive processes completely; only use of attributes, consistency and the effects of time pressure can be quantified, but it is a good starting point. In the future, the task could be developed to test rational and intuitive processing more comprehensively. Finally, the task runs on an openly available platform that does

not require an internet connection (once set up) and the code itself is freely available at https://gitlab.developers.cam.ac.uk/ajw283/decision_making_in_hd/.

4 Decision-Making Across the Lifespan in Healthy Adults

4.1 Summary

Decision-making is a problem-solving activity that results in an optimal or satisfactory solution, which usually defines a course of action. People make hundreds of decisions each day which range in importance: from deciding when and what to eat for lunch, to deciding who to marry and whether to sign a 30-year mortgage contract. Age-related changes in DM processes constitute a vital area of study. Age is the single largest predictor of cognitive decline (Cremers et al., 2020) and in the United Kingdom, there are predicted to be an additional 8.2 million people aged 65 years or older by 2068 (Coates et al., 2019). Building from dual-process theory described previously, older adults tend to make more intuitive decisions, perhaps based on a greater wealth of experience, nostalgia and attachment, or decreased cognitive flexibility and an associated reduction in engagement in new experiences. In contrast, younger adults are more likely to maximise utility through systematic deliberation (these studies are discussed in detail below). These observations may cause older adults to fail to use pertinent information in critical decisions, perhaps concerning their health or finances, whereas they may be more efficient in making routine, everyday choices. However, this has not been demonstrated experimentally to my knowledge.

This Chapter more formally validated the new Party Food task and measured the use of choice attributes, choice consistency, covariates and RT, alongside alternative tests for rational processing, across the adult lifespan. Older adults focused on fewer attributes than young adults and choices became significantly less explainable by the attributes as age increased. Older adults were more consistent to a trend level. The new task better explained group differences compared to existing tasks. These ecologically valid analyses in particular are used in future chapters where DM interventions have been trialled.

4.2 Introduction

4.2.1 Age-related cognitive changes

Age-related changes in cognitive ability have a fundamental effect on rational and intuitive DM. Research has shown that cortical thinning occurs, particularly in frontal regions, in healthy ageing, along with the loss of white matter integrity and the accumulation of toxic aggregated proteins (Charlton et al., 2010; Kaup et al., 2011). In addition, altered connectivity and reduced grey matter is apparent in the medial temporal lobes and hippocampus, especially in people with mild cognitive impairment and Alzheimer's disease (Grady, 2012). These structural changes are correlated with measurable declines in attention, task switching, working memory, processing speed, and long-term memory that begin from the age of 20 (Park et al., 2002). Generalising, it is the high level 'executive' functions that decline with age (Wiebe & Karbach, 2017). However, functions such as emotion regulation, well-being and stability, and semantic (knowledge) memory are spared (Carstensen et al., 2011; Laver, 2009). The preservation of semantic memory, versus working memory, further supports the selective decline of the prefrontal cortex, where activity is highest during tasks that require working memory (St-Laurent et al., 2011). In addition, research has found a reduced ability to ignore distracting information and a loss of inhibitory control (Healey et al., 2008; Motes et al., 2018). This suggests that specific suppression of neural activity is also an adaptive mechanism to combat the effects of ageing.

Counterintuitively, functional MRI studies have found increased activity in the prefrontal cortices of older adults. The "compensation hypothesis" goes some way to explain these results, where wider networks are recruited to support performance comparable to younger adults and sometimes positively correlated with behavioural performance in older (but not younger) groups. However, other studies have found the opposite, where more widespread BOLD signals are not compensatory (Grady, 2012). The Compensation-related utilization of neural circuits (CRUNCH) hypothesis provides explanation for this conflicting fMRI research. It states that older adults recruit more neural resources for easy tasks compared to young adults, and as tasks become more difficult, compensation cannot support continued performance and neural activity declines (Schneider-Garces et al., 2010). Functional networks across brain regions can be compromised with age, with ensuing effects on task performance, suggesting that a compensation strategy has its limits (Grady, 2012). It is important to note that changes in fMRI BOLD signal may be confounded by age-related changes in vasculature

because cerebral blood flow decreases by approximately 0.4% per year (Zhang et al., 2017), which was not measured directly in the aforementioned studies.
Of relevance to DM, it has been suggested that compensation may benefit general cognition, but not in specific tasks or choices (Zarahn et al., 2007), and therefore it could be expected that cognitively healthy older adults may still demonstrate impaired DM.

4.2.2 Complexity aversion and ageing

A recent review of life-like DM found that the elderly have "great difficulty in making optimal choices." The authors synthesized evidence across choice behaviour in health insurance, health care and retirement planning and found that older adults often act as if they are confused about the decision attributes, failing to understand them or process relevant payoff information (Keane & Thorp, 2016). Even in these specific instances, elderly consumers made suboptimal decisions, in keeping with the CRUNCH hypothesis for a decline in performance during difficult tasks, and is probably also underpinned by the aforementioned neural changes.

4.2.2.1 Consumer decision-making in Older Adults

Research into consumer DM was the first to dissect changes across the lifespan in efforts to serve older consumers (Carpenter & Yoon, 2011; John & Cole, 1986). Markets often assume that all consumers are rational, but as pointed out by Keane and Thorp, if a majority of elderly consumers have difficulty making rational choices during complex tasks there is serious concern for the well-being of this population (Keane & Thorp, 2016). Specifically, older consumers consider less information during their purchase decisions (Deshpande & Krishnan, 1981; Mata et al., 2008). They favour, and better recall, long-established brands in comparison to younger adults (Drolet & Yoon, 2020; see Chapter 8), and accordingly favour repeat purchasing. One explanation for this brand favouritism could be the smaller "consideration sets" used by older adults, and the observation that they make more optimal decisions when fewer options are available (Abaluck & Gruber, 2011). For example, older consumers spent less effort reviewing the nutritional information on cereal products than young consumers which led to less appropriate choices (Balasubramanian & Cole, 2002). This is also seen in finance where older and more experienced investors are more likely to use heuristics to their benefit, but demonstrate reduced investment dexterity (Korniotis & Kumar, 2011). The reduced consideration sets described in the consumer literature overlaps nicely with

reports of dedifferentiation in the neuroscience literature. Older adults fail to notice differences, and to show subsequent changes in neural activity, when faced with subtle changes in stimuli (Lee et al., 2011). As such, the reduction in consideration set size may occur because of reduced subconscious awareness of different stimuli.

In line with this, increasing age and decision complexity leads to more inconsistent decisions with increased comprehension errors (Finucane et al., 2005). However, in contrast, one study observed that older adults 'shopped around' more, considering more information before making healthcare choices (Boscarino & Steiber, 1982). One way to reconcile these contradictory findings might be that older adults are more efficient decision makers, mostly favouring strategies to reduce cognitive load, except on occasions when cognitive perseverance has a clear benefit. However, it is hard to ascertain from these findings whether rational processing does in fact decline with age, whether older decision-makers are choosing (rationally) to use heuristics gathered across substantial experiences, or perhaps that these samples are people with early neurodegenerative conditions that are yet to express themselves clinically.

4.2.3 The decision-making environment

Older adults are more susceptible to their decision environment and are more easily distracted during consumer decision tasks (Carpenter & Yoon, 2011). This is explained by the Inhibitory Deficit Hypothesis where older adults make less efficient decisions by failing to suppress goal-irrelevant information (Hasher, 2015; see Chapter 22), or to discard irrelevant information from working memory (Hasher et al., 2007). For example, distractors in a search environment lead older adults to make more errors and take more time to find an object (Madden, 1983). Indeed, poor inhibitory control is associated with greater susceptibility to biased DM (Coolin et al., 2016), however, this environmental influence can also be leveraged to optimise choice behaviour through carefully controlled environmental nudges (Kim et al., 2007; Service et al., 2014; Wood & Neal, 2009). One further consideration is the distraction caused by smartphones; it slows behavioural RTs and decreases the amplitude of event-related potentials during tests of cognition (Leynes et al., 2018). Screen time per hour is longer in young adults (Christensen et al., 2016) so may go some way to counteract the age-related increases in distractibility during real-life DM.

4.2.4 Methods to rehabilitate age-related decision-making impairments

There are ongoing effects to lessen and rehabilitate age-related cognitive decline. 'Brain training' was in vogue for a number of years in the early 2000s and continues to be popular especially among healthy older adults. It is evident that expertise has positive effects on performance but whether short term training induces similar benefits, or indeed provides more general performance rehabilitation, is questionable (Lampit et al., 2014). One study saw PFC activity restored to levels comparable to young adults following two weeks of training in a multitasking paradigm. The authors further found that older adults improved to the level of untrained young adults on an untrained working memory task (Berry et al., 2010). However, in other studies no evidence supported transferable improvements in cognition from computerised 'brain training' tasks to similar, untrained tasks (Owen et al., 2010), nor to everyday cognition (Borness et al., 2013). However, in this last study, Borness and colleagues found that "respite" sessions, where participants watched nature documentaries, significantly improved quality of life. To investigate causality in cognitive rehabilitation, a recent study used transcranial alternating-current stimulation (tACS) to improve working memory, and electroencephalography (EEG) to measure subsequent functional connectivity, to demonstrate restored working memory performance in older adults (Reinhart & Nguyen, 2019). Aerobic exercise has also been shown to have a small, yet significant, effect on cognitive flexibility and inhibitory control in adults over 60 years old (Xiong et al., 2020). Bilingual older adults are shown to have better white matter integrity than monolinguals, with associated stronger prefrontal functional connectivity, and importantly, superior cognitive function and a four-year delay in all-cause dementia diagnoses (Alladi et al., 2013; Gold et al., 2013). Given these findings, it is plausible that cognition and DM can be a target for rehabilitation but we do not currently have a sufficient mechanistic understanding of DM processes to design a highly specific and successful cognitive therapy.

4.2.5 Realistic, everyday tasks to measure decision-making

Of relevance to the task employed in this study, it has been shown that older adults are able to recall the prices of grocery products equally as well as younger adults. Building from earlier research which showed older adults' reliance on heuristics, the author concluded that this was due to their increased familiarity with the context (Castel, 2005). This finding highlights the importance of ecological validity in cognitive

testing of older individuals, more so than young adults, where context has a smaller effect on DM. Another study which used a price inference task in older and younger adults showed that older adults searched for less information but took longer to process it, and used simpler strategies overall, but performed equally as well as young adults (Mata et al., 2008). In complex environments simple strategies are often superior to integrate information and make predictions (Todd & Gigerenzer, 2000). These findings contribute to an overall picture of efficient DM in everyday situations for older adults. This is an encouraging finding given that most DM occurs in familiar contexts. Therefore, to understand where older adults may be impaired in DM, this study used the familiar context of supermarket choices to create a level playing field across ages.

4.2.6 The present study

To my knowledge, rational-intuitive DM processes have not been analysed in a carefully controlled experimental set up that considers the aforementioned variables, complexity aversion and the relevance of context. The bat and ball cost calculation, for example, is not a realistic scenario to measure an individual's DM, and nor are any of the currently available tools. Thus, this Chapter will present a carefully designed, yet realistic task to investigate the use of choice variables and choice consistency during time-unlimited and time-limited food-choice paradigms.

4.3 Objectives

The primary objective of this study was to use the Party Food task developed in the previous chapter to investigate how some aspects of rational and intuitive DM change across the adult lifespan. Secondarily, the objective was to investigate how differences in response inhibition, anxiety, depression, irritability and intelligence influence rational and intuitive processes. Furthermore, this study aimed to further validate the new Party Food DM task to detect differences in DM processing. Finally, a better understanding of these processes might, in the future, identify specific and tractable targets for intervention to support good DM.

4.4 Methods

4.4.1 Study Recruitment

Participants (N=62) were recruited into this study to gather a representative sample of DM across the lifespan, and later binarized into two groups, old (N=32, age 37-79) and young (N=30, age 19-29). Individuals met the following criteria prior to participating: 1) no known neurological or psychiatric condition that, in the opinion of the investigator, could impact on their ability to complete the study protocol, 2) age >18, and 3) willing and able to complete all assessments in the protocol. The following exclusion criteria were also applied: 1) non-native English speaker, whose level of understanding or fluency was likely to impact on their ability to complete the study assessments, 2) uncorrected sight or hearing impairment which would interfere with cognitive testing, and 3) known learning disability, special education need or medical problem that interferes with the individual's ability to complete the study procedures.

4.4.2 Ethical Approval, Insurance and Sponsorship

The study was conducted under approval from two separate research ethics committees. Firstly, approval was sought from the CPREC for the earlier participants (CPREC 2018.121). The University Finance Division insured the study (HVS/2019/2901) and the Research and Development department sponsored the protocol (G106773). Second, approval was sought from the Medical Health Research Authority (Project ID: 258455) and approved by the South Central – Oxford C Research Ethics Committee (19/SC/0153) to include patients and controls (for the subsequent study in Chapter 5). Insurance (HVS/2018/2503) and joint sponsorship (A095071) were through the University and Cambridge University Hospitals NHS Foundation Trust.

4.4.3 Data Storage

Sensitive data as defined as that which contained person-identifiable data (PID), for example name, contact details and date of birth. Such data was stored on the SDHS and used to contact participants only, after which an anonymous identification number was used. The code break between PID and ID number was also stored on the SDHS. This service is hosted at the University of Cambridge Clinical School and provides a dedicated network, separated from the production network by a firewall, for storing sensitive personal data and hosting computers involved in its management and analysis.

Access was via a secure Virtual Desktop (based on Citrix XenDesktop 7.6) and all data imported or exported to/from the SDHS was made via the secure transfer service.

4.4.4 Study Visit

The study was conducted during an in-person visit to the John Van Geest Centre for Brain Repair in Cambridge, United Kingdom. This study took place from April 2019 to December 2020 and each visit was conducted in a quiet clinic room. Despite the intermittent lockdowns that came as a result of the coronavirus pandemic, later visits were able to continue in a similar manner to earlier ones. Enhanced hygiene and sanitation procedures were used to ensure the safety of participants, including regular use of hand sanitiser, temperature and COVID-19 symptom checks prior to entering the building, cleaning of clinic rooms before and after each visit, masks worn by both myself and the participant, room ventilation, and a two-metre distance maintained. Each visit took approximately two hours to complete and Table 10 summarises the study procedures. Each study procedure is described in more detail in Appendix 2.

Table 10. Study procedures. Abbreviations: HADS+I = Hospital Anxiety and Depression and Snaith Irritability Scale; SDMT = Symbol Digit Modality Test; ACE-R = Addenbrooke's Cognitive Exam - Revised; NART = National Adult Reading Test; SST = Stop Signal Task; GDMS = General Decision Making Style; CRT = Cognitive Reflection Test.

Assessments	Time to complete (mins)
Informed Consent	10
HADS+I	5
ACE-R	15
NART	5
SST	10
Bees information sampling task	10
Trender reasoning task	10
Decision making experiences questionnaire	5
GDMS questionnaire	5
Party Food task	20
Supplementary decision making tasks (Jelly bean, Linda problem, CRT)	10
Rey complex figure drawing	5

Total (plus breaks, taken at the participant's discretion)	**110**

4.4.5 Statistical Analysis

R studio (version 1.2.5033 "Orange Blossom") was used to conduct the majority of analysis presented in this Chapter, including participant demographic analysis with the Arsenal package (Heinzen et al., 2020). To calculate participant verbal IQ I referred to the equation calculated by Bright and colleagues (Bright et al., 2016):

$$\text{Predicted WAIS-IV VIQ} = -0.9775 \times \text{NART error score} + 126.41$$

Shapiro-Wilk tests were used to determine normality of each variable and an F-test to determine equality of variance. Wilcoxon Rank Sum tests were used for non-normal variables and Chi-squared test was used for categorical variables.

Mann-Whitney U and Kruskal-Wallis tests were used to determine group (young vs. old adult) differences between decision attributes (cost, quantity, eco-friendliness) and choice consistency, instead of parametric tests because the coefficient distributions were non-normal. Dunn's post-hoc tests were applied where relevant. Parametric Welch's T-tests were used to quantify differences between binarized young and old groups where requirements for equality of variance and normality were met.

Validation of the Party Food task against traditional measures for rational-intuitive DM was with a non-parametric multivariate analysis of variance for task-based measures using the NPMV package (Burchett et al., 2017), and a separate Pearson's correlation for questionnaire-based measures.

4.4.6 Behavioural Modelling

MATLAB (version R2018.b) was used to write the logistic regression models, test multicollinearity and present the subsequent results. Dr Fabian Grabenhorst assisted with writing the initial scripts for these analyses and all scripts are available in the GitLab project link.

A Pearson's correlation was performed to quantify patterns in the output of behavioural models across the lifespan.

A linear model was applied to selected outcome variables (choice prediction and choice consistency) with relevant covariates (anxiety and depression, response inhibition).

4.4.7 Power Calculation

The central task used in this study (Party Food task) was novel and therefore no previous effect sizes could be used to calculate power and estimate sample size requirements. Instead, I aimed to recruit at least 30 participants per group to reach statistical normality assumptions under the Central Limit Theorem. Furthermore, an *a priori* correlation power analysis using a bivariate normal model in G*Power (version 3.1.9.4) suggested that with a generic medium effect size of 0.35, standard 0.05 chance of type I error and 0.80 power to detect a correlation, the sample size should contain 61 participants (Faul et al., 2007).

4.5 Results

4.5.1 Participants

The characteristics of each participant group are shown in Table 11. No significant differences, bar age, were found between young and old adults across the following variables: sex, verbal IQ, global cognition (measured by ACE-R total score), depression, anxiety, or irritability. Non-parametric tests were used for all continuous variables as they did not pass tests for normality and equality of variance. All participants scored within the clinically normal ranges for global cognitive and psychiatric variables. All participants met the effort and attention cut off scores in the Rey Complex Figure Drawing task.

Table 11. Participant demographics. (1) = Kruskal-Wallis Rank Sum test (equivalent to Wilcoxon Rank Sum test when the grouping has two levels). (2) = Pearson's Chi-squared test.

	Young (N=30)	Old (N=32)	p value
Age			
- Range	19.0 - 29.0	37.0 - 79.0	< 0.001 (1)
- Mean	23.4	57.7	
Sex, Female	15 (50.0%)	16 (50.0%)	1.000 (2)
Verbal IQ			
- Range	100.0 - 120.5	95.1 - 125.4	0.076 (1)
- Mean	112.7	115.0	
ACE-R Total Score			
- Range	91.0 - 100.0	86.0 - 100.0	0.433 (1)
- Mean	97.0	96.3	
Depression			

- Range	0.0 - 5.0	1.0 - 6.0	0.678 (1)
- Mean	1.4	1.2	
Anxiety			
- Range	0.0 - 17.0	0.0 - 13.0	0.188 (1)
- Mean	6.4	5.1	
Irritability			
- Range	0.0 - 10.0	0.0 - 8.0	0.804 (1)
- Mean	4.3	4.1	

4.5.2 Choice attributes can be parsed and weighted to explain individuals' decisions

From the Party Food task, multi-attribute trials (n=156) were analysed to understand which information participants based their choices on, using the methods described in Chapter 3. In these trials, individuals were faced with image, cost, quantity, cost per unit, and eco-friendliness information. I could not quantify image differences with this method and also did not include the cost-per-unit attribute due to collinearity with the cost and quantity attributes, therefore, coefficients for cost, quantity and eco-friendliness were calculated. It may be possible to quantify a coefficient for image in future analyses. The DM interventions (which are the ultimate goal of this work) will be unlikely to manipulate image, because they will not be able to control user's visual input, but rather to manipulate the written information presented. Therefore it is more important to understand how written attributes such as cost are processed.

Coefficients for each attribute were calculated using a logistic regression model and psychometric curves were generated to show the relationship between attributes and choices graphically at the individual level. Figure 30 shows four examples of such plots, where each graph represents the individual's sensitivity to left-right differences in the respective attribute across their choices. An inclining sigmoid shape indicates that attribute differences in favour of the left option would increase left-choice probability; a flat curve would indicate a weak or no relationship between attribute delta and choice probability. These plots support that the task captures common group effects for some attributes (e.g. low cost is favoured) but also that there is individual variation (e.g. weight placed on item's eco-friendliness).

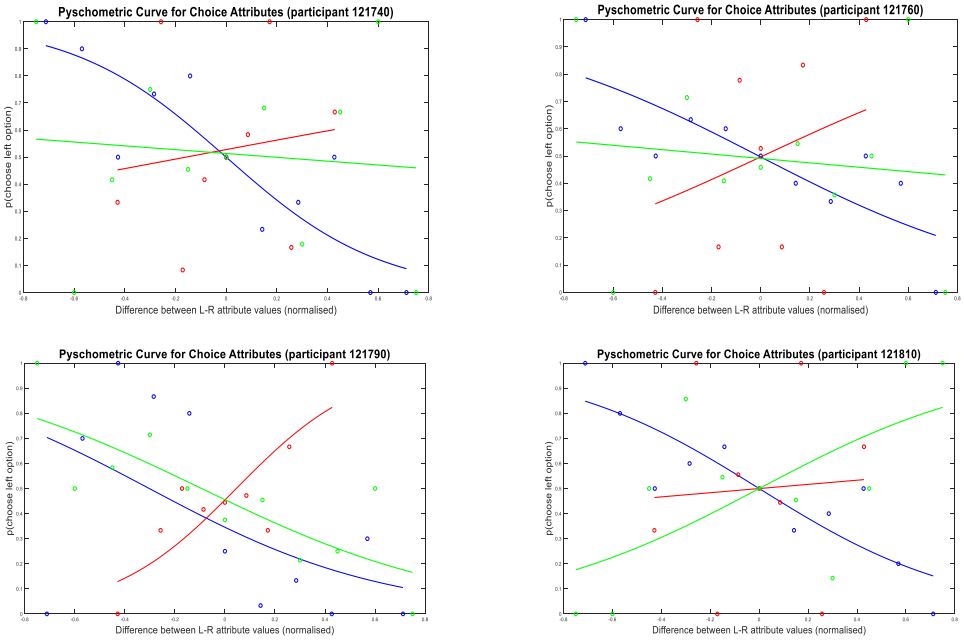


Figure 30. Individual psychometric curves based on logistic regression coefficients for three choice attributes. Blue = cost; red = quantity; green = eco-friendliness. The more sigmoid-shaped each curve, the better predictor that attribute is of a participant's choices. For example, the top left graph (participant 121740) has the largest coefficient for cost and does not use the quantity and eco-friendliness attributes as much to guide their choices. Across all four graphs it is clear that individuals display different preferences and strength of preferences for the three attributes. P-values and regression coefficients for these participants, for cost, quantity and eco-friendliness curves, respectively: 121740 (top left) p=0.000 (β=-3.95), 0.075(β=2.39), 0.644(β=-0.28); 121760 (top right) p= 0.006 (β=-1.47), 0.710 (β=0.38), 0.332(β=-0.52); 121790 (bottom left) p=0.000 (β=-4.75), 0.001(β=5.16), 0.002 (β=-2.04); 121810 (bottom right) p=0.000 (β=-2.20), 0.343 (β=1.04), 0.264 (β=-0.62).

4.5.3 Choice coefficients can be used to explain decision behaviour

It is further possible to generate an integrated decision variable, a sharper sigmoid graph with greater explanatory power, by calculating a linear sum of the weighted attributes (Figure 31, black graph). This provides a nice graphical explanation of how these attributes capture individual preference, and I have further confirmed this mathematically by comparing three different regression models to show that incorporating all attributes gives a substantially better model fit (Table 12).

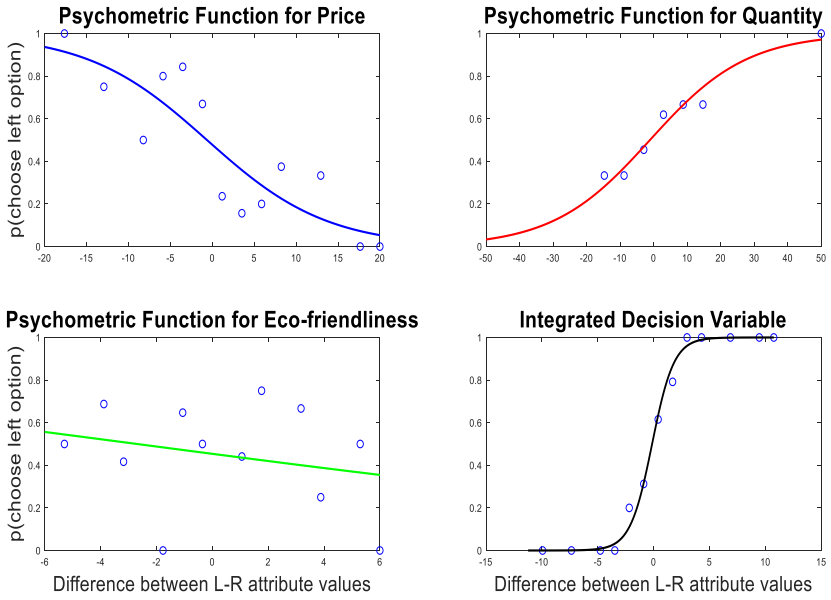


Figure 31. Psychometric functions for each attribute and subsequent integrated decision variable can be calculated for each individual, pictured is an example set of plots (participant 121740). The differences values (x-axis) for each attribute are not normalised in these plots, but when integrated they are calculated as a proportion of the maximum possible values for that attribute.

These data show that model fit is reasonable in terms of pseudoR^2 and choice percent prediction (above chance level). Interestingly, the best model fit is different for young and old adults: the full model which incorporates all attributes is best for the young group, while the model which includes only the cost attribute best fits the old group. In other words, the model with the lowest Akaike Information Criterion (AIC; an estimate of prediction error) is the most complex for young adults, and the most simple for older adults (Table 12).

Table 12. Logistic Regression Model fit for Party Food task attributes, comparing median values for young and old adults across three models of decreasing complexity. In bold are the best models for each group, in brackets the standard deviation.

	Young Adults			**Older Adults**		
	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC
Model 1 – Cost, Quantity, Eco-friendliness	**0.24 [0.19]**	**75.00 [11.6]**	**175.43 [41.2]**	0.11 [0.15]	65.38 [10.6]	204.10 [32.5]
Model 2 – Cost, Quantity	0.15 [0.18]	69.87 [13.4]	188.84 [40.2]	0.07 [0.13]	64.74 [10.3]	204.40 [29.1]
Model 3 – Cost	0.19 [0.20]	71.15 [14.7]	181.32 [44.4]	**0.11 [0.14]**	**66.35 [11.2]**	**201.13 [31.7]**

Plotting the coefficients of each choice attribute further supports this; the bars in Figure 33 are shorter in the old group compared to the young. Comparing the predictability of choices between groups shows that a significantly greater percentage of young adults' choices can be predicted when using the models that best fit each group ($t=2.54$, $p=0.01$; equal variances $F=1.20$, $p=0.61$; normal distributions for young ($W=0.98$, $p=0.85$) and old ($W=0.98$, $p=0.80$)). This suggests that the young group are using the attributes quantified in this model to make their choices during the task, more so than the older group. However, the somewhat weak model fit and relatively large standard deviations in Table 12 suggest some reservation about these results; there may be additional factors which influenced participants' decisions that have not be captured.

4.5.4 Decision behaviour becomes less explainable as age increases

Acknowledging the difference in age range between the two groups (young 19-29 years, old 37-79 years), it is important to understand whether these findings are due to group structure rather than actual differences in rational processing. By plotting a correlation for age against choice predictability (based on how the attribute coefficients explain left-right choice), the negative relationship is significant (Figure 32; Pearson's $R=-0.33$, $p=0.009$). For each year older, participants' choices become 0.33% less predictable, although a wide range of modelled choice predictions exist across all ages. This plot also demonstrates the dense group of individuals between 20 and 30 years.

The correlation appears to be driven by the difference between 20-30 and 65-80year olds, while an intermediate group, 30-60 years, is not visually different from the 20-30 year olds, but an larger sample size is needed to confirm this.

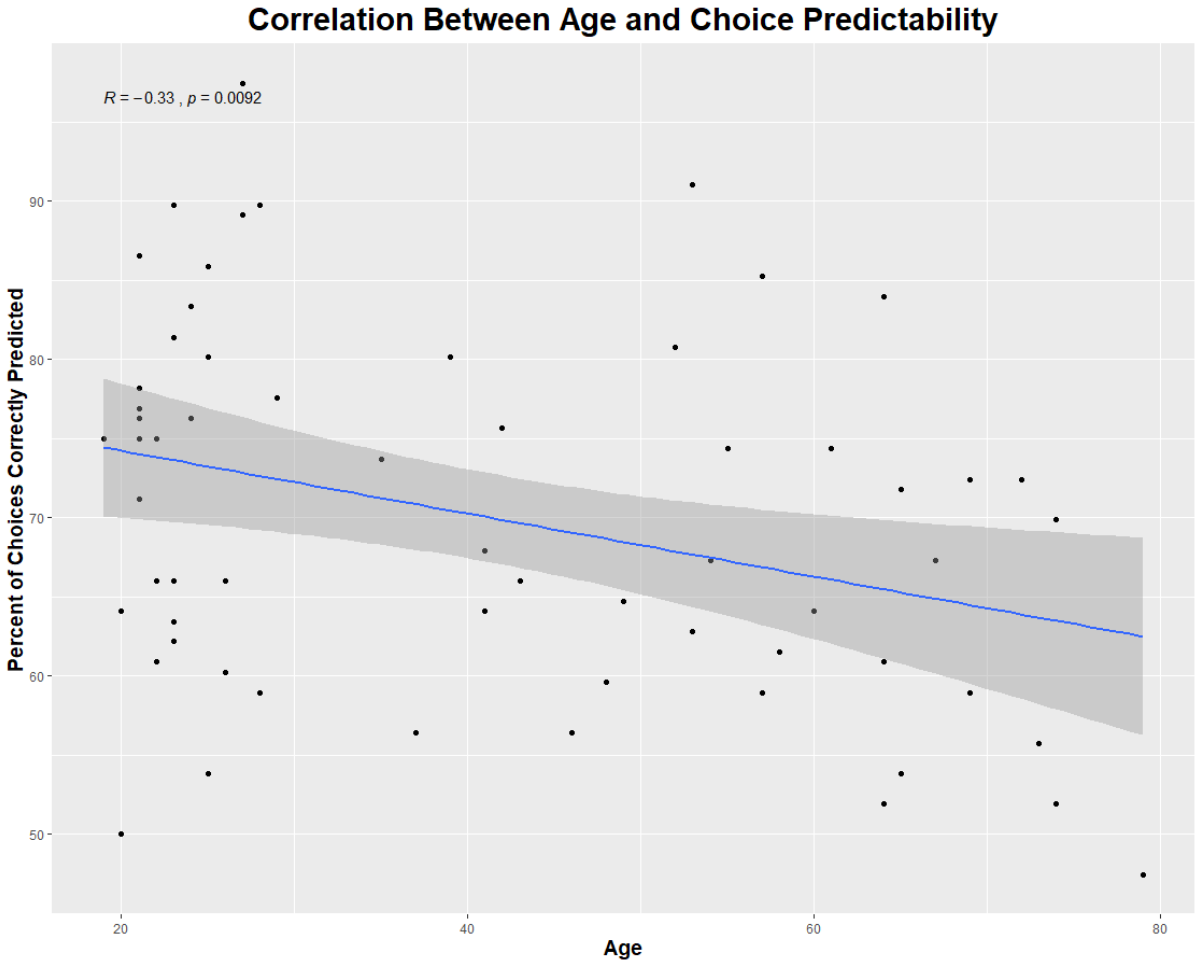


Figure 32. Correlation plot between age and choice predictability (how the attribute coefficients explain left-right choice) from the logistic regression model applied to the Party Food task. There is a negative correlation between age and choice predictability (Pearson's R=-0.33, p=0.0092).

4.5.5 Young and old adults do not value cost, quantity nor eco-friendliness attributes differently

A breakdown of the choice attributes showed that the young group used cost, quantity and eco-friendliness to make their choices and the older group used cost and quantity (but not eco-friendliness); the pooled regression coefficients were significantly non-zero. All attribute coefficients were non-normally distributed (Shapiro Wilk test p-values <0.01) thus I used non-parametric tests to compare means. (Young adults: cost

V=253, p=0.003, quantity V=274, p<0.001, eco-friendliness V=253, p=0.003; older adults: cost V=0, p<0.001, quantity V=330, p=0.002, eco-friendliness V=252, p=0.52).

However, there are no statistically significant differences between groups for the attribute coefficients. There were no differences in the coefficients for cost (W=7948, p=0.98), quantity (W=7920, p=0.98) nor eco-friendliness (W=7872, p=0.91). In other words, this suggests there are no differences in how sensitive young and old adults are to cost, quantity and eco-friendliness. Note that the y-intercept attribute is a proxy to measure the left-right choice bias, thus should not be different from zero, nor different between the groups (non-normal distribution W=0.91, p<0.01; One-sample Mann-Whitney U V=13820, p=0.15). No participants demonstrated significant left-right choice bias as measured by the y-intercept coefficient not being different from zero.

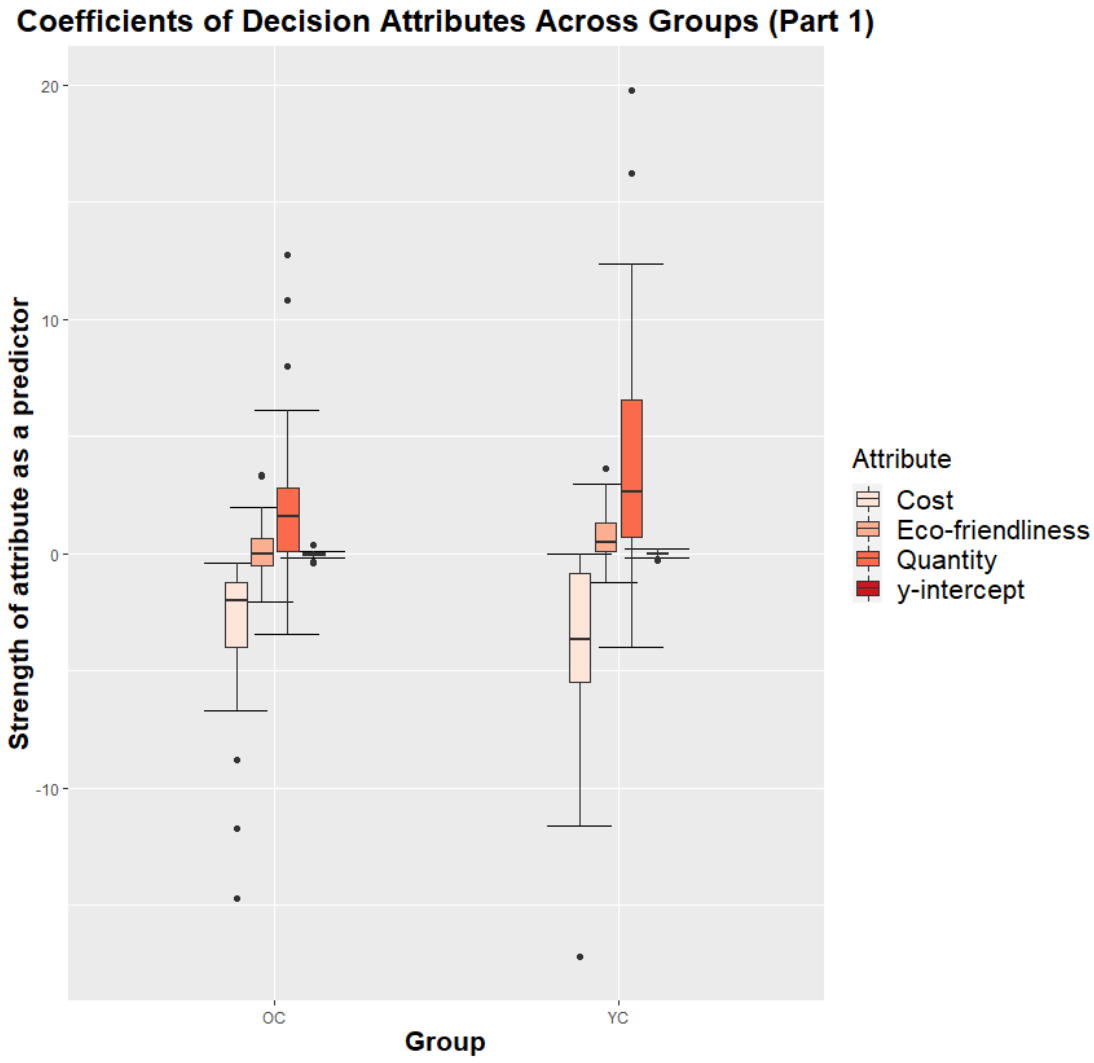


Figure 33. Bar plot of decision attribute coefficients (cost, quantity, eco-friendliness and y-intercept) for young against old adults. There were no differences between young and old adults for any of the attribute coefficients. OC = old adults, YC = young adults. For each box, the upper and lower hinges correspond to the first and

third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

4.5.6 Decision time limits cause neglect of choice attributes

The second part of the Party Food task gives the opportunity to analyse DM under time pressure, one method to manipulate the use of intuitive rather than rational processing (Phillips et al., 2016). This part of the task was not designed to pass tests for multicollinearity, given that the weighting of attributes is a process reserved for rational processing, thus it is only possible to observe relative coefficients between the groups and relative choice consistency. As in Part One of the task, the distributions of the three attributes are plotted below and normalised values are calculated as a proportion of the maximum for each attribute (Figure 34). The distributions are comparable, visually, to those in Part One.

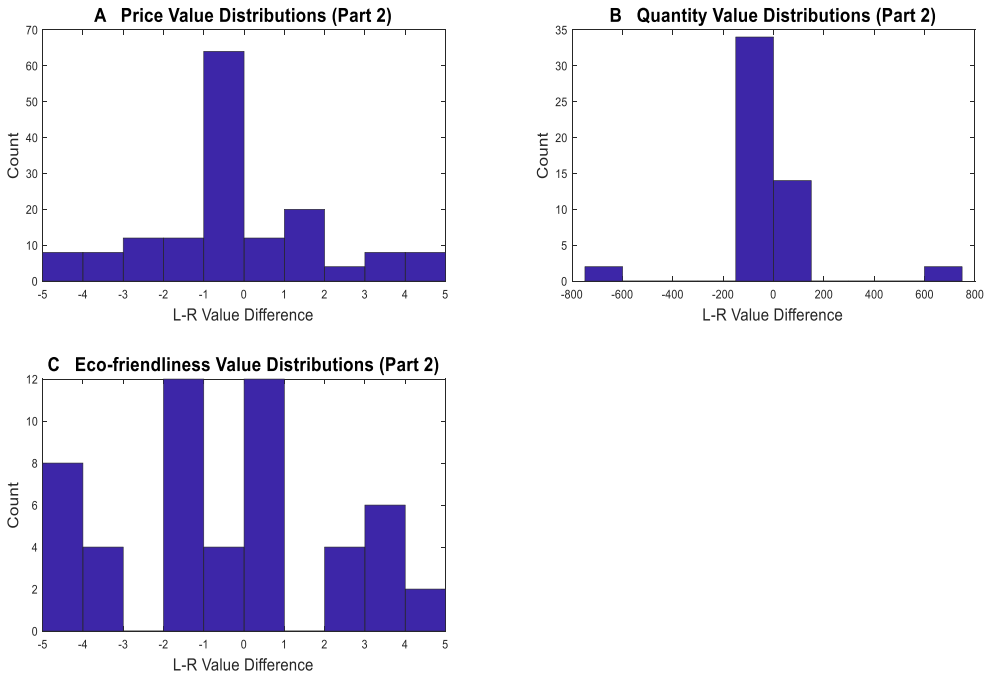


Figure 34. Value distributions for choice attributes quantified from the Party Food task (Part 2): A = Price attribute value distribution; B = Quantity attribute value distribution; C = Eco-friendliness attribute value distribution.

Data from ten participants was removed after calculating the regression coefficients as these participants demonstrated significant left-right bias, as measured by the y-intercept value being significantly non-zero. It was likely that these participants

were selecting left or right without considering the onscreen choice. Of the participants who demonstrated this bias, four were old controls and six were young controls. The remaining participants did not demonstrate left-right choice bias, as shown by the y-intercept coefficient values. Coefficients are not normally distributed (Shapiro-Wilk test: $W=0.91$, $p<0.01$) and are not significantly different from zero (one-sample Mann-Whitney U test: $V=17036$, $p=0.34$). As in Part One of the Party Food task, the coefficients are non-normally distributed (Shapiro-Wilk for cost ($W=0.75$, $p<0.01$), quantity ($W=0.54$, $p<0.01$) and eco-friendliness ($W=0.85$, $p<0.01$). Furthermore, there were no differences in the correlation coefficients between groups (Mann-Whitney U tests; Cost ($W=7936$, $p=1.00$), Quantity ($W=7908$, $p=0.96$) and Eco-friendliness ($W=8028$, $p=0.87$), and coefficients for all attributes are around zero (Figure 35) thus demonstrating that neither young nor old adults were using them to make choices while under time pressure, as they did in part one of the task (where time was unlimited).

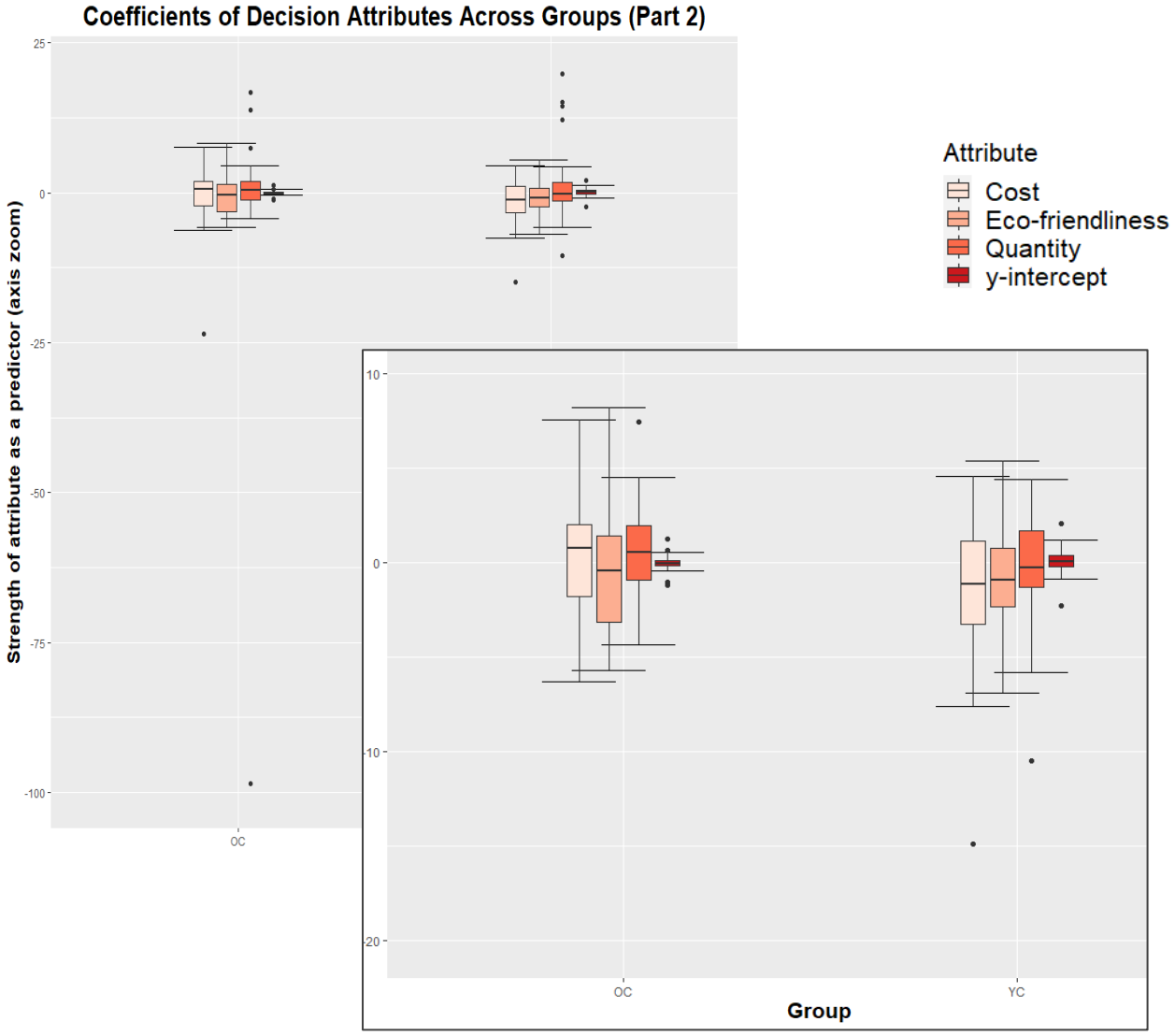


Figure 35. Coefficients of decision attributes across old and young adult for Part Two of the Party Food Task (where time to decide is limited relative to the participant's prior response times). The imposed time limit reduces the size of the coefficients, effectively demonstrating that the participants failed to use this attribute information in a time-limited situation. Overlayed plot shows axis zoom for the same plot. The coefficients are not statistically different from zero for any group or attribute. Data from ten participants is not plotted because after calculating the regression coefficients these participants demonstrated significant left-right bias. For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

Decision consistency varies across individuals

To further understand individual differences in DM when a time limit is applied, I have compared the consistency of choices between participants and groups. Each choice in parts one and two of the Party Food task was presented four times, in part to allow left-right counterbalancing. This provided the opportunity to calculate the variance between the 'same' choice and a lower variance is therefore a proxy measure for more consistent choice behaviour. Furthermore, the consistency calculation leverages another nuance of this task: three levels of complexity exist across the choices participants see. The simplest choices show just one attribute, the image. 'Medium' choices contain two attributes, cost and image. The most complex choices contain five attributes, image, cost, quantity, cost per unit, and eco-friendliness. Consistency is calculated separately across each level of complexity. First are four examples of individual choice consistency to demonstrate patterns across complexity levels in a representative set of individuals (Figure 36).

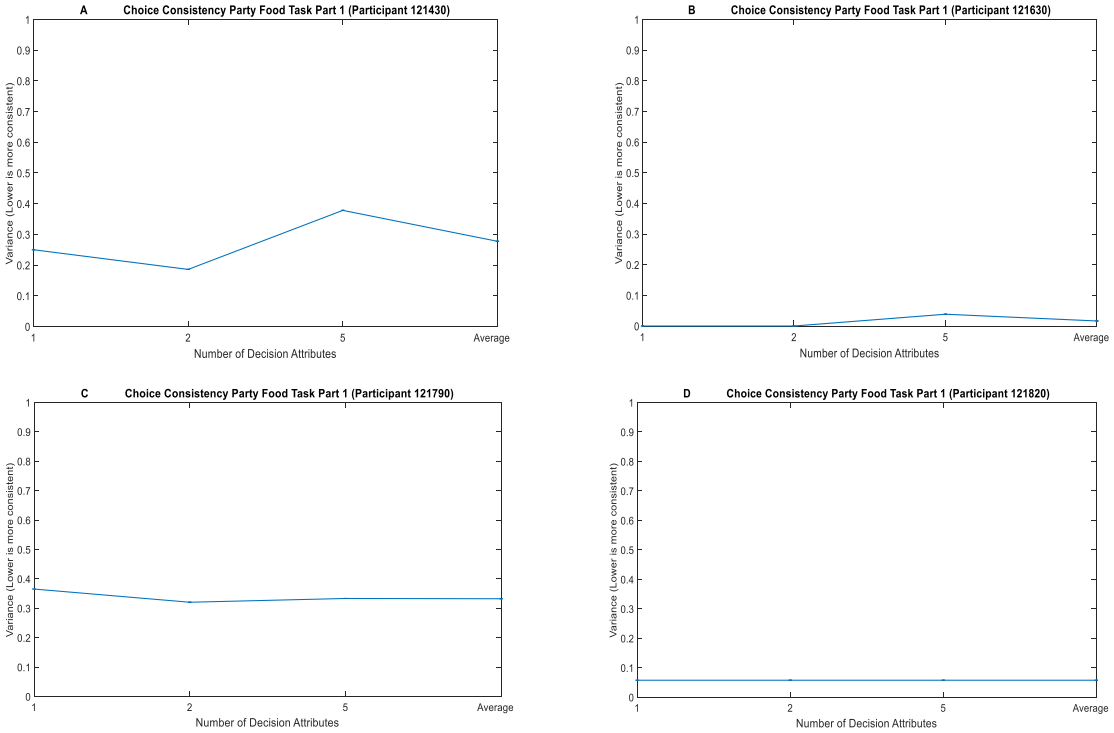


Figure 36. Four examples of individual choice consistency across the Party Food task, part one. Choices are divided into three levels based on the amount of information that was presented to the participant: 1, 2 or 5 attributes. One attribute is where the participant chose between two images, two attributes are where the participant has image and cost information for their choices, and five attributes include image, cost, quantity, cost per unit and eco-friendliness attributes. Every choice was presented four times, for side-of-screen counterbalancing. Consistency was measured as the variance across identical choices; where a lower variance indicates more consistent choice behaviour, and where zero indicates total consistency. Also included on the x-axis is the average variance across all choices for that participant. Four examples of task consistency are shown above which demonstrates that consistency is variable across individuals, for example, participant 121430 (A) is markedly less consistent than participant 121630 (B).

4.5.7 Decision consistency is not different between old and young adults, in deliberative nor intuitive decisions

Comparison between young and old adult groups shows that participants appear to become less consistent as the number of attributes increases (Figure 37). Using a Shapiro-Wilk test for normality, some levels for both young and old adults in part one are non-normally distributed, thus I used non-parametric tests to analyse these data (Young: one attribute W=0.86, p<0.01*, two attributes W=0.95, p=0.17, five attributes W=0.90, p=0.01*; Old: one attribute W=0.82, p<0.01*, two attributes W=0.89, p<0.01*, five attributes W=0.94, p<0.10). Variance was equal between groups for the

three levels of complexity (one attribute: F=2.07, p=0.05, two attributes: F=0.67, p=0.29, five attributes: F=1.68, p=0.16). Mann-Whitney U tests showed that there were no differences between groups for the most simple decisions (one attribute W=561, p=0.24), or for two-attribute decisions (W=578, p=0.17), but there was a trend towards older adults choosing more consistently when faced with the most complex, five-attribute choices (i.e. lower mean variance) (W=606, p=0.08, not corrected for multiple comparisons).

The same calculations were made for part two of the task, where time to decide was limited. Using a Shapiro-Wilk test for normality, most levels for both young and old adults in part two are normally distributed, thus I used parametric t-tests to analyse all data except comparisons which included older adults' five-attribute choices (Young: one attribute W=0.95, p=0.35, two attributes W=0.98, p=0.88, five attributes W=0.96, p=0.37; Old: one attribute W=0.95, p=0.18, two attributes W=0.93, p=0.05, five attributes W=0.93, p=0.04*). Variance was equal between groups for the three levels of complexity (one attribute: F=0.46, p=0.07, two attributes: F=0.76, p=0.48, five attributes: F=0.57, p=0.13). Welch's t-tests showed that there were no differences between groups for the most simple decisions (one attribute t=0.09, p=0.92), for two-attribute decisions (t=0.21, p=0.84), nor for the five-attribute choices (i.e. lower mean variance) (Mann-Whitney U test, W=526, p=0.26). From both parts one and two, this suggests that applying time pressure makes groups substantially and equally inconsistent. However, when faced with five attributes and an unlimited time-to-choose, older adults show a trend towards greater choice consistency than young adults.

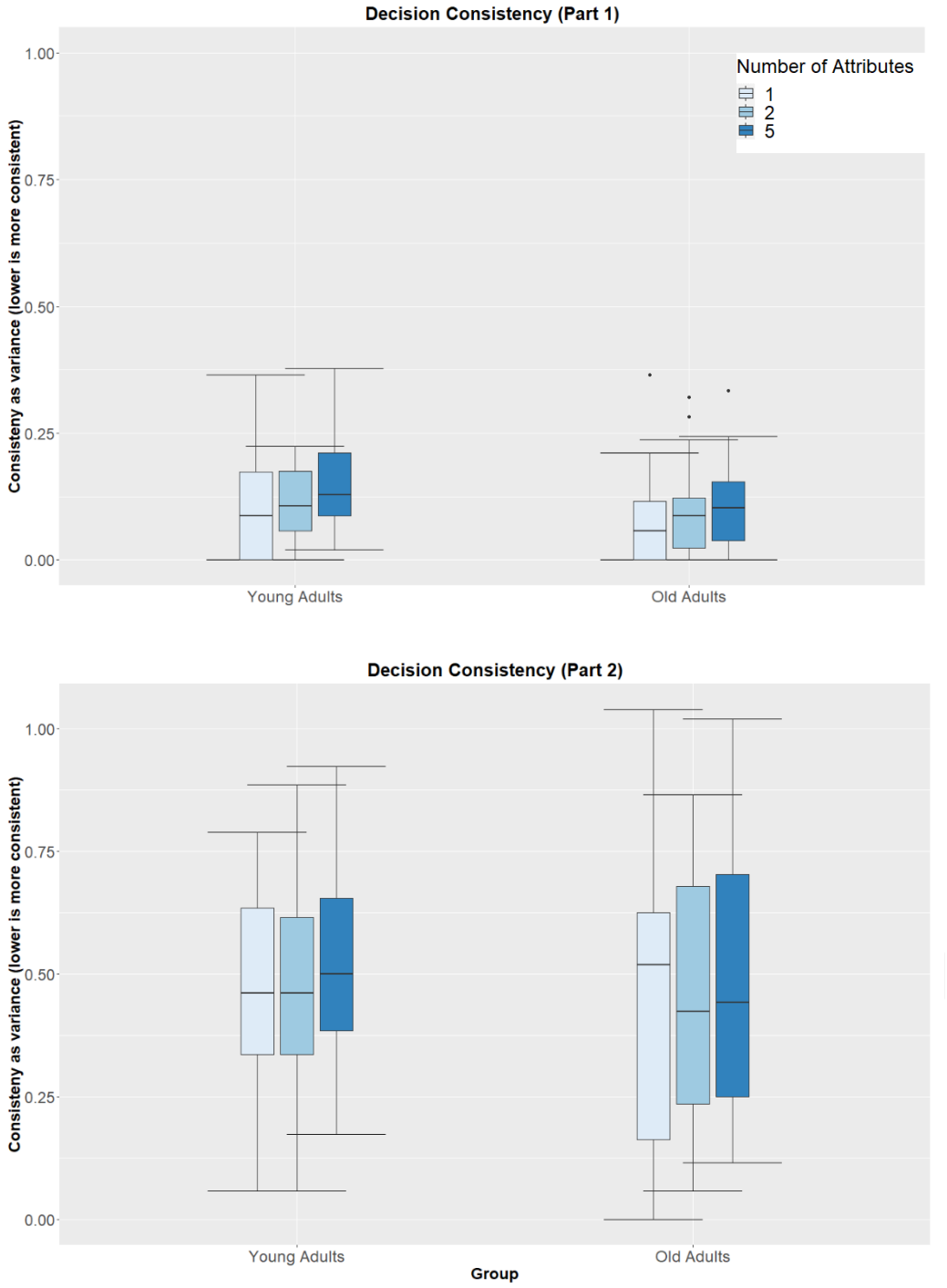


Figure 37. Decision consistency plotted across complexity levels (number of attributes) and between groups (young and old adults). Consistency is calculated as the amount of variance across identical decisions that were presented four times during the Party Food task (part 1 (top), part 2 (bottom)). When given an unlimited time to decide, both groups have relatively low variance in their choices, and variance increases when more attributes are included in the decision. Under time pressure (Part 2), both groups across all complexity levels show much higher variance. For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

4.5.8 Decision consistency is not different across choices with increasing complexity

Within-group comparisons showed that decision consistency is not different for young adults across the three complexity levels in part one (Kruskal-Wallis test statistic =4.16, p=0.12), nor in part two (Kruskal-Wallis test statistic =1.28, p=0.53). For older adults, there is a trend towards decreasing consistency under increasing complexity (Kruskal-Wallis test statistic =5.11, p=0.08), but there are no within-group differences in part two (Kruskal-Wallis test statistic =0.19, p=0.91).

4.5.9 Decision consistency is significantly worse during intuitive decision making

Finally, I compared within-group differences between parts one and two of the Party Food task, where time was unlimited and restricted, respectively. As is clear from the plots in Figure 37, there are significant differences in the choice variance in both the young group (Kruskal-Wallis test statistic =71.01, p<0.01), and in the old group (Kruskal-Wallis test statistic =50.0, p<0.01) driven by the decreased decision consistency when time was limited (Dunn's post-hoc test; result matrices not shown).

4.5.10 Depression, anxiety and response inhibition are not associated with choice predictability

There were no differences between old and young adults across measures of anxiety, depression and irritability (see Demographics, Table 11). The older group had significantly worse response inhibition as measured by the stop-signal task summary scores as has been shown in prior research on cognitive changes in older adults (higher is worse; non-normal distributions; Mann-Whitney U W=195, p<0.01).

Based on literature suggesting that affect and response inhibition plays a role in DM, a linear model with covariates was applied to the choice predictability data to understand if alternative variables could explain some of the observed group differences. Both groups' distributions for choice prediction (calculated previously using the logistic regression values with the best fit at group level) were normal with equal variance (Shapiro-Wilk test: young (W=0.98, p=0.79; old W=0.97, p=0.49; F-test F=1.14, p=0.72). Table 13 below shows that acute feelings of anxiety and depression and response inhibition (as measured by stop-signal task summary score) were not associated with predictability of choices.

Table 13. A linear model was applied to the choice predictability scores for each group (young and old adults) including two covariates: HADS (Hospital Anxiety and Depression Scale) and response inhibition, as measured by the Stop Signal Task. Neither covariate was associated with groups' choice predictability.

Term	Estimate	Std error	Statistic	P-value
Group (old/young)	-7.29	3.27	-2.22	0.02
HADS	-0.40	0.25	-1.59	0.12
Response inhibition	-0.00	0.03	-0.03	0.98

4.5.11 Cognitive reflection test and other measures of rationality and intuition show expected age-related changes and positive correlations with choice predictability

Additional tests were included in the visit to confirm that the new Party Food task was indeed capturing rational and intuitive DM. The following additional tests were included: CRT, Linda Problem, Jelly Bean Task, Trender (matrix) reasoning, Bees information sampling. The final two tasks measure rational processing alone, whereas the first three can ascertain whether rational or intuitive processing was used based on the answer given. Choice predictability values were used as the dependent variable for the Party Food task in these analyses because they are based on the rational process of attribute weighting and were significantly different between the old and young groups.

A non-parametric multivariate analysis of variance (MANOVA) was performed using the R package "NPMV" which found significant differences in these tests and the new Party Food task between the groups ($F=5.83$, $p<0.01$). Using this ranked-sum method it is not possible to calculate post-hoc comparison effect sizes and p-values, instead, relative group effects are defined as the probability that a randomly chosen participant from group "x" displays a higher score than any other participant. The relative treatment effects are listed in the Table below (Table 14) and show that groups differ in the Party Food task, Trender reasoning, Linda problem, and the Jelly Bean task such that the older group are less likely to use rational processing. The Bees Information Sample task and CRT have weaker relative group differences but suggest differences in the same direction.

Table 14. The relative effect sizes for a non-parametric MANOVA to compare additional rational-intuitive decision making tasks with the new Party Food task to show that all tests are comparable in that young adults perform more rationally than older adults

	Cognitive Reflection Test (number correct)	Linda Problem (number correct)	Jelly Bean Task (number incorrect)	Trender (matrix) Reasoning (number correct)	Bees Information Sampling (mean samples taken + mean difference)	Party Food Task (% correctly predicted)
Young	0.60	0.63	0.33	0.75	0.54	**0.68**
Old	0.40	0.37	0.67	0.25	0.46	**0.32**

Finally, the General Decision Making Style (GDMS) questionnaire was completed by all participants. It was designed to measure self-reported rational, intuitive, dependent, avoidant and spontaneous DM style. In this study, the intuitive sub-score was subtracted from the rational sub-score to give a proxy value for rational processing, and this distribution was compared to the Party Food task choice predictability values. The questionnaire-based scores were normally distributed (W=0.97, p=0.37), as were the choice predictability scores (W=0.98, p=0.40). Figure 38 indicates that the self-reported GDMS rational-intuitive scores were not correlated with choice predictability (rho=-0.06, p=0.67), which suggests that self-reported rational-intuitive decision style is not an effective method to quantify rational-intuitive processing.

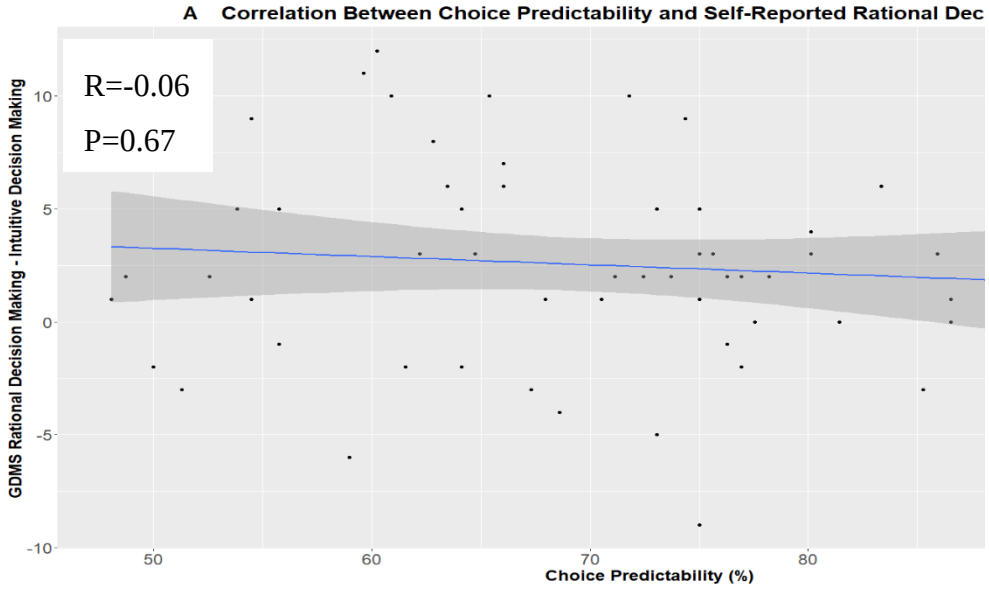


Figure 38. Correlation plot for choice predictability from the Party Food task and a self-report, questionnaire-based measure of rational/intuitive decision making (GDMS, General Decision Making Style). There is no correlation (R=-0.06, p=0.67) which suggests the self-report quantification of rational-intuitive is not a valid measure for rational/intuitive decision making.

4.6 Conclusions

Deconstruction of the Party Food task into its constituent attributes shows that young and old adults do not value cost, quantity or eco-friendliness of supermarket products differently. Modelling the attributes and left-right choice with a logistic regression suggests that older adults make more predictable choices when faced with fewer attributes; model fit (measured as 'choice predictability') for the older group is best when only cost information is included. However, the model fit in the young adult group is best when all three attributes are included. In the young group, all three attributes significantly explained left-right choice probability. In the older group, cost and quantity only explained choice probability. Furthermore, the older group had significantly reduced choice predictability. This is supported by a negative correlation between choice predictability and age.

By calculating choice consistency, both groups appear to become marginally less consistent as they face more choice attributes, but this observation was not significant. Older adults do, however, trend towards having greater decision consistency when given five-attribute choices and this is perhaps related to their focus on fewer attributes.

On the contrary, when intuitive processing is invoked by imposing a time limit on DM, there are no differences between the two groups. Both groups become significantly more inconsistent when the time-limit is imposed.

There was no effect of recent feelings of anxiety or depression (HADS questionnaire) nor response inhibition (Stop Signal Task) on the choice predictability between the two age groups. Finally, the new Party Food task did not correlate with self-reported questionnaire-based measures of rational-intuitive DM (GDMS). However, the Party Food task was able to distinguish young and old decision makers comparably to more established measures of rational processing.

4.7 Discussion

The primary objective of this study was to understand how aspects of rational and intuitive DM change across the adult lifespan in the sample of tested participants. Additionally, the study aimed to validate the task for use in clinical groups. The reduced ability to make use of multiple choice attributes in the older group is in agreement with past findings that rational processes decline as we age, whereas intuitive processes remain stable (e.g. Keane & Thorp, 2016). However, the use of choice attributes and choice consistency are only two factors of many which contribute to rational decision processing. Other factors could include cost relative to budget, product quality or the most appropriate selection of items for a known purpose. Moreover, it could also be optimal to neglect attributes in favour of others (as the older group did with eco-friendliness); perhaps one determines that for a small party, eco-friendly products will not make a difference to the environment and might even ruin the party because they are lower quality. On consistency, participants were not instructed to make consistent choices and high variance (across identical options) could be interpreted as novelty seeking behaviour, which again is optimal in some circumstances. The model fit and relatively large standard deviations suggest that there are indeed additional factors in these decisions that were not quantified and therefore conclusions regarding 'rational processes' are limited.

Additionally, the two-group split had very different age ranges (19-29 and 37-79 years). With a larger group size it would be informative to include an 'intermediate' age group: it appeared in Figure 32 that those aged between 30 and 60 did not perform differently to the young group. This would more accurately reflect the population, where middle-aged adults are generally proficient decision makers and able to manage multiple choice attributes. Age-related cognitive changes, such as cortical thinning in the PFC may play a role in the decline of rational processing (Kaup et al., 2011). Alternatively, in young adults PFC is not fully developed and it may be that the young group's approach was suboptimal (Gogtay et al., 2004). More robust measures of rational processing, mentioned above, could elucidate which approach is in fact optimal.

Unlike literature which suggested that affect plays a role in older adults' DM, this study did not find any relationship between recent (past 7 days) feelings of anxiety and depression and rational DM. However, the appropriateness of the Hospital Anxiety and Depression Scale must be brought into question, where perhaps a more acute and comprehensive measure of affect and/or mood may be more suitable. Past research has

investigated how the emotional salience of items affects choice behaviour, so a future study could ask participants the rate the items for their salience after completing the task.

The use of choice attributes was not affected by response inhibition (measured with a stop signal task), despite significant differences between the young and old groups (older adults performed worse as has been found previously, e.g. Carpenter & Yoon, 2011. . The Party Food task had no response time limit, unlike the stop signal task, which probably accounts for this difference. This suggests that allowing older adults more time to make choices might ameliorate any problems with inhibitory control.

This study also sought to confirm the efficacy of the new Party Food task in measuring aspects of rational and intuitive decision processing. The alternative, more established tasks showed comparable ability to distinguish the young and old groups. While promising, the aforementioned caveats suggest that there are several additional factors which should also be considered in the context of rational-intuitive DM research and perhaps this nomenclature (rational-intuitive) is not constructive for future research.

The questionnaire-based measure did not correlate with the Party Food task. Counterintuitively, this supports the efficacy of the new task to measure rational and intuitive processing. It is challenging for an individual to have conscious and accurate awareness of intuitive DM and their subconscious biases. Even experts succumb to their own biases without awareness, comparably to non-experts (Chin et al., 2019; Mizrahi, 2018). It follows that there should be no correlation between behavioural and self-reported measures of rational-intuitive processing, as was found in this study, further supporting the need for more experimental measures in this domain. However, this observation should be tested specifically in future studies. More generally, it is promising that the Party Food task upheld the rational-intuitive maxim: when participants made rapid, intuitive decisions their choices were less predictable and less consistent (Kahneman & Tversky, 1982).

Numerical ability, to understand and use numbers, has been the focus of previous DM research (Ramchandran et al., 2020). In the context of prescription decisions, numerical ability was more predictive of decision performance than age (Wood et al., 2011). This study did not quantify numerical ability, but it may be an important covariate especially in the Party Food task where preference calculated by numerical differences between left and right options was a primary outcome.

Another limitation of this study is that participants were not screened for medications, illicit drug or alcohol use or previous significant head injury; these variables can cause impairments in DM. Future studies into any kind of DM or cognition should be aware of these variables and either control for them or exclude such participants (Galandra et al., 2021; Giacino et al., 2020; Hanson et al., 2008).

The results of this study provide some support for the 'compensation-related utilization of neural circuits hypothesis (CRUNCH)' which states that older adults have greater neural activation at lower levels of cognitive load to compensate for reduced effective use of neural resources (Grady, 2012). Older adults' decisions were best fitted by a model that used one choice attribute whereas young adults' decisions were best represented by a model that use the maximum number of attributes analysed. Future studies could extend the scope of the task by including more than three attributes and using functional MRI to measure relative levels of brain activity. Generalising, the results from this study suggests that older adults could optimise their DM by using fewer pieces of information, whereas younger adults should consider all available information.

This task has three key differences to existing measures: it is realistic, allowing more generalizability to life-like decision processing, it takes account of subjective preference in the decision process, and the decision attributes can be carefully manipulated and analysed precisely at an individual level without adding complexity. The task is infinitely updateable with minimal learning and memory demands, theoretically minimising practice effects. It is also flexible in terms of the specific items that participants decide upon: products can be updated to reflect supermarket choices from any country or culture. However, the task choices do not have an objective correct answer so it is not possible to analyse if participants are 'right'. Instead it should be stressed that the Party Food task dissects the DM process rather than decision outcomes, although it may be adapted in future to assess utility, for example, shopping within a budget or buying for a specific purpose. There is room for improvement in the analysis of the Party Food task as model fit was somewhat weak, it explained ~65-75% of participant's choices, and standard deviations were relatively large. Quantification of additional variables, for example, the image or product brands will be investigated for this purpose in future task development.

With this in mind, the Party Food task could be used to test cognitive interventions to target DM. The finding that rational processing declines with age provides a starting point to build specific cognitive interventions. Given that it was only some aspects of

rational processing, and not intuitive processing, that decline with age, interventions could target the rational process towards the development of new habits. One caveat is context: this study doesn't provide information on real-life examples where older adults' DM may go awry. Analysis of health insurance, health care or financial management choices, for example, would provide useful information about where to target any such intervention. These studies would likely be difficult to conduct because even pseudo-anonymised data is personally sensitive and often privately held. This study does not support any such intervention being used in place of current interventions. Instead, it would be used in conjunction with the less specific interventions: aerobic exercise, bilingualism, brain training, and transcranial alternative-current stimulation.

This study supports the rational-intuitive theory of DM: participants were inconsistent and neglected choice attributes in intuitive compared to rational decisions. It further shows that healthy ageing is associated with a decline in use of choice attributes, whereas intuitive processing is unchanged across the adult lifespan. Further development of the Party Food task could help to understand rational processing more completely, as well as including a middle-aged group. To support autonomous, optimal DM, cognitive interventions should focus on simplicity to support older person's rational processing of consequential decisions.

5 Decision-Making in Huntington's and Parkinson's Diseases

5.1 Summary

Building on the results of the previous Chapter which showed age-related decline in the use of choice attributes and choice consistency, this Chapter uses similar methods to investigate the same features of DM in patients carrying the gene for HD as well as patients with Parkinson's disease (PD). Cognitive and behavioural impairments in neurodegenerative disease are the most impactful from a patient perspective (Simpson et al., 2016; Svenningsson et al., 2012). They are costly from a societal perspective given their implications for health and social care which are projected to double in the next 25 years (Leibson et al., 2015; Prince et al., 2014). Behavioural reports are used to infer cognitive processes in neurodegenerative disease (i.e. neuropsychological tests) but they have provided little direction for successful intervention. The purpose of this study was not to focus on any single type of cognitive impairment in patients, but to identify tractable targets for intervention by carefully studying DM behaviour. Disciplines such as behavioural economics and marketing are adept at the prediction and manipulation of human choice, and this expertise could serve people with emerging cognitive decline to remain independent and autonomous for longer.

This Chapter summarises the cognitive and behavioural problems described in HD and PD and expands on this towards the study of DM. While the subject of this thesis is HD, the PD group is included to validate the new task more widely, in addition to a control group. The Party Food task is used to quantify some aspects of rational and intuitive processing across the groups. These analyses show that it is increasing age, not disease status, that is associated with reduced use of choice attributes, but that controls made more consistent choices than the HD and PD groups. These results provide insight into decision processing in chronic neurodegenerative disorders and highlight specific areas for possible intervention and further specific research.

5.2 Introduction

5.2.1 Cognition and decision-making in Huntington's Disease

Cognitive problems in HD and PD are heterogenous but tend to become more severe over time as a result of the compounding effects age and neuropathological brain changes (Begeti et al., 2013; Grady, 2012; Yoon et al., 2019). This impairs the patients' ability to respond to increasing cognitive demands. In HD gene carriers, impaired prefrontal and connected striatal circuitry are responsible for some of these early behavioural dysfunctions (Duff et al., 2010; Georgiou-Karistianis et al., 2013). HD gene carriers show progressive impairments in executive functions such as forward planning, anticipation, judgment, reasoning, cognitive flexibility and working memory, as well as attention, and immediate and long term memory (Baake et al., 2017; Ho, Sahakian, Brown, Barker, Hodges, Ané, et al., 2003). There is evidence for disrupted emotional processing prior to motor onset which also progresses with the disease course (Tabrizi et al., 2013). In terms of DM-specific cognition, gene carriers can understand the tasks used to measure choice behaviour (Eddy & Rickards, 2012; Minati et al., 2011), but they tend to have slower RTs than controls (Enzi et al., 2012; Galvez et al., 2017; Vaportzis et al., 2015), although the choices they make are in accordance with expected value (Galvez et al., 2017; Watkins et al., 2000). However, HD groups demonstrate impaired performance in easier levels of DM tasks than controls (Vaportzis et al., 2015; Watkins et al., 2000), although there is not conclusive evidence for impairments in risky choice paradigms (Adjeroud et al., 2017; Campbell et al., 2004; Stout et al., 2001; van Wouwe et al., 2016). There is very little empirical research on DM in everyday settings, such as health, financial, consumer and social choices. One line of investigation into the decision to get a predictive genetic test has focused on effective counselling and the context around the decision, using narrative-based evidence (Arning et al., 2015; Etchegary, 2006; Smith et al., 2002). Targeted cognitive interventions such as brain training and physical exercise have been trialled to a limited extent in HD but not demonstrated clear feasibility nor benefit to patients (Mueller et al., 2019; Yhnell et al., 2020).

5.2.2 Cognition and decision-making in Parkinson's disease

Parkinson's disease differs from HD in that there is no absolute confirmatory test for diagnosis; it is instead based on expert neurologist opinion using established validated motor and cognitive criteria, sometimes supported by ancillary tests (Goetz et al., 2008;

Tolosa et al., 2006). In early PD, limbic and cortical Lewy body pathology and reduced nigrostriatal dopamine transmission are thought to be responsible for changes in cognition (Aarsland et al., 2017; Carbon & Marié, 2003). Neurocognitive deficits are common in recently diagnosed patients and span a number of domains: attention, executive, memory and visuospatial (Aarsland et al., 2017; Ding et al., 2015; Nombela et al., 2014). These dysfunctions may contribute to PD patients' more reserved DM profile: some patients are not good at using prior knowledge to make decisions in ambiguous circumstances (Herz et al., 2016), PD apathy is associated with reduced incentivised DM (Le Heron et al., 2018), and patients are more averse to risks across both low and high value choices, but this can be normalised by dopamine-replacement therapy (Cherkasova et al., 2019). Specifically, when choices involve large potential losses, unmedicated PD patients are more likely to overestimate the magnitude of loss but otherwise make decisions that are comparably similar to controls (Sharp et al., 2013). Everyday DM has received more attention in PD than in HD. One study with PD dementia patients found that semantic impairments were correlated with simulated tasks for everyday functioning (Roll et al., 2019). Investigations still tend to be qualitative, highlighting a need for decision support but not quantifying the extent of that need, for example, decisions about eating and drinking in PD and HD were found to be related to health literacy and planning style (Clarke et al., 2018). Interventions specific for cognition in PD have also received more attention than those in HD. Cholinesterase inhibitors such as rivastigmine, donepezil and memantine are supported to treat PD dementia (although with small effect sizes) (Dubois et al., 2012; Emre et al., 2004, 2010). No disease-modifying therapies for mild cognitive impairment in PD are available (Aarsland et al., 2017), although exercise (Reynolds et al., 2016), and cognitive training (Lawrence et al., 2017) may improve cognitive problems.

5.2.3 Realistic, everyday decision-making in Huntington's and Parkinson's diseases

Everyday DM has not been studied in HD or PD, for example, how patients spend their money or make health care decisions. The cognitive and DM impairments discussed above suggest that patients may make suboptimal choices. Anecdotal evidence from HD gene carriers at the John Van Geest Centre for Brain Repair certainly highlights problematic choice behaviour. For example, one patient who made consequential decisions in her job struggled to decide between similar options in the supermarket on low valence items such as choice of biscuits etc; another ordered 13 identical watches

online; one patient purchased multiple aquariums during a 2020 UK COVID-19 lockdown (but did not own any fish), and another bought a car despite having lost their driver's license. Indeed, it is not only gene carriers who demonstrate poor choice behaviour, there is evidence that healthy older adults can neglect choice attributes (see Chapter 4).

These problems highlight an important question: could DM problems emerge prior to cognitive decline, both in patients with chronic neurodegenerative disease and in older adults? If this is the case, patient DM could benefit from interventions to address behaviour instead of the disease-modifying interventions based on deep phenotyping of cognitive problems carried out to date.

5.2.4 A direction for decision-making interventions in patient cohorts

There are few precautions or policies in place to support poor DM behaviour in patient groups (Sugiura et al., 2020). The Mental Capacities Act (2005) supports patients with severe cognitive decline in the case of dementia (for example) while stressing that the individual should still be empowered to make their own decisions. Individual autonomy is preserved in decision aids informally known as 'nudges': they alter behaviour in a predictable way by relying on known biases but without forbidding or mandating options (Thaler, 2018). Behaviour nudges are widely used because they are not costly to test or implement, unlike traditional policy-based methods of changing behaviour (Benartzi et al., 2017; DellaVigna & Linos, 2020; Service et al., 2014). For example, a nudge can highlight the most commonly chosen or best option among a list to reduce the choice set. The application of behavioural nudges to patient cohorts might provide individual-level benefits similar to conventional clinical interventions, supporting potentially compromised DM while also maintaining autonomy. However, it is first necessary to confirm that rational and intuitive processes (the mechanisms of nudge theory) are comparable between patients and the healthy populations these nudges were designed for, given the aforementioned differences in decision behaviour and the possible influence of sub-clinical cognitive changes on DM.

5.2.5 The present study

This study sought to investigate some aspects of rational and intuitive processing in HD, PD and matched controls to understand whether decision behaviour could be the target of future nudge interventions. Importantly, the study design accounts for previously

observed differences between patients and controls. The Party Food task gives participants an unlimited amount of time to make rational decisions, accounting for the slower, more reserved DM behaviour observed in PD and, theoretically, the impaired perception of HD patients found in Chapter 2. The inclusion of the PD group (rather than HD alone) allows the new task to be validated more widely, and to understand if different pathogenic causes and sites of pathology in chronic neurodegeneration affects rational or intuitive processing.

5.3 Objectives

The primary objective of this study was to understand if and how rational and intuitive decision processes (namely use of choice attributes and choice consistency, with and without response time limits) differ between people with PD and HD, separate from clinically significant cognitive decline, and neurologically healthy age-matched controls. A secondary objective was to understand if common neuropsychological variables were associated with decision processing. This study also aimed to understand how the new Party Food task compared to other measures of rational and intuitive processing in these patient cohorts.

An exploratory objective of this study was to understand whether grouping premanifest and early-manifest HD gene carriers, based on functional and cognitive measures (and not motor impairments), might be of use in future studies to work towards cognitive and functional interventions.

Altogether, the study aimed to identify specific and tractable targets for DM interventions.

5.4 Methods

5.4.1 Study Recruitment

Participants (N=102) were recruited into this study in one of three groups: HD patients, PD patients, or controls. Patients with HD were recruited from the NHS Huntington's Disease Clinic at the John van Geest Centre for Brain Repair in Cambridge and met the following criteria: 1) Confirmed diagnosis of HD gene status with expanded allele > 36 CAG repeats, 2) age >18, 3) Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) Score > 10 (out of a possible 13), 4) ACE-R score ≥ 82 (out of a possible 100; above the normative dementia cut off) and MMSE score >24 (out of a possible 30; above the normative dementia cut off) (patients must pass both MMSE and ACE-R criteria for inclusion), and 5) willing and able to complete all assessments in the protocol.

Patients with PD were recruited from the Parkinson's Disease Research Clinic at the same Centre with help from Marta Camacho and Molly O'Reilly. The inclusion criteria were similar to the HD patients: 1) Confirmed diagnosis of PD by a qualified neurologist, 2) age >18, 3) Schwab and England Activities of Daily Living (ADL) score ≥ 70 (out of a possible 100), 4) ACE-R score ≥ 82 and MMSE score >24, and 5) willing and able to complete all assessments in the protocol.

Control participants were recruited from the local community or were companions of clinic patients. They met the following criteria: 1) no known neurological or psychiatric condition that, in the opinion of a neurologist, could impact on their ability to complete the study protocol, 2) age >18, and 3) willing and able to complete all assessments in the protocol.

The following exclusion criteria were also applied to all participants: 1) non-native English speaker, whose level of understanding or fluency is likely to impact on their ability to complete the study assessments, 2) uncorrected sight or hearing impairment which would interfere with cognitive testing, 3) known learning disability, special educational need or medical problem that interferes with the individual's ability to complete the study procedures, and 4) known and ongoing comorbid neurological condition (patients only). Participants were not screened for medication.

Notably, this study did not stratify HD gene-carriers based on motor features. Instead it focussed on functional and cognitive abilities as these are more relevant to the goals of this research, which were to understand DM and develop interventions. However, to understand the validity of this exploratory approach, UHDRS Total Motor

Score was investigated as a covariate in the DM tests, and gene carriers were binarized premanifest and early-manifest groups. This approach has been used before and termed "peri-manifest" where a study into autobiographical memory performance grouped patients who were "late premanifest or…early diagnosed" (Carmichael et al., 2019) although it is not a widely used method it may have promise for future cognitive interventions.

5.4.2 Ethical Approval, Insurance and Sponsorship

Approval was sought from the Medical Health Research Authority through the Integrated Research Application System (Project ID: 258455). The study was given favourable opinion by the South Central – Oxford C Research Ethics Committee (19/SC/0153). I applied for insurance cover through the University of Cambridge Finance Division (HVS/2018/2503), and approval from the University's Research and Development department as a joint sponsor (A095071). Joint sponsorship was with the Cambridge University Hospitals NHS Foundation Trust.

5.4.3 Study Visit

The study was conducted during an in-person visit at the John Van Geest Centre for Brain Repair in Cambridge, United Kingdom. This study took place from July 2019 to December 2020 and the same person conducted all visits in one of two quiet clinic rooms. Despite the intermittent lockdowns that came as a result of the coronavirus pandemic, later visits were able to continue in a similar manner to earlier ones. Enhanced hygiene and sanitation procedures were used to ensure the safety of participants, including regular use of hand sanitiser, temperature measurements of the participants with COVID-19 symptom checks prior to entering the building, cleaning of clinic rooms before and after each visit, masks worn by both myself and the participant, room ventilation, and a two-metre distance maintained. Each visit took approximately two hours to complete and Table 15 summarises the study procedures; details of each task are included in Appendix 2.

Table 15. Study procedures. Abbreviations: HADS+I = Hospital Anxiety and Depression and Snaith Irritability Scale; SDMT = Symbol Digit Modality Test; ACE-R = Addenbrooke's Cognitive Exam - Revised; NART = National Adult Reading Test; SST = Stop Signal Task; GDMS = General Decision Making Style; CRT = Cognitive Reflection Test.

Assessments	Time to complete (mins)
Informed Consent	10
HADS+I	5
ACE-R	15
NART	5
SST (*PD patients did not complete this task)	10
Bees information sampling task	10
Trender reasoning task	10
Decision making experiences questionnaire	5
GDMS questionnaire	5
Party Food task	20
Supplementary decision making tasks (Jelly bean, Linda problem, CRT)	10
Rey complex Figure drawing	5
Total (plus breaks, taken at the participant's discretion)	**110**

5.4.4 Measures of Disease Severity

5.4.4.1 Huntington's Disease

Unified Huntington's Disease Rating Scale (UHDRS)

This scale is comprised of four subscales which measure motor, cognitive and psychiatric abnormalities and levels of daily functioning. The UHDRS Total Motor Score (TMS) measures performance on a range of motor skills believed to be particularly vulnerable to HD pathology such as eye movements, dysarthria/oropharyngeal motor function, chorea, dystonia, gait/balance, rigidity/bradykinesia and repetitive hand movements and sequences. The maximum score (i.e. most severe) is 124 points and >5 is taken as being diagnostic as having manifest HD. There were no criteria for participation based on this test.

The UHDRS Total Functional Capacity (TFC) measures functional ability and includes the following domains: occupation, finances, domestic chores, activities of daily living and the care level required. The TFC is the clinical test which is used to

stage manifest HD according to the Shoulson and Fahn criteria (Shoulson & Fahn, 1979) and is measured on a 13-point scale where 13 indicates normal function. The minimum score required to participate in this study was 10.

5.4.4.2 Parkinson's Disease

Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS is formed of four parts and this study used Part III, the motor examination, which includes items for speaking, hand grips, finger taps, hand pronation/supination, leg ability, raising from a chair and walking with a maximum score (most severe) of 132 points. There were no criteria for participation based on this test.

Schwab and England Activities of Daily Living (SE-ADL)

This scale assesses a patient's independence between 0 and 100%, where 100% is 'completely independent: able to do all chores without slowness, difficulty or impairment' with no awareness of any difficulties. The minimum score required to participate in this study was 70%, 'mostly independent: faces more difficulty with some chores. One spends a large part of the day with chores and might take 3-4 times longer than normal with awareness of difficulties' (Schwab & England, 1969).

5.4.5 Statistical Analysis

R studio (version 1.2.5033 "Orange Blossom") was used to conduct the analyses presented in this Chapter. Analyses were similar to the previous Chapter.

Mann-Whitney U (for exploratory premanifest vs early-manifest HD and for HD vs control analysis of response inhibition differences) and Kruskal-Wallis tests were used to determine group (for control vs PD vs HD) differences between decision attributes (cost, quantity, eco-friendliness), choice consistency, RT and missed trials, instead of parametric tests because the coefficient distributions were non-normal. Pairwise comparisons were made where relevant, with false discovery rate adjustment for multiple comparisons. Mann-Whitney U tests were used to determine whether the coefficients were different from zero.

The ability of existing measures for rational processing to discriminate the three groups was analysed with a non-parametric MANOVA.

Pearson and Spearman correlations were used to understand if disease severity was related to outcomes of the decision tasks (both motor and functional tests).

5.4.6 Behavioural Modelling

MATLAB (version R2018.b) was used to write the logistic regression models, test multicollinearity, calculate model fit and choice variance, and present the subsequent results.

A Spearman's correlation was performed to quantify patterns in the output of behavioural models against age. A linear model was applied to selected outcome variables (choice prediction and choice consistency) with relevant covariates (verbal IQ, depression, response inhibition).

5.4.7 Power Calculation

Due to the novelty of the central task used to assess DM, no prior effect sizes could be used to calculate power and estimate sample sizes in clinical groups. As in the previous Chapter, I aimed to recruit at least 30 participants per group to reach statistical normality assumptions under the Central Limit Theorem.

5.5 Results

5.5.1 Participants

Thirty-seven participants with HD were recruited for the study but three were subsequently excluded. One person had a significant global cognitive deficit (MMSE score 24), one failed the final effort and attention test (Rey score 32 of 36) and the other demonstrated significant left-right bias in the Party Food task, part 1. A neurologist carried out the UHDRS on the day of the visit when possible, but for some participants the UHDRS scores from their closest clinic visit to my assessment was used with an upper limit of nine months before or after the study visit date. The same was later applied to UPDRS scores. Scores for UHDRS-TMS ranged from 0-31 (out of a possible 124), which represented no-to-low motor impairments. Scores for the UHDRS-TFC ranged from 10-13 (out of a possible 13), which represented no-or-low functional impairment.

Thirty-three participants with PD were recruited for the study but six were subsequently excluded. Four participants were found not to meet Schwab and England Activities of Daily Living criteria on the day of their visit (scores < 70%). One participant

had significant global impairment (MMSE score 24) and another participant did not finish the battery of tests. Patient UPDRS scores ranged from 10-66, out of a possible 132, spanning low to moderate motor impairment. The motor scores for two patients were excluded as they were collected >9 months prior to the study visits and thus unlikely to be representative of the patient's motor functioning at their visit with me. Independence scores measured by the SE-ADL scale ranged from 70-100%, or 'mostly independent (takes three to four times longer to do some chores) to completely independent'. All exceeded the effort and attention test cut off score. PD patients did not complete the task for response inhibition (stop signal task). PD patients tended to be slower to complete the task battery and, being the longest single task, it was removed to ensure the visit did not last longer than three hours.

Thirty-two controls were recruited for this study. This is the 'old control' group from the previous Chapter. The demographics Table below indicates that the groups have significantly different mean ages (Table 16). This is due to differences between the PD (older) and HD (younger) cohorts and is to be expected in these diseases. Thus, the control group was recruited to span both groups given previous findings that age was significantly correlated with rational processing (see Chapter 4) (age was non-normally distributed: Shapiro-Wilk normality test $W=0.97$, $p=0.04$. Equal variance: Levene test $F=1.98$ $p=0.14$. Kruskal-Wallis rank sum test: $H=29.85$, $df=2$, $p<0.01$. Post-hoc comparison matrix: control-PD $p<0.01$; control-HD $p=0.07$; PD-HD $p<0.01$ (with false discovery rate adjustment for multiple comparisons)). All controls exceeded the effort and attention test cut off score.

The three groups were not matched for verbal IQ and this was driven by lower scores in the HD cohort (non-normal distribution: Shapiro-Wilk normality test $W=0.95$, $p<0.01$. Equal variance: Levene test $F=0.63$, $p=0.54$. Kruskal-Wallis rank sum test: $H=9.8$, $df=2$, $p<0.01$. Post-hoc comparison matrix: control-PD $p=0.75$; control-HD $p=0.01$; PD-HD $p=0.01$ (with false discovery rate adjustment for multiple comparisons)). However, the groups were matched for cognitive function as measured with the ACE-R.

Finally, the groups were not matched for HADS depression scores, as the PD group reported more severe features of depression, although no participants met clinical depression criteria (non-normal distribution: Shapiro-Wilk normality test $W=0.85$, $p<0.01$. Equal variance: Levene test $F=0.21$ $p=0.81$. Kruskal-Wallis rank sum test: $H=10.9$, $df=2$, $p<0.01$. Post-hoc comparison matrix: control-PD $p<0.01$; control-HD $p=0.95$; PD-HD $p=0.01$ (with false discovery rate adjustment for multiple comparisons)).

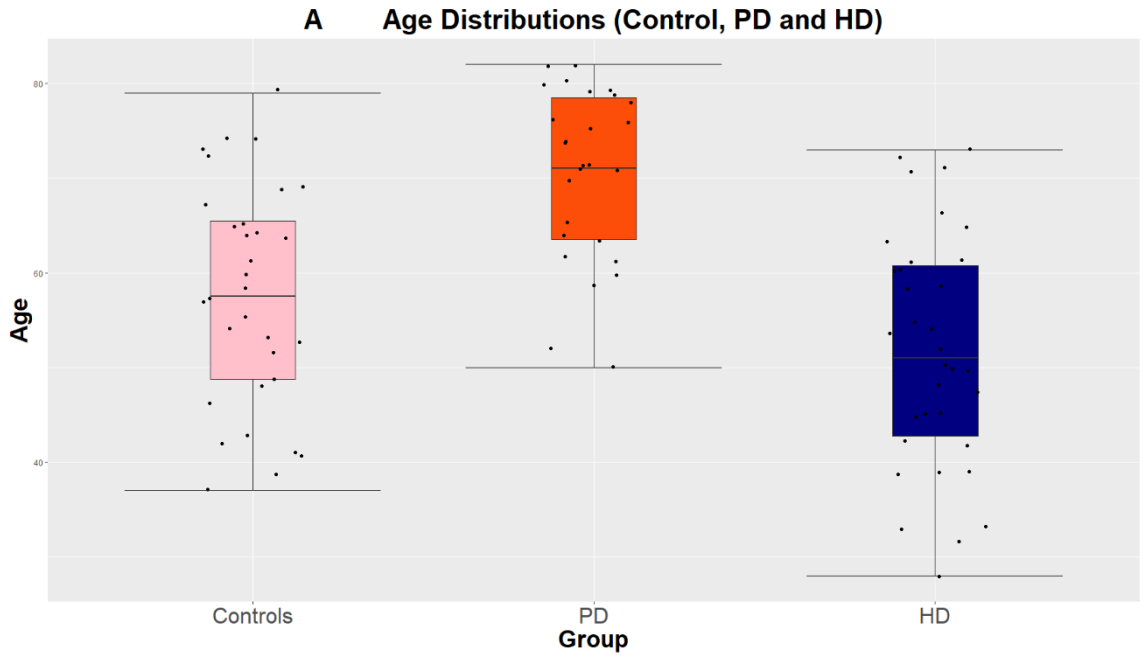
These group differences are addressed as covariates for DM performance, however, it should also be noted that some of the HADS depression scale questions overlap with PD symptoms. For example, "I feel as if I am slowed down" can be a feature of depression but bradykinesia is also a cardinal PD symptom.

Table 16. Participant demographics. Groups were not matched for age (p<0.01) but this is to be expected due to the different neurodegenerative disease groups. However the ages of the controls spanned both groups. Groups were matched for sex, cognitive function, anxiety and irritability (both measured by the Hospital Anxiety and Depression Scale) but were not matched for verbal IQ (measured by the National Adult Reading Test) or depression (measured by the Hospital Anxiety and Depression Scale). Abbreviations: PD=Parkinson's disease; HD=Huntington's disease; ACE-R=Addenbrooke's Cognitive Exam – Revised; SE-ADL=Schwab and England Activities of Daily Living independence scale; UPDRS TMS=Unified Parkinson's Disease Rating Scale Total Motor Score; UHDRS TFC=Unified Huntington's Disease Rating Scale Total Functional Capacity; UHDRS TMS= Unified Huntington's Disease Rating Scale Total Motor Score. (1) Kruskal-Wallis rank sum test, (2) Pearson's Chi-squared test. Test statistics are included in body text where significant.

	Controls (N=32)	PD (N=27)	HD (N=34)	p-value
Age				< 0.001 (1)
- Range	37.0 - 79.0	50.0 - 82.0	28.0 - 73.0	
- Mean	57.7	70.5	51.8	
Sex, Female	16 (50.0%)	14 (51.9%)	18 (52.9%)	0.971 (2)
Verbal IQ				0.007 (1)
- Range	95.1 - 125.4	95.1 - 125.4	89.3 - 125.4	
- Mean	115.0	115.3	109.5	
ACE-R Total Score				0.566 (1)
- Range	86.0 - 100.0	83.0 - 100.0	82.0 - 100.0	
- Mean	96.3	95.2	95.0	
Depression				0.004 (1)
- Range	0.0 - 12.0	1.0 - 11.0	0.0 - 11.0	
- Mean	2.6	4.3	2.9	
Anxiety				0.979 (1)
- Range	0.0 - 13.0	0.0 - 13.0	0.0 - 14.0	
- Mean	5.1	4.9	5.3	
Irritability				0.097 (1)
- Range	0.0 - 8.0	0.0 - 12.0	0.0 - 17.0	
- Mean	4.1	3.6	5.7	
SE-ADL				
- Mean	NA	85.2	NA	
- Range	NA	70.0 - 100.0	NA	

UPDRS III Motor Score			
- Mean	NA	35.3	NA
- Range	NA	10.0 - 66.0	NA
UHDRS TFC			
- Mean	NA	NA	12.6
- Range	NA	NA	10.0 - 13.0
UHDRS TMS			
- Mean	NA	NA	5.2
- Range	NA	NA	0.0 - 31.0

Boxplots below show the age distributions across the three groups (Figure 39A) and below that, the distributions when the control group is split in half to match each patient cohort (Figure 39B). Comparison between the HD patients and control group showed that age did not differ significantly between groups, although the HD patient group had greater variance (normal distribution: Shapiro-Wilk test W=0.98, p=0.69. Non-equal variance: F-test F=0.3, p=0.01. Mann-Whitney U W=215, p=0.24). Similarly, comparison between the PD and control group showed that age was matched (normal distribution: Shapiro-Wilk test W=0.96, p=0.18. Equal variance: F-test F=2.4, p=0.08. Welch's T-test t=1.39, p=0.17).



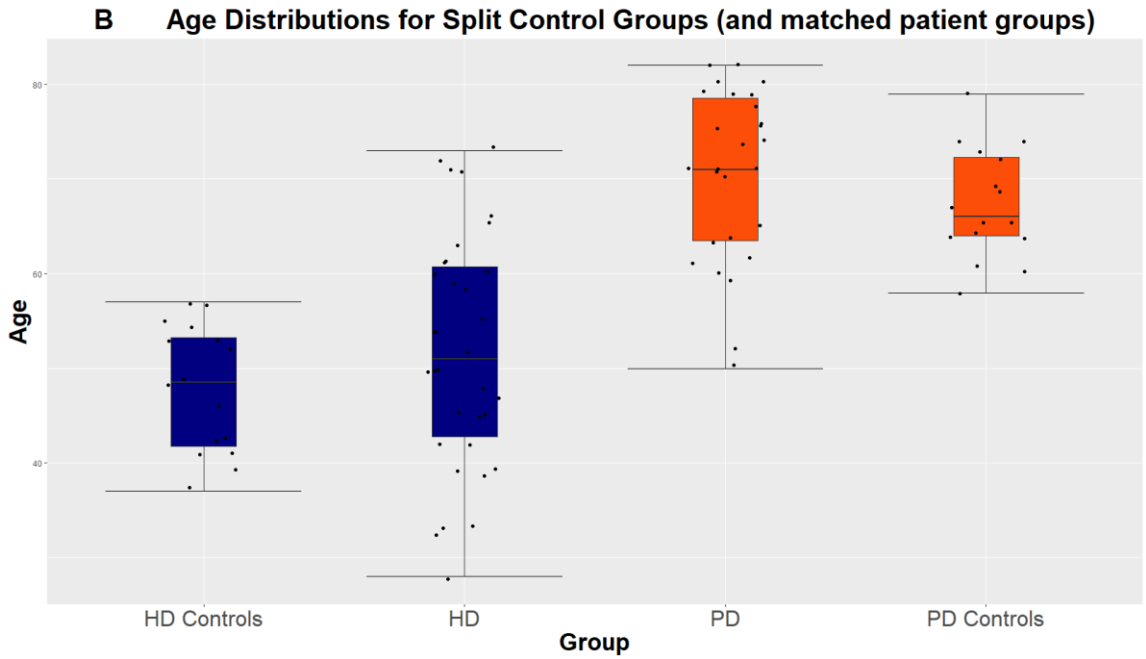


Figure 39. Age distributions for patients versus controls. Age is a significant predictor for rational processing but controls in this study were not matched to both patient groups. Instead the control group spanned the range of ages for PD and HD patients together (A). Splitting the control group in half at the median age creates two smaller control groups (N=16 per group) that are age-matched to their respective patient cohort (B). For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

5.5.2 Decision behaviour is not less predictable in Parkinson's and Huntington's disease cohorts compared to controls

Similar to the previous Chapter, choice attributes from the Party Food task multi-attribute trials (N=156) were parsed to understand which information participants based their choices on. A logistic regression model was used to calculate coefficients for each attribute (cost, quantity and eco-friendliness) which were normalised and not predictive of one another (see Chapter 4, Results).

Previous results showed that young adults' decisions were better explained by the model coefficients than older adults'. Furthermore, after comparing the fit of the regression models, it was found that young adults' choices were better explained by a model which used all three attributes, whereas the older adults' choices were best explained by the simplest (cost only) model. The same analyses of model fit were carried out in the patient groups and matched controls. Based on median AIC, the best fitting model in all groups (controls, HD and PD) was the simplest, cost-only model

(Table 17). Comparing choice predictability across groups for the simplest model (i.e. using choice attribute coefficients to predict choices, and comparing those predictions to the participants' actual choices), the HD patients made the most predictable choices, followed by the healthy control group and then the PD patients. However, pairwise post-hoc tests revealed that the patient groups were not different from the control group (Shapiro-Wilk test shows non-normal distribution: W=0.97, p=0.03; Levene Test shows equality of variance: f=1.61, p=0.21; Kruskal-Wallis test shows significant group mean differences h=8.93, p=0.01; Post-hoc tests show HD-PD difference (p=0.01) but not control-patient differences, control-PD p=0.13, control-HD p=0.13 all with false discovery rate adjustments for multiple comparisons). However, it should be noted that measures of model fit are somewhat weak and standard deviation is relatively high, together indicating that there could be additional variables not captured by this psychometric model.

Table 17. Logistic Regression Model fit for Party Food task attributes, comparing median values [standard deviation in brackets] for young and old adults across three models of decreasing complexity. In bold are the best models for each group (lower AIC indicates better model fit) which suggests that HD patients' choices were best fit by this model, followed by controls, and the PD cohort had the worst fit.

	CONTROLS (ALL)			**HD**			**PD**		
	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC
Model 1 – Cost, Quantity, Eco-friendliness	0.11 [0.15]	65.38 [10.6]	204.10 [32.5]	0.15 [0.14]	73.40 [10.9]	196.75 [31.6]	0.07 [0.08]	62.18 [7.5]	213.2 [18.1]
Model 2 – Cost, Quantity	0.07 [0.13]	64.74 [10.3]	204.40 [29.1]	0.13 [0.15]	70.51 [11.5]	192.19 [32.5]	0.03 [0.07]	57.69 [8.5]	214.2 [15.6]
Model 3 – cost	0.11 [0.14]	66.35 [11.2]	**201.13 [31.7]**	0.11 [0.14]	71.79 [11.8]	**193.90 [31.9]**	0.06 [0.07]	60.90 [9.0]	**211.1 [17.3]**

5.5.3 Age, not disease status, correlates with individual differences in rational decision processing

This prompted further investigation into the effects of age, acknowledging that HD patients had the lowest mean age (51.5 years), followed by the controls (57.7 years)

and the PD group (70.5 years), and that increasing age has been significantly correlated with reduced choice predictability in a cohort of healthy adults. By splitting the control group based on median age to age-match the groups (see Participants, Figure 39B), the logistic regression model fit (AIC) was comparable between the PD group and age-matched control group (Table 18A), and also for the HD group and age-matched control group (Table 18B) (HD and matched controls: normally distributed, Shapiro-Wilk test W=0.98, p=0.64; equal variance, F=1.04, p=0.90; Welch's t-test t=0.41, p=0.69. PD and matched controls: normally distributed, Shapiro-Wilk W=0.96, p=0.12; equal variance F=0.75, p=0.51; Welch's t-test t=0.49, p=0.63). This suggests that age, not disease status, is driving the differences in the use of choice attributes seen in these participants.

Table 18. By splitting the control group at the median age, two age-matched control groups can be separately compared to the patient groups. Model fit comparison suggests that there are no differences based on disease status, but that age is responsible for differences in model fit. Table A compares PD patients and age-matched controls, while Table B compared HD patients and different age-matched controls. Standard deviation in brackets.

Table A	**CONTROLS (matched to PD age) (mean age 67.4, n=16)**			**PD (mean age 70.5)**		
	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC
Model 1 – Cost, Quantity, Eco-friendliness	0.08 [0.11]	62.82 [10.1]	209.2 [25.5]	0.07 [0.08]	62.18 [7.5]	213.2 [18.1]
Model 2 – Cost, Quantity	0.05 [0.11]	62.50 [8.8]	209.1 [25.6]	0.03 [0.07]	57.69 [8.5]	214.2 [15.6]
Model 3 – Cost	0.08 [0.11]	63.46 [10.4]	**206.4 [24.4]**	0.06 [0.07]	60.90 [9.0]	**211.1 [17.3]**

Table B	**CONTROLS (matched to HD age) (mean age 47.9, n=16)**			**HD (mean age is 51.5)**		
	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC	Median Pseudo R^2	Median Correctly Predicted (%)	Median AIC
Model 1 – Cost, Quantity, Eco-friendliness	0.14 [0.17]	66.67 [10.5]	197.61 [37.4]	0.15 [0.14]	73.40 [10.9]	196.75 [31.6]
Model 2 – Cost, Quantity	0.08 [0.15]	66.35 [11.4]	202.80 [32.6]	0.13 [0.15]	70.51 [11.5]	192.19 [32.5]
Model 3 – Cost	0.13 [0.17]	69.55 [11.3]	**196.91 [37.0]**	0.11 [0.14]	71.79 [11.8]	**193.90 [31.9]**

A correlation plot that compares age and choice predictability, based on the choice coefficients from the regression model 3 described above (Table 18; best fit across all participants), supports the effects of age and not disease status. Figure 40 shows that choice predictability declines significantly with age (Spearman's Rho= -0.29, p=0.0045; Shapiro-Wilk test for normality of choice predictability: W=0.96, p=0.029). The group membership of individuals' data is superimposed on the graph, and visual inspection suggests there is no clear grouping of either disease. For each year older, participants' choices become 0.29% less predictable, although there is a wide range of modelled choice predictability across all ages.

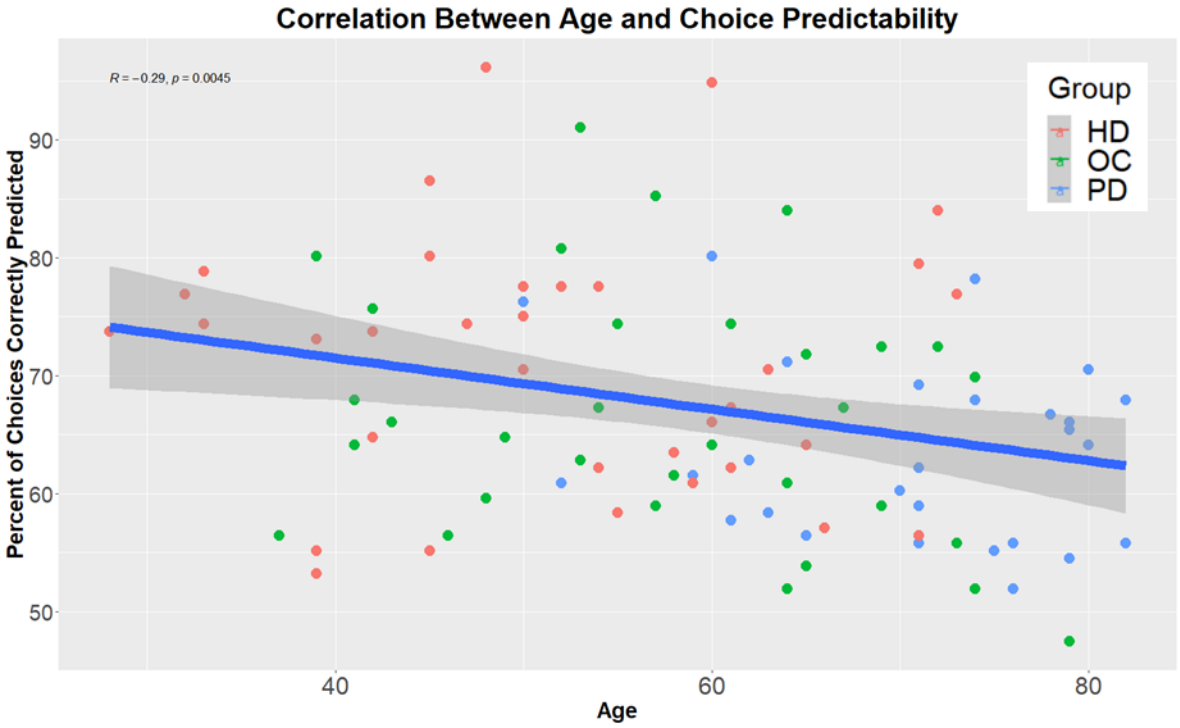


Figure 40. Correlation between age and choice predictability in the Party Food decision task. Logistic regression was used to calculate choice attribute coefficients which were used to predict choices (based on the model with the best fit across groups, model 3, which used only the cost attribute), and those predictions compared to the participants' actual choices to give 'percent of choices correctly predicted'. Coloured dots indicate group membership: red=HD, green=controls (OC), blue=PD. A Spearman correlation was applied due to the non-normal distribution of choice predictability, R=-0.29 P=0.0045 (Shaded area indicates 95% confidence interval).

5.5.4 Groups do not value cost, quantity nor eco-friendliness attributes differently

There are no statistically significant differences between groups in the size of attribute coefficients. A non-parametric Kruskal-Wallis test was used given none of the coefficients were normally distributed (Shapiro-Wilk tests for normality: Cost W=0.74, p<0.01; quantity W=0.92, p<0.01; eco-friendliness W=0.96, p=0.01. Kruskal-Wallis tests: Cost H=0.03 p=0.98; quantity H=0.38, p=0.82, eco-friendliness H=0.68, p=0.71). The similarity across groups for each attribute is also evident in Figure 41. All participants value cost negatively (that is, they are averse to higher cost) and value quantity positively (they prefer options with greater quantity) and the regression coefficients are significantly non-zero (Wilcoxon signed rank test for cost V=222, p<0.01, median=-2.12; for quantity V=59042, p<0.01, median=1.95). However, by calculating whether the coefficients are significantly different from zero, participants across all groups did not use the eco-friendliness attribute to discriminate between the two options (Wilcoxon signed rank test for eco-friendliness V=35628, p=0.43, median=-0.01).

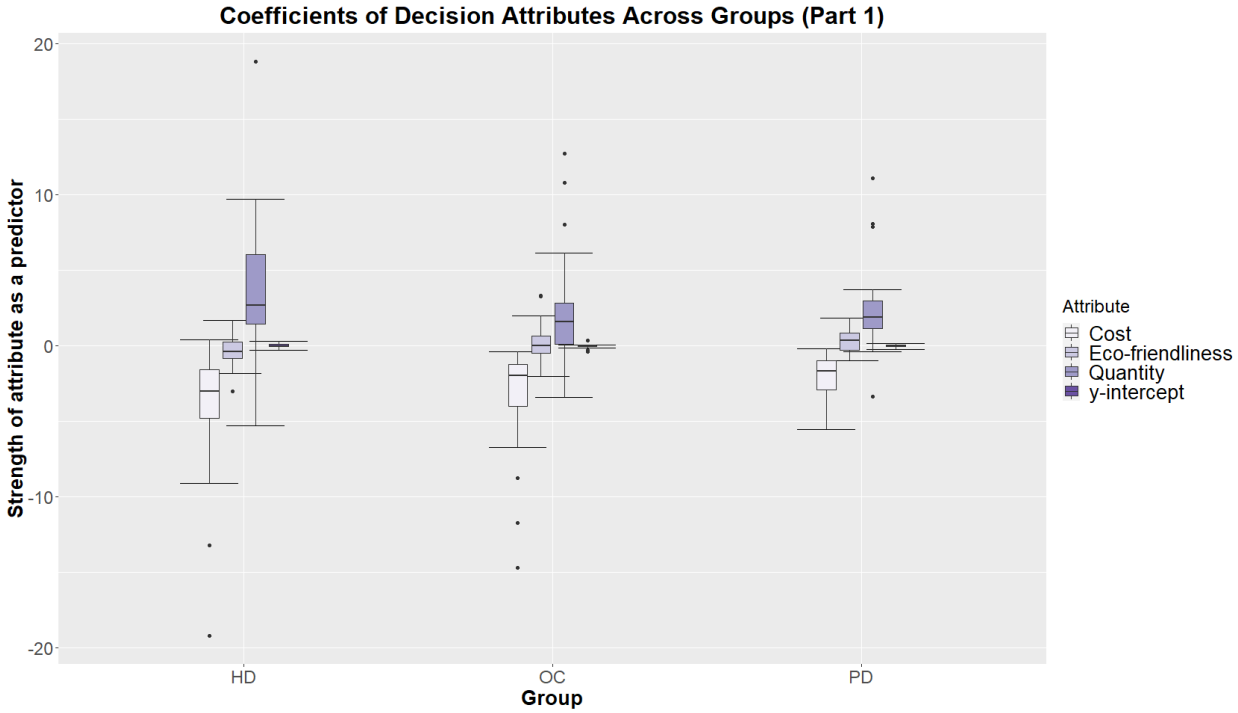


Figure 41. Box plots of decision attribute coefficients per group (cost, eco-friendliness, quantity and y-intercept). There are no between-group differences for how each attribute is valued. All groups value higher cost negatively, higher quantity positively, and do not value the eco-friendliness attribute. HD=Huntington's disease; OC=Controls; PD=Parkinson's disease. For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

Additionally, one HD patient with a y-intercept coefficient that was significantly non-zero (i.e. indicated that they were only selecting the left option) was removed from these analyses. The remaining y-intercept coefficients were also non-normally distributed but did not differ between groups and were not significantly different from zero with a median value of 0.00 (Shapiro-Wilk test for normality y-intercept $W=0.97$, $p=0.03$. Kruskal-Wallis test for group comparisons $H=0.25$, $p=0.88$. Wilcoxon rank test for y-interceptV=31020, $p=0.15$).

5.5.5 Intuitive decision processing causes neglect of choice attributes across groups

The second part of the Party Food task gives the opportunity to analyse DM under time pressure, one method to manipulate the use of intuitive rather than rational processing (Phillips et al., 2016). This part of the task was not designed to pass tests for multicollinearity, given that the weighting of attributes is a process reserved for rational processing, thus it is only possible to observe relative coefficients between the groups and relative choice consistency.

Behavioural data from nine participants were removed after calculating the attribute coefficients because they showed significant left-right bias, as measured by the logistic regression y-intercept value being significantly non-zero. It was likely that these participants were selecting left or right without considering the onscreen choice. Of the participants who demonstrated this bias, four were controls, four were PD patients and one was a HD patient. The remaining attribute coefficients are plotted below for relative comparisons between the groups and do not differ across the three groups (Figure 42) (Shapiro-Wilk tests for normality: Cost $W=0.16$, $p<0.01$; quantity $W=0.51$, $p<0.01$; eco-friendliness $W=0.30$, $p<0.01$. Kruskal-Wallis tests to compare means: Cost $H=1.05$, $df=2$, $p=0.59$; quantity $H=3.21$, $df=2$, $p=0.20$; eco-friendliness $H=0.57$, $df=2$, $p=0.75$).

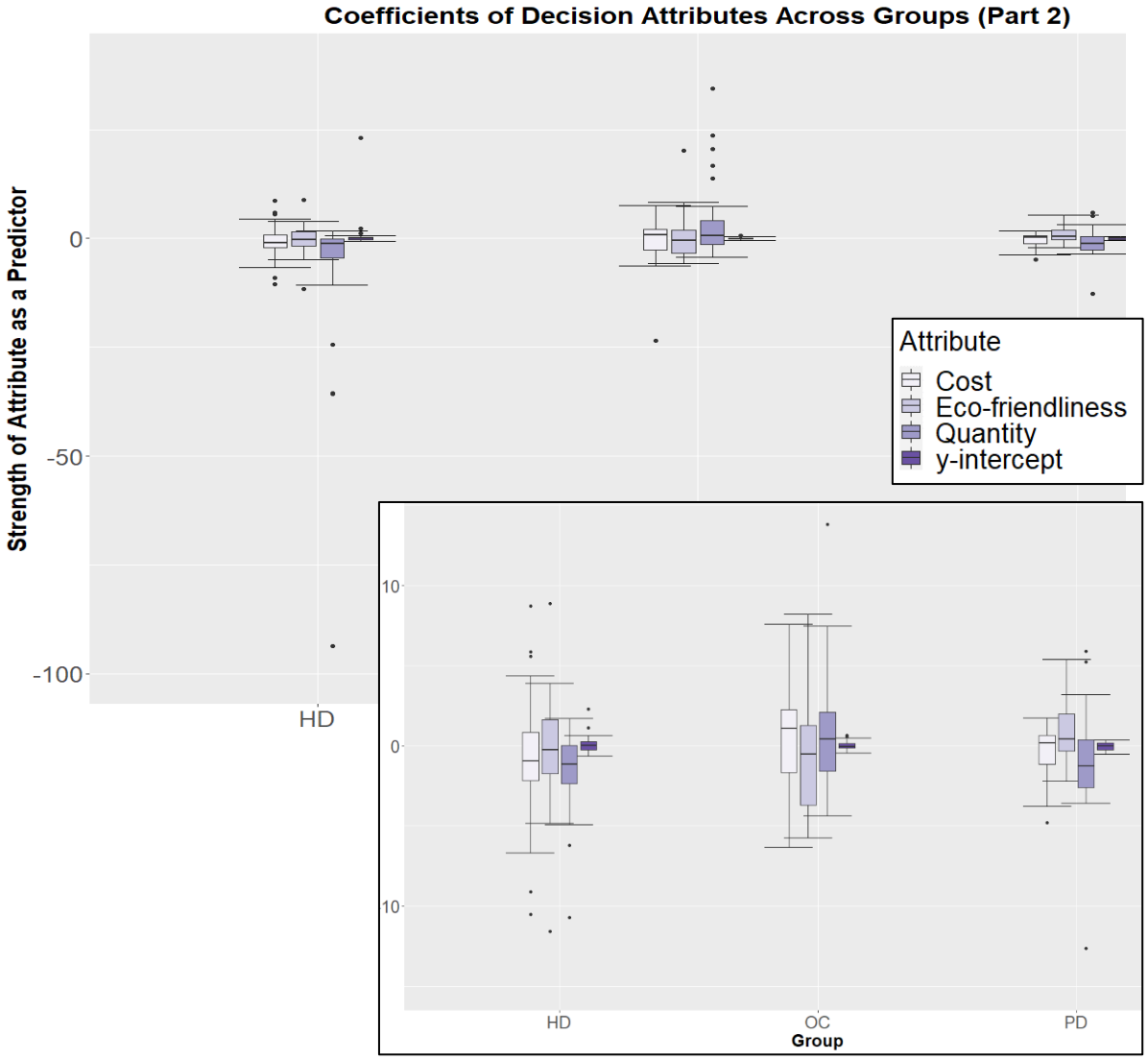


Figure 42. Coefficients of decision attributes across HD and PD patients and matched controls (OC) Part Two of the Party Food Task (where time to decide is limited relative to the participant's prior response times). The imposed time limit reduces the size of the coefficients, effectively demonstrating that the participants failed to use this attribute information in a time-limited situation. Overlayed plot shows axis zoom for the same plot. Data from nine participants is not plotted because after calculating the regression coefficients these participants demonstrated significant left-right bias. For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

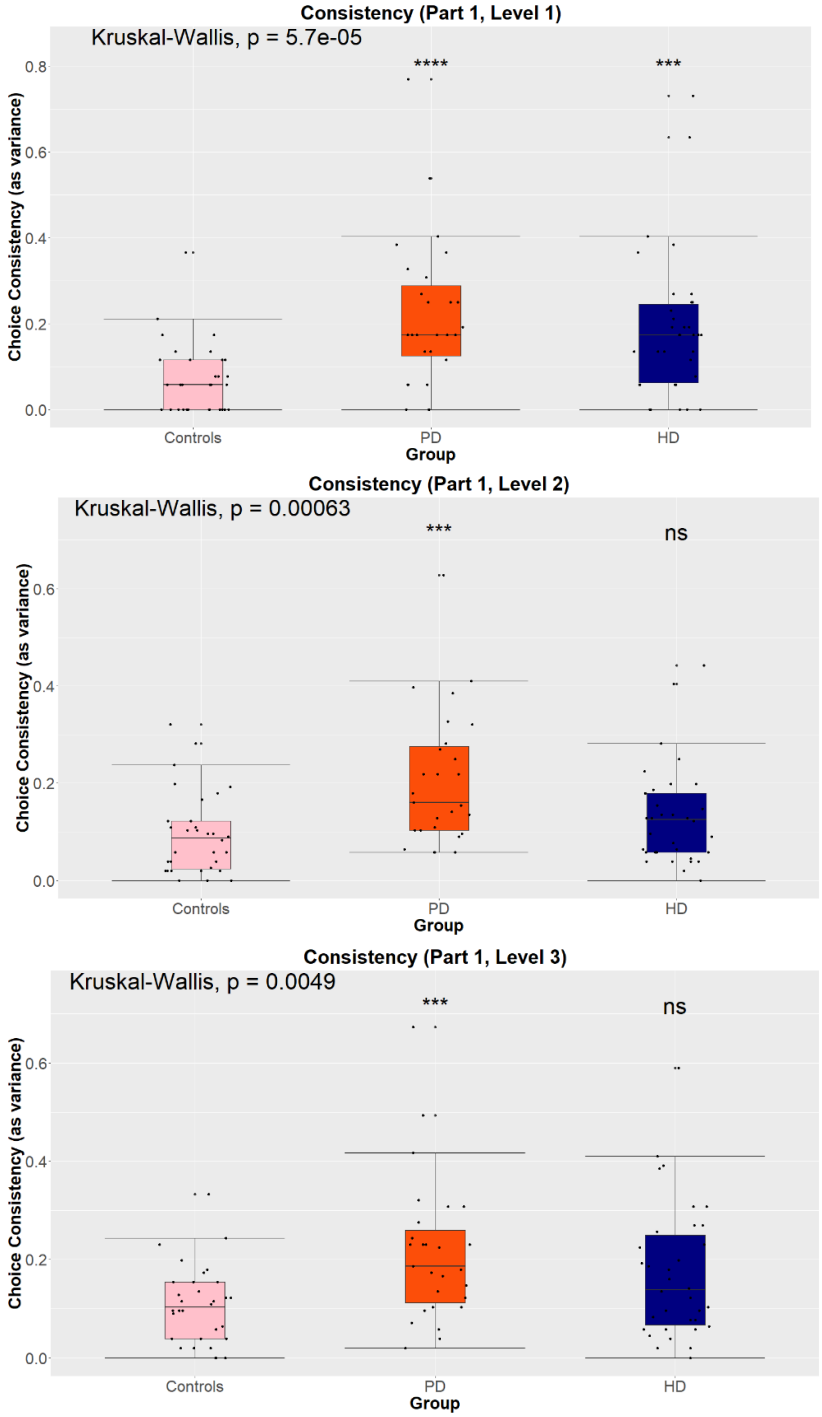
5.5.6 Controls make more consistent choices during rational decision-making than PD and HD groups

The Party Food task presents each choice to participants four times, from which variance between choices can be calculated as a proxy for choice consistency. Greater

variance across identical choices suggests less consistent choice behaviour. Furthermore, choice consistency is compared over three complexity levels: the easiest choice is between images only (level one), the next level presents image and cost attributes, and the most complex level contains image, cost, quantity, cost per unit and eco-friendliness attributes (level three).

In part one of the Party Food task (where participants had an unlimited time to decide), controls made the most consistent decisions. This finding was the same across all three complexity levels. Non-parametric comparison of group means suggests the three groups were significantly different from one another (Figure 43), and subsequent post-hoc tests indicated that the PD group were always less consistent decision-makers than the controls, and the HD group were less consistent than the controls in only the simplest (level one) decisions (Shapiro-Wilk tests for normality: level one $W=0.84$ $p<0.01$, level two $W=0.88$ $p<0.01$, level three $W=0.89$ $p<0.01$; Levene tests for equality of variance: level one $F=2.91$ $p=0.06$, level two $F=2.27$ $p=0.10$, level three $F=2.98$ $p=0.06$; all non-normally distributed with equal variance. Kruskal-Wallis tests to compare group means: level one $H=19.56$ $p<0.01$ and post-hoc pairwise Wilcox tests (with false-discovery rate adjustment) Control-PD $p<0.01$ Control-HD $p<0.01$ PD-HD $p=0.44$, level two $H=14.75$ $p<0.01$ post-hoc pairwise Wilcox tests Control-PD $p<0.01$ Control-HD $p=0.07$ PD-HD $p=0.02$, level three $H=10.63$ $p<0.01$ post-hoc pairwise Wilcox tests Control-PD $p<0.01$ Control-HD $p=0.10$ PD-HD $p=0.17$).

Figure 43. *Below.* Comparison between groups for choice consistency across the three levels of complexity in the Party Food task, part one. Controls make more consistent choices across all three levels compared to the PD group and are more consistent than the HD group in the simplest choices but comparably consistent in the more complex levels. Included on the plots are p-values for a Kruskal-Wallis comparison of group means and post-hoc significance stars to indicate pairwise comparisons with the control group – note these are prior to false discovery rate adjustments which have been made in the body text and remain significant ($p\leq0.0001$=**, $p\leq0.001$=***, $p\leq0.01$=**, $p\leq0.05$=*, $p>0.05$=ns). Top=level one, simplest choices; Middle=level two, two attributes to consider; Bottom=level three, most complex choices with five attributes to consider. Pink=controls; Orange=PD; Navy=HD. For each box, the upper and lower hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentiles). The whiskers extend from the hinge to ±1.5 * IQR.**



5.5.7 There are no differences in choice consistency between controls, PD and HD groups during intuitive decision-making

In part two of the Party Food task (where participants had a limited time to decide: 75% of their average time in part one), the groups could not be distinguished on consistency (Figure 44). This finding was the same across all three complexity levels and, as seen previously in healthy controls from 18-79 years, shows that applying time

pressure to the decision process makes groups substantially and equally inconsistent (Shapiro-Wilk tests for normality: level one W=0.97 p=0.11, level two W=0.95 p<0.01, level three W=0.96 p<0.01; Levene tests for equality of variance: level one F=3.10 p=0.051, level two F=0.02 p=0.98, level three F=0.87 p=0.42; all non-normally distributed with equal variance. Kruskal-Wallis tests to compare group means: level one H=1.70 p=0.43, level two H=2.47 p=0.29, level three H=5.46 p=0.07).

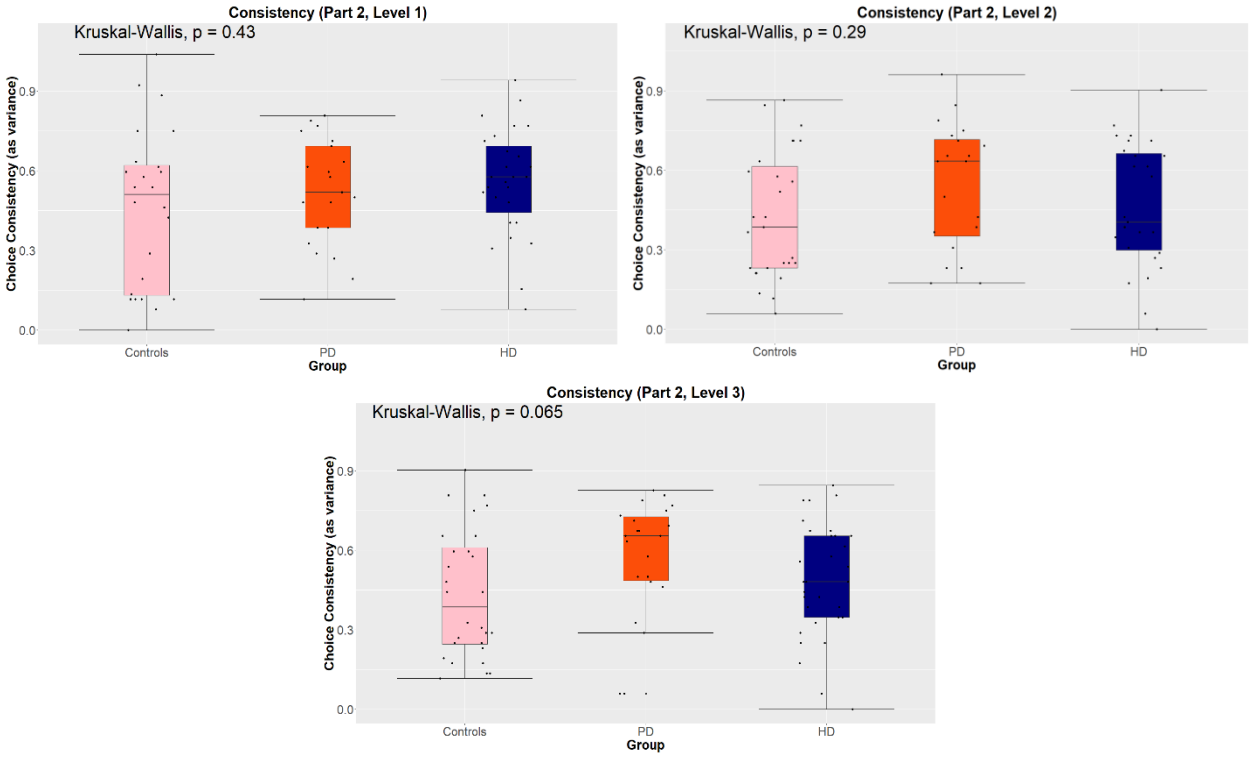


Figure 44. Comparison between groups for choice consistency across the three levels of complexity in the Party Food task, part two. There are no differences between groups in choice consistency across all three complexity levels. Included on the plots are p-values for a Kruskal-Wallis comparison of group means. Test statistics are included in the body text. Top left=level one, simplest choices; Top right=level two, two attributes to consider; Bottom=level three, most complex choices with five attributes to consider. Pink=controls; Orange=PD; Navy=HD. For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

5.5.8 Decision consistency is not different within groups across choices with increasing complexity for rational nor intuitive decisions

As choices become more complex (i.e. there are more attributes to decide with) the choice consistency does not change within any group. Controls alone demonstrate a trend towards becoming less consistent as decisions become more complex in part one of the task (unlimited time to decide) (Kruskal-Wallis comparison of group means: Controls

H=5.11 p=0.08, PD H=0.07 p=0.96, HD H=2.19 p=0.33). Additionally, there are no within-group differences in part two of the task (Kruskal-Wallis comparison of group means: Controls H=0.03 p=0.98, PD H=1.06 p=0.59, HD H=2.32 p=0.31), shown visually by the overlapping bar plots within each group (Figure 45).

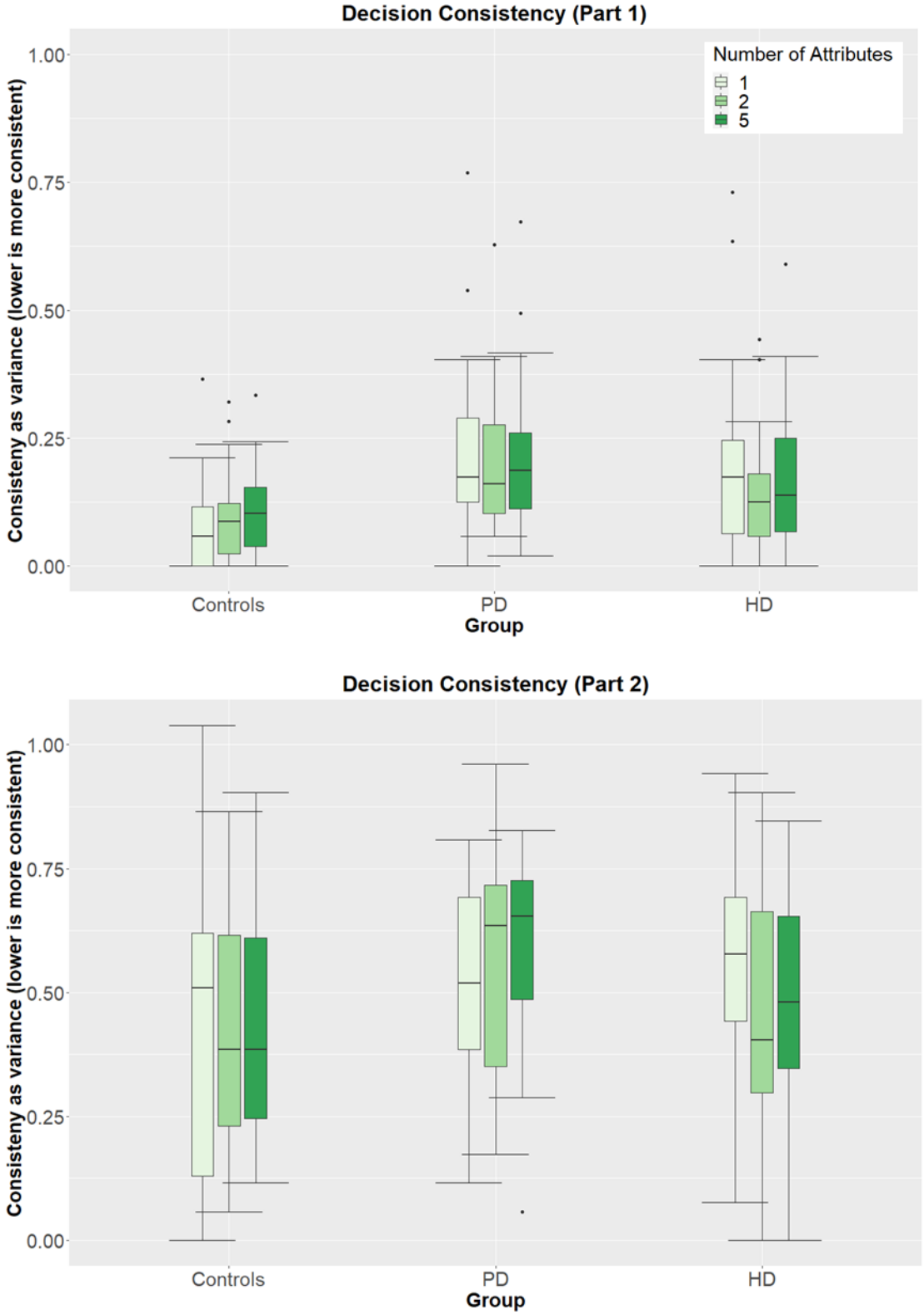


Figure 45. Decision consistency plotted across complexity levels (number of attributes) and between groups. Consistency is calculated as the amount of variance across identical decisions that were presented four times during the Party Food task (part 1 (top), part 2 (bottom)). When given an unlimited time to decide (top), both groups have relatively low variance in their choices, and in the control group, variance increases as more attributes are included in the decision. Under time pressure (bottom), both groups across all complexity levels show much higher variance. For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

5.5.9 Decision consistency is significantly worse during intuitive decision-making

Finally, the differences in choice consistency between parts one and two of the Party Food task were compared. It is clear by visual comparison that there are differences in consistency between part one, which tests rational DM, and part two, which tests intuitive DM, where the choice variance is approximately 10-20% across the groups versus approximately 50%, respectively (Figure 46). Having found no significant differences across the complexity levels, these were collapsed within each group and compared across parts one and two with a Kruskal-Wallis comparison of means test. There were significant differences between the rational and intuitive parts of the task for all three groups, driven by the decreased consistency in intuitive decisions (Controls $H=93.4$, $p<0.01$; PD $H=60.3$, $p<0.01$; HD $H=86.6$, $p<0.01$; Dunn's post hoc tests results matrices not shown).

5.5.10 Verbal IQ, depression and response inhibition do not covary with choice predictability

There were significant differences between the groups for measures of depression and VIQ (see Table 16, demographics). The PD group had higher (worse) depression scores, as measured by the HADS, and the HD group had lower VIQ, as measured by the National Adult Reading test. To confirm that these differences were not affecting the DM task results described above, a generalised linear model (GLM) was run in which choice predictability was modelled (using model 3 with the best fit for choice attributes to explain left-right choice probability) for each group with depression and VIQ included as covariates. The GLM was used instead of a standard regression

linear model because the vectors were not normally distributed (Shapiro-Wilk tests for normality: choice predictability W=0.97 p=0.04; depression W=0.86 p=<0.01; VIQ W=0.95 p<0.01). Neither depression nor VIQ were significantly associated with the relationship between choice predictability and group (depression t=0.22 p=0.83; VIQ t=1.52 p=0.13).

Finally, the response inhibition test scores were assessed for covariance with the DM task results. Only the HD and control groups completed the SST because of time restrictions; it was the longest test and PD patients tended to be slower in completing the task battery, and they found the SST particularly difficult to complete, thus it was removed for this cohort. Additionally, seven participants did not record scores for the SST due to either the task crashing (four participants) or them opting not to complete the task (three participants). Even so, there were significant differences between the HD and age-matched control group for response inhibition, with HD patients performing less well (scores were non-normally distributed, Shapiro-Wilk test W=0.93 p<0.01; Mann-Whitney U test to compare means, test statistic=116, p=0.01). A second GLM was calculated to check that response inhibition did not covary with choice predictability in the HD and age-matched control group (response inhibition t=-0.55, p=0.59). The difficulties with the SST task suggest that it may not be appropriate for cohorts with neurodegenerative disease, especially in extended neuropsychological batteries such as this.

5.5.11 Disease severity for PD and HD is not associated with choice predictability

Given the clinical features of both PD and HD, it is important to understand if choice predictability is affected by motor severity or general functional differences in activities of daily living. For the PD group, motor features were quantified with part three of the UPDRS and general functioning with the SE-ADL. To be included in the study, PD patients were required to have 70% or greater independence so the range for this data is limited. For the HD group, motor features were quantified with the total motor score from the UHDRS and general functioning with the UHDRS total functional capacity scale. Similar to the PD group, the latter test was an exclusion criteria for this study such that patients were required to score 10/13 or higher to be included. Both tests for motor function were carried out by qualified examiners and I am grateful to Dr Caroline Williams-Gray and Marta Camacho for their help with the UPDRS, and Dr Roger Barker, Sam Hewitt and Dr Tagore Nakornchai for their help with the UHDRS

assessments. The tests for each disease are independent and cannot be directly compared, therefore each patient cohort was independently assessed to understand whether measures of disease severity correlated with the percent of choices correctly predicted. All measures of disease severity are non-normally distributed except for the UPDRS motor scores (Shapiro-Wilk tests: UPDRS motor $W=0.97$, $p=0.55$; SE-ADL $W=0.86$, $p<0.01$; UHDRS TMS $W=0.75$, $p<0.01$; UHDRS TFC $W=0.53$, $p<0.01$). Therefore, a Pearson correlation was calculated for the UPDRS motor scores which were not correlated with choice predictability ($R=0.17$, $p=0.41$). Spearman's correlations were calculated for the remaining measures and none were correlated with choice predictability (SE-ADL $Rho=-0.32$, $p=0.10$; UHDRS TMS $Rho= 0.10$, $p=0.58$; UHDRS TFC $Rho=-0.28$, $p=0.11$).

5.5.12 Exploratory findings for cognitive and functional stratification in HD gene carriers

It is not common practice to group pre- and early-manifest HD gene carriers, as I did in these analyses. The motor features which define this stratification may not be relevant in the cognitive and functional requirements of DM, and ultimately may not be relevant for future interventions, thus I stratified patients based on cognitive (ACE-R and MMSE) and functional measures (UHDRS TFC). The previous paragraph showed that measures of disease severity (UHDRS TMS and TFC) were not correlated with choice predictability. However, further analyses are required, given the significant differences in TMS and TFC between the pre- and early-manifest groups such that early-manifest patients have higher motor scores and lower functional capacity (non-normal distributions, Shapiro-Wilk tests: UHDRS TMS $W=0.75$, $p<0.01$, UHDRS TFC $W=0.53$, $p<0.01$. Mann-Whitney U tests: UHDRS TMS $W=0.5$, $p<0.01$; UHDRS TFC $W=210$, $p<0.01$) and premanifest patients may be close or far from disease onset. There were 20 premanifest and 14 early-manifest gene carriers in this cohort.

All outcome measures for the Party Food task were compared across gene-carrier-groups using t-tests or Mann-Whitney U tests, where appropriate. The only significant difference observed was between pre- and early-manifest patients for choice consistency at the most complex level during rational DM (part one, level three of the task). The early-manifest patients had reduced decision consistency than the premanifest individuals. However, when multiple comparisons were adjusted for, this difference disappeared (Shapiro-Wilk tests for consistency, part one level three $W=0.91$ $p<0.01$; Mann-Whitney U test $W=82$ $p=0.04$, after adjustment for multiple comparisons using

false discovery rate p=0.31). Thus, it is reasonable to consider this cohort of HD gene carriers as a single "peri-manifest" group in this instance as they do not differ on any outcome measure of the task. However, the small sample sizes do not provide unequivocal evidence that the "peri-manifest" categorisation is valid in other instances.

5.5.13 Alternative measures of rationality and intuition show similar differences between groups, but the Party Food task best distinguishes groups

The patient cohorts both completed the alternative tests of rationality and intuition which, as described, were some of the best measures for this purpose but not entirely suitable for patient cohorts. These include two alternative tasks, the Trender stepwise reasoning test and the Bees information sampling task where higher scores suggests the participant engaged in more rational processing. The remaining three tests were word problems, designed such that the answer given was indicative of the type of processing used to come to a decision (rational, intuitive or neither). All five variables were non-normally distributed so a non-parametric MANOVA was applied to approximate test statistics and to calculate the relative effects. The five alternative tests were compared in the first instance (Table 19) across four different test statistics to show significant or trend-level group differences. The relative effects table below shows that each measure can distinguish the groups as I would expect: PD patients perform the worst (as also seen in the Party Food task consistency analysis) and controls tend to perform the best, although the HD cohort are relatively close. Those tasks which best distinguish the groups are the CRT and the Trender stepwise reasoning task.

Table 19. Non-parametric MANOVA (results and relative effects) to compare the alternative tests of rational and intuitive processing in decision making across HD, PD and a control cohort. The tests could distinguish the groups significantly or to a trend-level of certainty, with the Trender stepwise reasoning task and the Cognitive Reflection Test best distinguishing group-level performance.

Test statistics	**Test Statistic**	**P-value**	**Permutation Test p-value**
ANOVA type test p-value	2.573	0.01	0.012
McKeon approx. for the Lawley Hotelling Test	1.735	0.08	0.092
Muller approx. for the Bartlett-Nanda-Pillai Test	1.705	0.081	0.084
Wilks Lambda	1.726	0.079	0.089

Relative effects

Group	**Trender reasoning number correct**	**Bees Information Sampling score**	**CRT number correct**	**Linda Problem correct**	**Jelly Bean task number incorrect**
	Higher is more rational	*Higher is more rational*	*Higher is more rational*	*Higher is more rational*	*Lower is more rational*
Controls	0.56	0.50	0.62	0.52	0.42
PD	0.37	0.49	0.42	0.50	0.57
HD	0.54	0.50	0.44	0.49	0.53

Interestingly, a second MANOVA which included the choice predictability measure from the Party Food task is significant across all four tests statistics and the choice predictability variable shows the strongest discrimination in relative effects in this model (Table 20). These findings suggest that the Party Food task is an improved measure of rational and intuitive decision processing in these patient groups in comparison to controls. Finally, a reduced model with the Party Food task choice predictability variable, CRT and Trender stepwise reasoning task gives a higher-still set of test statistics (ANOVA type test=5.346; McKeon approximation for the Lawley Hotelling Test=4.627; Muller approximation for the Bartlett-Nanda-Pillai Test=4.614; Wilks Lambda=4.632) which suggests that this reduced set of tasks would be most useful in future patient studies of rational-intuitive DM.

Table 20. Non-parametric MANOVA (results and relative effects) to compare to alternative tests of rational and intuition decision processing in HD, PD and control cohorts, with the Party Food task outcome measure 'choice predictability' also included. This variable improved the model's ability to distinguish the three groups (see test statistics and p-values) by providing the largest relative difference between the groups (see bold column in bottom Table).

Test Statistics: with additional choice predictability variable	**Test Statistic**	**P-value**	**Permutation Test p-value**
ANOVA type test p-value	3.213	0.001	0.002
McKeon approx. for the Lawley Hotelling Test	2.221	0.014	0.018
Muller approx. for the Bartlett-Nanda-Pillai Test	2.234	0.011	0.013
Wilks Lambda	2.236	0.012	0.017

Relative Effects: with additional choice predictability variable

Group	Trender reasoning number correct	Bees Information Sampling score	CRT number correct	Linda Problem correct	Jelly Bean task number incorrect	Choice Predictability
	Higher is more rational	*Higher is more rational*	*Higher is more rational*	*Higher is more rational*	*Lower is more rational*	*Higher is more rational*
Controls	0.56	0.50	0.62	0.52	0.42	**0.51**
PD	0.37	0.49	0.42	0.50	0.57	**0.36**
HD	0.54	0.50	0.44	0.49	0.53	**0.60**

5.5.14 Response times are slower in patients but number of missed trials does not differ

Previous studies have reported that patient groups respond more slowly in decision tasks than controls. The same finding is reported in this study: there were differences between the groups for RT during rational processing (as measured in the Party Food task, part one), but not for intuitive processing of decisions (Figure 46). During rational processing, group differences were driven by PD patients responding more slowly than controls (levels 1 and 2), and by HD patients responding more slowly than controls for the five-attribute choices (level 3). For the level 2 and 3 choices, significance was at a trend level and is reported below. To calculate these group differences, RTs were averaged for each participant in both parts of the Party Food task and within each complexity level (i.e. each participant had six average times, 2 parts x 3 levels). Average RT was used instead of all RTs so as not to falsely inflate significance (all RTs are not independently varying data points, therefore would falsely increase the degrees of freedom and drive greater significance). The RT distributions were non-normally distributed ($p<0.01$, Shapiro-Wilk tests) and thus Kruskal-Wallis tests were used to determine significance for part one (one attribute (level 1 complexity) $h=6.87$, $p=0.03$, post-hoc tests with false discovery rate adjustment Control-HD $p=0.20$, Control-PD $p=0.02$, PD-HD $p=0.34$; two attributes (level 2) $h=5.74$, $p=0.06$, post-hoc tests Control-HD $p=0.16$, Control-PD $p=0.06$, PD-HD $p=0.48$; five attributes (level 3) $h=4.84$, $p=0.09$, post-hoc tests Control-HD $p=0.07$, Control-PD $p=0.37$, PD-HD $p=0.37$)

and for part two of the Party Food task (one attribute (level 1) h=3.57, p=0.17; two attributes (level 2) h=2.25, p=0.32; five attributes (level 3) h=1.38, p=0.50).

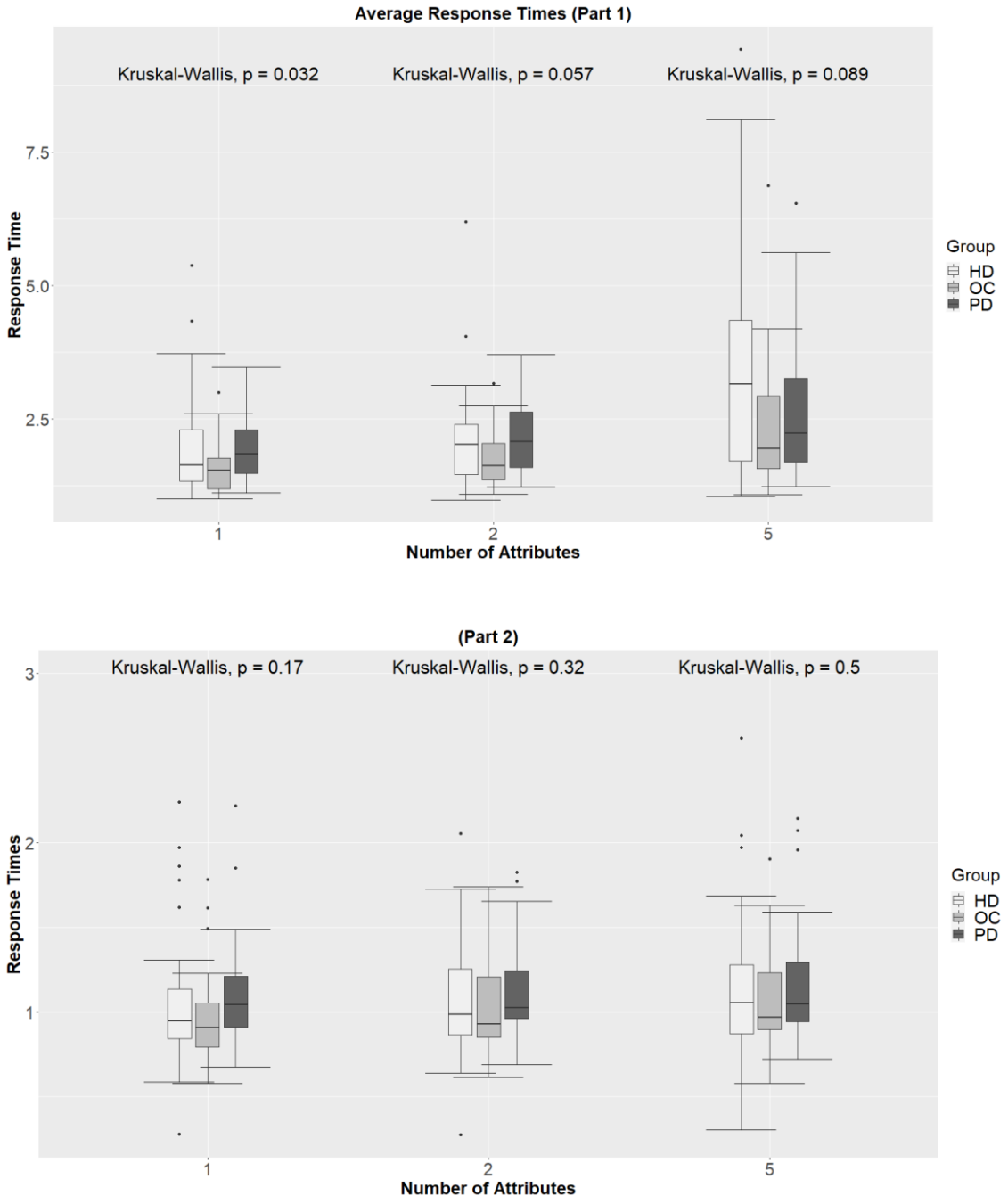


Figure 46. Response time (RT) boxplots for the Party Food task. Six sets of boxplots are plotted: two parts of the Party Food task and each of the three levels of choice complexity within those. The average RT for each individual was included for analysis, not every RT. Times were slower for PD patients during rational decision processing as shown by post-hoc calculation reported in text (Kruskal-Wallis tests, reported on plot and in text). HD=white; OC=controls, light grey; PD=dark grey. For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

There were no differences in the number of missed trials across groups in part two of the task (Figure 47). When the time limit was imposed, most participants missed some trials (i.e. the screen went blank before they could select left or right) which suggests the time limit was effective in preventing rational processing of choices. The time limit was different for each participant, calculated based on 75% of their average RTs across each level of part one. Number of missed trials across the three levels was non-normally distributed ($p<0.01$, Shapiro-Wilk tests) and Kruskal-Wallis tests confirmed that no group differences were present (one attribute (level 1) $h=0.82$, $p=0.66$; two attributes (level 2) $h=0.49$, $p=0.78$; five attributes (level 3) $h=3.14$, $p=0.21$).

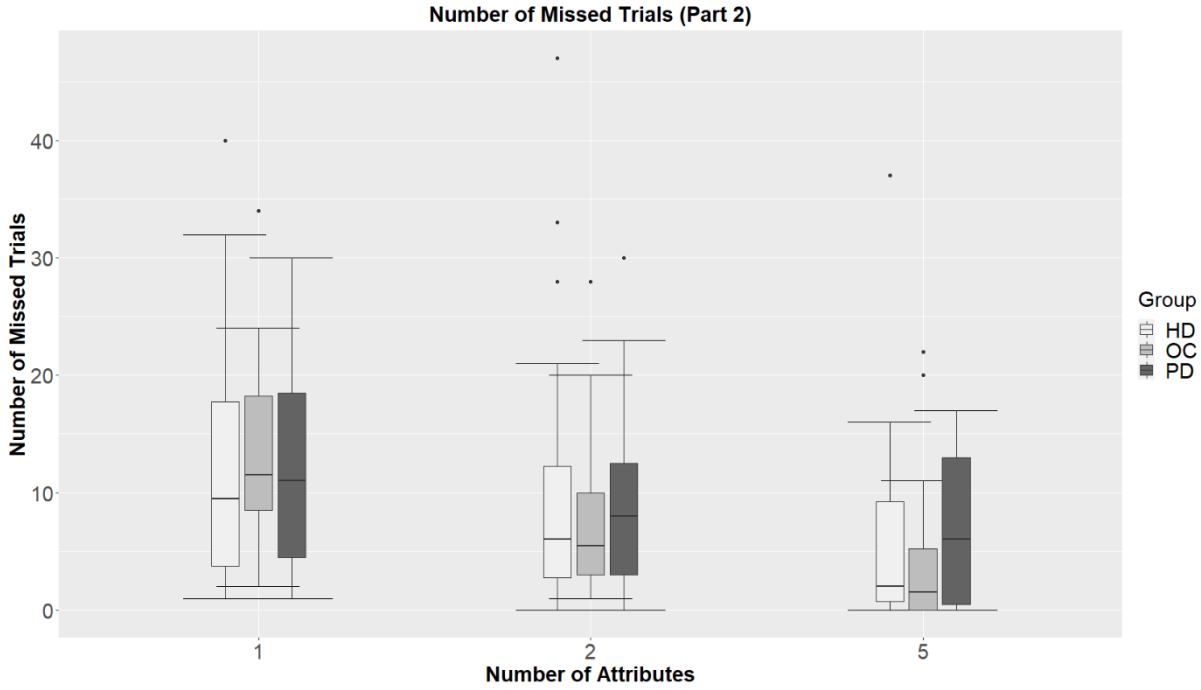


Figure 47. Number of missed trials in the time limited part of the Party Food task (part 2). The number of missed trials was not different across the groups in any of the three complexity levels (Kruskal-Wallis test p-values>0.1, reported in text). HD=white; OC=(controls) light grey; PD=dark grey. For each box, the upper and lower hinges correspond to the first and third quartiles (25th and 75th percentiles). The whiskers extend from the hinge to ±1.5 * IQR.

5.6 Conclusions

In this study, aspects of rational and intuitive processing were investigated through a food choice task. Under a rational processing paradigm where participants

had an unlimited time to make choices, choice attributes were quantified to understand what drove participant's choices and choice consistency was also measured. Cost, quantity and eco-friendliness attributes were not valued differently across the three groups (HD, PD, control); cost and quantity, but not eco-ratings, were significant coefficients in a regression model across participants in each of the groups.

This study also found that age, and not disease status, was related to individual differences in the use of attributes to make decisions. Based on the attributes, Neither HD nor PD patients made less predictable choices than controls, but PD patients made less predictable choices than HD patients. However, when the control group was split by age to match the HD and PD cohorts separately, the patient and control groups were not found to use the choice attributes differently. This finding was compounded by a correlation which showed that together, participants demonstrated a significant decline in the use of choice attributes of 0.29% per year, irrelevant of disease status, a value similar to the decline in healthy controls across the life span (19-79 years) of 0.33% per year (see Chapter 4, Results).

Choice consistency in the rational processing paradigm was different between the groups, such that controls demonstrated reduced variance in their choices. Pairwise post-hoc tests revealed that HD patients were comparably consistent to controls in all but the simplest decisions, whereas PD patients made less consistent decisions than controls at all complexity levels. The intuitive processing paradigm, where time to respond was limited, found that DM was poor across all groups: choice attributes were neglected and decision consistency was significantly worse. Furthermore, in both rational and intuitive paradigms, there were no within-group differences for consistency as the choices increased in complexity. Slower RTs were observed in PD and HD patients than controls during rational processing, but there were no group differences in RT for intuitive processing, nor number of missed trials in the Party Food task part 2.

Neuropsychological test results which differed across the groups (VIQ, depression and response inhibition) were not found to covary with choice predictability during rational DM. Motor and functional measures of disease severity in both PD and HD were similarly not associated with the rational processing paradigm outcomes, though the patients were at early disease stages. The exploratory sub-study into stratification of HD patients based on cognitive and functional measures, rather than motor scores, was successful such that premanifest and early-manifest gene carriers did not demonstrate differences in their use of choice attributes.

The study did not analyse the results of the DM questionnaire despite the participants completing it during their visit. This is because the self-report measure was found not to correlate with any behavioural measure of rational-intuitive processing in the larger cohort of controls and it would be inappropriate to draw conclusions based on its analysis.

Finally, alternative tests for rational-intuitive processing were found to be comparable, although with a weaker ability to distinguish group differences, compared to the Party Food task. Future studies could use a reduced set of tasks to understand these outcome variables in patient cohorts which would include the Party Food task, Trender stepwise reasoning task, and the CRT.

5.7 Discussion

The primary objective of this study was to understand how aspects of rational and intuitive DM differed among HD and PD patients and controls. It concluded that processing of choice attributes was reduced in older participants, irrelevant of disease status, but choices were more consistent in the control group. Decisions made under time pressure, a proxy for intuitive decision processing, were poor as expected, regardless of age or disease status. This matches the finding from Chapter 4, where use of choice attributes declined across the lifespan, but it was unexpected that disease status did not play a role in this as well. This is because studies in premanifest HD patients find cognitive impairments in a range of domains (Baake et al., 2017), as do early-stage studies of cognition in PD (e.g. Williams-Gray et al., 2013) and it is reported that neurodegenerative processes begin many years prior to a clinical diagnosis (Estevez-Fraga et al., 2020; Mahlknecht et al., 2015).

The Party Food task, specifically designed for completion by people with neurodegenerative disorders, is a useful starting point to understand rational and intuitive processing. It was completed without problems by PD and HD patients and it introduces ecological validity and formal choice modelling not previously seen in DM tasks for these groups. However, there is still room to improve the task, specifically the model fit. It was able to predict ~60-72% of participants' choices based on three choice attributes, which suggests that some variance in choice behaviour was not captured. Quantification of image attributes as a fourth covariate in the logistic regression model may help here, while

retaining the suitability of the task for neurological patients. With these improvements in mind, the lack-of-difference between patients and controls might be captured by the variance not explained by the model. It is also worth considering that this study was restricted to participants with normal cognitive functioning so perhaps differences in the processing of choice attributes beyond age were not to be expected.

Choice consistency did distinguish control and PD participants such that the PD cohort made less consistent choices during rational DM. However, participants were not instructed to 'make consistent choices', thus it is possible that increased variance (across identical options) was driven by a novelty seeking behaviour which is optimal in some circumstances. Relatively speaking however, these group differences in consistency and not in use-of-attributes suggests that these two constructs capture different aspects of rational DM. In future studies, it might be useful to build upon these with more constructs to get a fuller picture of rational DM in these groups. It is important, however, that future studies also measure use-of-attributes and choice consistency to determine how these are different.

This study also found that choice complexity did not affect choice consistency. This is a somewhat counterintuitive finding. It was expected that more complex decisions would lead to less consistent choice behaviour - more attributes means more unique factors on which to base one's decision - and considering that these groups' choices were best modelled by a single attribute (cost), this finding suggests that the participants could focus on cost and ignore other attributes, regardless of their number. However, the most complex decisions in this study were relatively straightforward with only five attributes and future investigations might set up decision paradigms with more realistic complexity.

This study found differences in RT between patients and controls for rational decision processes as has been previously shown in HD (e.g. Enzi et al., 2012; Galvez et al., 2017; Vaportzis et al., 2015) and PD decision research (e.g. Smith & McDowall, 2011), which is logical given the motor impairments demonstrated by these participants, although fairly minor. Although the patient groups used choice attributes comparably, they took longer to make these decisions. It might be that requiring HD and PD patients to make decisions under the same time limits as controls would impair their use of choice attributes, forcing patients to use intuitive processing, and future research or intervention development should be aware of this. As shown in the previous Chapter, RTs were also different between groups, where young controls had significantly reduced RTs than older controls. It may be insightful for further analysis of this task to interrogate the RT

distributions, for example, application of a drift diffusion model (as in Chapter 2) or linear ballistic accumulator would give insight into the latent neural processes (Wiecki et al., 2013). One would expect these to be different between the groups considering the effects of neurodegenerative pathology and age.

More generally, choice attributes, consistency and RTs capture only a small part of what it means to make rational decisions, as discussed in the previous Chapter. Utility and outcome-focused quantification could contribute a fuller picture of how rational processing changes with age and disease. There now needs to be work to build on these findings to gain a more thorough understanding about how rationality changes with both age and disease.

This study has several further limitations. The disease scores (i.e. UPDRS and UHDRS) were not always taken on the same day as the visit. When it wasn't possible to conduct both a clinic and study visit on the same day, I had planned to use clinic scores within six months of the study visit. However, with the COVID-19 pandemic, most in-person visits where these scores would normally have been collected were cancelled or conducted online and therefore some participants had missing data for these tests. Also missing from this study is the medication status of the PD cohort. PD patients were mostly in the ON state when assessed (i.e. on usual medication or not usually on any medication for their PD) but this was not formally recorded in the study. Previous studies have found that dopamine-replacement therapy can normalise DM to control performance (Cherkasova et al., 2019; Sharp et al., 2013), but these therapies are short-acting and dopamine levels fluctuate over a day. It would better for future studies with PD cohorts to either plan visits only during the ON or OFF states, or at least record the state and determine whether it affects choice behaviours. The PD cohort also did not complete the SST, a measure of response inhibition, primarily because the battery was too long for PD patients when this task was included. Future studies could use fewer DM tests and incorporate this task, or consider an easier task to measure response inhibition. Three other participants (two HD and one control) were not comfortable with the sustained, rapid, computer mouse responses required to complete the SST and a task more suitable for participants with a movement disorder may be more appropriate.

Overall, this investigation into aspects of rational and intuitive processing has found few differences between controls and patients with Parkinson's and Huntington's

diseases. The motor and functional features of these chronic neurodegenerative diseases were not associated with differential use of choice attributes. Similarly, HD gene carriers with normal cognition performed comparably despite different motor and functional abilities between premanifest and manifest individuals. With a few caveats, this finding suggests that any behavioural interventions that target thinking in older adults are also applicable to PD and HD groups. This is promising in light of there being no successful interventions for cognition in either group, nor in mild cognitive impairment or even in healthy older adults. 'Nudge' interventions, as described previously, might be useful to support declining cognition. For any such intervention, it is important to remember that HD patients have reduced perception (Chapter 2) and it has been found here, and reported previously, that both PD and HD patients respond more slowly in clinic-based DM tasks. Perhaps the next step is to confirm that patient groups share the same specific biases as controls: the results of this study would suggest so, given that intuitive processes were not different across groups.

Future studies that investigate the efficacy of 'nudge' interventions would benefit from using a slimmed-down test battery, consisting of the party food task, Trender Stepwise Reasoning task, and the CRT. This considerably shorter battery would be more appropriate for longitudinal studies in terms of time and repetition: each task can theoretically be altered with minimal practice effects.

This study did not characterise cognitive impairments in patients as many studies have done this previously, but it identified a target for intervention through the rational-intuitive metaphor for DM. The new task is a good starting point from which to understand this paradigm further. The functional effects of age and early cognitive decline could be rescued by nudges which leverage the intact intuitive processing to support everyday DM. How these interventions might look and exactly which decisions should be their target are the subjects of Chapters 6 and 7 in this thesis, and hopefully, of future research to support older adults and patient groups to remain independent and autonomous for longer.

6 A Study into the Effects of Dopamine and Noradrenaline Neurotransmission on Decision-Making in Adults Across the Lifespan

6.1 Summary

The results of the previous Chapters found that age leads to declines in some aspects of rational processing in healthy adults, Huntington's (HD) and Parkinson's (PD) patients. Research suggests that the dopaminergic medication for HD and PD has effects on DM, indeed the dopaminergic system plays a central role in all of our DM activities. These effects appear to change across the lifespan. This study sought to investigate the role of dopamine in aspects of rational and intuitive processing using the tasks from Chapters 4 and 5, by administering drugs which acutely increase or decrease dopamine neurotransmission.

Three drugs, amisulpride, bromocriptine and methylphenidate, were administered in a randomised, double-blind, placebo-controlled, within-subjects study. The objective was to gain mechanistic insight into how modulation of neurotransmission by these drugs affected use of choice attributes and choice consistency. The study utilised the much shorter battery to measure DM that was refined over the previous three Chapters. This study also served to understand how the medication prescribed to HD and PD patients might affect real life DM and to act as a pilot to directly study such effects in a more formally powered study with patient cohorts. Dopaminergic medication might support

rational processes in chronic neurodegenerative disease, but also in individuals where the effects of healthy ageing on rational processes are particularly severe.

6.2 Introduction

6.2.1 A role for dopamine in rational and intuitive DM

In the previous Chapter I showed that HD, PD and age-matched control groups performed comparably in their use of choice attributes. The differences observed were associated with increasing age rather than disease status. It has been shown computationally (Keramati et al., 2011) and in animals (for a review see Balleine & O'Doherty, 2010) that rational thinking processes (such as use of choice attributes) in particular map closely to dopamine (DA) neuron firing. Tonic midbrain DA neuron firing (continuous, slower release of DA) balances competition between rational and intuitive responses by assessing the cost of deliberation, rate of reward and motivational strength to overcome those costs. Phasic firing (intermittent, faster DA release) encodes a value function to compute future rewards. Critically, changing DA levels with medication can alter the willingness to process choice attributes and outcomes (Hamid et al., 2016). This link between DA, rational decision processes, and the results from Chapter 5raises a question: how might DA levels play a role in the decision behaviour measured in the Party Food task? Both HD and PD pathology affects the dopaminergic system, therefore to better understand DM in these conditions it is important to address DA as well.

6.2.2 Dopamine in Parkinson's and Huntington's diseases

People with PD are given DA agonists or dopamine replacement therapy in the form of L-dopa to restore the depleted nigrostriatal DA supply and support basal ganglia motor pathways (Bernheimer et al., 1973). People with HD, on the other hand, are prescribed DA antagonists to reduce striatal DA levels that are thought to be responsible for their chorea (Richfield et al., 1991). Furthermore, dopamine is clearly implicated in cognition in these disorders. In non-demented patients, increasing L-dopa dose is associated with a *delayed* decline in cognitive function (Ikeda et al., 2017). In HD, DA-reducing medication *increased* the rate of cognitive decline (Harris et al., 2020). The mechanisms of changes in cognition are not understood completely, but these two studies suggest that modulation

of DA that is commonplace in HD and PD has incidental effects on cognition, and by relation, may also affect DM. It is difficult to ascertain exactly how DA medication affects DM in these conditions without first characterising the effects of specific medication on healthy controls. A multitude of different drugs are used for symptomatic relief in HD and PD, each of which has a slightly different profile of action on different types of receptors (Tomlinson et al., 2010; Wyant et al., 2017). This study therefore focuses on healthy controls, to understand how altered DA affects DM, but will serve as a pilot study to directly study the effects of DA medication in PD and HD on DM in the future.

6.2.3 What is the optimal level of dopamine for cognition?

According to the inverted-U theory for cognition, both low and high DA levels (as in unmedicated PD and HD, respectively) result in suboptimal cognitive performance whereas a middle amount of DA (as in control participants) is optimal (Figure 48, black line) (Cools & D'Esposito, 2011; Williams & Goldman-Rakic, 1995). Therefore, it could be argued that each disease provides a lesion model for a point on either side of the inverted-U schematic of optimal DA levels for cognition. As demonstrated in Chapter 5, participant performance in the DM task was more similar to the red line in Figure 48. This might suggest that it is independent of changes in dopamine levels in the CNS, or perhaps that PD and HD medication is indeed normalising DM (or at least normalising those DM processes measured).

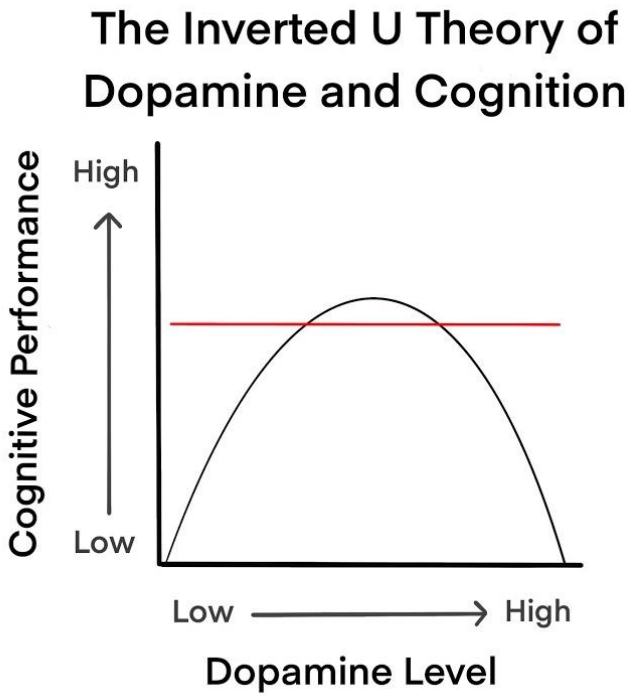


Figure 48. The inverted-U theory of dopamine and cognition states that high and low levels of dopamine are suboptimal for cognitive performance (black line). However, the results from previous Chapters suggest that participants with Huntington's and Parkinson's diseases and matched controls perform similarly on tests of rational and intuitive decision processing (red line). Figure adapted from Cools and D'Esposito, 2011.

However, of importance to our discussion is the fact that it is the dopamine D2-type receptors that are especially important for the inverted-U theory and are consistently implicated in cognitive functioning (Takahashi, 2013) probably in part because their levels are easy to manipulate with oral medication and thus easier to study in people.

6.2.4 How do dopamine levels change with age?

The previous Chapters have suggested that age and not disease status is associated with decline in some aspects of rational processing of everyday decisions. As we age we lose dopamine D1- and D2-type receptors and transporters in the striatum and frontal cortex – the two main destinations of the DA pathways (Eusebio et al., 2012; Karalija et al., 2019; Karrer et al., 2017). Coupled with volume loss in the striatum and prefrontal cortex (Marschner et al., 2005) there is good evidence to suggest that loss of dopaminergic neurotransmission occurs not only in disease, but also in healthy ageing at a rate of 3.7-14.0% per decade (Karrer et al., 2017). The causative factors have not been determined but it appears that healthy older adults are resilient and use dopaminergic resources more effectively (Braskie et al., 2008; Reeves et al., 2002; Samanez-Larkin & Knutson, 2015).

Modulation of D2 receptors with medication in healthy older adults may conform to the inverted-U theory described above, for which most research has relied on young adult participants. Increasing DA transmission improves episodic memory, especially in participants with low baseline scores, while reducing DA levels impairs it (Morcom et al., 2010). Conversely, a study with the same medications in post-menopausal women of similar age found no differences in working memory performance (but did see increased BOLD signal after DA activation with the agonist bromocriptine; Dumas et al., 2017). Genetic differences in DA receptor and transporter types (i.e. single nucleotide polymorphisms (SNPs) in COMT, Taq1A or DAT1) in the two cohorts might explain these divergent results, but genotyping was not conducted in either study. In fact, the genetic effects of functional polymorphisms in these DA genes are found to be enhanced in healthy older adults (compared to younger; Papenberg et al., 2013), such that age-related decline in cognition is not only lessened in people with alleles which confer

greater DA neurotransmission, but to a greater magnitude in older compared to younger adults (Li et al., 2013). To date it is not clear whether this genetic benefit confers protection against age-related receptor and volume losses. From this emerges the central question of this study: How does dopamine affect DM across the lifespan? In this study, the effects of amisulpride (a D2/D3 antagonist), bromocriptine (D2 agonist), and methylphenidate (a DA and noradrenaline (NA) reuptake inhibitor) taken prior to testing aspects of rational and intuitive DM are investigated in healthy young and old adults.

6.2.5 What are the specific cognitive and behavioural effects of these dopaminergic medications?

6.2.5.1 Amisulpride

Amisulpride is a selective post-synaptic receptor antagonist with high affinity for D2/D3 receptors (Leucht, 2004). It reduces DA neurotransmission. Initially I sought to use sulpiride, a more established, less specific dopamine D2/D3 antagonist, however there were problems with supply.

Past studies tend to show impairments when DA levels are reduced in keeping with the inverted-U relationship (Figure 48). Impaired executive functions (for example, problem solving, pattern recognition and generation) are observed following DA receptor blockade by sulpiride and the dopamine D2 receptor antagonist haloperidol (Mehta et al., 1999; Naef et al., 2017; Saeedi et al., 2006). These results suggest that blocking D2 receptors could impair rational processing although no study has specifically investigated this. However, focusing specifically on amisulpride suggests otherwise. Administration for seven days (200mg/day) led to improved local connectivity in the midbrain dopaminergic pathway, substantia nigra and putamen, which correlated with amisulpride plasma levels, and increased global functional connectivity (Metzger et al., 2015). An acute dose of 400mg, however, reduced DA neuron firing in learning tasks and led to reduced learning behaviour (Jocham et al., 2014). These experimental manipulations differed in their time course and it could be that compensation occurred after 7 days of reduced DA neurotransmission and increased activity, but no such changes occurred after a single acute dose. However, cognitive performance after one-off amisulpride is improved in some studies. A single administration of 400mg in young adults decreased RT in psychomotor tasks and increased word fluency, despite common side effects of sedation, headache and cognitive slowing (Chung et al., 2012). Another study in healthy young adults administered 200mg amisulpride and saw improvements in reinforcement

learning for high-value rewards, but no change in low-value rewards nor in the initial learning phases (compared to placebo; Jocham et al., 2011).

Alternatively, a healthy control group who received 400mg amisulpride prior to completing several tests of working memory did not perform differently compared to placebo performance (Morein-Zamir et al., 2010). Healthy older adults were similarly unimpaired in tests of general cognition after 50mg and 200mg amisulpride (Legangneux et al., 2000). These contradictory results are difficult to interpret in the context of rational-intuitive processing. One which studied information sampling found that administration of 400mg amisulpride led to marginally increased sampling, but significance was lost after multiple comparison adjustment (Vicario-Feliciano et al., 2019).

If anything, it appears that the lower 200mg dose is sufficient to see an effect on cognition (if there is any) without participants experiencing negative side effects. These studies did not use the same tasks, nor participants of a similar demographic type, which suggests the mechanism of action for amisulpride is specific and complex. Importantly, none of the aforementioned studies accounted for the genetic differences known to affect DA neurotransmission. It is likely that individuals have different baseline DA levels and therefore manipulation with amisulpride may differentially shift individuals along the DA-cognition curve (Figure 48).

6.2.5.2 Bromocriptine

Bromocriptine is a dopamine receptor agonist which increases dopamine transmission. It does not target the same receptors as amisulpride (i.e. D2/D3 receptors); it is a strong agonist for neurons expressing D2 receptors (i.e. the indirect striatal pathway which is affected by the very early stages of in HD; (Glass et al., 2000)), and a partial agonist for neurons expressing D1 receptors (i.e. direct pathway neurons, affected later in HD; (LiverTox, 2012)). Of relevance to DM and HD, D1 and D2 receptors are equally dense in the striatum but D1 receptors are four to seven times more abundant in limbic and cortical regions (Hall et al., 1994). It would be useful to study separately the effects of specific D1 receptor agonists, but these are not yet available for studies in healthy humans (Furman et al., 2020).

Activation by striatal D2 receptor agonists facilitates flexible cognition (Frank & O'Reilly, 2006; van Holstein et al., 2011), perhaps the kind required for rational processing of information during DM. In early studies using healthy volunteers,classic

neuropsychological tests and an acute dose of bromocriptine (1.25-2.5mg), it was shown that this drug improved working memory performance (Luciana et al., 1992) which was refined in later experiments to show specifically that improvements were during distraction in impulsive individuals (Cools et al., 2007). Bromocriptine administration also improved cognitive flexibility (van Holstein et al., 2011) and learning from reward (Cools et al., 2009). However these benefits were typically seen in individuals with low baseline DA levels (and this phenomenon first noted by Kimberg and colleagues; Kimberg et al., 1997): a specific example is in individuals with high impulsivity who have low baseline D2/D3 receptor binding (Cools et al., 2007; Dalley et al., 2007).

Other studies in healthy adults with the same doses have found no effects, or even impairments, after bromocriptine administration. Similar to the differential effects of amisulpride administration, this might be explained by the inverted-U relationship shown in Figure 48 or through specific behavioural effects of bromocriptine. For example, one study assessed working memory using a pattern location task and found no changes in performance after bromocriptine (Müller et al., 1998). However, participants were not stratified on their baseline DA levels nor baseline performance and differences may have been present at the individual level. A later study found improved spatial working memory but impaired learning (Mehta et al., 2001). More recently, it has been shown that bromocriptine reduced the ability to ignore distracters, which was modulated by higher functional connectivity with the prefrontal cortex (Bloemendaal et al., 2015)—this finding might explain why learning is impaired (it requires focus) but also why working memory can be both unaffected or improved in different tasks (there may be excess capacity to cope with distracters, or not). The divergent effects of the D2 receptor agonist bromocriptine might be due to specific effects of bromocriptine, but individual differences in the DA system may also play a significant role.

Focusing more specifically on rational and intuitive processing suggests a clearer role for D2 antagonism such that increasing DA neurotransmission does not alter rational processing of decisions. Bromocriptine administration did not alter participant's speed-accuracy trade off in a perceptual DM task, underpinned by there being no change in participant's decision thresholds parameter estimated with an accumulator model similar to that used in Chapter 2 (Winkel et al., 2012). In a large cohort of healthy adults bromocriptine had no effect on the amount of information sampled (Strube et al., 2020). Taken together, decisions that require rational consideration of attributes are likely to be unaffected by bromocriptine until the number of attributes reaches the limits of a person's

working memory capacity (and assuming they don't require learning). Dopamine levels in an optimal range are likely to best support rational processing of decisions, whereas "overdosing" DA levels might impair the cognitive controls required (Cools et al., 2019).

6.2.5.3 Methylphenidate

Considerable research has focused on the cognitive effects of methylphenidate due to its effectiveness in attention deficit hyperactivity disorder (ADHD), especially in children (Kimko et al., 1999). In adults it improves response inhibition, error detection, and mediates frontostriatal brain activation in ADHD patients by blocking dopamine and noradrenaline transporters to reduce synaptic reuptake and increase the availability of both neurotransmitters in frontostriatal pathways (Loureiro-Vieira et al., 2017; Volkow et al., 2001). People with ADHD have reduced dopamine receptors in the brain's reward pathways. Compared to healthy adults, dopamine ligand binding is greater across D2/D3 receptors in the nucleus accumbens, midbrain, left caudate, hypothalamic region which also correlates with behavioural measures of attention (Volkow et al., 2009).

However, its success in treating ADHD has also led to its widespread misuse as a cognitive performance enhancer in healthy adults, which usefully led to in depth study of methylphenidate's effects in healthy adults. One study in healthy adults found that methylphenidate decreased cortical inhibition and increased cortical facilitation measured by transcranial magnetic stimulation (Gilbert et al., 2006) which might support claims of cognitive enhancement. However, behavioural evidence is in conflict. A study which used the stop-signal task (which measures response inhibition) found almost no differences between placebo and drug, except that methylphenidate led to reduced variance in RTs on correct trials (Costa et al., 2013). It was found more recently that healthy adults with relatively lower dopamine synthesis capacity saw increases in cognitive motivation after taking methylphenidate by increased striatal DA signalling, but not improved performance *per se* (Westbrook et al., 2020).

Focussing more specifically on rational and intuitive processing, one study explored methylphenidate as a cognition enhancer in chess players and found that it improved reflective DM when players were not under time pressure but it had no, or detrimental, effects under time constraints (Franke et al., 2017). Another study suggests a mechanism for this: perceptual DM was enhanced specifically by increasing drift rate (evidence accumulation), but not other latent DM variables (Beste et al., 2018). A second computational-model-based study supported methylphenidate-enhanced rational DM,

where the quality of evidence was increased and variability in the accumulation processes reduced (Weigard et al., 2019). Taken together, methylphenidate might increase the likelihood to engage in rational processing by sharpening evidence accumulation, but an increased likelihood doesn't lead always lead to measurable behavioural change. As in modulation by bromocriptine and amisulpride, it may be that some individuals remain at an optimal DA level and any effects are not measurable with cognitive tasks. If the reason for misuse of methylphenidate lies in its ability to enhance rational processing of choice attributes, it might be an appropriate intervention for individuals who particularly struggle in this domain.

6.2.6 The present study

This was a double-blind, placebo-controlled, within-subject design, in which a D2/D3 dopamine agonist (bromocriptine), D2 antagonist (amisulpride) and dopamine and noradrenaline transport blocker (methylphenidate) were administered over four separate visits three weeks apart. After a two-hour wait period, participants completed DM tasks, refined from the previous studies described in this thesis. Of particular interest are the measures of rational processing: use of choice attributes, choice consistency (both from the Party Food task), and number correct in the Trender Stepwise Reasoning task and CRT. The Bees Information Sampling task was also included given the reported effects of dopamine manipulation on information sampling.

Studies in patients are useful to understand the mechanisms for therapeutic intervention, but are affected by factors such as clinical heterogeneity, comorbidities, long term medication, and selection biases. These can be avoided in studies of healthy subjects. As in Chapters 3 and 4, this study was conducted in healthy controls to initially understand the role of DA in aspects of rational and intuitive decision processing, but also to serve as a pilot study for investigations in patient cohorts.

I predicted that DA levels within an optimal range (see Figure 48, central area of black curve) are required to support normal DM (i.e. normal compared to those of a similar age). Rational-intuitive processes has not been studied during acute dopaminergic manipulation. In the case of amisulpride, past studies showed increased, decreased and unchanged performance in cognitive tasks, therefore I could not make educated *a priori* predictions. Given the compounding effects of genetic influences on DA neurotransmission, I predicted that any effects would be larger in older adults. Bromocriptine would have no effect in some participants, and lead to improved

performance in those with low baseline scores (e.g. Morcom et al., 2010). Methylphenidate would enhance rational processing, possibly by increasing motivation rather than the ability to rationalise choices directly (Westbrook et al., 2020).

Due to start in March 2020, this study was first delayed for seven months due to the COVID-19 pandemic. It started in October 2020 and I saw one set of participants before being put on hold again because of a resurgence of COVID-19. The study has not yet resumed (as of March 2021).

6.3 Objectives

The primary objective of this study was to investigate how acute modulation of DA and NA levels with medication affected rational and intuitive decision processing in healthy adults. The secondary objective was to understand whether neuromodulation with methylphenidate might serve as an intervention to improve rational decision processing. This study could therefore inform a future study in HD and PD cohorts to understand how DA medication affects DM.

6.4 Methods

6.4.1 Study Recruitment

Participants were recruited from the local community and through posters at Colleges and the Cambridge Biomedical Campus. Recruitment was remote, through the University SONA-Systems account where participants signed up online for all visits at once. The exclusion criteria were applied to filter potential participants prior to their signing up, and their pre-screen surveys were further screened for inclusion/exclusion criteria. After signing up, participants were screened again via email to confirm their study visit dates and the study criteria, particularly ongoing medical conditions, allergies and medication. All participants met the following criteria:

1) Aged 18-30 or 45-80
2) Willing and able to complete all assessments in the protocol

The following exclusion criteria were applied

1) Non-native English speaker
2) Uncorrected sight or hearing impairment which would interfere with cognitive testing
3) Documented learning disability or existing diagnosis of dementia
4) Other significant neurological condition affecting the brain
5) Lactose intolerance
6) Contraindications to receiving amisulpride, bromocriptine or methylphenidate
7) Ongoing medical condition that is poorly controlled in the opinion of the PI

6.4.2 Study Procedures

The study was conducted over four in-person visits at the John Van Geest Centre for Brain Repair in Cambridge and participants were paid after each visit. Reasonable travel costs were reimbursed if required. Participants maintained their normal routines outside the study. Each visit was three weeks after the previous, chosen to allow complete drug washout and minimise practice effects. A new version of each task was used at each visit to further minimise practice effects, and neither task had complex learning or memory requirements. Each visit lasted approximately three hours in which the participant arrived, took the study drug, waited for two hours, then completed 45 minutes of tasks (Table 21). Order of drug was randomised using an online tool (https://www.sealedenvelope.com/simple-randomiser/v1/lists) prior to the first visit. The drug was administered by a separate member of the study team (Dr Tagore Nakornchai) to maintain participant and experimenter blinding.

The drugs and doses were as follows:

1) Amisulpride, 200mg

   This is the standard dose as defined by the British National Formulary (BNF) https://bnf.nice.org.uk/drug/amisulpride.html (last accessed 28/09/2020) and is shown to provide clinical efficacy without side effects (Rosenzweig et al., 2002) with peak plasma concentrations that do not differ between old and young adults (Hamon-Vilcot et al., 1998).

2) Bromocriptine, 2.5mg

   This dose was within a range indicated by the BNF https://bnf.nice.org.uk/drug/bromocriptine.html (last accessed 28/09/2020) did

not induce sleepiness in comparison to other dopamine agonists (Micallef et al., 2009) but is higher than or equal to doses in past research.

3) Methylphenidate, 30mg

   This dose was above the range indicated by the BNF https://bnf.nice.org.uk/drug/methylphenidate-hydrochloride.html (last accessed 28/09/2020) for methylphenidate-naive individuals but considered safe in individuals with ADHD after titration. Previous studies also used higher doses than that suggested on the BNF website, 30-40mg instead of 10mg (Costa et al., 2013; Gilbert et al., 2006; Manktelow et al., 2017; Marquand et al., 2011). Discussion with Dr Anne Manktelow and her colleagues Dr Emmanuel Stamatakis and Alex Peattie confirmed that 30mg was safe and efficacious in their studies in healthy controls and patients with traumatic brain injury. Two neurologists also confirmed that this dose was safe (Drs Roger Barker and Tagore Nakornchai). Drug dose response is optimal when titrated over time with regard to bodyweight, however it has also been shown that dose-response curves do not differ significantly across body weights (Kimko et al., 1999).

4) Lactase placebo

   These tablets were purchased from Holland and Barrett https://www.hollandandbarrett.com/shop/product/milkaid-lactase-enzyme-tablets-raspberry-flavour-120-tablets-60018132 (last accessed 04/03/2021). They are similar in appearance to the other tablets (small, white, round) but have a raspberry flavour.

A Consultant Neurologist (Dr Roger Barker) prescribed the study drugs and the prescription was filled by Fitzwilliam Pharmacy in Cambridge. Although participants were blind to the order of administration, they were asked to guess the order in which they had received the drugs on their final visit to understand whether the tablets' appearance, odour or taste was indicative of their purpose.

During the visit, participants were provided with snacks (food consumption has not been shown to alter drug absorption) but asked to refrain from consuming caffeinated drinks due to the possible effects of caffeine on cognition (Franke et al., 2017; Kimko et al., 1999; Kopitar et al., 1991). They were allowed to go for a walk during the wait period but asked to remain nearby, on the Biomedical Campus. After completing visits 1-3,

participants were paid £7 per visit and then paid £12 after completing the final visit. The tasks in Table 1 below were completed two hours after drug administration in keeping with the peak plasma concentrations of the three drugs. For bromocriptine this is 1-2 hours, for amisulpride 2-3 hours, and for methylphenidate the peak concentration is 2 hours (Kimko et al., 1999; Mehta et al., 2004; Mehta & Riedel, 2006).

Table 21. Study procedures took approximately three hours at each visit with two free hours after taking the tablet but before cognitive testing. Abbreviations: HADS+I = Hospital Anxiety and Depression and Snaith Irritability Scale; VAS = Visual analogue scale; CRT = Cognitive Reflection Test.

Assessments	Time to complete (mins)
Informed Consent	5
HADS+I	5
Oral administration of drug (by non-blinded member of study team)	5
Two-hour wait period	-
VAS questionnaire	5
Trender Stepwise Reasoning task	5
Bees Information Sampling task	5
Party food task	20
Supplementary DM tasks (Jelly bean, Linda problem, CRT)	5
Rey complex figure drawing	5
Total (including wait period)	**180**

Study procedures not yet described in this thesis are below. Additional task descriptions are in Appendix 2.

6.4.2.1 Visual Analog Scale (VAS):

Fifteen slider-scale questions to provide a subjective measure of alertness, anxiety, tiredness, restlessness and ability to concentrate which could influence subsequent task performance (Bond & Lader, 1974; Figure 49). Participants completed the scale immediately prior to the cognitive tasks, after the drug administration and wait period. This version of the VAS is designed and has been implemented by Dr Adam Hampshire at Imperial College, via his website (www.cognitron.co.uk). William Trender and Peter Hellyer were also instrumental in building these tasks and maintaining them on the Cognitron website.

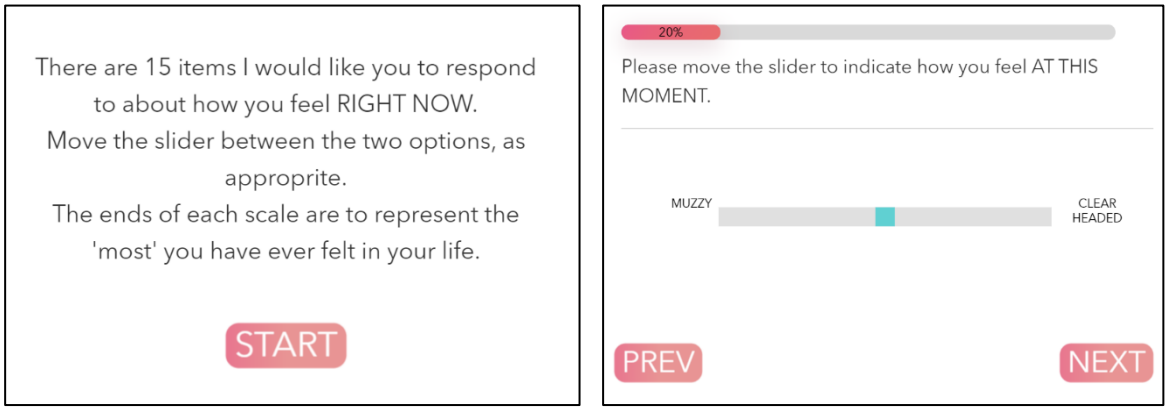


Figure 49. Schematic of the Visual Analogue Scale (VAS) where participants used a sliding scale to measure their immediate feelings prior to completing the task but after the two-hour wait period.

6.4.2.2 Methylphenidate

The prescription of methylphenidate, as a controlled drug, required a special prescription. To be eligible to write this an application was submitted to the NHS Business Authority for the study doctor (R.A.B) to be given a private prescriber identification number, which itself required a risk assessment and two standard operating procedures for the prescription, storage and administration of CDs. Methylphenidate must be stored in an approved controlled drug cabinet which fits the following criteria, and as part of continued use and storage or the drug, weekly audits are required to monitor use and supply. The supply of all three drugs was closely monitored by a register, completed at each visit, and a weekly audit. I am grateful to Dr Tagore Nakornchai for completing these in order to maintain experimenter blinding.

6.4.3 Ethical Approval, Insurance and Sponsorship

Approval was sought from the CPREC and linked to the previous study (CPREC2018.121) in which a larger set of tasks were used to understand DM in healthy controls across the lifespan (This study: CPREC2019.074). I applied for insurance cover through the University of Cambridge Finance Division (HVS/2019/2702), and further approval from the University's Research and Development department. External peer review was by Dr Caroline Williams-Gray.

6.4.4 Statistical Analysis

Due to the significant impact of the COVID-19 pandemic, this study is only 10% complete and data has not been analysed as planned. Below are the analyses plans once the study is complete.

R studio will be used to conduct analysis. Demographic variables will be tested for normality and equality of variance using Shapiro-Wilk and F-tests. Depending on these results, old and young groups will be compared using Welch's t-tests or Mann-Whitney U tests, and chi squared or Fisher's exact tests for categorical variables (sex).

For the effects of drug, each task will be independently analysed using a repeated measures MANOVA or non-parametric equivalent, with covariates, included if these differ between the groups (e.g. age). Practice effects will be analysed using two-way ANOVAs with group and session processing (first, second, third or fourth) against combined-Z-scored rational processing, regardless of drug taken. A script is included in the Gitlab project for the analysis conducted in this Chapter.

Identical methods to analyse and model participants' choices in the party food task as described in previous Chapters 3-5 are used. This includes MATLAB software, psychometric modelling of individual choices and calculating the variance between choices as a proxy measure of choice consistency.

6.5 Results

6.5.1 Participant Demographics

Five individuals have participated in this study at the time of writing. Six were recruited but one dropped out prior to the first visit due to uncertainties around intermittent lockdowns. It is expected that 50 individuals (25 young adults and 25 older adults) will complete the study when it is safe to do so from a COVID perspective.

6.5.2 Descriptive Results

The twenty visits that were completed are described below including qualitative feedback (Table 22). It is hard to draw any conclusions from this early stage in the study. However, it appears that the visit and study protocols are successful and do not require major changes. There is variability among the test scores at each visit within each individual (Figure 50) . I am concerned that practice effects between visits one and two

are present in the Trender Stepwise Reasoning and Bees Information Sampling tasks for some participants (for example, participant 2 in Trender graph, Figure 50). Scores for all tasks are within the expected ranges and are similar to those reported in Chapters 3-5. For example, it was expected that older adults would make fewer predictable choices which appears to be true in the case of the single older adult who has so far completed this study (participant 4, blue in Figure 50). Results for choice consistency were not calculated as these require group comparisons to be meaningful.

Table 22. Five participants completed the study prior to pausing recruitment. Their sex, age, and the drugs they took at each visit are listed below. Abbreviations: AMI=amisulpride; PLA=placebo; MPH=methylphenidate; BRO=bromocriptine.

Participant	**001 (F, 19)**	**002 (F, 19)**	**003 (F, 26)**	**004 (M, 69)**	**005 (M, 27)**
Visit 1	AMI	AMI	PLA	MPH	MPH
Visit 2	PLA	PLA	AMI	BRO	PLA
Visit 3	MPH	BRO	MPH	AMI	BRO
Visit 4	BRO	MPH	BRO	PLA	AMI

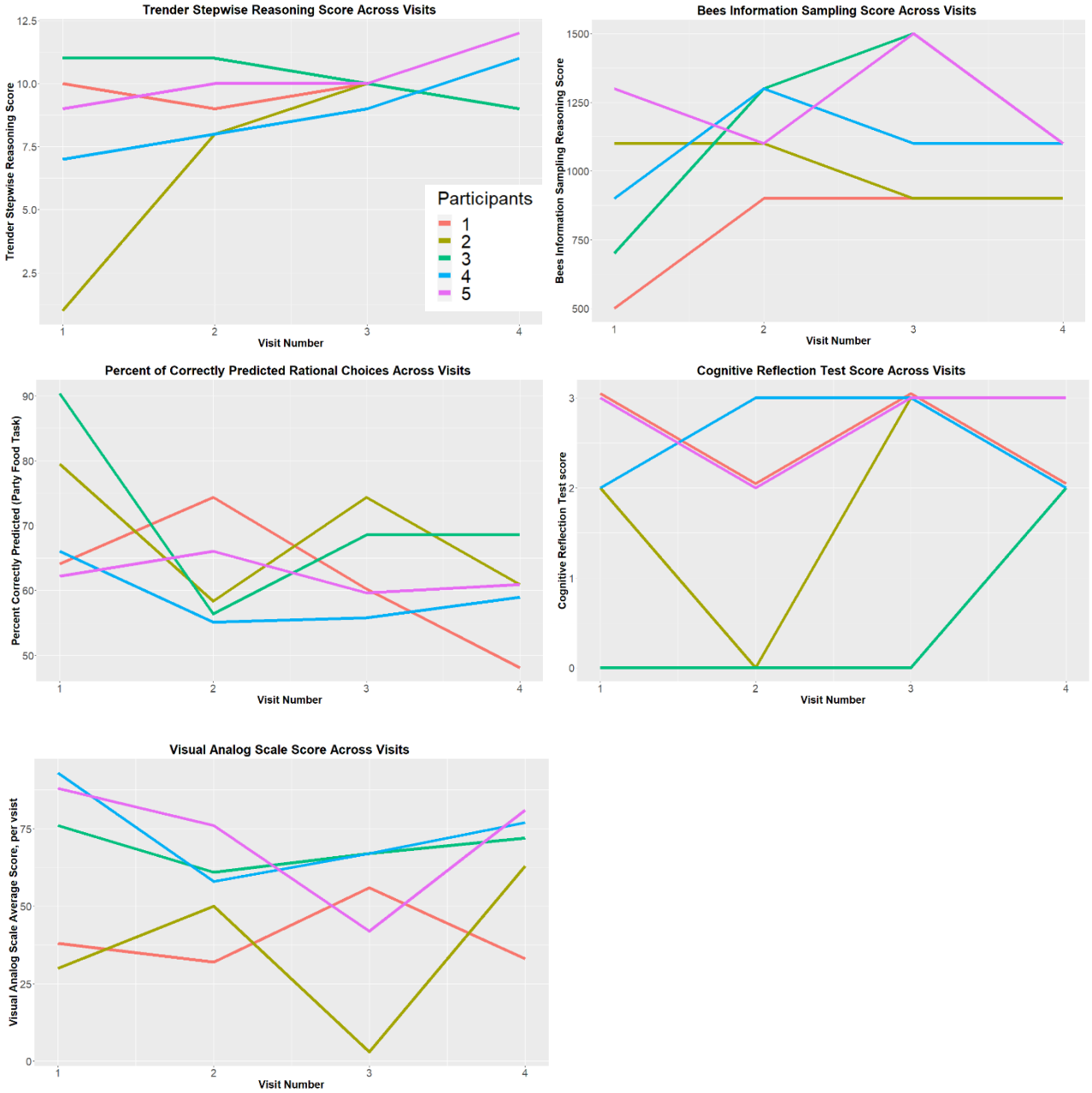


Figure 50. Scores for each participant across visits for each task in this study. Colours are for each participant. X-axis is visit number (1-4) and y-axis is the score. Top left = Trender stepwise reasoning task, scores out of 12; top right =Bees information sampling task, scores out of 1500; middle left = percent of choices correctly predicted by logistic regression model, out of 100%; middle right = Cognitive reflection test scores, out of 3; bottom = visual analog scale score aggregate across all questions, out of 100.

6.5.3 Recruitment

Recruitment via SONA-systems was superior to manually contacting and booking in participants. It saved time organising visit dates, provided an extra level of screening, and enable the recruitment process to be entirely remote.

Visits were not always three weeks apart. Rebooking visits became commonplace amidst requirements for participants to self-isolate, to work or attend virtual meetings at short notice and there were difficulties in securing clinic room space.

6.5.4 Side effects

All side effects were mild and transient. One participant reported feeling dizzy and warm during their wait period after taking bromocriptine but chose to continue with the visit, and did not disclose the side effect until the end of their visit (despite being asked how they felt several times).

6.5.5 Participants did not guess their medication but guessed placebo visits correctly

On their final visit, participants were asked to guess which medication they had received on each visit. This was important to ask because, while each visit used two tablets of similar size and shape, the placebo had a raspberry flavour and odour and placebo visits saw participants take two identical tablets (rather than similar). It is expected that each participant could make one correct guess, given that they had a 1 in 4 chance of being correct and four attempts. All five participants guessed one medication correctly and two participants guessed two of their medications correctly. Of the seven correct guesses, four were the placebo visit (i.e. 4 of 5 participants guessed when they were in the placebo visit). The remaining three correct guesses were for methylphenidate (2 participants) and bromocriptine (1 participant). Notably, one participant was a retired physician (nephrologist and dermatologist) familiar with the drugs' side effects but guessed only the placebo visit correctly.

The participants' awareness of their placebo visit is a problem as this study continues. A solution could be to have placebo tablets manufactured to look identical to one of the other three tablets, however, this is costly and may take a long time. A second solution is to purchase alternative placebo tablets, specifically those without a noticeable odour and taste.

6.5.6 Additional insights from participants

Comments made by the participants suggested that they were happier to participate when they could use the two-hour wait period effectively. For those participants who were undergraduate students, this meant having a desk and a quiet place to work. For postgraduate research students, this meant being able to go back to the their lab or office. For the retired participant, it meant being allowed to go for a walk or read. All participants took advantage of the snacks on every visit and were happy to abstain from caffeinated drinks during their visit.

6.5.7 Effects of drug

A repeated measures MANOVA and prerequisite assumption tests were conducted to ensure the analysis pipeline was functional. The assumptions were not met with the current sample, but they included: adequate sample size (cell n > number of dependent variables), no univariate or multivariate outliers, normality, no multicollinearity between dependent variables, equality of variances and equality of covariances. The subsequent MANOVA found no effects between the four levels (drugs and placebo) ($F = 0.412$, $p=0.83$). At this stage, age was not included as a covariate.

6.6 Discussion

6.6.1 Could methylphenidate improve the rational processing of decisions?

There is early evidence to support methylphenidate-enhanced evidence accumulation during DM, particularly in the case of perceptual DM in HD gene carriers, which was found to be impaired in Chapter 2 (Beste et al., 2018; Weigard et al., 2019). This suggests that it improves the processing of choice attributes and therefore the ability to make rational decisions. This study is designed such that any individual's rational processing can be meaningfully quantified with individual-level logistic regression and calculation of choice variance. However, parameters in the HDDM (if applied) are calculated at a group level without the ability to make conclusions at an individual level. The hierarchical Bayesian method assumes that individuals are similar, but not identical to their group (young or older) and therefore constructs group-level distributions which are representative of the individuals within them. Group comparisons are made with a 95% high-density interval which quantifies the overlap between group distributions similarly to a two-tailed t-test. Once completed, it would be useful for this study's analysis

protocol to be updated to include HDDM to understand whether these group-level differences are present. However, the HDDM traditionally requires choices to be classified as correct or incorrect (i.e. as 0 or 1) and in the Party Food task there are no correct answers. The algorithm which infers latent choice parameters might need to be altered if it does indeed treat correct choices differently to those which are defined as incorrect, however, a post on the HDDM forum by the author of the MATLAB package suggests that, "HDDM has no concept of correct or incorrect. Only upper and lower boundary. How you interpret and code responses is up to you" (Thomas Wiecki, June 24 2015, https://groups.google.com/g/hddm-users/c/aWQsLtBJfTU/m/8_hV3MgDBQAJ?pli=1, last accessed 09/03/2021). Further investigation into this by a person with computational modelling experience would add value to this study.

If group differences are observed and methylphenidate is shown to enhance rational processing, this study may serve as a pilot for an equivalent study in HD patients or other patients with chronic neurodegenerative disease. There is little empirical understanding about the effects of methylphenidate in HD patients. One published case study in a patient with juvenile HD, an early-onset form due to increased CAG repeat, found that methylphenidate worsened motor symptoms significantly (Waugh et al., 2008). It is logical to assume that increasing DA levels by inhibiting synaptic DA transport (i.e. the mechanism of action for methylphenidate) would worsen the motor features of HD, given the hypothesis that excess DA causes these (Richfield et al., 1991) and that anti-dopaminergic medication leads to improvements (Coppen & Roos, 2017). If methylphenidate is found to worsen motor features in traditional HD patients it is possible that more targeted drugs could provide a solution. For example, those which act on the prefrontal DA receptors but not the motor pathways within the basal ganglia and striatum may be helpful (i.e. D1 receptor agonists, but none are currently approved for use in the UK), or perhaps drugs which specifically inhibit noradrenaline reuptake, e.g. desipramine), although the corticostriatal white matter pathway means the regions are closely functionally connected which makes any interpretation difficult. Other options could be to use low-dose methylphenidate (e.g. 10mg instead of 30mg) or to recruit only patients with very few, or stable, motor features by stratifying recruitment based on UHDRS motor score and closely monitoring motor changes throughout the study.

Putting aside the problem of worsening motor features, methylphenidate has been tested for therapeutic use in Alzheimer's disease for apathy, which affects up to 70% of patients (Mega et al., 1996). If methylphenidate enhances motivation as concluded by Westbrook and colleagues, it is logical that apathy can be improved with methylphenidate (Westbrook et al., 2020). A small study found that every AD patient had improved apathy scores in a 12 week study with daily methylphenidate (titrated to 10mg MPH, twice daily; Padala et al., 2010). This was followed up by a better-controlled study which, in addition to apathy, saw improvements in cognition and functional status (titrated to 10mg MPH, twice daily; Padala et al., 2018). However, while another study also saw improvements with methylphenidate for apathy, 3 of 13 participants also had adverse events including delusions, agitation, anger, insomnia and irritability (10mg MPH; Herrmann et al., 2008). Similar positive results were found for apathy in cerebrovascular disease (2.5-7.5mg MPH; Spiegel et al., 2009) and vascular cognitive impairment (10mg MPH; Leijenaar et al., 2020), normal pressure hydrocephalus (10mg MPH; Keenan et al., 2005) and in geriatric patients (5mg MPH; Jansen et al., 2001). Furthermore, one report proposed methylphenidate as a treatment for apathy in patients with HD, although the potential impact on motor features was not discussed (Krishnamoorthy & Craufurd, 2011) and no such trial has been carried out to date. As such, any future study should include apathy rating scales (e.g. the Apathy Evaluation Scale), but also confounders which are often considered in this area of research, for example, daytime sleepiness, sleep apnoea, and elevated body mass index (Padala et al., 2018).

6.6.2 Uncertainties in the peak plasma concentrations of dopaminergic drugs

While this study has been designed to maximise the blood levels of each drug, this may not relate directly to levels in the brain. Between methylphenidate, bromocriptine and amisulpiride, there is likely to be differential penetration of the blood-brain barrier. Indeed, it is reported that amisulpiride has poor penetration in animals where even very high doses lack the physical effects seen in similar antipsychotic drugs (Natesan et al., 2008).

Furthermore, it is difficult to know how the peak plasma and brain concentrations for each drug vary in older versus younger adults because there is little published data on the pharmacokinetics across the lifespan. Only one study in amisulpride had this data (Hamon-Vilcot et al., 1998) and found that differences were non-significant but it should

not be assumed that this is the case for bromocriptine and methylphenidate. It is not within the scope of this study to monitor plasma concentrations during visits, but it would be useful to be aware of any such research which becomes available in the next few years.

6.6.3 Practice effects

This study may suffer from practice effects as they have not been studied explicitly in the selected tasks. A new version for each task was used at each visit without changing the task premise or instructions (for example, figure out the next pattern in the sequence, or choose your preferred food item), but the specific stimuli were different. The tasks are all straightforward without complexities such as multiple steps to learn and remember. However, one study found that very few tests are non-susceptible to practice effects, and effects are largest early on (e.g. between visits one and two; Bartels et al., 2010). If drug effects are minor, practice effects might mask or amplify true findings in this study. It is promising though that the same study found that confounding variables had minimal influence on practice effects (e.g. age, IQ). When this study is resumed, it might be of benefit to include an initial screening visit with a fifth version of each task to minimise any practice effects that are present between visits one and two, or to run a separate study to quantify the shape of learning curves in each task.

6.6.4 Continuation of Study

This study will be continued when it is safe to do so under UK Government and University of Cambridge guidelines, led by another PhD student, Miriam Schaepers. There is ethical approval in place to extend the end date of the study. Upon evaluation of these results, it is recommended that the study restarts with a more specific cognitive task in which the role of dopamine is better known. For example, the foraging task used by LeHeron and Colleagues which assessed cost-benefit DM for reward maximisation in an ecological context (Le Heron et al., 2020). Such a task will assist in the interpretation of results in this study where practice effects or imperfect blood-brain barrier penetration may interfere.

7 "Triage" Smartphone Application as a Specific Intervention for Problematic Decision-Making

7.1 Summary

Research described previously in this thesis suggests that impaired perception and an aversion to complex choices is evident in HD gene carriers and older adults, respectively. This Chapter outlines the development of an app called Triage which puts this information to use to support good DM about letters, emails and other documents. The intervention is not restricted to patients, nor to older adults, but is found to have merit across all individuals. Triage is used to scan photographs of letters, screenshots and PDFs to highlight the most pertinent terms and classify documents in terms of the action they require. For example, a letter from the bank which includes the term 'payment due' will alert the user to act urgently. As of March 2021, it is a functional app which has shown great promise and will now undergo further testing for its efficacy in reducing inaction related to decisions about letters and emails.

7.2 Introduction

7.2.1 The intervention: Triage app

Triage helps users to understand and respond appropriately to letters and emails, for example, bills, advertising material and appointment letters. The app scans all of the words in an email or letter and compares them against a reference dictionary, then presents the user with a traffic light rating: red, yellow or green. Within this pop-up are

short chunks of text which contain the most pertinent information – allowing users to focus on fewer attributes. Triage makes it easy for users to make good decisions and avoid bad ones by knowing which letters and emails require action, and which do not. It was designed based on previous findings from this thesis: HD patients had impaired perceptual DM but intact metacognition, and older adults', HD and PD patients' decisions were best explained by one choice attribute (compared to young adults who were using three choice attributes to decide). Finally, Triage supports autonomy. It allows all users to better perceive and process information contained in their letters and emails without the help of a family member or carer, or a customer service employee. To support good DM, users can choose to send the document summary (the chunks of text) to a trusted contact.

Given all this, the use of this new app does not necessarily have to be restricted to this patient group given the wide problems with DM that occur as we age and also in other neurodegenerative disorders.

7.2.2 A recipe for Triage

Triage was built to support good DM by specifically targeting the impairments evidenced in this thesis. It was refined under five criteria and these are discussed in more detail below.

1) To support many types of decisions
2) To support user autonomy, not take it away
    a. Not to ostracise or victimise users for making ‘bad’ decisions
3) To have as few barriers to uptake as possible
    a. Use nudge theory to make it easy to make good choices
    b. Capitalize on the ubiquity of smartphones
    c. Have a purpose that can be explained in one sentence
4) To involve others in the DM process
5) To support and try and offset the functional declines reported in chronic neurodegenerative disorders

7.2.3 Capitalise on the ubiquity of smartphones

To address the findings of this thesis and be accessible to as many people as possible, Triage capitalises on the prolific rise in smartphone use. The smartphone is

easily accessible, portable and widely used in contexts of personal and work life. It is socially acceptable, and considered normal, to own and use a smartphone (Barnes et al., 2019). In 2020, there were 6.1 billion smartphone subscriptions, forecast to increase to 7.5 billion in 2026 (*Ericsson Mobility Reports*, 2020). It has even been found that separation from ones smartphone induces behavioural and physiological stress, much like separation from loved ones (Konok et al., 2017), that addiction to smartphone devices exceeds addiction to social network services (Barnes et al., 2019), and recently 'problematic smartphone use' is considered to be a disorder (Busch & McCarthy, 2021). While not wanting to promote disordered use of smartphones, these data suggest that an app intervention is accessible (and testable) for large groups, and therefore Triage could support many different people.

7.2.4 Learning from scam prevention data: victims, contexts and methods

Development of Triage was strongly informed by data collected about scams which are used to prevent fraudsters from amassing more victims. A 2019 report concluded that the best way to combat common scams is to, "…pause, talk it over with others, and do some research before sending any money or sharing personally identifiable information" (DeLiema et al., 2019). Triage enables this by alerting the users to consider the letter or email in more detail and involve a trusted contact if desired.

Interventions for poor DM overwhelmingly address scams, particularly cybercrime, where malicious individuals target people's vulnerabilities on computers, other devices and networks to make money. In the United Kingdom there is unease and mistrust around online information and 81% of British people fear themselves, their friends or family falling victim to cybercrime. As a result, tools to reduce cybercrime are always in development (*New Web Tool to Test Your Cyber Risk as Survey Exposes 80% of British People Fear Online Attacks*, 2021). While preventing cybercrime is important, Triage has a broader application. If older adults struggle to process complex choice attributes, it is not only scams where their DM could be impaired, but in all kinds of choices.

Fifty three percent of elderly individuals in the UK have been targeted by fraudsters (Button et al., 2014; *Over Half of People over 65 Have Been Targeted by Fraudsters Say Age UK | Action Fraud*, 2015, p. 5). However, fraudsters target anyone (Sutherland, 2014) and use a huge range of contexts to engage potential victims: online purchases, tech support, employment, fake cheques or money orders, sweepstakes or lotteries, debt collection, phishing, health care and tax collection (DeLiema et al., 2019). Victims are

targeted over the phone, online and by mail, specifically by sending official-looking letters, by downloading fake antivirus software, persuading victims to give remote access to their device, sending phishing emails (which impersonate a trustworthy entity to obtain sensitive information), and asking victims to update their bank or credit card information on a fake website (DeLiema et al., 2019; National Council on Aging, 2021). The broad range of contexts and methods employed by fraudsters are addressed by Triage in its ability to evaluate all forms of written text and provide wide support for good DM, without addressing scams specifically.

7.2.5 Functional decline in chronic neurodegenerative disorders and patient autonomy

Cognitive decline can result in a change in the ability to make everyday decisions. The earliest functional declines in HD include occupational decline (55-65%) and an inability to manage finances independently (35-49%) (Beglinger et al., 2010). In Alzheimer’s disease, fluctuating cognitive ability causes patients’ daily DM to become unreliable from the perspective of family and carers (Davis et al., 2017). Anecdotally, patients in the Cambridge NHS HD Clinic sometimes misinterpret or miss entirely information contained in their appointment letters, although this has not been studied formally. Together, the empirical and anecdotal evidence, and the previous findings in this thesis, suggest that responding to letters and emails might also be impaired. Triage may help; by highlighting pertinent terms in such texts it could support the independent management of finances and decisions at work to allow the decision-maker to be more reliable, reducing these reported functional declines.

By supporting independent DM, Triage also gives users autonomy. Taking away an individual’s autonomy can be upsetting and ostracising. People with mild cognitive impairment and dementia are vulnerable to negative assumptions which undermine their rights to make decisions about their lives and can lead to lasting reductions to quality of life (Lai et al., 2008; Sabat, 2005). Studies in chronic neurodegenerative disorders also suggest that interventions which facilitate independence are sought after, “patients [with ALS] perceived their care as a burden on family and had concerns about the adverse effects that caring had on family caregivers” (Foley et al., 2016). It is of course tricky to manage autonomy; giving it can improve quality of life, but at the same time, could lead to poor decisions which reduce quality of life (Levy, 2014). Triage, therefore, supports

autonomy by keeping decisions within control of the user, but also facilitates the involvement of a trusted individual if desired.

7.2.6 A successful intervention involves other people

As mentioned above, one feature of Triage is the ability to share a text summary with a named, trusted contact. This feature is built from data which affirm the integration of others into successful DM processes. One study concluded that interventions designed to support cognitively impaired patients often fail because they do not involve family or other individuals (Foley & Hynes, 2018). A second study concluded that autonomy is key for patients, indeed it is highly valued in Western medicine, and that social relationships are required for autonomous capability (Entwistle et al., 2010).

7.2.7 Make the best decision the easiest one

Triage supports users to make better decisions for themselves by being aware of the relevant information. Nudges are interventions that alter behaviour in a predictable way without mandating or forbidding any options, and attempt to reduce irrational DM (Hausman & Welch, 2009; Thaler & Sunstein, 2008). Triage can be considered a nudge: an easy-to-implement, simplification of decision variables which respects autonomy but should lead users to evaluate their mail correctly. A successful nudge meets four key criteria: easy, attractive, social and timely (Service et al., 2014). Triage is easy to use: it requires only one tap to analyse the document and produce a traffic-light-rating summary. It is attractive: the user interface is simple, using colours and contrast to direct user's actions. It is social: the user can involve a designated trusted person to help understand and address any problems with the document. Finally, the app is timely: users can immediately take a photo of their post, or scan an email, and receive an outcome in less than a second.

Nudge interventions have been implemented in chronic disease populations with success. They intend to promote the self-management of disease through information provision. A systematic review found that promoting rational choices through reminders, feedback and planning prompts led to improved disease control, but noted that studies were sparse, with heterogenous methods and outcomes (Möllenkamp et al., 2019). While Triage isn't related to disease management *per se*, these findings suggest that it can work in healthy and disease groups alike. However, it is important to keep in mind that nudge interventions are not a silver bullet and have been criticised as being manipulative, cost

saving alternatives where rigorous policy changes would be more appropriate (Mols et al., 2015; *Nudge Theory Is a Poor Substitute for Hard Science in Matters of Life or Death | Sonia Sodha*, 2020). Nudge interventions fail to cause the intended behaviour change more often than they succeed (Osman et al., 2020). This may be due to suboptimal intervention design or an incomplete understanding of the underlying rational-intuitive paradigm in the relevant context. To have the best chances of success, a nudge intervention needs to be designed with careful regard to the population it is targeted toward (Hollands et al., 2013), therefore Triage should be iteratively tested and refined in its target population.

7.2.8 This present study

After six months of developing the app and testing it with my co-developer, Taketomo Isazawa (a PhD student working in the Department of Physics at the University of Cambridge on an project unrelated to this work), I applied to test it in a cohort of HD patients. The study is described in the methods section below but was ultimately rejected by a Research Ethics Committee. A subsequent study was set up in healthy controls only and was given permission to be carried out remotely (remotely because of the COVID-19 pandemic). The methods and results of this study are included in detail. Finally, a third study is being designed to test Triage in cohorts of older adults and any patient with a neurodegenerative or psychiatric disorder. This is covered in the discussion section and has grown from the findings of the prior two studies and continued development of Triage.

7.3 Objectives

The primary objective of this study was to build a DM intervention tool which could support all individuals, but particularly older adults and patients with neurodegenerative disease. The second objective was to design a study that could adequately test the efficacy of the app.

7.4 Methods

7.4.1 App Development Timeline and Narrative

7.4.1.1 July 2018: Initial idea

Triage began as an idea to build a tool to scan terms and conditions' documents, to search for words like 'liability' and help the user to determine whether they should click 'Agree'. With the arrival of the General Data Protection Regulation (GDPR) across Europe, I hoped such an app would support patients in particular to be more aware of what they were agreeing to. At the time I had no awareness of any such support services already being in place.

From this grew a plan to use optical character recognition (OCR) to read PDF documents downloaded (by the user) from any company or product. It would alert users with a traffic light system to represent severity. I researched open-source OCR software (and decided on Tesseract, https://github.com/tesseract-ocr/) and began to build a list of terms that may be cause for concern (for example, https://www.dacs.org.uk/knowledge-base/factsheets/understanding-social-media-terms-and-conditions). I met with a software developer at the Apple Office in Cambridge to try to understand how Apple currently approach the public's general ignorance to terms and conditions. Áine Cahill (Apple) said that she had never come across this problem with terms and conditions for apps or related products. I decided against attempting to fix a problem that did not exist and stopped working on the idea.

7.4.1.2 July 2019: An app to support rational decision-making

Early results from the Party Food task study in controls suggested that older adults were using fewer choice attributes to make decisions (Chapter 4). I therefore decided to build an app to scan documents but this time to support older adults, and HD patients who reported instances of being scammed and, in my experience, who also misread appointment letters.

7.4.1.3 August-October 2019: Work with co-developer to build an early version of Triage

Apple and Android phones use different operating systems and therefore require different underlying app software. We chose to build the app to work on Apple's iOS software after conducting informal research into the most common type of phones used

by the target group at our work places. Apple devices were overwhelming the most common.

Further discussion with Áine Cahill made clear that Apple’s encryption software is superior to that of Android phones. This is known as sandboxing. Intra- and inter-phone security is also more restricted on Apple devices, for example, one app cannot use information from another app within the user’s device, and user data which leaves the phone via an app is encrypted such that no one can find the user’s identity (not even Apple). Through an Apple Developer account we began building the app. Taketomo led on the app build, collating open-source software, writing code to connect it and ensuring there was a clear user interface. He used the Swift programming language which has been developed by Apple and open-source contributors (https://swift.org/) and therefore is free to use, and no data produced in the app is shared with a third party. Triage also has several components that were not developed by us:

1. Open-source code
    a. Overlay Container: used to implement the part of the user interface where the traffic light rating is shown (https://github.com/applidium/OverlayContainer)
    b. Onboard Kit: used for the onboarding process to provide a smooth experience when the user opens the app (https://github.com/NikolaKirev/OnboardKit)
    c. Camera Manager: provides the configurations to create a custom camera interface (https://github.com/thejohnlima/CameraManager)
2. Closed-source code
    a. Firebase ML kit: The on-device text recognition software (https://firebase.google.com/docs/ml-kit/recognize-text). Tesseract was initially used but Firebase ML was faster to recognise text.

I researched the ethical considerations for app development and software use in patient populations. For patients to be allowed to test the app formally, an observational study for qualitative and quantitative feedback required approval from the Medical and Health Research Authority and a Research Ethics Committee. A European Commission investigation stated that mobile health software can be considered as a medical device and require stricter review, but as Triage provides no clinical benefit it is exempt. Apps targeted towards patient populations are generally in early phase development and more legislation may emerge in the future (European Commission, 2020).

We developed a version of the user interface (Figure 51). Our primary aim in this early iteration was to make Triage extremely easy to use. A report found that removing one click from the process of filing a tax return increased the number of people who filed their tax returns on time by 20% (Service et al., 2014).

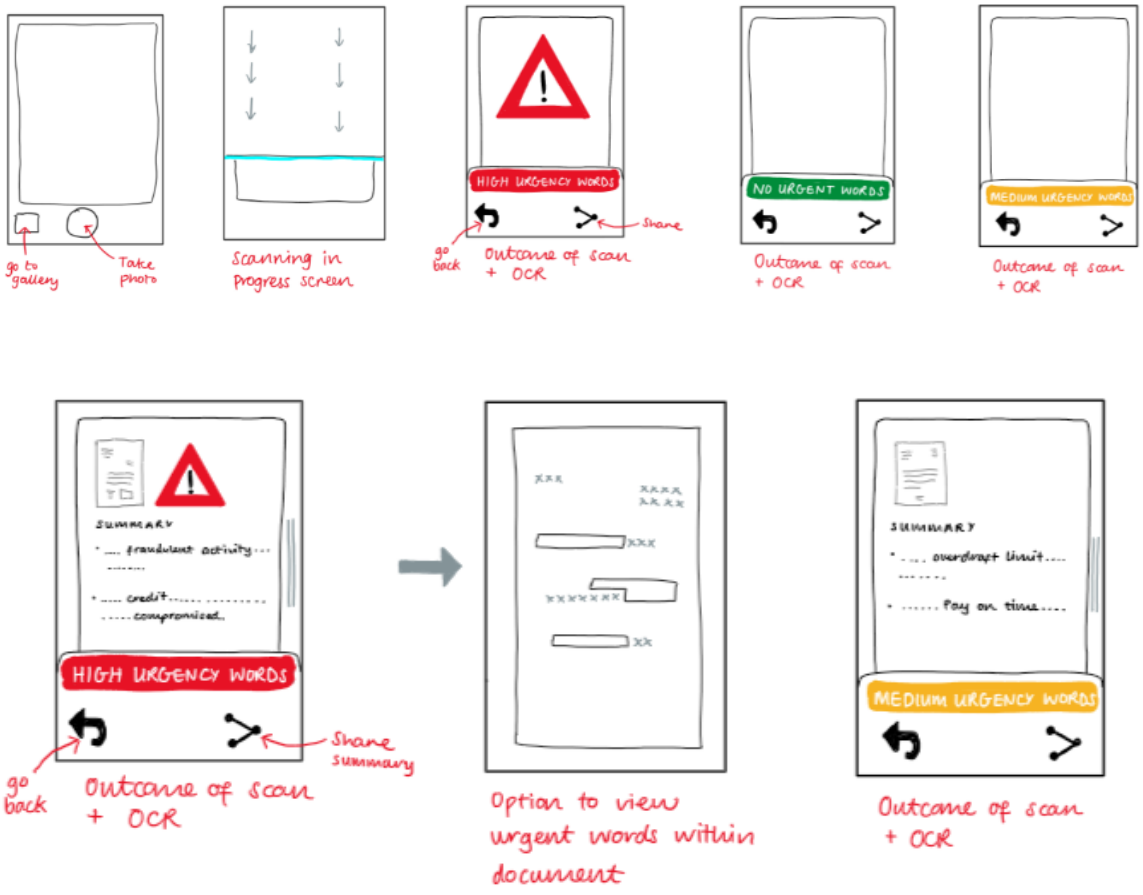


Figure 51. An early mock-up of the user interface for Triage. In the top panel users photograph a letter. Photos are saved within the app so that users can find previously scanned documents and rescan them ("gallery", top left). Triage scans the photo to look for a pre-programmed dictionary of words that are rated as highly urgent, urgent or not urgent. The output is one of three possibilities: red is highly urgent, yellow is urgent, and green is not urgent. In the bottom panel is this process in more detail. Users can share a summary which includes the urgent words (from red or yellow outputs) or return to the photo to see these words highlighted. Private information such as bank account numbers, date of birth and postcode are hidden from view, replaced by a series of 'X's. OCR=Optical character recognition.

Taketomo then improved the functionality of Triage. The scan time using the Tesseract OCR was initially 10 seconds but made four times faster by parallelisation (scanning different parts of the document at the same time). He developed a scanning graphic, similar to how a photocopier scans documents, to display while scanning was in progress (Figure 51). He built a user interface (UI) for the onboarding, camera screen and

urgency outcome for documents. We decided that a 2-3 second scan time was too slow, this on an iPhone X with up-to-date operating software and not a more realistic older device, so Taketomo tested alternative OCR software and found the Firebase ML kit to be superior (listed above). This change improved scan time such that it appeared to be instantaneous, as well as improving the accuracy of letter-matching to make Triage more reliable. We also began testing on an older Apple iPhone 6 running iOS 11 and an iPad Pro to understand how alternative devices, operating systems and screen sizes might influence the functionality of Triage.

Finally, I conducted research to gather a list of ‘urgent’ words that might require action should they be included in letters and emails. Christiane Barker at the Citizen’s Advice Bureau, Cambridge, was instrumental in compiling this list, as were members of the Barker Research group. This research also included collecting documents which required action such as reports of fraud, information about opening a new credit card account (for example, https://www.santander.co.uk/csdlvlr/BlobServer?blobtable=MungoBlobs&blobkey=id&blobcol=urldata&blobheader=application%2Fpdf&blobheadervalue1=inline%3Bfilename%3DCC+T%26Cs+and+important+information+do-ec-177.pdf&blobwhere=1314021010209&blobheadername1=Content-Disposition, last accessed 17/03/2021), invoices and notices for arrears. I included terms listed in advice articles included on the UK Government website, especially those which pertained to “Money and tax”, “Working, jobs and pensions” and “Housing and local services” as these are particularly relevant to the target audience (https://www.gov.uk/, last accessed 17/03/2021). Table 23 below details the first list of these words that were recognised as highly urgent (red) or urgent (yellow). We recognised at this point that the list was not comprehensive but provided a platform from which to build and test the functionality of the app.

Table 23. Key terms in letters and emails, primarily related to finance in this instance, which indicate that the person who received the correspondence should act upon it. Red indicates terms which may require highly urgent action, while yellow is for terms which may require urgent action. In parentheses are additional words that may or may not be included in the letter, and Triage recognises terms with and without these words.

YELLOW	RED
Credit card limit	Unarranged overdraft
Credit limit	Alert
Overdraft	Overdraft limit
Fees	Insufficient funds
Fraudulent (activity)	Debt
Future-dated payment	Illegal
Default fee	Actual unauthorised (activity)
Cash limit	Temporary suspension (of the card/of the account)
Ability to repay	Unlawful
Credit limit increase	Lost
Interest	Stolen
Suspected fraudulent (activity)	Unusual activity
Risk	Normal spending pattern
Not responding	Broken your agreement (with us)
Cancel(ling) your right	Account in credit
Suspend(ing) your right	Payment is due
Threat to security	Suspicious spending pattern
Fraud prevention	Bankrupt
Suspect fraud	Final notice
Increased risk	Council tax arrears
Minimum monthly payment	Second reminder notice
Restrict the use	Missed payment
Warning	Liability order
Unauthorised (use)	Bailiff
Lost	Enforcement agent
Stolen	Insolvency
Third party provider or TPP	Creditor
Required by law	County court judgement or CCJ
Personal information	Rent arrears
Tax(es)	Possession (seeking)
Cost(s)	Eviction (warrant)
Deadline	Antisocial (behaviour)
Unpaid	Breach of your tenancy
Pay on time	
Trust deed	

Letter before action	
Time limit	
Special offer	

7.4.1.4 November 2019: Early feedback from research group and software developer

With Triage in an early but useable format, I presented the concept and app and sought feedback from the general public, including colleagues and clinic attendees, which raised four issues about privacy, simplicity and wider usability. First, concerns were raised about access to the user’s photos by the developer and third parties. We met with Áine Cahill to discuss data movement transparency and she suggested writing data block diagrams to keep track of this (Figures 52 and 53). She also confirmed that Apple apps must adhere to strict privacy standards; access to the gallery is granted by the user on a photo-by-photo basis, and storage (if required) is provided by the developer and not Apple servers. More feedback from this consultation period provided a useful solution: scan the photo to extract the key chunks of text but never save it. A third point was to disregard the photo and key text, instead only rating the document (i.e. red, yellow or green) to suggest an impetus to respond. This suggestion was not implemented as we would like the user to have some awareness about how the app rates documents, but instead a focus on extreme simplicity taken forward. Finally, there were suggestions to use Triage to scan screenshots and PDF documents due to reported instances of fraud through email, links and attachments. We implemented this feature but were aware that it enabled the photo gallery to communicate with Triage in a user’s device. This is not problematic in itself, but if Triage photos become accessible by the photo gallery, they may be accessed by other apps with possible consequences. A bonus of this additional feature was that already-digitised documents do not require OCR and therefore can be processed faster by Triage.

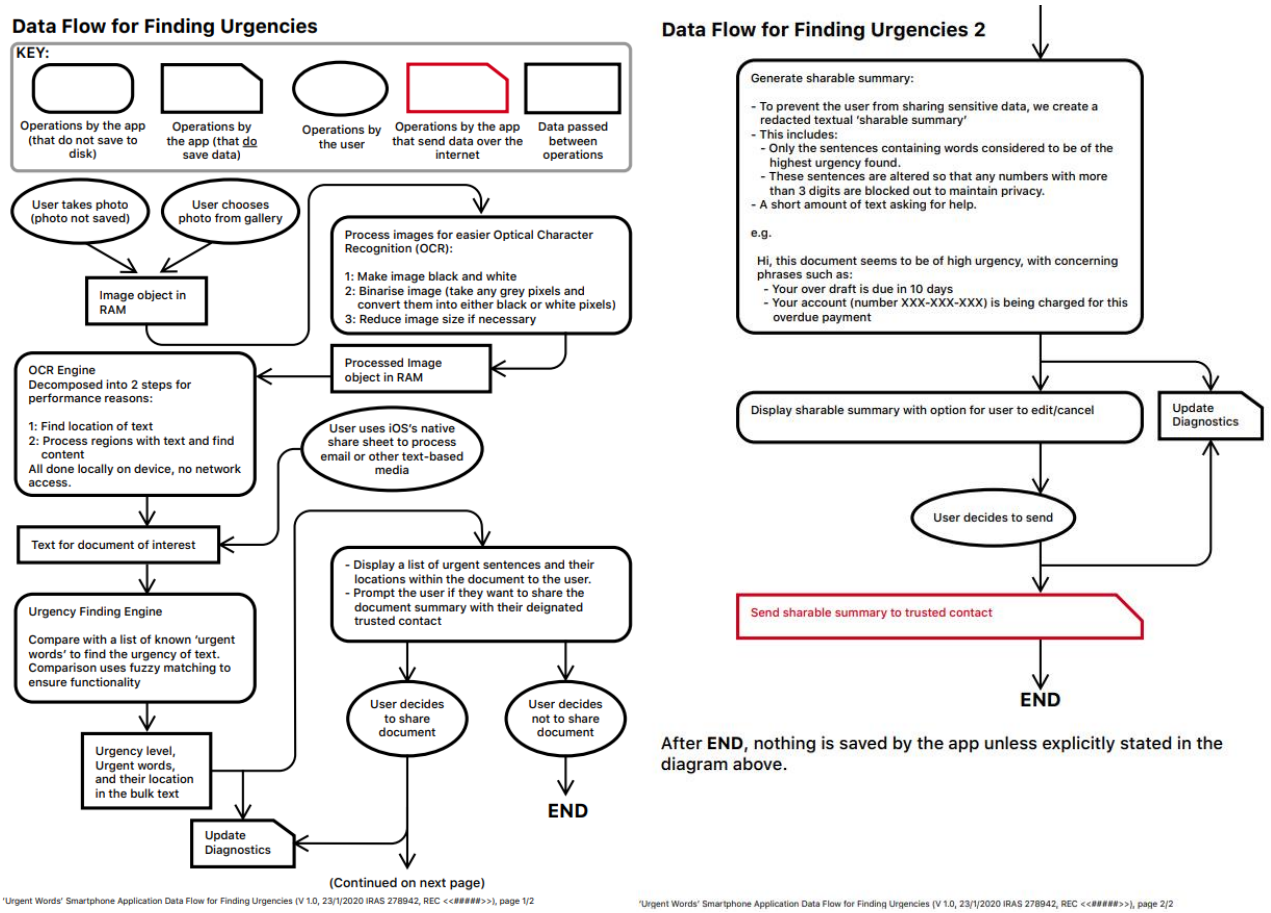


Figure 52. Low-level data block diagram produced by Taketomo Isazawa. It describes data movement in the back end of Triage (the part users do not see). Most importantly, there is only one instance in which data could leave the user's phone. This is at the discretion of the user, and in a redacted format that includes only the urgent terms and nearby chunks of text. It can also be edited by the user prior to being sent. The photo of the document is not saved by the user.

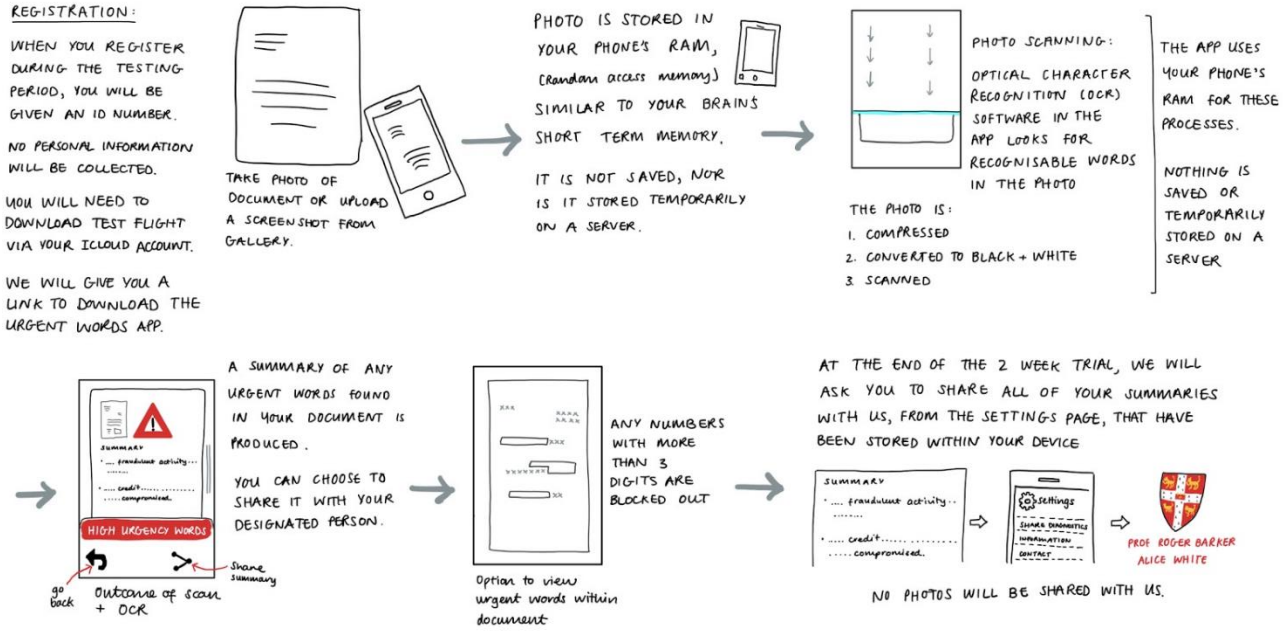


Figure 53. High-level data block diagram. It describes how data moves within Triage from the perspective of the user and highlights that the app doesn’t save any scanned photos (it uses RAM, random access memory) to “read” the document and provide a summary. Private information such as date of birth, account numbers and postcode are blocked with ‘X’s by Triage. Any diagnostic data (e.g. crash statistics) for app development are stored within the app and shared at the user’s discretion. The diagram is hand drawn to improve understanding and readability, as user’s understanding of this process is critical to their trusting of the software. This diagram was also included in the participant information sheet.

7.4.1.5 January 2020: Triage features to date

At this stage, the app functioned to take a photo and scan it using the OCR. The photo was not saved and was processed using the device random access memory (RAM). Scanning involved compression of the file and conversion of the pixels to black or white for maximum contrast, again, not requiring communication with an external server. The OCR software compares pixels to a database of letters and words to identify text, which is then compared to our dictionary of urgent terms (Table 23). It could also import single photos from the user’s photo gallery, as selected by the user, for example, screenshots of emails or other text. The urgency ratings and summary outcomes remained as above, and a user could share the summary text with a named trusted contact via iMessage. We also continued to collect our own documents to further test and refine Triage.

7.4.1.6 February 2020: Protocol and ethics application for first study

Given this feedback from several groups, we set up the app for testing by including a registration screen, where users input their trusted contact (to share summary information). The participant information sheet would initially serve as the privacy policy (Appendix 3 for an example). We added an option to contact the app developers and also the clinic team at the John Van Geest Centre for Brain Repair, as well as contact information for the Citizens Advice Bureau. We added notification dots to appear every two days and remind the participant to use Triage. Finally, Taketomo submitted the build to TestFlight, Apple's app testing platform. This allowed us to monitor anonymously app usage and details on its functionality (e.g. crash statistics), and also if large files were being exported by the app. Large file sizes are indicative of photos being shared, thus monitoring file size was a proxy for unintentional photo sharing.

We next sought to test Triage in patients carrying the HD gene but ethical approval was declined. The planned study included two stages: first, people with HD (both premanifest and manifest patients; no controls included) would attend small focus groups to discuss instances of misreading documents, phone use habits and financial independence; secondly, those within the focus group would be introduced to Triage, given a demonstration and the option to download it and become a beta tester for a two week trial period, and then have a follow up call to discuss their thoughts on the app. The study was primarily observational to ensure that Triage was effective in doing what we expected. Along with the low and high level data block diagrams, the information sheet made clear that data is stored by Triage and sent to Taketomo and I for development purposes only. Only anonymous bulk diagnostics are ever stored locally on the device. These could be shared with the developers given additional user consent. The diagnostic information is composed of statistics and preferences. Preferences are the user's trusted contact. The statistics stored are:

- Time stamps for when the app was opened.
- Time stamps for when the app scanned a document and the corresponding urgency ratings.
- Time stamps for when the app processed a document shared from a different app and corresponding urgency ratings.
- Time stamps about whether and when the user decided to share the results and the corresponding urgency rating.
- The number of hits for each urgency keyword.
- Processed "sharable summaries" (detailed in the data flow diagram) for documents scanned by the user
- The user's IP address

The statistics can be shared by the user at any time through the settings screen, and users were also asked to do this at the end of the two week trial. Any shared information is pseudo-anonymised under a unique study ID number, and never alongside data such as the patient name, date of birth, address, etc. The ethics committee rejected the application for reasons covering data access, wording, a control group, safeguarding, intellectual property and research experience; amendments to the application were not permitted, instead a new study was required. The protocol was updated based on this feedback and I subsequently wrote a new study to be conducted in healthy controls.

7.4.1.7 February 2020: Continued functional development for word categorisation; User interface development

Triage was functioning well but continued testing with our own documents found that it did not always provide accurate feedback. For example, a letter from a bank was accurately interpreted as being urgent, with the relevant terms highlighted (see Figure 54, left image; actual letter not shown for privacy). However, another letter which informed local residents about a fireworks show was also categorised as highly urgent (Figure 54, centre image) when ‘non-urgent’ would have been a more appropriate outcome (Figure 54, right image). The underlying dictionary was updated to reflect the growing body of test documents.

The UI was also continually improved. Clear logos and high contrast colours were used to enhance understanding and simplicity. For example, highly urgent documents have a bright red rating with an exclamation mark in a white circle (similar to a cautionary road sign). The chunk of text which contains the highly urgent term is also highlighted in red (Figure 54).

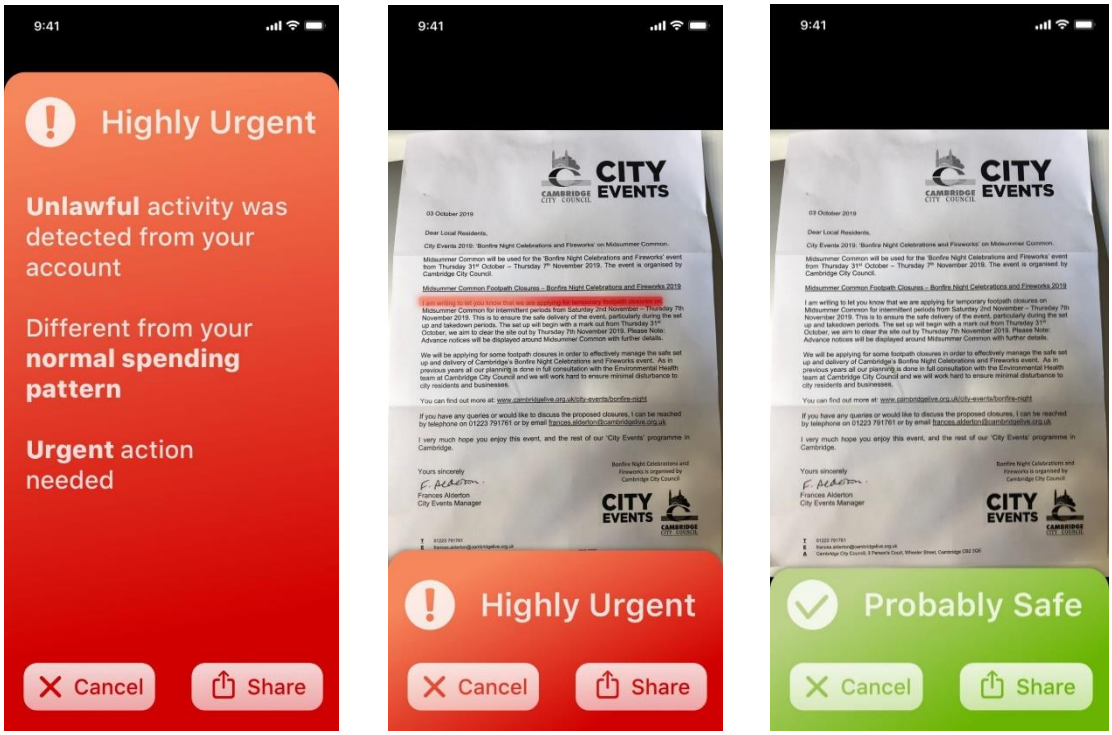


Figure 54. Examples of the Triage app during testing in February 2020. The dictionary did not always classify accurately the letter's urgency level. For example, the left image is the rating for a bank letter which correctly described an instance of fraud (letter not shown for privacy). However, the centre image is a letter from the Council which informed residents of a fireworks event and was also classified as highly urgent. It would have been more accurate to classify this letter as safe (green, right image). The underlying dictionary was updated to reflect the growing body of test documents.

To gather more feedback, I sought advice from Dr Christelle Langley, a postdoctoral researcher developing remote cognitive training and test tools. She recommended a focus group to discuss the issue of misreading documents so as to ensure that Triage was fit-for-purpose. She also suggested a less dense participant information sheet. Regarding the app functionality, she recommended that summary information shared with a trusted contact be monitored carefully and during testing and ideally the contact should also have their own information sheet and consent form. On data security, she indicated that feedback should be sent via the SDHS or REDCap with an additional code break to ensure absolute anonymity, and not through email. Finally, she suggested that the consent should include an optional open data statement allowing for future anonymous data sharing as is required by many journals.

7.4.1.8 April 2020: Logo development; In-app wording

We next finalised the Triage logo (Figure 55) and worked to refine the words used to describe Triage's outcomes. In particular, given that we could not be certain how Triage would respond to all documents (see Figure 54), we chose to encourage a sense of reservation in the messages, for example, "probably safe" instead of "safe". This should also prompt users to check for themselves the contents of the document. Below is all text used within Triage.

- High Urgency Message (used in the title for the red pop-up): *"Highly Urgent"*
- Medium Urgency Message (used in the title for the yellow pop-up): *"Potentially Urgent"*
- Low Urgency Message (used in the title for the green pop-up): *"Probably Safe"*
- Urgency Information Title (used as the title for the infobox "*i*" information logo also on the pop-up):
  "What does this mean?"
  - Low Urgency Information (the content of the green information pop-up):

    "A "Probably Safe" rating means that we didn't find any cause for concern in this letter. \n

    However, this does not mean that we are 100% sure that this letter will be safe."
  - Medium Urgency Information (the content of the yellow information pop-up):
    "A "Potentially Urgent" rating means we found some text that might be problematic. \n
    We recommend sending this to your trusted contact if you are unsure about how to respond."
  - High Urgency Information (the content of the red information pop-up):
    "A "Highly Urgent" rating means we found text that could indicate a problem.\n
    We recommend sending this summary to your trusted contact."
- Infobox Dismissal Title (the text on the button to dismiss the information on what each level of urgency means for the user):

  "OK"
- Medium Urgency Initial Message (the sentence at the start of a text sent by the user with a summary of the document they just scanned):
  "Hi, this document might contain some information that requires urgent action. I'd appreciate if you could have a look at it. It contains concerning messages such as:"
- High Urgency Initial Message:

  "Hi, this document might contain some information that requires urgent action. I'd appreciate if you could have a look at it. It contains concerning messages such as:"
- Support Mail Subject (initial subject of email created when the user taps the "Contact Healthcare Team" button in the settings):

  "Urgent Words app query"

  The email is sent to the NHS HD Clinic email address, monitored by staff at the John Van Geest Centre for Brain Repair.

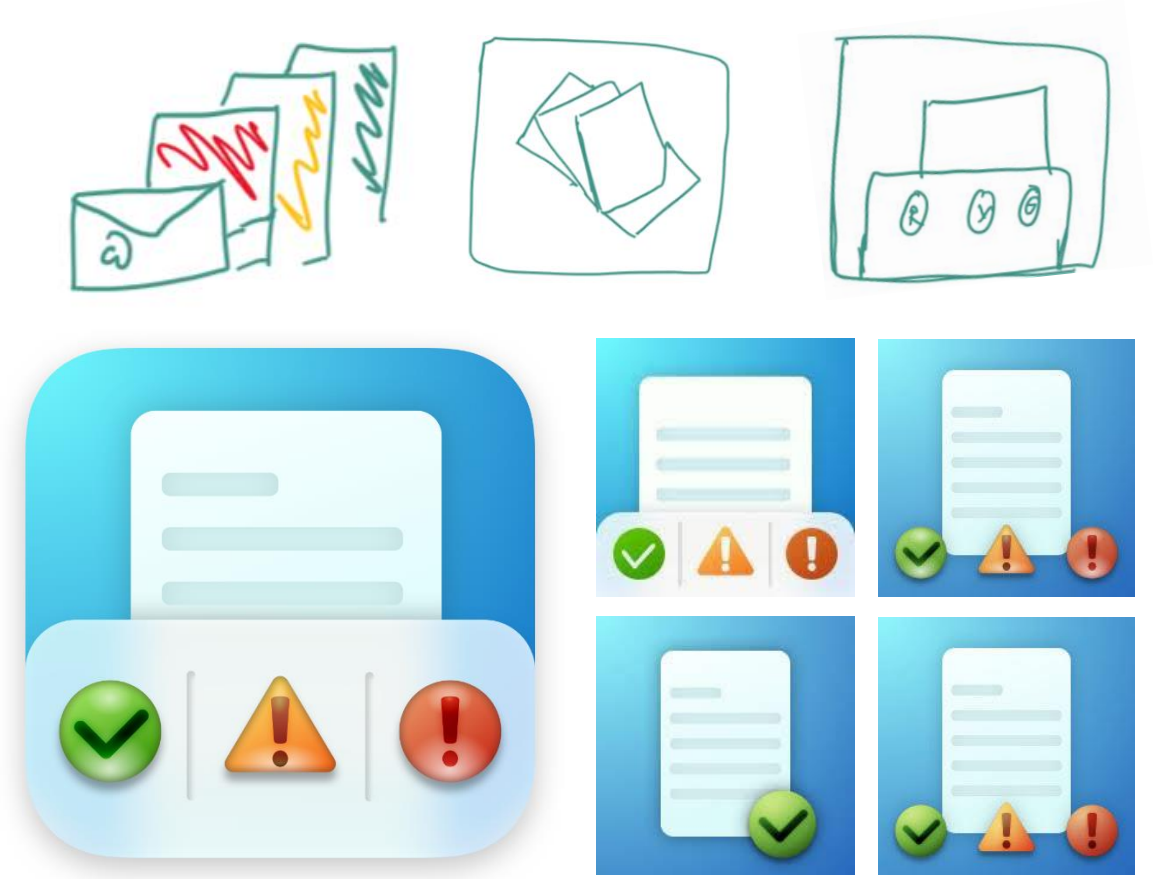


Figure 55. Logo development for Triage. The large logo on the left is the current Triage logo (March 2021). The smaller logos were iterations for development in which colour, shape, simplicity, highlights and shadow were altered.

7.4.1.9 June 2020: Intellectual property and liability; A new study in healthy controls

After receiving feedback from the REC and Cambridge Enterprise, I submitted a new study protocol and application to the CPREC to test Triage in healthy controls. At this point remote working was the norm due to the COVID-19 pandemic and the study was designed to be entirely virtual. The study was approved and began in July. The study objectives and methods are described at the end of this methods section, and the results follow from it.

7.4.1.10 July 2020 – March 2021: New Features; Ongoing troubleshooting for Triage

We made improvements and added new features to Triage in real-time as we received feedback from beta testers. At build 1.0.2, early responses were positive and we were able to harvest bulk statistics to confirm that Triage was working as expected on users' devices (i.e. it followed the data flow diagrams). We added multiple image

selection where users could access and scan more than one document from their photo gallery if desired.

At build 1.0.3, a new functionality was added to scan PDF documents from the ‘Share’ menu within other apps (e.g. Mail). Beta testers reported that non-English documents caused the app to freeze, which led to the addition of a new feature at build 1.0.4 to recognise language and inform the user that Triage had found non-English text. Some users also asked to see introductory explanation screens which was unexpected because the onboarding process was functioning on our test devices. It was also reported that the multiple select option did not function smoothly; once in-gallery photos were selected, there was no ‘button’ to return to Triage and scan them. Furthermore, after scanning was complete, there was no option to return to ‘home’ and select new photos/documents to scan.

At build 1.0.4 more features were added and more problems arose. Language recognition prevented Triage from crashing, however, it now failed to recognise handwritten text and recognised drug names as foreign (and therefore didn’t provide an urgency rating for either). This fix involved a second comparison against the English dictionary post-scan to confirm if the text was still non-English and was implemented in build 1.0.5. Landscape mode was supported in this build which allowed Triage to scale more gracefully to larger screens (e.g. iPad).

At build 1.0.5 an update to the dictionary of urgent words was added based on participant feedback.

At build 1.0.6 a new logo within the ‘Share’ menu was also added that was visible when documents were scanned through other apps (Figure 56).

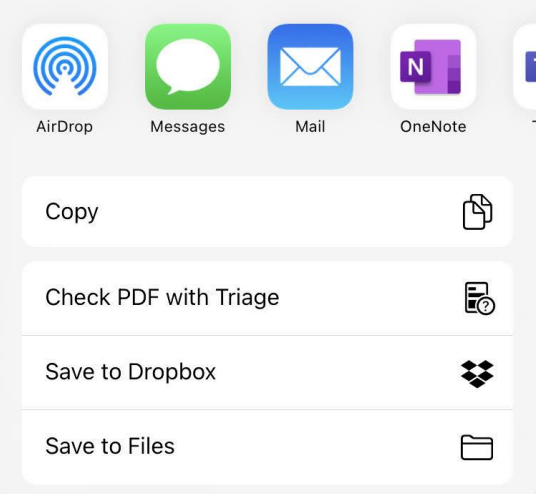


Figure 56. A new feature was added to Triage for build 1.0.6 where users could scan documents from the 'Share' menu of another app, for example, the Mail app. A new logo in black and white was designed for this menu.

For build 1.0.7 we added the ability to photograph documents in landscape mode (as only portrait mode was previously available).

At build 1.0.8 the multiple select feature was polished; it no longer required a special dialogue box to activate and the issues where users got 'stuck' in the photo gallery were resolved. Multiple PDF documents from outside apps could also be scanned at once in this build. The foreign language feature was improved to acknowledge words which appeared to be foreign, but Triage now scanned the remaining (English) text and provided an urgency rating. Further additions were made to the dictionary.

The most recent build (1.0.9 as of March 2021) involved simple bug fixes which were identified through ongoing testing, where the scan graphic was not showing and where older devices sometimes crashed when processing multiple documents.

7.4.1.11 A study to test the functionality and user-friendliness of Triage

7.4.1.11.1 Objective

To understand whether the app is feasible, useful and user-friendly in a control cohort and provide information for further development of it.

7.4.1.11.2 Outcomes

1. User feedback: Short video call or email with each participant to conduct a six-question, semi-structured interview.

2. Software feedback: Usage statistics and app diagnostics.

7.4.1.11.3 Participants

Thirty-six individuals were recruited for the study and 13 participants completed it. Inclusion criteria were individuals that were at least 18 years old, fluent English speakers and in possession of and a user of an appropriate Apple iOS device (usually iPhone 5 or newer, or iPad). Exclusion criteria were self-reported dementia or neurodegenerative disorder, or problems with using a device (e. poor vision or arthritis). Participants were recruited by word of mouth by the researchers. Potential participants were sent a link to the information sheet and subsequent consent form, hosted within the University of Cambridge Qualtrics survey account.

7.4.1.11.4 Protocol

Consented participants were sent a link to install TestFlight, a standard, controlled beta testing application provided by Apple, and subsequently install the Triage app. Further information about the TestFlight process is available here https://developer.apple.com/testflight/ (last accessed 18/03/2021). After approximately two weeks of testing, users were asked to undertake a short video call with the researcher to give their feedback via a semi-structured interview. If a video call was not possible, feedback was collected over email. App usage statistics were shared by participants via the settings screen in Triage and diagnostics collected automatically via TestFlight. No data collected during this study contained sensitive or person-identifiable information, aside from the aforementioned email addresses.

The following questions were used to gather feedback after a participant had tested Triage.

1. What are your thoughts on the concept of what we are trying to create here with the Triage app?
2. Do you think that the app provided the support it was meant to and did you find it useful?
3. Roughly how many times did you use Triage over the last two weeks?
4. Do you think you would use it in the future? Recommend it to a friend?
5. I’m going to show you the list of words that we have put together from different sources which are recognised by Triage as being ‘amber’ or ‘red’ level urgency.
    a. Are you surprised to see any of these words on the list?

   b. Can you think of any additional words that might be useful to include in this list?
6. Are there other things you would like to say before we finish?

7.4.1.11.5 Analysis

Quantitative (for example, number of crashes) and qualitative data (for example, user feedback) was monitored in real time so as to allow fixes to be made as needed as quickly as possible. For example, if the app was crashing due to a known bug, it was fixed as soon as possible rather than waiting until the study had finished. Upon termination of the study, descriptive statistics were the primary assessment of feasibility and user-friendliness. Qualitative data was analysed to improve usefulness. This information was used to decide whether patient group testing should proceed.

7.4.1.11.6 Data Storage and Access

We paid special attention to the storage of participant data to ensure that it was within GDPR guidelines. To this end, we ensured that patients had access to information about what happened to their data and this was detailed in the information sheet. There were three types of data:

1. Qualtrics consent data were collected and stored automatically on the University of Cambridge Qualtrics system in an account in my name. This data was saved to the SDHS. Participants were made aware before they consented that Qualtrics were a third party in this study who could hypothetically access their data.
2. App functioning data were sent by the user to TestFlight if they encountered a problem or wanted to provide feedback with a screenshot.
3. App diagnostics data were automatically recorded by TestFlight and connected to the email account which they used to download TestFlight. Any data containing PID was stored on the SDHS server.

All data were anonymised prior to analysis. All PID were deleted permanently after the completion of the study. Fully anonymised research data will be stored for 15 years in the University of Cambridge data repository as is standard policy, accessible only to the research team.

7.4.1.11.7 Ethical approval and sponsorship

The study was given favourable ethical review by the CPREC (2020.078) and sponsorship confirmed by the Research Governance Office within the School of Clinical Medicine at the University of Cambridge for protocol version 1.1 (G106773).

7.5 Results

7.5.1 Demographic information

Detailed demographic information was not recorded in this study. The inclusion criteria meant that all participants were over 18 years old, fluent English speakers who used Apple iOS devices, and they didn’t have dementia or a neurodegenerative disorder, nor did they have a visual impairment, arthritis, or condition which limited their phone use.

The age range of the 13 participants was 23-65 years. Twenty-three participants were recruited but did not download the app; four of these did not meet inclusion criteria. All participants were in full-time employment or in full-time education and recruited from the Cambridge University community which has a high socioeconomic status. Individuals were recruited by word of mouth, therefore there may have been bias in their responses given this. Finally, this study was conducted between July and December 2020 during the COVID-19 pandemic and two separate lockdown periods in the UK, an unusual time for many people.

7.5.2 Qualitative user feedback

Where possible video calls were organised to gather feedback from participants, but sometimes scheduling problems meant that email was used. Feedback is summarised below.

1. What are your thoughts on the concept of what we are trying to create here with the Triage app?

Responses: All but two participants understood the purpose of Triage, which was included on the information sheet. Overall the feedback suggested that the concept for Triage had merit.

Of the participants who did not understand the purpose of the app, one admitted to not reading the information sheet or instructions within the app and the other misunderstood the purpose, having assumed it was to assist physician DM and not adults in general.

2. Do you think that the app provided the support it was meant to and did you find it useful?

Responses: Again, the response to this question was positive. Comments from participants suggested that they themselves didn't require help with determining how to respond to documents, but they tended to name individuals (e.g. mum or grandad) who would benefit from using Triage. Several participants did though suggest that Triage would be more useful if it could recognise scams and junk mail. Based on this feedback, Taketomo and I have investigated the addition of a feature to recognise documents which may be spam or scams. These would still be considered as 'urgent' but instead of mandating a response, they would mandate the user *not* to respond. We have not implemented this feature yet because we do not have a method to reliably identify such documents, and current spam identification seems to target email specifically rather than all documents. Finally, this test period allowed us to understand that the multiple select feature, where users could select documents from the gallery, was not functioning as intended so it was improved in subsequent builds.

3. Roughly how many times did you use Triage over the last two weeks?

Responses: Triage was not used regularly by the participants and the study required reminders for each participant. The fairly low rate of use is partly due to the fact that participants did not feel the app was aimed at them (it is not) and did not feel as if they needed it. This is the flaw in testing an intervention in healthy controls. To remedy this, future participants were reminded during the two-week period to use Triage.

4. Do you think you would use it in the future? Recommend it to a friend?

Responses: Echoing the previous questions, participants were positive about Triage and would recommend it to their older relatives, or if they themselves experience cognitive impairments. One participant suggested that Triage could be useful for people with visual impairment.

5. I'm going to show you the list of words that we have put together from different sources which are recognised by Triage as being 'amber' or 'red' level urgency.
    a. Are you surprised to see any of these words on the list?
    b. Can you think of any additional words that might be useful to include in this list?

Responses: It was useful to share with participants how Triage works and several people thought it would be better to know this information prior to using the app (for example, in the introduction information screens) as a point was made by one participant that people will be more likely to trust something that they understand, and this is probably even more true for older users. One participant read the word list and commented, *“The vast majority of words are related to financial problems. Could you add in ‘appointment’ to amber?”* This highlights again that Triage may be useful in more contexts than we currently describe, and that there is an appetite for wider applicability. As the corpus of test documents grows we make additions to the reference dictionary.

6. Are there other things you would like to say before we finish?

Participants made comments about uptake, user-friendliness and wider development. The biggest concern that was raised concerned the incorporation of Triage into daily routines, so using reminder emails and banner notifications may be helpful. To improve the accuracy of Triage, one participant suggested, *“Could you add a function where testers can send their photo to you [the developers]? Especially when it is green and they think it should be red, to help improve the app.”* Although it would be useful to have this information, it would violate our goal to protect private information. There is however an option within TestFlight for users to send a screenshot with any feedback for the developers but we do not highlight this outside of the information sheet. Finally, and as mentioned above, participants had suggestions for wider uses of Triage such as managing appointments.

7.5.3 Software feedback: Usage statistics and app diagnostics

TestFlight recorded between 2 and 13 sessions per user across each of the builds. This is fairly low but enough to gather some useful feedback. In future, studies should use the suggestions made by participants to promote regular use and testing in the population it was designed for, should help here too.

Surprisingly only four instances of Triage crashing were recorded by TestFlight. All were at build 1.0.3 and occurred during selection of multiple pictures in the photo gallery. This feature has since been refined. Five screenshots and comments were sent to the developers via TestFlight which also all concerned multiple select. These issues are described above and have since been fixed.

7.6 Discussion

Triage is currently a functioning app which supports users to recognise and understand actionable information within letters and emails. It provides a safety net for impaired DM by changing the choice architecture – the context around a choice – to make it easier for users to know which of their letters require action and which don't. This might allow users to make decisions more autonomously without the need for assistance from family members, carers or customer service employees. The previous Chapters in this thesis (particularly 2, 4 and 5) showed that impaired perception, using only one attribute to make choices, and intuitive processing of choice attributes can impair DM. However, the ability to make consistent choices, deliberate on attributes, and use metacognitive judgement can be used to support good DM. Therefore, by making pertinent information very clear, Triage can support users to make good decisions themselves.

We plan to continue to develop Triage after the completion of my PhD towards the wider applications suggested by users. This includes summarising and rating documents, but also alerting users to payment deadlines, appointment times, recognising scams and spam, and user-friendliness for a wider target audience. While we research methods to recognize scams and spam documents, we plan to add a reminder not to click on a link (if present in a scanned document) until the user is confident it is safe. This is similar to some email accounts which remind mail recipients not to click on external links. We would like to develop the language feature further to support detection of dubious documents, for example, by naming the languages present in the scanned text.

Triage relies heavily on language. The reference dictionary used to indicate yellow or red outcomes is central to the function of Triage and needs to be considered carefully. Legitimate use of these terms can prompt the recipient to act (or to ignore, in the case of scams). However, illegitimate use of words like 'tax arrears' and 'due date' in scams might also lead users to engage in a scam. For this reason, the list of terms may need to be restricted, not published and treated as proprietary. Future development might also require the expertise of a linguist to understand how terms are used across different industries, across time, whether there are synonyms we have not considered, and how different cultures might understand some words to have different meanings.

To improve the reliability of Triage, several new features are being explored. Firstly, when character mismatch is high, as in the case of some handwriting, the user will

be alerted that ‘Triage does not understand handwriting well’. While we cannot be certain of the reliability of Triage for every potential document, we can make users aware of uncertainties to prompt them to exercise their own judgement. A further improvement could use sentiment analysis. Sentiment analysis uses natural language processing, a form of artificial intelligence, to systematically identify subjective information within a piece of text. It is commonly applied to customer feedback. For example, text which uses short sentences and adjectives such as ‘terrible’ is likely to have negative sentiment. For Triage, this could involve searching for specific terms and applying a rating based on them, for example ‘concern’, ‘support’ and ‘health’ might together suggest there is action to be taken. Sentiment analysis could also include more sophisticated algorithms where a sentiment training set of data is compared with user’s documents during scanning.

Greater reliability could also be found by comparing scanned texts against a dictionary of ‘probably safe’ terms, as well as the current yellow and red dictionaries. This is related to one participant’s comment where personal correspondence is probably safe regardless of what is included. Colloquial terms are often used to start and end personal correspondences, for example ‘hey’ or ‘xxx’, and perhaps even the use of emojis could suggest that documents are safe. However, because it would be more consequential to misclassify an urgent document as safe, Triage will default to yellow or red classification unless safe is a certainty.

There is potential for Triage to support the identification of misinformation with further developments. Similar to a the red and amber reference dictionaries, a reference set of terms and features common to unreliable information sources could be compared against the scanned text. Recently, misinformation around vaccinations and mask wearing has led people to use false information to make decisions which undermine public health (Vaidyanathan, 2020). The wrong information, even when considered thoughtfully or rationally, can still lead to poor decision outcomes. “Cognitive inoculation” interventions against misinformation have already been designed and implemented to show that simply increasing awareness of how misinformation spreads and how to recognise it is effective in reducing its negative effects on DM (Basol et al., 2020; Linden et al., 2017; Vaidyanathan, 2020).

To develop Triage further, it is important to test it in the population it is designed for. A new research protocol is being written and will include a wide range of participants: healthy older adults, people with neurodegenerative disorders such as Parkinson’s and Huntington’s disease, people with psychiatric conditions such as depression and

schizophrenia, and people with sensory impairments such as glaucoma and hearing loss. The groups are not selected based on evidence for impairment, rather that the involvement of a wide range of people will better inform future functionality and usability. One specific source of beta testers is patient advocate groups, such as Parkinson's UK, which includes a network of engaged individuals with wide experiences of what would best help patients.

The study will be a form of challenge trial. Baseline ability to respond to documents will be measured by asking participants to respond to fabricated documents. Participants will then use Triage for two weeks and receive links to UK Government advice about responding to documents. They will be able to send feedback if desired, and anonymous diagnostics and usage statistics will be collected. A second challenge will then be completed with a second set of fabricated documents to quantify changes in ability to respond. A control arm will involve both challenge sets but rather than trying the new app, participants will only be sent links to publicly available UK Government advice for responding accurately to documents. The provision of information in this way is not considered to be a nudge intervention (Möllenkamp et al., 2019). The control participants will be given the opportunity to try Triage after the second challenge.

A study which used fabricated documents was presented at the 2020 Society for Judgement and Decision Making by Alycia Chin, David Zimmerman and colleagues (http://www.sjdm.org/presentations/2020-Poster-Chin-Alycia-disclosure-overdraft-consumer.pdf). They investigated how understanding was affected by the format of information disclosure for overdraft on bank accounts. Triage will be deemed effective if using it can increase the accuracy of response to documents, both in the qualitative user feedback and in the challenge trials.

Before this study can proceed, a body of fabricated documents will be constructed and piloted to ensure they are sufficiently realistic, representative of real documents for the target audience, and not too easy or too hard to interpret to avoid floor and ceiling effects. Additional theoretical problems that are considered include:

1. A threshold problem where the perceived benefits do not exceed the costs required to learn about and download Triage.
2. A habituation problem where it is cognitively difficult (for anyone) to learn a new piece of software unless you are familiar with software. It is akin to online food shopping, where the first use is inordinately more difficult than the tenth.

3. A defence decision problem where users feel they do not have problems that need to be addressed.
4. A signalling problem, related to (3), where users do not want to demonstrate to others that they have a DM problem thereby losing pride or reputation. Social norms, particularly regarding one’s autonomy, will be considered to overcome this problem and one solution is to recruit participants through patient advocacy groups like Parkinson’s UK.

Potential commercialisation will continue to be explored, primarily as a method to increase dispersal of Triage to refine functionality. Some options for this might include banks, charities or the National Cyber Security Centre. As new features are developed, it may be beneficial to collaborate with other individuals or companies, both to increase the trustworthiness of Triage (for example, work with NHS Digital) and where closed source code is necessary, as might be the case with the classification of spam and scam documents.

The foundations and current functionality of Triage are a good platform from which to develop it further. Future testing in the target groups is vital to understand whether it does support DM, and continued involvement from a number of individuals will ensure that Triage is refined to serve this purpose.

8 Final Discussion

The studies in this thesis have shown how DM is affected in HD. Perceptual DM was impaired in gene carriers, a novel finding especially in the case of premanifest individuals where behavioural differences are rarely reported. By applying a computational model, I found that this was due to a reduced rate of evidence accumulation and decision thresholds. However, gene carriers had intact metacognition such that their ability to accurately reflect on their choices was intact. I subsequently designed a novel cognitive task to quantify some aspects of rational and intuitive processing in a realistic context, the Party Food Task. This task was effective in its purpose, determined by iterative pilot testing, then in a cohort of healthy controls I showed that use of choice attributes declined across the lifespan, while intuitive processing led to poor DM regardless of age. Furthermore, I showed that increasing age, and not disease status in HD and PD patients, conferred a gradual decline in the use of choice attributes. Intuitive processing was comparable across all groups, but inconsistent compared to rational DM. The Party Food task is a step in a new direction, to combine ecological validity and suitability for neurological patients with a formal choice-modelling approach, although these studies have highlighted several ways in which it should be refined further.

I went on to investigate two interventions that might support good DM in patients and older adults. Both studies were affected by closures due to the COVID-19 pandemic and neither was completed prior to March 2021 (the time when this thesis is being written). The first studied how acute modulation of dopamine affected aspects of rational and intuitive processing in healthy controls across the lifespan. It further investigated whether methylphenidate could enhance use of choice attributes and choice consistency. Only five participants completed the four-visit study and results so far show that this study is feasible and could be continued in the second half of 2021. A smartphone app called Triage was the second intervention, designed to support accurate perception and action regarding email and letters. Initial tests with control participants showed that Triage functions well, is user-friendly and has strong grounds to be of use for patients and older adults, although efficacy has not yet been explicitly tested. A challenge trial is in preparation to do this.

Taken together, these results prompt some noteworthy conclusions and questions. First, there are impairments in DM between HD gene carriers and controls, but these are specifically in perceptual DM. The use of choice attributes, consistency, intuitive processing and metacognitive reflection post-choice was not different to age-matched controls. Impaired perceptual DM might explain the anecdotal and empirical reports of poor choices made by some HD patients in some studies. Therefore, successful interventions might target low-level perception and not high-level cognitive problems. Such solutions could therefore be very simple, like the Triage app, for example.

Furthermore, by including premanifest HD gene carriers without clinical cognitive or functional impairments, this research suggests that perceptual evidence accumulation might be the earliest measurable change in DM due to cognitive decline. Indeed, changes in perceptual DM might predict future cognitive progression in HD though longitudinal studies are needed to confirm this.

However, a caveat in this study is that DM was investigated independently of reward processing: the central tasks, Metadots and Party Food, do not provide feedback to participants about their performance. However, everyday DM almost always involves some kind of feedback, which is used to reflect on past choices and adapt for future ones. Behavioural deficits in primary reward-related behaviour are not reported in HD but reward-related brain activity is different to controls (Enzi et al., 2012; McLauchlan et al., 2019; Minati et al., 2011; Perry & Kramer, 2015). This therefore suggests that the addition of another variable (i.e. reward information) in any decision could lead to suboptimal choices as the reward might not be perceived accurately, or the additional attribute might be ignored in favour of another more discernible or salient attribute.

The minimal differences observed in aspects of rational and intuitive DM between HD gene carriers and matched controls were unexpected given the neurobiological overlap between goal-directed and habitual decisions and early HD pathology. By testing behaviour independent of reward in the Party Food Task, it might be that those regions were not sufficiently activated. Alternatively, the relatively high-functioning gene carriers in the study (with cognition and daily functioning within normal ranges) may have been able to compensate for subtle neurodegeneration, possibly similar to the CRUNCH hypothesis where age-related overactivation is compensatory and cognitive performance remains equivalent (Reuter-Lorenz & Cappell, 2008). Selection biases in the HD group might also have contributed: a disposition towards cognitive diligence is a feature of rational DM (Stanovich, 2011), and HD gene carriers are known for ‘symptom

hunting' or being more attuned to their cognition, understandably so, compared to controls. In general, groups such as those I tested have an intrinsic bias because only the most motivated and able individuals will participate. Selection biases aside, the Party Food Task design eliminated several confounding variables that were present in past research. It controlled for psychomotor and motor effects on RT, required minimal learning and working memory, and allowed individual preferences to vary independently of measures of rational processing. Any one of these confounders may have driven group differences in previous HD DM experiments. It might be useful in future studies to develop more challenging tests of rational and intuitive processes, and/or to complete measures during functional neuroimaging to confirm this.

The findings from Chapters 2 and 5 are interesting to consider in parallel. HD gene carriers demonstrated no impairments in metacognitive ability nor in the use of choice attributes compared to controls. Could high metacognitive efficiency perhaps be associated with a superior ability to think rationally? There is recent and novel evidence to connect the two concepts. In a BioRXiv preprint, Schulz, Fleming and Dayan suggest that metacognitive judgements drive information gathering, such that low confidence justifies the potentially costly acquisition of new information (Schulz et al., 2021). For example, and of relevance to this research, if we suspect that an email is untrustworthy we tend to look for more information to determine whether it is a scam. The new task constructed by the authors to test this theory is similar to the Metadots task such that participants see a stimulus, make a decision about it, rate their confidence, then choose whether to see the stimulus again to gather more information (at a cost), after which they receive a reward based on their accuracy. This task would have merit if applied to HD, not only to connect metacognition and rational processes, but also to understand the effects of reward on these processes.

It is worth considering whether there are more fundamental explanations for these findings. First, RT might explain DM ability. Strict time limits forced participants to respond intuitively, to make inconsistent choices in which choice attributes were neglected. So, might allowing more time to decide, support better rational DM? In the case of older versus young adults, Chapter 4, old controls had slower RTs in spite of using fewer attributes to make their decisions. More time did not support better DM in this instance. In the case of patients versus controls in Chapters 2 there were no significant differences in RT, but HD perceptual performance was worse. In Chapter 5, PD and HD patients responded more slowly than controls but their use of choice attributes was not

different to controls. Together, these results suggest that DM speed declines with age, that perhaps patients require more time to respond equivalently, but that use of choice attributes cannot be improved by giving participants more time to respond (although to confidently assert this would require explicit manipulation of RT). Secondly, it is worth considering the effect of apathy on rational processing of decision variables. As discussed in Chapter 5, an apathetic person is one who has little interest in people or their environment. It follows that such a person would be less motivated to process choice attributes. Prevalence of apathy is higher in people with mild cognitive impairments (Ma, 2020) and in cognitively normal adults, apathy increases with executive dysfunction (Kawagoe et al., 2017; Montoya-Murillo et al., 2019) but no study has directly measured both apathy and DM. HD and PD patients tend to be more apathetic than controls (Martinez-Horta et al., 2016; Sousa et al., 2018), so despite not measuring apathy in this research, equivalent performance between patients and matched controls in Chapter 5 suggests that apathy may not affect rational choice processing, but again future investigation would provide useful confirmation.

Given more time, I would like to have investigated the real-life DM outcomes in HD gene carriers. The present research was motivated by anecdotal reports and observations from the Cambridge HD Clinic, as well as laboratory-based DM tasks in gene carriers. Quantitative evidence such as the number of missed appointments, systematic reports of fraud or unwise spending, or even the number of reminder emails required would better characterise the effects of this research. It is difficult to objectively access such private information, but alternatively, well-designed laboratory studies might suffice. For example, by providing fictitious letters and asking gene carriers how they would respond, or an out-of-order sequence of everyday decisions for participants to order correctly (similar to Roll et al., 2019), or even by creating advice-giving scenarios about how best to make everyday decisions. Systematically characterising everyday DM function could also be informative for healthy cognitive ageing in general, and perhaps could be used to predict the onset of cognitive impairment. Interrogation of these real-life DM outcomes might also circumvent the selection biases mentioned previously by observing such effects rather than requiring experimental participation.

Finally, this research begins to explore the effects of nudge interventions on patient populations. To date, this has not been systematically interrogated, yet nudges are widespread for population-level intervention around the world. The studies in this thesis suggest that intuitive processing of decisions is not different in young or old adults,

patients with PD or HD gene carriers, and therefore provides early evidence that nudges have comparable effects in these groups. Testing nudges in patient groups would confirm this. Nudges are a good treatment option for cognitive decline: they are cheap to test and implement while preserving autonomy.

In conclusion, this thesis discussed how DM is affected in HD gene carriers, building from known neurobiological overlap between DM and HD pathology to investigate perception, metacognition and aspects of rational and intuitive processing. It found gene carriers' perceptual DM was impaired in premanifest individuals, and markedly more so in early-manifest patients, a novel result particularly to find behavioural differences between premanifest individuals and controls. In their intuitive processing and use of choice attributes, gene carriers' performance was comparable to age-matched controls: increasing age, not disease status, was associated with decline in the use of attributes. Controls were more consistent decision makers than HD and PD patients in some decisions. Built from these findings are two interventions to support autonomous and optimal DM, although both require further investigation. The roles of dopaminergic and noradrenergic neurotransmission in DM might be leveraged with acute medication to support the rational consideration of choice attributes, while an app-based intervention called Triage may prompt accurate perception of and action toward letters, emails and other documents.

Conclusions from this thesis provide a more thorough understanding of HD-specific cognitive changes on DM, of the effects of subtle cognitive decline and ageing on DM, and finally, and how good DM can be supported.

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10 APPENDICES

APPENDIX 1 COGNITIVE TASKS CONSIDERED PRIOR TO CREATING A NEW DECISION-MAKING TASK

Task	Reference of applied task
National Adult Reading Test (NART)	(Nelson & O'Connell, 1978)
Tower 3 and 4 tasks	(Goel & Grafman, 1995)(Stout et al., 2011)
Tower of Hanoi	(Goel & Grafman, 1995)
Serial response time task	(Stout et al., 2011)
Verbalised category learning tasks	(Stout et al., 2011)
Associative learning of categories	(Cantwell et al., 2017)
Facial emotion recognition	(Stout et al., 2011)
Dynamic emotion recognition	(Stout et al., 2011)
N-back task	(Georgiou-Karistianis et al., 2014)
Self-timed finger tapping	(Stout et al., 2011)
Speed tapping task	(Stout et al., 2011)
Cued movement sequence task	(Stout et al., 2011)
Psychological refractory period tasks	(Janczyk et al., 2015)
Simple and two-choice response times	(Hecht et al., 2008)
Letter-Number sequencing	(Stout et al., 2011)
Digit span	(Egeland, 2015)
Benton facial recognition test	(Stout et al., 2011)
University of Pennsylvania Smell Identification Test (UPSIT)	(Stout et al., 2011)
Stroop colour naming	(Stout et al., 2011)
Stroop word naming	(Stout et al., 2011)
Stroop interference	(Stout et al., 2011)
Symbol digit modalities test (SDMT)	(Stout et al., 2011)
Trail making A and B	(Stout et al., 2011)
Phonemic verbal fluency	(Stout et al., 2011)
Categorical verbal fluency	(Baake et al., 2017)
Hopkins verbal learning test, revised (HVLT-R)	(Stout et al., 2011)
Matrix reasoning test	(Stout et al., 2011)
Vocabulary subtest of the WASI	(Stout et al., 2011)
Iowa gambling (IGT)	(Denburg et al., 2009)
Game of Dice (GDT)	(Bridge et al., 2012)
Cambridge gambling	(Cambridge Cognition, 2006)
Ultimatum game	(Phelps et al., 2014)
Wisconsin card sorting	(Marschner et al., 2005)
Yoni Task	(Adjeroud et al., 2016)
Basic empathy scale (BES)	(Adjeroud et al., 2016)

Interpersonal reactivity index	(Adjeroud et al., 2016)
Empathy Quotient	(Maurage et al., 2016)
Social story sequencing	(Maurage et al., 2016)
Faux-pas	(Maurage et al., 2016)
Complex mental state decoding	(Maurage et al., 2016)
Paired associates learning (PAL)	(Begeti et al., 2016)
Tower of London	(L. H. Watkins et al., 2000)
Virtual Morris water maze	(Begeti et al., 2016)
Utrech thrift	(Abell et al., 2000)
Sally Ann task	(Abell et al., 2000)
Toronto alexythymia scale	(Trinkler et al., 2013)
Bell Lysaker Emotion recognition (BLERT)	(Pinkham et al., 2017)
Penn emotion recognition task (ER-40)	(Pinkham et al., 2017)
Reading the mind in the eyes task (RMET)	(Pinkham et al., 2017)
Awareness of social inferences test (TASIT)	(Pinkham et al., 2017)
Hinting task	(Pinkham et al., 2017)
Mini profile of nonverbal sensitivity (MiniPONS)	(Pinkham et al., 2017)
Social attribution Task-Multiple choice (SAT-MC)	(Pinkham et al., 2017)
Intentionality bias task (IBT)	(Pinkham et al., 2017)
Public goods games	(Fosgaard et al., 2017)
Montreal Cognitive Assessment (MoCA)	(Lagravinese et al., 2017)
Olfactory discrimination and identification test	(Larsson et al., 2006)
Barratt impulsiveness scale (BIS)	(Patton et al., 1995)
Sensation-seeking scale	(Shulman et al., 2016)
Problem behaviours assessment (PBA)	(Tabrizi et al., 2013)
Circle tracing annulus length	(Tabrizi et al., 2013)
Frederick's cognitive reflection test (CRT)	(Frederick, 2005)
Probablistic object reversal task (pORT)	(Marschner et al., 2005)
Self-ordered pointing task	(Marschner et al., 2005)
Balloon Analog Risk Task (BART)	(Phelps et al., 2014)
Monetary incentive delay (MID)	(Perry & Kramer, 2015)
Bayesian alternatives - Doctor/diagnosis on screen task	(Hayes et al., 2016)
Object detection tasks	(Newell & Shanks, 2014)
Wonderlic Personnel Test (WPT)	(Toplak et al., 2011)
Need for cognition task (NFC)	(Cacioppo et al., 1984)

Wheel of fortune	(Shad et al., 2011)
Matching and Maximising Marble task	(Koehler & James, 2010)
Urns task	(Koehler & James, 2010)
Jelly bean task	(Denes-Raj & Epstein, 1994)
Rational–Experiential Inventory	(Epstein et al., 1996)
Wason card selection	(Pohl, 2016)
Information sampling task	(Cambridge Cognition, 2006)
Motor screening	(Cambridge Cognition, 2006)
Big/Little circle	(Cambridge Cognition, 2006)
Delayed matching to sample	(Cambridge Cognition, 2006)
Pattern recognition memory	(Cambridge Cognition, 2006)
Spatial recognition memory	(Cambridge Cognition, 2006)
Intra-Extra dimensional set shift	(Cambridge Cognition, 2006)
One touch stockings of Cambridge	(Cambridge Cognition, 2006)
Stockings of Cambridge	(Cambridge Cognition, 2006)
Spatial span	(Cambridge Cognition, 2006)
Spatial working memory	(Cambridge Cognition, 2006)
Match to sample visual search	(Cambridge Cognition, 2006)
Choice reaction time	(Cambridge Cognition, 2006)
Rapid visual information processing	(Cambridge Cognition, 2006)
Reaction time	(Cambridge Cognition, 2006)
Simple reaction time	(Cambridge Cognition, 2006)
Graded naming test	(Cambridge Cognition, 2006)
Verbal recognition memory	(Cambridge Cognition, 2006)
Affective go/no go	(Cambridge Cognition, 2006)
Stop signal task	(Cambridge Cognition, 2006)
Implicit association test (IAC)	(Cambridge Cognition, 2006)
Faith in Intuition(FI)	(Epstein et al., 1996)
Base rate neglect task	(Pohl, 2016)
Actively Open-minded Thinking scale (AOT)	(Stanovich & West, 1997)
argument evaluation test (AET)	(Stanovich & West, 1997)
Addenbrooke's cognitive exam-revised (ACE-R)	(Begeti et al., 2013)
The Linda problem	(Kahneman & Tversky, 1982)
Brief Moral Decision-Making Questionnaire (BrMoD)	(Carmona-Perera et al., 2015)

APPENDIX 2 DETAILED EXPLANATIONS OF DECISION-MAKING TASKS USED IN THIS THESIS

These tasks are in addition to the Party Food task developed in Chapter 3.

Informed Consent

Participants were given a Participant Information Sheet (example in Appendix 3) at least one week prior to the visit. They were given the opportunity to ask questions via phone or email, and again in-person prior to signing the consent form (example in Appendix 3). In some instances, participants chose to partake at short notice, for example, if they were in the building to accompany their partner for a clinic visit.

Screening tasks

- Stop Signal Task (SST): This test is part of the Cognitron battery (www.cognitron.co.uk) and measures impulse control. The participant is presented with an arrow stimulus and must respond with the direction of the arrow using the mouse to select 'left' or 'right'. If the red dot above the arrow is present, the subject must withhold their response. Time to respond, ability to inhibit response, and number of correct trials are recorded by the computer (Trender et al., 2018); paradigm originally developed by (Logan et al., 1984).

- Rey Complex Figure Drawing: This task measures effort and attention. Participants are given a complex line drawing to copy on paper. It was administered at the end of the battery and participants who did not complete the figure sufficiently (i.e. scored 34/36 or higher) were assumed to lack either effort or attention, and their scores for the visit were excluded. The similarity to the original figure is scored based on 18 different components, each worth 2 points (Rey, 1964).

- National Adult Reading Test (NART): This test is a measure of premorbid verbal IQ. Fifty irregular and mostly unfamiliar English words are presented and participants are instructed to read each word aloud. Verbal IQ are estimated from the number of errors made in the NART (Nelson & O'Connell, 1978).

Anxiety and depression

- Hospital Anxiety and Depression Scale (HADS): The HADS is a 14 item self-rated questionnaire (7 items pertaining to depression and 7 to anxiety) which is designed to determine the levels of anxiety and depression experienced by the participant in the past 7 days. There are 8 additional questions which can be included in determine irritability levels (Zigmond & Snaith, 1983).

General cognition

- Addenbrooke's Cognitive Exam – Revised (ACE-R): The ACE-R is a measure of global cognition and assesses performance in five neuropsychological

domains (orientation and attention, memory, verbal fluency, language and visuospatial function). The ACE-R has normative data from an elderly population and established cut-off scores that are indicative of dementia with a high degree of sensitivity and specificity. It has been used in a number of neurodegenerative disorders. A total score is obtained out of a maximum 100 (Davies et al., 2008).

Rational processing tests

- Bees Information Sampling Task (IST): This test is part of the Cognitron battery (www.cognitron.co.uk) developed by Dr Adam Hampshire and colleagues. The "Bees" task measures the deliberative information gathering aspect of DM. Participants are presented with a 'hive' array of yellow boxes and must reveal them one at a time to show the underlying colour (of two possible colours). Revealed boxes remain 'open' once selected, and participants must decide which colour makes up the majority by revealing subsequent boxes. There are 15 trials preceded by one practice trial. The outcome measures are latency, errors, mean number of boxes selected, total correct trials, participant's confidence in their decision, and probability of the participant's decision being correct based on the available evidence at the time of decision. Importantly, all participants were verbally instructed to reveal as few boxes as possible while still getting the answer correct and mediating their uncertainty through the use of the confidence rating scale (Trender et al., 2018)

- Trender reasoning task: A form of this test is included in the Weschler Adult Intelligence Scale (sometimes called Matrix Reasoning), but this version is part of the Cognitron battery (www.cognitron.co.uk). It measures non-verbal abstract problem solving. Participants must identify patterns in a series of designs and select the next image in the series from a choice of three. There are 12 such choices to make in this test (Trender et al., 2018).

Questionnaires

- Faith in intuition (FI) scale: This self-report questionnaire measures an individual's tendency to engage in type one processing. It assess how much individuals trust their intuitions with statements such as, "I believe in trusting my hunches" on a Likert scale (Epstein et al., 1996; Pacini & Epstein, 1999).

- Need for cognition (NFC): This self-report questionnaire measures an individual's tendency to engage in type two processing. It assesses how much individuals enjoy and engage in effortful thinking (Cacioppo et al., 1984).

- Rational-Experiential Vignettes: This activity measures an individual's preference to engage in intuitive or rational processing. It consists of one scale on which participants evaluate the thoughts of the individuals described in the vignettes. The scale is related to the FI and NFC scales, such that one end represents a more intuitive answer, and the other end a more deliberative answer. Four two-part vignettes are included in this questionnaire (Epstein et al., 1996).

- General Decision-Making Style Questionnaire (GDMS): This questionnaire was developed to capture individual DM style across five types: rational, intuitive, spontaneous, avoidant, and dependent. It consists of 25 questions (5 per type) that are answered on a Likert scale (Scott & Bruce, 1995).

- Decision-Making Experiences Questionnaire: This questionnaire was developed in the Department of Psychiatry (University of Cambridge) to capture difficulties across real-life decisions in Autism Spectrum conditions. It includes 43 questions where participants rate how difficult they would find a given decision, and how various parameters affect decision difficulty to provide subjective insights into participants' thoughts about their own DM (Luke et al., 2012).

Rational-intuitive processing in conflict tests

- Cognitive reflection test (CRT): Initially designed as a measure of individual differences in cognitive ability, the CRT characterises three groups of people based on the responses they make to three short questions. Each question has a correct answer, an intuitive but incorrect answer, and an answer that is entirely incorrect. It is inferred from these questions that rational processing is required to respond correctly (Frederick, 2005).

- Jelly bean task: This task interrogates the finding that people ignore statistical concepts and instead rely on judgmental heuristics to make decisions, in this case, the ratio bias effect. Participants are presented with two 'bowls' on a screen. Initially, one bowl is said to contain 10 jelly beans, one of which is red. The second bowl contains 100 jelly beans, 10 of which are red. The probability of choosing a red jelly bean is identical in each case (10%), but when instructed to pick a bowl to choose a red bean from for a monetary reward, participants choose the bowl with 100 beans two thirds of the time. The second part of the task alters the probabilities such that the second bowl now contains 9 red jelly beans and 91 non-red, with the probability clearly stated. Participants must then choose the bowl from which they have the greatest chance of selecting a red jelly bean. In this task, intuitive processes are associated with choosing the second bowl, and rational with the first bowl (Denes-Raj & Epstein, 1994).

- The Linda Problem: This task was developed to systematically diagnose the nature of processing errors made due to the conjunction effect. Errors in this case defy the statistical rule that the probability of a conjunction between A and B cannot exceed the probability that A or B will occur alone. The Linda Problem asks: "Linda is 31 years old, single, outspoken, and very bright. She majored in philosophy. As a student, she was deeply concerned with issues of discrimination and social justice, and also participated in anti-nuclear demonstrations. Which statement is more probable? (A) Linda is a bank teller, or (B) Linda is a bank teller who is active in the feminist movement." In this task, rational processes are associated with option (B) and intuitive processes with option (A) (Kahneman & Tversky, 1982)

APPENDIX 3 EXAMPLE PARTICIPANT INFORMATION SHEET AND CONSENT FORM USED FOR THE RESEARCH PROJECTS IN THIS THESIS

UNIVERSITY OF CAMBRIDGE
JOHN VAN GEEST CENTRE FOR BRAIN REPAIR
The E. D. Adrian Building, Forvie Site, Robinson Way, Cambridge CB2 0PY, UK

Cambridge University Hospitals NHS
NHS Foundation Trust

Participant Information Sheet (Version 1.1 03.10.2018)
Part 1 - CONTROLS

Study title: Decision Making in Huntington's Disease
REC reference: PRE.2018.090
Chief Investigator: Prof Roger Barker

We would like to invite you to take part in the above research study. Before you decide you need to understand why the research is being done and what it will involve for you. Please take the time to read the following information carefully. Part 1 tells you the purpose of the study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
The striatum is a region of the brain that is involved in making decisions. It is also an area that is affected by Huntington's (HD) disease. This study aims to identify if patients with Huntington's disease differ in how they make decisions, compared to people without the disorder. We will do this by asking participants to carry out a series of different decision making tasks either on the computer or on paper. The information we learn from this study will be important as it may enable us to better understand the factors which influence how people with HD make decisions.

Why have I been invited?
You have been invited to participate in this study because you do not have a family history of HD and are not known to carry the gene for HD, and you have expressed an interest to be involved in research. Your role in the study is to act as a healthy control and your performance will be compared to that of the HD participants.

Do I have to take part?
It is up to you to decide whether to take part or not. We will describe the study and go through this information sheet with you, which we will then give to you. We will then ask you to sign a consent form to keep. You are free to withdraw at any time, without giving a reason.

What will happen to me if I take part?

If you take part, you will be asked to visit the Brain Repair Centre (BRC) in Cambridge for one visit which will last approximately 2 hours, although this may be slightly longer or shorter depending on how difficult you find the tasks. You will be asked to carry out several decision-making tasks on the computer, on paper or verbally. We will endeavour to make your time with us as enjoyable as possible and you will be allowed to take a break at any point.

Tasks:
During your visit you will complete a series of games that are designed to help us understand the way in which you make. Broadly speaking the assessments that you complete will fall into the following groups:

- Measures of **impulsivity** which look at how quickly you make decisions and how much information you take into consideration before committing to a particular choice.
- Tests of **planning** which require you to think through a problem in advance and evaluate different ways to solve it before you can find the most efficient solution.
- Tests of **pattern recognition** which look at how well you can identify the key aspects of a sequence
- Assessments that look at your **global cognitive performance** for example how well you remember information, direct your attention, orientate yourself in time and space, process and use language.

We will also give you questionnaires to see how you think you would respond in hypothetical scenarios and how you think about decisions. There will also be some questionnaires to see how motivated you are, your education level and whether you are depressed, as all of these factors can influence how you perform on the games above.

Expenses and payments
You will be paid £15 for completing the tasks and questionnaires.

What will I have to do?
There are no lifestyle restrictions for participating in this study. We ask that you provide us with a means of contacting you (e.g. to confirm an appointment). To preserve your privacy, we will not identify ourselves as having any connection with a medical facility if we contact you using this means.

What are the possible disadvantages and risks of taking part?
There will be no disadvantages or risks to anyone involved in the study. However, you are free at any time to stop the assessment or pass on any part of a task. The way you perform on these games will NOT be used to stop you making decisions in your real life.

What are the possible benefits of taking part?
We cannot promise that this study will help you personally but the information we get from this study may help improve the understanding of this aspect of Huntington's disease in the future.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. More detailed information about this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participating, please read the additional information in Part 2 before letting us know if you'd like to participate.

Data sharing:
It is important that research is conducted in an open and transparent way. To help achieve this we support the open sharing of research data to allow our peers to scrutinise our analysis and interpretation, to support policy making and to optimise the use of good quality research data. The results of this study will be shared with our collaborators and members of the wider research community upon their request. This means that there is a potential that your data will be shared with researchers from abroad including countries outside of the European Economic Area (EEA). You should be aware that these countries often do not offer the same level of protection of peoples' privacy as that demanded by law in the UK however, each request will be reviewed on an individual basis to ensure its integrity and all data shared will be fully anonymised. Information about how the University uses your personal data can be found at: https://www.information-compliance.admin.cam.ac.uk/data-protection/research-participant-data

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The E. D. Adrian Building, Forvie Site, Robinson Way, Cambridge CB2 0PY, UK

Cambridge University Hospitals NHS
NHS Foundation Trust

Participant Information Sheet (Version 1.1 03.10.2018)
Part 2 – CONTROLS

Study title: Decision making in Huntington's disease
REC reference: PRE.2018.090
Chief Investigator: Prof Roger Barker

What will happen if I don't want to carry on with the study?
You are free to withdraw at any point during the study, without giving a reason. If you decide to withdraw you will not be asked to attend any further study visits however, we will ask your permission to continue to use the information that we have already gathered up to your withdrawal. If you decline all of your information will be destroyed.

What if there is a problem?
In the unlikely event that you are harmed by taking part in this research project, there will be no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it yourself. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). Indemnity is also provided by Cambridge University.

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (Dr Roger Barker 01223 331160 or Alice White 01223 331160). If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure. Details can be obtained from the hospital. The Patient Advice and Liaison Services (PALS) can also be contacted on 01223 216 756.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential and will only be seen by members of the Cambridge Centre for Brain Repair. Personal Identifiable Data (PID) will be stored independently of all other data collected during the study and will only be linked on a single file which will be stored securely on the Department of Clinical Neuroscience secure server.

All data will be held in accordance with the Data Protection Act and will be accessible to a member of the study team, regulators and the study's sponsors, Addenbrooke's hospital and Cambridge University for audit and monitoring purposes. Any information about you which leaves the Brain Repair Centre will have your name removed so that you cannot be recognised.

Data will be stored at, and be under the custody of, the Cambridge Centre for Brain Repair for at least 15 years after the study has finished and possibly indefinitely in accordance with good research practice. If you have consented to it, the data that we have collected may be used in further studies.

What will happen to the results of this study?
Results may be published in scientific and neurological journals and may be presented at conferences or local groups (including Huntington's Disease Association meetings). All identifying characteristics of the data will be removed before the results are published; none of your information will be able to be traced back to you.

Who is organising and funding the research?
The Brain Repair Centre is organising this research and donations made to the department will provide the small funding required for this study.

Who has reviewed the study?
All the research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable ethical opinion by the Psychology Research Ethics Committee.

If you have any questions relating to this study please contact:

Alice White
Cambridge Centre for Brain Repair
Forvie Site
Robinson Way
Cambridge CB2 0PY

Telephone: 01223 331160
Facsimile: 01223 331174
Email: ajw283@cam.ac.uk

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JOHN VAN GEEST CENTRE FOR BRAIN REPAIR
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Cambridge University Hospitals NHS
NHS Foundation Trust

Participant Identification Number for this trial:

CONTROL CONSENT FORM

Decision Making in Huntington's disease

Name of Participant: _____

Please initial boxes

1. I confirm that I have read and understand the information sheet version 1.1 03.10.18 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that information collected about me during the course of this study will be kept securely in the Study Centre. It will be treated in the strictest confidence, with Prof. Roger Barker acting as custodian. Data will be kept for at least 15 years. ☐
4. I agree to allow the study investigators to contact me in the future in respect of follow-up this study. ☐
5. In the future I understand that I may not be in a position to give my consent to participate in follow-up of this study. In this circumstance, I understand that I will no longer be eligible to continue to participate in the study however, I am happy for the researcher to continue to use any data previously collected. ☐
6. I agree for any anonymous data collected to be sent to other academic collaborators and peers to facilitate open science within and outside of the UK. ☐
7. I agree to take part in the above study. ☐

Name of Participant	Date	Signature

As a study investigator, I confirm that I have explained the nature and purpose of the research study and have supplied a study information sheet for the participant to retain

Researcher	Date	Signature

1 each for participant, researcher and study notes