Subjective time perception in healthy ageing and dementia

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Declaration

I, Maï-Carmen Requena-Komuro, confirm that the work presented in this thesis is my own. Where information is derived from other sources, I confirm that this has been referenced appropriately.

To my parents and Jim

Abstract

Our ability to experience the passage of time is fundamental to our lives. Consequently, disruptions to temporal processing may have adverse effects on the normal conduct of everyday life activities, particularly in the elderly. In fact, difficulties with temporal perception have been consistently described in healthy ageing and can be clinically significant in common dementias, such as Alzheimer's disease and frontotemporal dementia syndromes. However, they remain poorly defined and have not been systematically compared. In this thesis, I describe several changes in subjective time perception resulting from healthy ageing and different neurodegenerative diseases by presenting behavioural and structural brain imaging evidence.

In chapter 3, I demonstrate the modulation of perceived duration by the emotional and perceptual characteristics of a range of everyday life sounds and show that healthy ageing impacts the perceived duration of environmental sounds and overall duration discrimination sensitivity. In chapter 4, I present a remote testing protocol developed during the COVID-19 pandemic and show comparable performance to face-to-face testing on several neuropsychological and neurolinguistic tests for healthy control participants and patients diagnosed with canonical Alzheimer's disease and frontotemporal dementia syndromes. In chapter 5, I evaluate the impact of these neurodegenerative diseases on timing abilities using the paradigm presented in chapter 3 and the remote testing protocol from chapter 4. I highlight differences in perceived duration and discrimination sensitivity that reflect syndromic characteristics and present neuroanatomical correlates that shed light on the mechanisms of time perception. In chapter 6, I establish distinct profiles of abnormal long-range temporal behaviours of everyday life in a similar dementia cohort and present the associated neuroanatomical substrates, furthering our understanding of temporal awareness.

Overall, investigating subjective time perception in both healthy and pathological ageing opens a new avenue for a more quantitative, functional, and ecological approach to assessing ageing.

Impact Statement

As the world faces a growing ageing population, identifying ways to meet the health challenges of older people becomes critical. Notably, the mechanisms underlying brain ageing and neurodegenerative diseases of later life remain poorly understood. Investigating time perception could provide novel valuable insights into these mechanisms. Indeed, our ability to perceive time supports our everyday life activities in countless ways. Accumulated experimental evidence further shows that time is encoded in large brain networks overlapping those disrupted in major dementias. Given that each dementia has a unique neuroanatomical signature, different dementias are therefore likely to be characterised by distinct temporal profiles.

The work presented in this thesis broke several new grounds: first, by demonstrating the feasibility of using remote testing protocols in these research fields; second, by using a psychophysical approach not often used in dementia research but which can provide precise measurements of timing abilities in patients; third, by establishing quantitative differences in subjective temporal coding of naturalistic sounds of everyday life across large cohorts of healthy young and older adults, as well as diverse types of dementia; fourth, by linking altered temporal behaviours to specific neuroanatomical substrates in dementia.

These findings could bring further benefit both within and outside academia. Specifically, future research exploring the neurobiological mechanisms underlying time perception changes in these clinical populations may help identify future therapeutic targets that would broadly and tangibly improve the quality of life of people living with dementia. Moreover, characterising their temporal difficulties manifesting in their everyday lives may help design better support systems for these patients and reduce caregiver burden. In addition, longitudinal approaches, especially to compare cognitive trajectories of healthy and pathological ageing, would not only contribute to detecting early signs of neurodegeneration, but may also help identify areas of cognitive reserve. This is even more promising for temporal processing given that time encoding is a fundamental property of neurons and that the human brain is highly plastic. Research in this avenue may therefore pave the way to the development of specific behavioural training

programs aimed at improving timing abilities in individuals at risk of developing neurodegenerative diseases.

Currently, time perception remains a relatively unexplored topic in these research fields, despite its potentially wide-ranging impact. The research described in this thesis may therefore offer an interesting starting point for future work. Notably, there is a need to correlate different forms of timing across different scales and paradigms to better bridge the gap between experimental testing and real-life behaviour. This would help raise awareness among clinicians and academics from multiple disciplines on the importance of developing novel ecological cognitive biomarkers reflecting the daily-life experience of older people. Multidisciplinary research of this kind may also represent a valuable opportunity to foster collaborative initiatives with the wider public to demonstrate the potential of science to provide tangible solutions to real-life problems.

Acknowledgements

About three years and a half ago, I officially started my PhD at the Dementia Research Centre. Three years and a half, that represents 42 months of constant self-reinvention, 168 weeks of intense thought-provoking work and sun-seeking holidays to recharge batteries, 1176 days of planning, planning, planning, without ever really thriving at it, 28 224 hours of staring at the screen, looking out the window, at the ceiling, into other people's brains and sometimes my own for answers to all kinds of questions. I also must admit I spent these 28 224 hours complaining (many apologies to those who patiently listened), but also, thankfully, celebrating food, creating music, and most importantly, sleeping. Three years and a half, that also represents 1,693,440 minutes of riding an emotional roller coaster (or rather, being taken onto one). But that is simply 101,606,400 seconds of living as a sensitive human being.

As I reach the finish line, I am convinced that doing a PhD is not about the destination, but it is about the journey and mine was a very transformative one. I rejoice in having to thank so many people because it proves that I was not alone, despite having felt so, sometimes.

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Abbreviations

AD	Alzheimer's disease
BG	basal ganglia
BNT	Boston Naming Test
BPVS	British Picture Vocabulary Scale
bvFTD	behavioural variant frontotemporal dementia
C9orf72	chromosome 9 open reading frame 72
CI	confidence interval
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
DARTEL	Diffeomorphic Anatomical Registration using Exponentiated Lie algebra
D-KEFS	Delis-Kaplan Executive Function System
dlPFC	dorsolateral prefrontal cortex
DS-F	digit span forward
DS-R	digit span reverse
fMRI	functional magnetic resonance imaging
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
FUS	fused-in sarcoma
FWE	family-wise error
GABA	gamma-aminobutyric acid
GDA	Graded Difficulty Arithmetic
GNT	Graded Naming Test
GRN	progranulin
IFG	inferior frontal gyrus
Ins	insula
IPL	inferior parietal lobule
IQ	Intelligence Quotient
lvPPA	logopenic variant primary progressive aphasia

MAPT	microtubule associated protein tau
MMSE	Mini Mental State Examination
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MSN	medium spiny neurons
NART	National Adult Reading Test
nfvPPA	non-fluent primary progressive aphasia
OR	odds ratio
PAL	Paired Associate Learning test
PALPA	Psycholinguistic Assessment of Language Processing in Aphasia
PET	Positron Emission Tomography
PPA	primary progressive aphasia
PSE	point of subjective equality
RMT	Recognition Memory Test
ROI	region of interest
s	seconds
SBF	Striatal Beat Frequency
SMA	supplementary motor area
SNc	substantia nigra pars compacta
STQ	Subjective Time Questionnaire
svPPA	semantic variant primary progressive aphasia
TDP-43	transactive response DNA binding protein 43
TIV	total intracranial volume
T-MMSE	Telephone Mini Mental State Examination
TMT	Trail Making Test
VBM	voxel-based morphometry
VOSP	Visual Object and Spatial Perception battery
VTA	ventral tegmental area
WASI	Wechsler Abbreviated Scale of Intelligence
WMS-R	Wechsler Memory Scale

Epigraph

« Le temps ne va pas vite quand on l'observe. Il se sent tenu à l'œil. Mais il profite de nos distractions. Peut-être y a-t-il même deux temps, celui qu'on observe et celui qui nous transforme.

[*Time does not go fast when we observe it. It feels watched. But it takes advantage of our distractions. Perhaps are there even two times, one that we observe and one that transforms us.*] »

Albert Camus

Les Carnets II

Janvier 1942 - Mars 1951

1. General Introduction

1.1. Defining subjective time perception

1.1.1. Subjective or 'psychological' time

In order to interact with the world, our brain builds a *representation* of it. In other words, it does not faithfully copy the world "exactly as it is", rather it creates an image of it in a way that is most adaptive and useful to us. A perfect example of this is our colour vision. Most humans benefit from trichromatic vision, i.e., we can see blues, greens, and reds. However, most species in the animal kingdom cannot see reds because they lack the corresponding cone photoreceptor (though they have other cones that allow them to see other hues or regions of the electromagnetic spectrum, including the ultraviolet domain). It has been argued that our trichromatic vision is the direct result of evolution, allowing us to assess when fruits are ripe (since ripe fruits are often red) or to find the most suitable mates (Gerl & Morris, 2008).

Similarly, our perception of time is not exact. That is, time in our minds does not flow at the same pace as the physical clock time, and as a result, any interval that is labelled as one second, two minutes, or three hours in the external world does not necessarily match our own experience of those intervals. This is "psychological time" and is exemplified in many of our everyday life sayings, such as "time flies when you're having fun". Furthermore, all individuals experience time differently, although we are exposed to the same fluctuations (for example, we may all feel that a certain time interval flew by, although the exact perceived duration of that time interval may be different from one individual to another). In addition, our subjective perception of time can change over the years, such that time seems not to flow at the same speed when we are seventy compared to when we were thirty or ten years old. Despite all these variations, we all possess an internal timekeeping mechanism that is accurate most of the time and enables us to carry out our everyday life activities in a world regulated by the physical clock. A key challenge of time perception research is therefore to understand how our brain encodes time in a way that fully supports our interactions with the external world, while accommodating individual variations.

1.1.2. Investigating subjective time in healthy ageing and dementia

As will be described throughout this introduction, our ability to perceive time is essential for many of our everyday life activities and is supported by several core cognitive functions (namely executive function, working memory, attention, and decision-making). In addition, accumulated evidence on the neural basis of psychological time implicates a large network of cortical and subcortical brain areas, further endorsing temporal processing as a key brain function. Time perception is therefore an ideal candidate for tracking age-related cognitive dysfunction (Balci et al., 2009), especially given that some of the brain areas and cognitive functions supporting time perception are susceptible to healthy ageing (Matthews & Meck, 2016; Turgeon et al., 2016). Initial studies assessing timing in pathological ageing, specifically in neurodegenerative diseases, highlighted time disorientation as a key symptom (Dumurgier et al., 2016; Folstein et al., 1975). However, given the distinct brain atrophy patterns associated with each neurodegenerative disease, it is likely that each disease will be differentiated based on its uniquely associated temporal profile.

In this thesis introduction, I will first provide a basic overview of the terminology and methodologies that have been used to describe and assess timing abilities in humans, covering the cognitive processes (memory, attention, emotion) that impact time perception. I will then address the timing models and neuroanatomical findings that are most relevant to this thesis's work. I will also present the current perspective on time perception in healthy ageing and major dementia syndromes. Finally, I will consider key unresolved questions relevant to subjective time perception in healthy and pathological ageing that emerge from this survey of the literature and outline how I have addressed these questions experimentally in this thesis.

1.1.3. A brief psychological taxonomy of time

Time is central to our lives, as almost any task requires some degree of temporal processing. A few examples include speech comprehension, playing a musical instrument, planning a future holiday, and social interactions. Several distinct timing processes have therefore been outlined to reflect the diversity of temporal requirements in those tasks. Based on the survey of the timing literature (Paton & Buonomano, 2018), possible distinctions can be drawn along the following dimensions:

- the temporal scale at which a particular task operates. Notably, different neural mechanisms seem to govern sub-second and supra-second timing, although some brain areas have been implicated in both (Hayashi et al., 2014; M. Wiener et al., 2010);
- the temporal content, that is whether the task involves measuring the duration of an interval or analysing the temporal structure of a sequence of multiple intervals (Teki et al., 2011);
- and finally, whether the task is more perceptual or motor in nature. For example, the temporal bisection task, which will be further described in the next section, is essentially a perceptual task. Indeed, although participants make a motor response (a keypress) to indicate their answer at the end of each trial, the choice of the answer is informed by the processing of incoming sensory stimuli. On the other hand, producing an interval of one second long for example is essentially a motor task because it involves internally generating a motor response based on prior knowledge of how long one second lasts. Again, neuroimaging evidence suggests distinct neural mechanisms for perceptual and motor timing (M. Wiener et al., 2010), although a recent study demonstrates that motor processes can influence perceptual duration judgements (De Kock et al., 2021)

Importantly, the neural mechanisms underlying sub-second/supra-second, duration/pattern, and perceptual/motor timing tasks have not been fully resolved and it is therefore still unclear how much they may overlap. The present terminology has therefore been developed over the years as a necessity to use a common language to better compare and contrast the wide variety of published timing studies in order to

resolve these mechanisms. Accordingly, I will follow the perceptual/motor timing dichotomy when I present findings pertaining to healthy ageing and dementia, focusing particularly on interval timing which the main experimental work of this thesis addresses. I will also describe separately findings related to mental time travel as this notion is relevant for **Chapter 6** of this thesis. Mental time travel is defined as our ability to use our mental timeline to "travel" at different points in the past to reminisce past autobiographical events (also known as past prospection) or to collect information from our past and present to imagine future scenarios (also referred to as future prospection or episodic future thinking) (D. Bernsten & A.S. Jacobsen, 2008; Bonato et al., 2012b; Brunec et al., 2015; Pathman et al., 2018). Unlike motor and perceptual timing, mental time travel is therefore not directly relevant to the present (i.e., it does not require immediate processing of sensory input or immediate action). However, it supports our sense of self-continuity from past to future (Tulving, 1972; Wheeler et al., 1997).

On the next page, **Table** 1-1 presents the different timing processes related to motor timing, perceptual timing, and mental time travel, specifying the different time scales at which they operate along with concrete examples.

Table 1-1 A psychological taxonomy of time

Motor timing	Perceptual timing	Mental time travel
Milliseconds/seconds	Hundreds of milliseconds /seconds/minutes	Episodic events
Producing an interval or a sequence of intervals (e.g., saying the word "time" or the phrase "time is a flowing river")	Estimating the duration of an interval, also known as interval timing (e.g., measuring how long the red traffic light will last for)	Estimating the duration of an event in the past or in the future (e.g., the duration of a previous or future walk)
Synchronising to a beat/meter/rhythm (e.g., clapping along to a song)	Determining the duration between two events (e.g., evaluating the time between seeing and hearing a thunder)	Determining the temporal distance between two events (e.g., evaluating the time between two meals)
Synchronising to an external event (e.g., laughing with your friends)	Determining the order of two events (e.g., hitting your toe before feeling the pain)	Evaluating the speed of time's passing (e.g., feeling that time passed slowly as a child compared to now)

A summary of timing processes described in the literature for motor timing, perceptual timing, and mental time travel, with the time scale at which these operate and concrete examples from everyday life specified in parentheses.

1.1.4. Measuring timing abilities in humans

The way experimenters measure how humans experience time largely depends on the timing processes being addressed. Here I will present a brief overview of the experimental tasks typically used in timing research.

To assess motor timing, the following experimental tasks are often used:

i. **Production task**: participants are instructed to produce an interval of a certain duration (specified by a verbal label, for example "2 seconds"), often using key presses to signal the onset and offset of the interval.

ii. **Reproduction task**: participants are first presented with a stimulus that lasts for the duration to be reproduced (for example, a blue circle lasting for two seconds), and are then given the opportunity to produce that duration using key presses.

iii. **Finger-tapping task**: there are two versions of this task: either the participant listens to a regular beat and is asked to tap their finger at the same pace (externally triggered), or, after an initiation phase where they are asked to tap their finger to the beat, they continue to tap their finger at the same pace without hearing the beat (self-triggered).

To assess perceptual timing, there is a larger set of tasks available of which the following are most relevant to the work presented in this thesis:

i. **Verbal estimation task**: participants are asked to provide a verbal estimate of the duration of an interval (for example by saying "five seconds"). The interval may be "empty" (the duration of the interval would be defined by its onset and offset, usually indicated by an auditory beep), or "filled", either with a stimulus (for example a blue circle or a musical sequence) or with an activity (for example reading or counting). For this task, participants can either be instructed beforehand that the task assesses timing abilities (prospective timing) or are asked to evaluate the time only at the end of the interval (retrospective timing).

ii. **Temporal discrimination task**: participants are asked to discriminate two intervals, i.e., they attend to two successively presented stimuli, the first being the standard interval and the second varying in duration compared to the standard to a degree that differs from trial to trial. Participants are then asked to indicate if the second interval is shorter or longer than the first.

iii. **Temporal bisection task**: on each trial, participants attend to a single stimulus and are asked to categorise it as "short" or "long". Usually, the "short" and "long" references are defined in a preceding practice phase where participants learn to associate a verbal label to the correct duration ("short" for the shortest duration of the two references, and vice versa), but this is not necessary (see partition method in **section 3.3.3**).

For the experimental work presented in this thesis, I chose the temporal bisection task. Initially developed for animal studies of timing (Church & Deluty, 1977), this paradigm has been later adapted for human participants (Wearden, 1991) and has been extensively used to evaluate the impact of emotion on duration estimation (Droit-Volet & Gil, 2009), one key aspect of this thesis work. In addition, language is strongly impacted in some of the neurodegenerative diseases studied here (**section 1.6**). In that regard, the temporal bisection task was found particularly suitable as it requires minimal verbal output (choosing "short" or "long" categories experimentally defined during the practice phase), as opposed to a verbal estimation task which would require intact conceptual knowledge of and ability to use temporal labels (seconds, minutes). Finally, as will be explained in **Chapter 2**, the analysis of performance on the temporal bisection task is primarily inspired by visual psychophysics and involves two key measures: the bisection point, which also corresponds to the point of subjective equality (PSE) and can indicate the direction of temporal distortions (over or under estimation of a duration), and the Weber's ratio, which signals discrimination sensitivity for a specific duration range. These measures can provide complementary information on the integrity of timing functions in healthy and pathological ageing.

Studies of mental time travel usually investigate past and future prospection separately. Past prospection in dementia patients has traditionally been assessed using different interview protocols (Graham & Hodges, 1997; Kopelman, 1989; Levine et al., 2002; P. Piolino et al., 2000). The procedure remains largely similar, however, and consists in asking patients to recall personal memories from different periods of their lives (from childhood, teenage years, through to adulthood) using prompt words defined by the experimenter prior to the interview. The collected speech samples are then analysed to identify internal or episodic details (pertaining to the actual re-experiencing of the event), separately from external or semantic details (referring to the facts that are not specific to the event). To assess future prospection, a modified version of the Autobiographical Interview known as the Past-Future task has been used (D. R. Addis et al., 2008). In this task, patients are asked to recall events from the past year and to generate personal events that are likely to happen in a year's time, so as to keep an equal temporal distance.

To assess our general sense of the speed of time, other questionnaires have been developed, the most widely used one being the Subjective Time Questionnaire (STQ) (Wittmann & Lehnhoff, 2005a). It will be further described in **section 3.3.4**.

1.2. Models and neural substrates supporting interval timing in humans

Before considering how subjective time perception may be impacted in dementia, it is first necessary to consider the neural mechanisms that underpin temporal perception. However, how psychological time is encoded in the brain remains a matter of debate. The difficulty in elucidating a biological mechanism lies in the fact that there is no time "organ". In other words, unlike the visual system for example, where neurons localised in the occipital lobe are specialised in processing visual input, there is not one single brain area that processes temporal information. In fact, over the years, research based on lesion as well as structural and functional neuroimaging techniques has shown that many cortical and subcortical areas participate in mediating our sense of time, probably reflecting the diversity of tasks requiring temporal processing (Paton & Buonomano, 2018).

Two distinct views propose to explain these findings. The first is illustrated in state-dependent models which present timing as an intrinsic property of neural ensembles. Using simulations, one of those models demonstrates that durations in the milliseconds range can be encoded directly in the dynamic state of those ensembles through synaptic changes, such that each duration is encoded within its wider context in the form of a "temporal object" (Karmakar & Buonomano, 2007). The second perspective proposes a "core" timing network formed of distributed brain regions that have been consistently implicated in temporal processing independently of the computation at stake, with additional brain areas activated based on the context (Merchant et al., 2013). I will describe more extensively the latter approach since it fits most naturally with the current network paradigm of dementia and therefore helps me anticipate how neurodegenerative diseases may be differentially affected by timing impairment.

In this section, I will focus on interval timing, by first describing its defining psychophysical property, and then explaining the main pacemaker-accumulator models. Those are the most widely adopted by the timing research community and have been improved over the years to incorporate biological evidence, which I will succinctly present. I will also mention a few complementary models originating from experimental findings and which offer a different perspective on interval timing.

1.2.1. Weber's law or the scalar property of interval timing

Similarly to other sensory processes, interval timing follows Weber's law. This law states that the variability associated with estimating the magnitude of a certain stimulus is proportional to the magnitude of that stimulus itself. The temporal equivalent is known as the scalar property (Gibbon et al., 1984; Gibbon et al., 1997) and states that intervals of short durations are measured with less variability compared to intervals of longer durations, which mathematically translates into the ratio of the standard deviation over the corresponding interval being constant. This constant, also called the Weber's fraction or the coefficient of variation, has been demonstrated over several hundreds of milliseconds for a variety of tasks in both animals and humans (Allan & Gibbon, 1991; Gibbon et al., 1997), though later experiments have shown that the scalar property may not hold for longer durations above one second (Grondin, 2014).

1.2.2. Basic information processing models of interval timing

The first information processing models of interval timing date from the early 1960s, the "internal clock model" being the most widely cited (Creelman, 1962; Treisman, 1963). It decomposes temporal processing into three separate stages or modules: clock, memory, and decision-making (**Figure** 1-1). Briefly, the clock is composed of a pacemaker which emits pulses at a regular rate and of an accumulator which accumulates those pulses for the duration of the interval to be timed. The accumulation process is controlled by a switch such that it starts when a salient event is detected. Once the event ends, the clock reading is passed on from the accumulator to the memory module (also known as the reference memory) where it is stored. When the duration of a following event needs to be predicted, its corresponding clock reading is compared to previous readings extracted from the memory module. A decision is then made to indicate the perceived duration of that event.

While the original internal clock model describes the clock stage as the main source of duration estimation variability, the Scalar Expectancy Theory developed by Gibbon defines all three modules as potential sources of errors (Gibbon, 1977; Gibbon & Church, 1984). In the first module, the latency between the onset of an interval to be timed and the switch closure or between the offset of the interval and the switch opening may lead

to counting errors in the accumulator. Errors may also occur when the clock reading is transferred from the accumulator to the memory module. Notably, in several duration discrimination tasks, internal representations of comparison durations were shown to be affected by the trial history, such that previous durations were held in memory long after they were presented (Dyjas et al., 2014; Gamache & Grondin, 2010; Ogden et al., 2008). These errors are considered to largely contribute to the scalar property (illustrated by a memory distribution of time intervals that is wider for long durations compared to shorter ones) and may further impact the decision-stage since accurate estimates must derive from accurate encoding and storage of intervals.

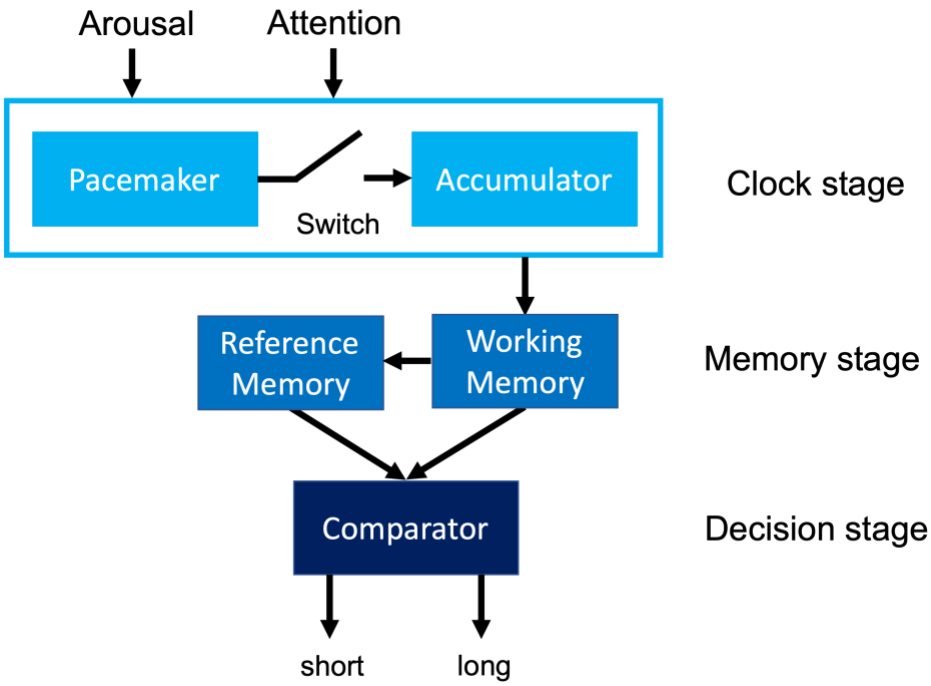


Figure 1-1 Overview of the pacemaker-accumulator model

The figure illustrates the basic components of the pacemaker-accumulator model with its three modules. The clock module is composed of the pacemaker, emitting pulses at a specific rate, and of the accumulator which starts to accumulate those pulses while the intermediate switch is closed. Though the closing and opening of the switch is hypothesised to be governed by attention, the pacemaker pulsing rate is said to depend on physiological arousal levels (see **sections 1.3.1** and **1.3.2**). In the memory stage, the number of pulses accumulated during a to-be-timed interval is transferred to working memory for immediate comparison and to reference memory where all the previously timed durations are stored. In the decision stage, the comparator module uses information from both reference and working memory to make a decision about the current interval (in a temporal bisection task, this decision would be “short” or “long”). Figure adapted from (Droit-Volet & Gil, 2009; Gibbon & Church, 1984).

1.2.3. Striatal Beat Frequency (SBF) model

The Striatal Beat Frequency (SBF) model is the neural instantiation of the Scalar Expectancy Theory (Buhusi & Meck, 2005; Matell & Meck, 2004). It is based on a pacemaker-accumulator model where any given duration is encoded by a specific set of high frequency oscillators selected via Hebbian learning (Miall, 1989). In the SBF model, those oscillators are located in the cortex (each one oscillating at a relatively stable frequency) and project onto medium spiny neurons (MSNs) in the striatum (the input structure of the basal ganglia). These project onto the thalamus via GABAergic projections, which in turn projects back to the cortex, forming multiple parallel cortico-striatal-thalamo-cortical loops.

The SBF model proposes that any given duration is encoded in the strengths of the cortico-striatal synapses as follows (**Figure** 1-2):

i. At the start of the interval to be timed, the cortical oscillators reset their phase and start to oscillate.
ii. They gradually desynchronise and return to their intrinsic oscillating frequency, such that, at the end of the interval, they are not all in their firing phase. A given duration will therefore correspond to a specific oscillatory firing pattern.
iii. MSNs learn to associate these oscillatory patterns with their corresponding durations by acting as coincidence detectors through Hebbian learning. In other words, cortical oscillators that were firing at the offset of the interval will have their synapses strengthened, while the synapses of those that were silent will be weakened. This process is thought to be mediated by dopaminergic input to the MSNs from the substantia nigra pars compacta (SNc).
iv. After repeated exposure to an identical duration, dopaminergic neurons may even signal the start of that interval and MSNs fire when they detect the oscillatory pattern corresponding to that duration. This firing results in the inhibition of the basal ganglia outputs, which in turn disinhibit the thalamus. This triggers cortical excitation which either translates into the generation of a specific (motor) response or feeds back into the cortico-striatal loops.

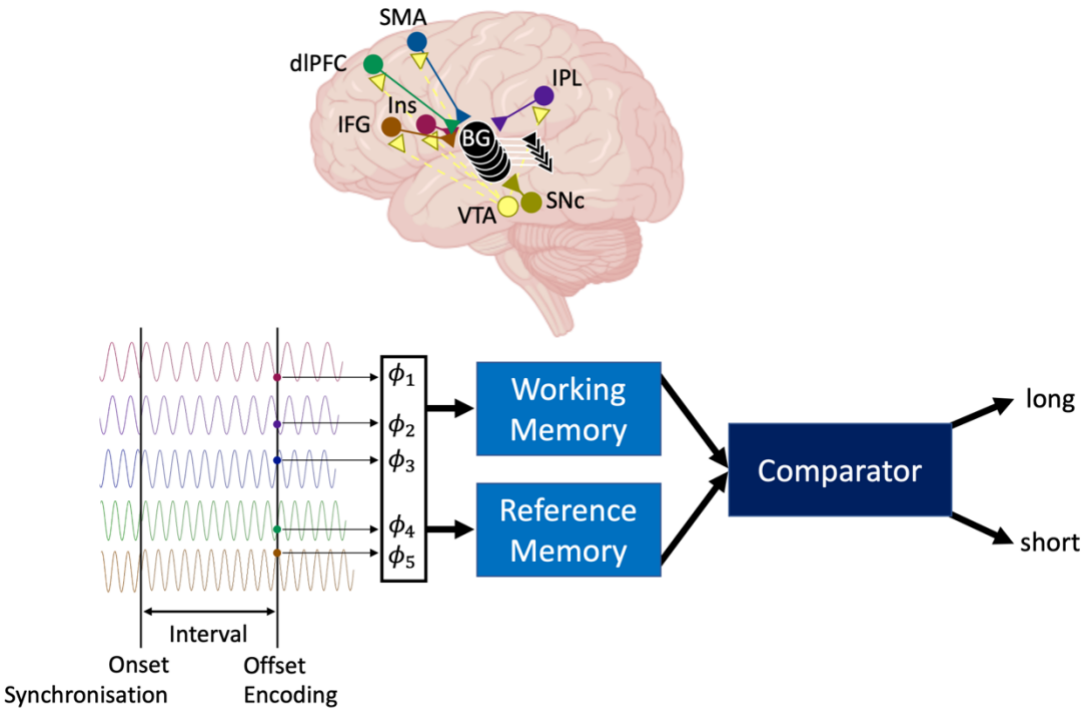


Figure 1-2 Striatal Beat Frequency model and its neural substantiation

According to the Striatal Beat Frequency model, each duration is encoded in the strengths of cortico-striatal synapses and is associated with a unique pattern of oscillatory phases. Indeed, at the start of a to-be-timed interval, dopaminergic neurons, possibly in the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc), excite cortical oscillators which then start to synchronise. Their locations on the figure are approximate but have been chosen to reflect current literature implicating several cortical areas in interval timing, namely the dorsolateral prefrontal cortex (dlPFC), the supplementary motor area (SMA), the inferior frontal gyrus (IFG), the insular cortex (Ins), and the inferior parietal lobule (IPL). Because they each have a specific oscillatory frequency, they gradually desynchronise such that, at the end of the interval, they will be at a different phase (ϕ). Medium spiny neurons in the basal ganglia (BG), shown here in black, then learn to associate this oscillatory phase pattern with the duration. They can later compare this pattern with all previously encoded durations using coincidence detection mechanisms to make a decision relevant to the current task (for example, in a bisection task, the participant must choose between a short and a long response). Figure adapted from (Buhusi & Meck, 2005).

The SBF model can be directly compared to the pacemaker-accumulator models previously described:

- Cortical oscillators act as the pacemaker, where the oscillatory phase pattern generated by those cortical ensembles replaces the pulse count but is likewise associated to a unique duration.

- This association is ensured by Hebbian learning. The reinforcement of a particular pattern of synaptic strengths is equivalent to the clock reading transfer from the accumulator to the reference memory in the pacemaker-accumulator models. The cortico-striatal synapses are therefore central to the memory stage.
- The firing of MSNs represents the decision stage where, based on the decision rule, the action associated with the timed duration can occur.

1.2.4. Current evidence in favour of the SBF model

Over the years, the SBF model has received significant support from experimental evidence in both animals and humans (Coull et al., 2011; Meck et al., 2008). For example, Matell et al showed that about 20% of dorsal striatal neurons shape their firing patterns according to trained durations (Matell et al., 2003). In addition, several pharmacological manipulations have highlighted the influence of dopaminergic inputs on clock speed and of cholinergic inputs on the memory storage (Meck, 1996). Specifically, the administration of dopaminergic agonists (such as methamphetamine or cocaine), resulting in an increased dopamine release, induces motor responses that occur earlier than the offset of an interval, suggesting a faster clock, while the administration of dopamine antagonists (such as haloperidol) has the opposite effect (Cheng et al., 2006; Lake & Meck, 2013; Maricq & Church, 1983; Maricq et al., 1981; Matell et al., 2006). Moreover, the administration of anticholinesterases (thereby inhibiting the degradation of acetylcholine) increases temporal discrimination sensitivity and accelerates the speed of memory storage such that remembered clock readings are shorter than their actual duration, while the administration of a cholinergic antagonist (atropine) has the opposite effect (Meck & Church, 1987).

Numerous functional neuroimaging studies further underlined the importance of the basal ganglia as part of a wider network including several cortical areas, all crucial to interval timing (Coull et al., 2004; Ferrandez et al., 2003; Harrington et al., 2004; Harrington et al., 2010; S. M. Rao et al., 2001). These cortical areas are the dorsolateral prefrontal cortex (dlPFC, often with a right-sided activation) (Lewis & Miall, 2006b), the supplementary motor area (SMA) and pre-SMA (Coull et al., 2004; Macar et al., 2006; Mita et al., 2009), the right inferior frontal gyrus (IFG) (M.J. Hayashi et al., 2013; Livesey

et al., 2007; M. Wiener et al., 2010), the insular cortex (Livesey et al., 2007; Van Wassenhove et al., 2011; Wittmann, Simmons, et al., 2010), as well as the parietal cortex, specifically the inferior parietal lobule (IPL) (Hayashi et al., 2014). However, the precise function of these cortical areas within the SBF model and their potentially differential contributions to the clock/memory/decision-making modules have not been fully elucidated. Both frontal and parietal areas have been suggested to support maintenance of intervals in working memory (Harrington et al., 2004; Lewis & Miall, 2003; Ustun et al., 2017), thereby contributing to decision-making processes (Pouthas et al., 2005; S. M. Rao et al., 2001; van Rijn et al., 2011). However, parietal areas may be more specifically in charge of allocating appropriate attentional resources to time (Ferrandez et al., 2003; M. J. Henry et al., 2015; Lewis & Miall, 2006a). Interestingly though, the parietal cortex has been shown to host neurons processing temporal, numerical, and spatial information in an interactive way, suggesting a broader role in encoding magnitude (M.J. Hayashi et al., 2013; Walsh, 2003). The right IFG has been specifically implicated in categorical decision-making in a duration discrimination task (M.J. Hayashi et al., 2013). Finally, the insular cortex, which represents the physiological condition of the body (interoception) and receives homeostatic, hedonic, and motivational signals from other brain areas, has also been conceptualised as the ideal locus for the emergence of subjective time awareness (Craig, 2009; Wittmann, 2009; Wittmann, Simmons, et al., 2010). This is particularly relevant as internal emotional states have been consistently shown to modulate our perception of time, as we will see later in **section 1.3.2**.

Overall, these findings provide strong evidence in favour of a distributed network supporting subjective time perception.

1.3. Important factors modulating interval timing

Over the years, research has shown that the perceived duration of an interval can be modulated by several factors. First, differences have been highlighted between prospective and retrospective timing tasks, that is whether the subject is aware of their requirement to make a duration judgment (prospective) or not (retrospective). While prospective timing has been shown to largely rely on attentional processes, retrospective timing is mainly dependent on intact memory (Block et al., 2018). Second, the perceived duration of an interval is naturally influenced by its content. For example, a filled interval (a continuous tone for example) is experienced as longer in duration that an empty interval (delimited by onset and offset tones) (Thomas & Brown, 1974). Other stimulus characteristics, such as the modality (auditory, visual, tactile) (Grondin, 2003), its temporal structure (N. K. Horr & M. Di Luca, 2015) and its predictability (Pariyadath & Eagleman, 2007), as well as task characteristics, such as the concurrent presentation of non-temporal information of magnitude (M. J. Hayashi, A. Valli, et al., 2013; M. Zhang et al., 2019) or external social cues (Colonnello et al., 2016), and task relevance (Uusberg et al., 2018; M. Zhang et al., 2019) have all been identified as critical factors. Finally, internal signals strongly influence perceived duration as demonstrated by studies on physiological arousal and emotion (Droit-Volet et al., 2013), agency (Imaizumi & Asai, 2017), and interoceptive awareness (Teghil, Boccia, et al., 2020).

In the next paragraphs, I will focus mostly on prospective timing tasks describing the impact of three factors that are most relevant to my thesis work and that have been extensively studied in timing research, namely attention, emotion, and modality.

1.3.1. Attention

The impact of attention on time perception is well known in everyday living (“A watched kettle never boils”) and is often experimentally assessed using tasks of divided attention where participants are either asked to perform two tasks at the same time (for example estimating the duration of an interval while reading numbers) or by including within an interval of time a distractor selected for its potential to divert attention away from time (for example a visual object that appears at an unexpected time). No matter the method, findings have revealed that timing shares common attentional resources with other

(non-temporal) cognitive tasks and that paying more attention to time lengthens the perceived duration of an interval (Brown, 1997; Burle & Casini, 2001; Macar et al., 1994; Polti et al., 2018; Pouthas & Perbal, 2004; Tse et al., 2004). These findings have been contextualised in the pacemaker-accumulator models by including an attentional "gate" (Zakay & Block, 1996), such that, when paying more attention to time during a specific interval, the gate would open more widely or frequently, which would directly increase the number of pulses accumulated during that interval, thereby lengthening its perceived duration.

1.3.2. Emotion

There is a breadth of literature on the effects of emotion on time perception (Droit-Volet & Gil, 2009; Droit-Volet & Meck, 2007). Most studies employed a temporal bisection task where the perceived duration of faces displaying different emotions was compared against the perceived duration of neutral faces. The most consistent finding is that of facial expressions of anger, fear, threat, or happiness, being perceived as lasting longer than a neutral one (Droit-Volet et al., 2004; Effron et al., 2006; Tipples, 2008, 2011). This effect has often been attributed to changes in physiological arousal, such that an increase in arousal triggers an increase in the pulsing rate of the pacemaker, in turn leading to a higher number of accumulated pulses, thereby prolonging the perceived duration (Treisman, 1963). A dynamic presentation of faces has further been shown to accentuate the difference in perceived duration between emotional (anger and sadness) and neutral conditions, as well as between highly arousing (anger) and less arousing (sadness) emotional expressions (Fayolle & Droit-Volet, 2014). In addition, Angrilli and colleagues showed that negatively valenced pictures are perceived as lasting longer than positively valenced pictures only in a state of high arousal, while a state of low arousal led to opposite results (Angrilli et al., 1997). This modulation has been attributed to an attentional mechanism such that, in a state of low arousal, when a presented stimulus diverts attention away from time, its perceived duration is shortened.

A few studies have been conducted in the auditory domain. For example, a musical melody played in major mode seems to last shorter than if played in minor mode (Droit-Volet et al., 2010). Similarly, words expressed with anger or joy are perceived as shorter than words pronounced with a neutral tone, and the underestimation is accentuated for a joyful tone compared to an angry one (Fallow & Voyer, 2013; Voyer & Reuangrith, 2015). No other complex sounds of differing emotional valence have been used to investigate the impact of emotion on interval timing in the auditory domain. The current findings are in apparent contradiction with results from the visual domain but have mostly been accounted for by attentional mechanisms (as previously described). They may also point to sensory specificities in timing processes.

1.3.3. Modality

The comparison of timing abilities across modalities (often visual against auditory) raises a much broader question on whether the representation of time is essentially amodal (van Wassenhove, 2009). A consistent finding is that auditory stimuli are judged longer than visual stimuli across the sub-second and supra-second scales and are discriminated with higher precision (Grondin, 2003; Penney et al., 2000; Wearden et al., 1998). The lengthened duration of sounds is already experienced by young children and persists into late adulthood (Droit-Volet et al., 2007; Lustig & Meck, 2011). Different theories have been put forward to explain this effect. While Wearden and colleagues argue that auditory stimuli induce an acceleration of the pacemaker rate (Wearden et al., 1998), Penney and colleagues discuss the modality dependent efficiency in maintaining a closed switch (thereby loosing less pulses during the timed interval for auditory compared to visual stimuli) (Penney et al., 2000). Though these two explanations are both compatible with a modality specific internal clock (i.e. with modality specific pacemaker pulsing rate and switch opening/closing properties), other findings highlighting cross-modal interferences with duration judgements suggest the opposite, at least in the milliseconds range (Van Wassenhove et al., 2008).

1.4. Models and neural substrates supporting mental time travel

1.4.1. Defining mental time travel

As stated earlier, mental time travel refers to our ability to both recollect personal memories from the past, thereby stimulating our autobiographical or episodic memory, and use our previous life experiences to imagine future possible scenarios, also known as episodic future thinking (Atance & O'Neill, 2001; Tulving, 2002). These processes have been assumed to rely on the existence of a mental timeline (Bonato et al., 2012b), influenced by previous ideas of a shared neural code for time and space (Walsh, 2003).

Mental time travel can be decomposed into several processes: an initial step where the individual projects themselves in time (self-projection), which is distinct from temporal orientation, a process where they orientate themselves within their new immediate temporal context (e.g., in relation to the events belonging to the past or future bubbles they now find themselves in) (Arzy et al., 2008); a final step consists in the actual mental construction of a reimagined or novel scene (Hassabis et al., 2007). Two additional functions therefore support mental time travel: the ability to evaluate temporal distances (e.g., the amount of time between the present and a specific time in the past or in the future), as well as temporal order (e.g., defining which event happens before the other).

A recent review attempts at describing how different models of time perception may support mental time travel, though they have not been mechanistically validated against experimental evidence (Buhusi et al., 2018). I will now briefly explain how they work, focusing on those I previously mentioned in **section 1.2**. First, according to the general framework of pacemaker-accumulator models, information about the temporal order between two events is encoded together with the duration of both events and can therefore be directly accessed from memory later. Similarly, information about the temporal distance can be deducted from memory by subtracting the respective timestamps associated to both events (Church, 1984; Gibbon & Church, 1990). However, both the Striatal Beat Frequency model and state dependent models currently lack a neurobiological mechanism for mental time travel, as it is not clear how neural activity can encode the unidirectional aspect of time.

Despite the absence of mechanistic models that can biologically explain mental time travel processes, a recent study demonstrated that presenting temporal (rhythmic) cues at the same time as to-be-encoded visual objects improves their recall, probably by directing attentional resources during encoding (Hickey et al., 2020). These results suggest that temporal information naturally embedded in the environment may support and influence the formation as well as the activation of memories.

1.4.2. Associated neural substrates

Current research strongly anchors mental time travel processes to the default-mode network (Buckner & Carroll, 2007; Spreng & Grady, 2009), and more specifically to the hippocampus. Indeed, the hippocampus has initially been implicated in episodic memory formation, by encoding events in their spatiotemporal context as well as representing the temporal sequence of several events (Eichenbaum, 2017b). It has since been involved in the construction of future events by utilising episodic details from previous personal experiences (Schacter & Addis, 2009; Zeidman & Maguire, 2016). Besides the hippocampus, several other brain regions have been identified, each associated with a distinct role. For example, the lateral temporal cortex is activated earlier than the hippocampus, reflecting the chronology of mental time travel processes, namely that self-projection occurs before temporal orientation (Schurr et al., 2018). This is in line with current evidence suggesting that semantic information is also crucial for the representation of the self at different timepoints (M. Irish & Piguet, 2013; Strikwerda-Brown et al., 2019). The medial and rostrolateral prefrontal cortices have also been associated with mental time travel, with a possible role in integrating experienced or imagined events in the ongoing narrative of the self (Demblon et al., 2016; Kurczek et al., 2015). The parietal cortex has been consistently involved as well (Arzy et al., 2008; Demblon et al., 2016; Gauthier & Van Wassenhove, 2016; Nyberg et al., 2010), with a role in remapping temporal experiences from an egocentric perspective by extracting temporal and spatial information encoded in distinct neural networks (Gauthier et al., 2019; Gauthier & Van Wassenhove, 2016; Nyberg et al., 2010).

1.5. Interval timing: from infancy to late adulthood

1.5.1. Timing is not innate, it is a learning experience

When we are born, we do not know what time is, that is we are not conscious of what it is. Like for any other senses, however, our brain learns how to time through our interactions with the external world. Indeed, our environment is full of temporal information, from the basic day/night cycles to the temporal regularities of complex sounds like speech and music. In fact, a study using behavioural conditioning has shown that 1 months old infants are already able to learn temporal information (Brackbill & Fitzgerald, 1972). Using a modified version of the temporal bisection task, another study showed that 4 months old infants are able to categorise durations similarly to adults (Provasi et al., 2010). Overall, these findings suggest that timekeeping mechanisms begin to develop at an early age.

Starting from the ages of 3 to 5 years old, children are then able to time durations that they are familiar with, such as the duration of daily activities (Friedman, 1990a). It is only much later, between the ages of 7 and 10 years old, that children develop an *explicit* sense of time, that is a conscious experience of time supporting overt estimation of different time intervals independent of context (Droit-Volet, 2013; Fraisse, 1982).

1.5.2. Maturation of timing abilities in adulthood

Timing abilities continue to improve throughout childhood, with children estimating intervals more accurately and with less variability (Droit-Volet, 2013). A performance plateau may be reached sometime during adolescence, given that children aged 8-11 years old have been shown to perform similarly to adolescents aged 14-15 years old on a duration discrimination task in the hundreds of milliseconds range (Neufang et al., 2008). However, neural circuits supporting interval timing continue to mature during late adolescence/early adulthood. An fMRI study compared a group of children and adolescents aged between 10 and 16 years old with a group of adults aged between 20 and 53 years old on a duration discrimination task in the seconds range (A. B. Smith et al., 2011). While the two groups performed similarly, significant changes in functional connectivity were identified. Specifically, adults had an increased functional

connectivity between right inferior fronto-striatal and inferior parietal regions, as well as between the right and the left inferior frontal cortices, while adolescents relied more on midline paralimbic, limbic and posterior structures less specialised in timing. These results echo previous findings of maturation of fronto-parietal circuits subserving attentional processes (Booth et al., 2003; Rubia et al., 2010), and may explain the increasing ability to pay attention to time from children to adults.

1.5.3. Aging effects on time perception

The question of whether timing abilities decline with age or whether ageing affects our temporal experience in general has not been fully elucidated. Folk wisdom suggests that "time goes faster as we grow older". This sense of temporal acceleration has been confirmed in several cohorts using surveys where young and older adults were asked to rate on a five-point Likert scale their subjective perception of the speed of time's passing for different periods of the past (Friedman & Janssen, 2010; Janssen et al., 2013; Wittmann & Lehnhoff, 2005a). Older people have been consistently found to judge the last 10 years of their lives as having passed the quickest. However, it is quite difficult to experimentally determine the cognitive mechanisms of that effect. While some suggest that our perception of these long intervals depend on their relative duration in comparison to our entire lifetime, such that a specific time interval will represent a decreasing proportion of our lives as we grow older (Lemlich, 1975), others suggest that this temporal acceleration is due to memory mechanisms. Indeed, retrospective duration judgements are longer when more events are recalled (**section 1.4.1**) and performing routine activities has been shown to shorten the perceived duration of time (Avni-Babad & Ritov, 2003). Therefore, if more memorable and novel events have been experienced and stored in the past compared to the present, they would be more likely recalled, and the duration of the corresponding past period would appear longer than the present.

However, the neural mechanisms supporting interval timing are different from those implicated in retrospective judgments of episodic events (see **sections 1.2.4** and **1.4.2**). Therefore, one cannot assume that healthy ageing will also impact the perception of shorter time intervals. Nevertheless, the brain areas supporting interval timing,

specifically the fronto-striatal circuits as well as thalamic and dopaminergic neurons, have been shown to degrade with age (Bäckman et al., 2010; Bauer et al., 2015; Fama & Sullivan, 2015; Klostermann et al., 2012). This is likely to further contribute to the age-related decline observed in attention, working memory, and processing speed, all crucial to interval timing (McDowd & Shaw, 2000; Zacks et al., 2000).

In fact, an early meta-analysis showed that healthy older adults overestimate and under-produce time intervals (Block et al., 1998). These findings have been attributed to increased attention resulting in a higher number of accumulated ticks during temporal encoding as per information processing models of timing. However, later studies using estimation, production, and self-paced finger-tapping tasks all showed underestimation and overproduction of time intervals, as well as a slower tapping rate, which would be consistent with the hypothesis of a slower internal clock in healthy older adults (Baudouin et al., 2004; M. Carrasco et al., 2001; Craik & Hay, 1999; Perbal et al., 2002; Turgeon et al., 2011; Vanneste et al., 2001). These apparently contradictory findings have been largely accounted for by effects of task complexity and attentional load (Craik & Hay, 1999; Lustig & Meck, 2001; Perbal et al., 2002; Pouthas & Perbal, 2004; Vanneste & Pouthas, 1999), such that healthy older adults would produce shorter time estimates only for complex task or tasks of high attentional load (imposing high demands on divided attention). Further, poorer timing performance in healthy older adults has been attributed to a slower processing speed (Baudouin et al., 2004; Perbal et al., 2002) as well as reduced attentional and working memory capacity (Balci et al., 2009; Baudouin et al., 2019; Baudouin et al., 2006). It is worth noting however that studies using a temporal bisection task or a discrimination task have failed to identify differences in timing performance between healthy young and older adults (Lamotte & Droit-Volet, 2017; McCormack et al., 1999; Rammsayer et al., 1993; Wearden et al., 1997). Separately, healthy older adults have been shown to produce more variable estimates compared to healthy young adults (Block et al., 1998; McCormack et al., 1999; Wearden et al., 1997), suggesting impaired duration discrimination sensitivity in healthy ageing. This is further corroborated by correlations between lower discrimination sensitivity and reduced working memory and attentional capacities (Gagnon et al., 2018; Ogden et al., 2019).

Overall, current evidence tends to suggest that, when observed, impaired time perception in healthy older adults is not a result of true dysfunction in timing mechanisms, but may instead be attributable to domain-general cognitive limitations (Turgeon et al., 2016). To explain previous findings of null age-differences in certain timing tasks, Turgeon and colleagues exploit the notion of “degeneracy”, which refers to the ability of neural circuits to produce similar overall outcomes even when the primary circuits are malfunctioning. Accordingly, healthy older adults may be able to compensate any timing deficits by recruiting additional neural and cognitive resources (Turgeon et al., 2016).

1.6. Time perception in dementia

1.6.1. Improving dementia diagnosis

Ageing is the primary risk factor for dementia, with the number of reported cases doubling every six years of life (Prince et al., 2015). Alarmingly, about 55 million people across the globe currently live with dementia, and with an ageing population steadily increasing, dementia cases are expected to keep rising (WHO, 2017).

Dementia is an umbrella term encompassing several types of neurodegenerative diseases, including Alzheimer's disease (AD) and Frontotemporal dementia (FTD) syndromes which are the focus of this thesis. Although the exact pathophysiological mechanism underlying each type is still unclear and may differ from one type to another, the general model describes abnormal protein accumulation in a specific area of the brain that leads to toxicity and subsequently drives neuronal loss, which gradually spreads to different brain regions as the disease progresses. The identity of the protein(s) involved, the region(s) of atrophy, and the associated symptoms all contribute to the definition of a diagnostic framework for each dementia type (Dubois et al., 2014; M.L. Gorno-Tempini et al., 2011; Rascovsky et al., 2011). However, there is no exact correspondence across those three levels (molecular, neuronal network, behaviour) and as such, many cases remain undiagnosed or misdiagnosed (Dubois et al., 2014; H. Sivasathiaseelan et al., 2019).

Efforts to expand and deepen our knowledge of these neurodegenerative diseases should therefore continue. In that regard, investigating subjective time perception, specifically in AD and FTD, would offer a novel window on disease neurobiology and an improved understanding of the associated clinical symptoms, as will be discussed in more detail in **section 1.7**. In the upcoming sections, I will first describe the clinical symptomatology and brain atrophy patterns associated with AD and FTD syndromes, with a view to inform hypotheses regarding subjective time perception changes which can be expected in these diseases.

1.6.2. Alzheimer's disease

1.6.2.1. Typical amnestic variant (AD)

Alzheimer's disease is the most common form of dementia, accounting for 60 to 70% of adults developing dementia over the age of 65 years old worldwide (WHO, 2017). Patients diagnosed with AD primarily present with episodic memory impairment (Dubois et al., 2014), often in addition to reduced spatial navigational skills, attentional deficits, executive dysfunction, and linguistic impairment (Weintraub et al., 2012). Neuropsychiatric symptoms, such as anxiety and depression, are also prevalent (Mendez, 2021). Altogether, this symptomatology relentlessly impacts the performance of daily living tasks, increasing caregiver burden.

Brain atrophy in AD patients is first localised in the hippocampus and entorhinal cortex (**Figure** 1-3) and later spreads to the lateral temporal, parietal and frontal lobes, in areas that form part of a core "default-mode network" and that are key to the cognitive functions highlighted above (Seeley et al., 2009).

In earlier stages, however, laboratory investigation remains instrumental in the diagnosis, with an increased total tau to beta-amyloid 1-42 ratio and raised phospho-tau in the cerebrospinal fluid (CSF) and amyloid deposition on ligand PET brain imaging indicative of AD pathology (Dubois et al., 2014).

1.6.2.2. Logopenic variant primary progressive aphasia (lvPPA)

Logopenic variant primary progressive aphasia (lvPPA) is classified as the language variant of AD (Dubois et al., 2014) but can also be placed under the umbrella of primary progressive aphasias (PPA) (M.L. Gorno-Tempini et al., 2011; Marshall, Hardy, Volkmer, et al., 2018). This is because despite prominent language difficulties, the brain atrophy profile is similar to memory-led AD and most cases have an underlying AD pathology.

The defining linguistic deficits in lvPPA are word-finding difficulties and pauses in speech, which are often accompanied by phonological errors, though grammar remains intact (Marshall, Hardy, Volkmer, et al., 2018). lvPPA patients characteristically exhibit reduced phonological working memory, which manifests as difficulties in repeating phrases as

opposed to single words and polysyllabic words compared to shorter words (Leyton et al., 2014; Meyer et al., 2015).

Clinical and neuropsychological examination of lvPPA reveals additional features that are more typical of AD: impaired episodic memory (Mendez, Monserratt, et al., 2019; Piguet et al., 2015), reduced auditory verbal working memory (Giannini et al., 2017), impaired visuospatial awareness (Meyer et al., 2015; Watson et al., 2018), as well as deficits in attention and arithmetic skills (Kamath et al., 2020). Neuropsychiatric symptoms, such as anxiety, apathy, and depression have also been reported (Magnin et al., 2013; J. D. Rohrer & Warren, 2010; Singh et al., 2015).

The associated brain atrophy profile presents as an asymmetric atrophy involving the left temporo-parietal junction, which can be identified as a widening of the left Sylvian fissure on a coronal T1 MRI scan (**Figure** 1-3) (M. L. Gorno-Tempini et al., 2008; J. D. Rohrer, G. R. Ridgway, et al., 2010). In contrast to typical AD, the hippocampi may be relatively spared, especially in the early stages (Phillips et al., 2018; Win et al., 2017), and atrophy tends to spread anteriorly as the disease progresses, although with considerable individual variation (M. L. Gorno-Tempini et al., 2008; J. D. Rohrer et al., 2013).

Analysis of CSF biomarkers is often indicative of underlying AD pathology (M. L. Henry & Gorno-Tempini, 2010; Mesulman et al., 2008; Spinelli et al., 2017), though not all lvPPA patients show AD positive biomarkers (Matías-Guiu et al., 2015; Norise et al., 2019).

1.6.3. Frontotemporal dementia syndromes

Frontotemporal dementia (FTD) is the second major form of young onset dementia after Alzheimer's disease (Ratnavalli et al., 2002), with typical age of onset falling in the sixth decade of life, although clinical signs can be detected any time between the third and the ninth decades (J. D. Warren, Rohrer, & Rossor, 2013). It is much rarer than AD, with a prevalence of 11/100,000 and incidence of 1.6/100,000 (Coyle-Gilchrist et al., 2016), though it is likely that many cases remain undiagnosed (Leroy et al., 2021).

Three syndromic FTD groups have been defined, all broadly targeting the frontal and temporal lobes but marked by their distinct clinical presentation at early stages, as well as by their neuroanatomical and pathological profiles (H. Sivasathiaseelan et al., 2019).

The most common FTD syndrome is known as behavioural variant FTD (bvFTD) (Hogan et al., 2016; Leroy et al., 2021), followed by semantic variant primary progressive aphasia (svPPA) and non-fluent variant primary progressive aphasia (nfvPPA), which are also both classified under PPA due to their language dominant profiles of cognitive deficit (Marshall, Hardy, Volkmer, et al., 2018).

The complexity of FTD lies in its heterogeneity and the extensive overlap between the different molecular histopathology profiles and clinico-anatomical phenotypes. Most cases are due to tau or transactive response DNA binding protein 43 (TDP-43) pathology, and a minority of cases to fused-in-sarcoma (FUS) pathology (J.D. Rohrer et al., 2011). FTD also has an important genetic component, bvFTD being the most heritable syndrome and svPPA the least (J. D. Rohrer et al., 2009). The most common FTD-causing mutations have been found in the microtubule associated protein tau (MAPT) gene, the progranulin (GRN) gene, as well as abnormal expansions of the hexanucleotide repeat on the open reading frame of chromosome 9 (C9orf72).

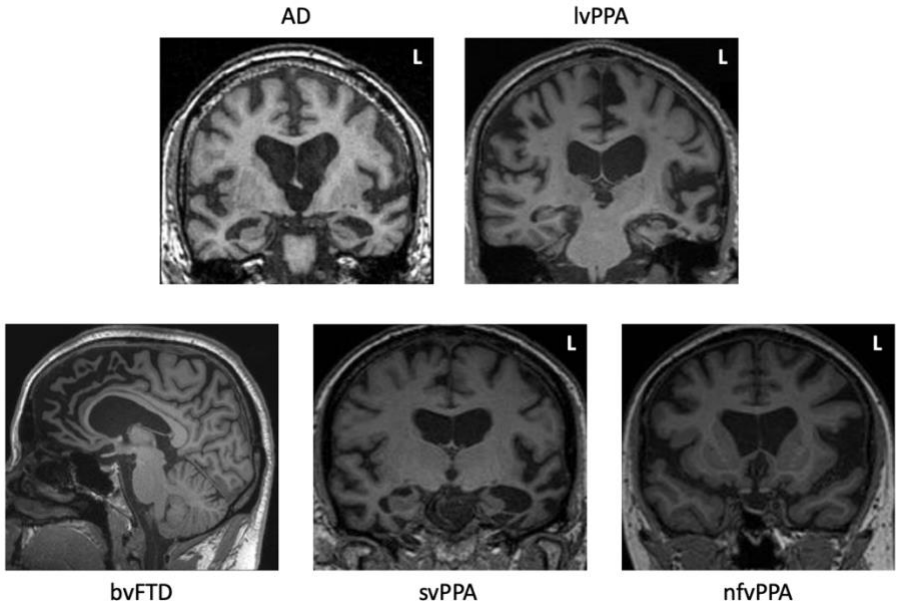


Figure 1-3 Atrophy profiles of in AD and FTD

The figure shows representative T1-weighted brain magnetic resonance imaging (MRI) sections from patients diagnosed with typical AD and logopenic variant of AD (lvPPA) (top), and canonical syndromes of FTD (bellow), namely behavioural variant FTD (bvFTD), semantic variant (svPPA), and non-fluent variant PPA (nfvPPA). Coronal sections display the left hemisphere on the right (indicated with an "L").

1.6.3.1. Behavioural variant frontotemporal dementia (bvFTD)

Behavioural variant FTD is primarily characterised by a socio-emotional dysfunction involving symptoms such as disinhibition and impulsivity, apathy, reduced empathy, stereotypical or ritualistic behaviours and dietary changes (sweet tooth, or craving for sweet food) (Nyatsanza et al., 2003; Radakovic et al., 2021; Rascovsky et al., 2011), which can all be framed as disrupted goal-directed behaviours (Wong et al., 2018). The predominance of behavioural disturbances makes diagnosis challenging, and patients may be misdiagnosed with a psychiatric condition before reaching the final diagnosis of bvFTD.

Executive dysfunction is also significant and strongly impacts the execution of daily-living tasks (Moheb et al., 2017), while episodic memory and visuospatial functions are often intact (Rascovsky et al., 2011). Further, bvFTD patients show limited insight into their disease, thereby increasing care burden (Guger et al., 2021).

Brain MRI shows predominantly frontal and/or anterior temporal lobe atrophy of widely variable distribution and severity (**Figure** 1-3) (H. Sivasathiaseelan et al., 2019). The bvFTD histopathological profile corresponds to the FTD one, which has been described in the previous section (J. D. Rohrer et al., 2009; J.D. Rohrer et al., 2011).

1.6.3.2. Semantic variant primary progressive aphasia (svPPA)

As the diagnostic label suggests, the semantic variant of PPA is uniquely characterised by insidious disintegration of the semantic memory system which stores word, object, and concept knowledge (M.L. Gorno-Tempini et al., 2011; Marshall, Hardy, Volkmer, et al., 2018). In the early disease stages, svPPA patients usually present with progressive erosion of vocabulary and word comprehension. As the disease progresses, additional impairment in visual recognition of familiar faces (prosopagnosia) and/or visual objects (visual agnosia) supervenes. Prosody and word articulation are preserved however, resulting in a fluent, even garrulous speech, which often sounds circumlocutory.

In striking contrast to their semantic deficits, svPPA patients often show an increased interest in numbers and puzzles, such as Sudoku, at least in the early stages (Green & Patterson, 2009; Midorikawa et al., 2017; Papagno et al., 2013; H. Sivasathiaseelan et

al., 2021). Similarly to bvFTD patients, svPPA patients often exhibit ritualistic, obsessional and stereotypical behaviours (Nyatsanza et al., 2003; Snowden et al., 2001). Emotional disturbances are also significant. Deficits in emotion recognition are associated with abnormal physiological reactivity and interoceptive awareness (Bertoux et al., 2020; Hua et al., 2019; Marshall, Hardy, Russell, et al., 2018; Marshall et al., 2017). Neuropsychiatric symptoms, such as anxiety, depression, apathy, and anhedonia, are also common (J. D. Rohrer & Warren, 2010; Shaw et al., 2021; Wong et al., 2020). Tragically, svPPA patients often develop suicidal thoughts, which can be exacerbated by depressive symptoms and retained insight (Sabodash et al., 2013). svPPA patients' inability to project themselves into the future (**section 0**) has further been hypothesised to encourage their suicidal behaviour (Hsiao et al., 2013).

The corresponding MRI profile is highly consistent, with asymmetric focal atrophy predominantly affecting the left anterior temporal lobe (**Figure** 1-3), including the amygdala and anterior hippocampus (Chan et al., 2001; Huang et al., 2020). Over time, atrophy spreads more posteriorly in the temporal lobe and anteriorly in the frontal lobe, around the inferior frontal gyrus and orbitofrontal cortex as well as the contralateral temporal lobe (J. D. Rohrer et al., 2008). Pathology is also homogeneous, as most cases have an underlying TDP type C pathology (H. Sivasathiaseelan et al., 2019).

1.6.3.3. Non-fluent variant primary progressive aphasia (nfvPPA)

Non-fluent variant primary progressive aphasia (nfvPPA) is clinically characterised by slow and effortful speech, frequently punctuated with speech sound errors (M.L. Gorno-Tempini et al., 2011; Marshall, Hardy, Volkmer, et al., 2018; H. Sivasathiaseelan et al., 2019). These mispronunciations are accentuated with word length and either correspond to phonemic or articulation errors. This linguistic phenotype is largely attributed to difficulties in executing speech motor commands, which also relate to patients' difficulties with orofacial movements and swallowing. Non-fluent speech is often associated with incorrect grammar (usually manifesting as missing function words) and syntax comprehension is also impaired. While general intellect remains usually intact, most nfvPPA patients also show some degree of executive dysfunction (J. D. Rohrer, M. N. Rossor, et al., 2010). Apathy and depressive symptoms (exacerbated by

preserved insight) are another area of concern in nfvPPA (Quang et al., 2021; J. D. Rohrer & Warren, 2010; Wong et al., 2020).

Brain MRI in nfvPPA patients reveals asymmetric atrophy of the inferior frontal gyrus, insular cortex, and anterior superior temporal gyrus, illustrated by the widening of the left Sylvian fissure on a coronal view (**Figure** 1-3). However, there is wide individual variation in atrophy patterns (J. D. Rohrer, D. Paviour, et al., 2010).

The underlying pathology in nfvPPA is heterogenous. Most cases, especially those with additional parkinsonian features, are tauopathies, though some patients have a TDP-43 pathology (Graff-Radford et al., 2012; J.D. Rohrer et al., 2011; Spinelli et al., 2017).

1.6.4. Known time perception abnormalities in targeted diseases

1.6.4.1. AD and lvPPA

Behavioural evidence

i. Clinical observations

Episodic memory impairment is a cardinal feature of AD (Dubois et al., 2014). Time disorientation is another typical AD symptom (Grewal, 1995). It refers to patients' inability to locate themselves in time and is typically assessed using the Mini-Mental State Examination (MMSE) which incorporates five questions where patients are asked to provide the year, the season, the month, the day of the week, and the precise date at the time of examination (Folstein et al., 1975). Notably, the MMSE is frequently used in clinical and research settings to measure disease severity in dementia patients.

ii. **Motor timing**

Evidence accumulated so far indicates motor timing deficits in AD (M. C. Carrasco et al., 2000; El Haj et al., 2014; Henley et al., 2014; Nichelli et al., 1993). One study used a production task and showed that AD patients produced longer and more variable estimates at the scale of seconds compared to healthy age-matched controls (M. C. Carrasco et al., 2000). In another study, a larger AD cohort also reproduced estimates of one-second-long intervals that were longer and more variable than the healthy control group (Nichelli et al., 1993). In both studies, the higher variability in temporal estimates in AD has been attributed to attentional deficits, which may have been particularly apparent considering prospective timing relies on attention (Block et al., 2018; Zakay &

Block, 2004). In addition, El Haj and colleagues have shown that when instructed to retrospectively reproduce the duration of 15-seconds-long intervals during which they either fixated a cross (low attentional load) or performed a Stroop interference task (high attentional load), AD patients under-reproduced those intervals in the high compared to low attentional load condition, more so than did healthy older adults, again reflecting their attentional deficits (El Haj et al., 2014). Moreover, the difference in direction (under-reproduction instead of over-reproduction as shown by Nichelli and colleagues) may be attributed to the use of a retrospective timing task, which, unlike for prospective timing tasks, depends on memory processes (Block et al., 2018), another domain of difficulty in AD.

Another important aspect of motor timing is rhythm. In the study by Henley et al, patients performed a finger-tapping task, by either following an external trigger or generating their own pace (Henley et al., 2014). Here, the AD group performed similarly to controls, suggesting preserved processing of rhythmic auditory stimuli in AD.

iii. Interval timing

Several studies have investigated time perception over short intervals in AD patients, but with varied methodology. An initial study in 1993 by Nichelli et al found that AD patients produced verbal temporal estimates that were, on average, similar to healthy age-matched control participants, but with a significantly higher variability. However, later studies have yielded mixed results on this specific aspect of temporal processing (**Table** 1-2). While some revealed similar performance between AD patients and control participants on a group level (Caselli et al., 2009; Rueda & Schmitter-Edgecombe, 2009), others found significant differences, with some showing AD patients overestimate the duration of intervals compared to controls (Barabassy et al., 2007; Papagno et al., 2004; Ranjbar Pouya et al., 2015) and one the opposite (El Haj et al., 2013). However, this is not surprising, as those studies used a diverse range of experimental designs, which differed in procedures (verbal estimation vs temporal bisection), modality (visual vs auditory), interval type (empty vs filled) and interval content (single vs dual tasks, to evaluate attentional effects). All these factors have been shown to modulate time perception in healthy controls (Bratzke & Ulrich, 2019; Droit-Volet, Wearden, et al., 2015; N.K. Horr & M. Di Luca, 2015; Lamotte et al., 2012). Of particular relevance is the

impact of attention on timing, considering attentional deficits are another hallmark of AD. Interestingly, attentional effects have been established both in the perceptual and motor domains (El Haj et al., 2014; Papagno et al., 2004). Overall, what is mostly consistent across studies is the variability of performance in AD cohorts, suggesting a lower discrimination sensitivity compared to the healthy control group (although Caselli and colleagues have shown similar discrimination sensitivity between AD patients and control participants in the supra-second range (Caselli et al., 2009)). This is further consistent with the finding that lower attentional and working memory capacities are associated with reduced discrimination sensitivity in healthy participants (Gagnon et al., 2018; Ogden et al., 2019).

To date, only one study assessed temporal performance in lvPPA (Grube et al., 2016) and showed that lvPPA patients were relatively intact on the perceptual processing of tone sequences. These findings were surprising given their deficits in phonological working memory but suggest that phonological working memory may be distinguishable from non-verbal auditory working memory. However, findings should be taken with precaution given the small sample size for this study (n=4).

iv. Mental time travel

Regardless of the interview methodology, most studies conducted so far revealed deficits in recollecting past personal events (i.e., with fewer details) in AD patients compared to healthy older adults. However, whether this recollection disability follows a temporal gradient is much less clear. Some studies showed that AD patients recall more episodic details for events that are more remote (e.g., they remember where they spent their childhood but not where they went on their last holiday) (Eustache et al., 2004; Graham & Hodges, 1997; Greene et al., 1995; Kirk & Berntsen, 2018; Leyhe et al., 2009; Muller et al., 2013; Nestor et al., 2002; Seidl et al., 2011), sometimes to the extent that the number of episodic details produced by AD patients is comparable to controls for the past period related to early years of life (M. Irish et al., 2011a; Ivanoiu et al., 2006). However, others fail to show a difference (D.R. Addis & Tippett, 2004; Barnabe et al., 2012; Hou et al., 2005; Meeter et al., 2006; Nestor et al., 2002; Philippi et al., 2015; P. Piolino et al., 2003; Thomann et al., 2012). This inconsistency is likely due to a combination of differences in interviewing and scoring methodologies.

More recently, several studies have revealed that AD patients may have similar difficulties in projecting themselves into the future, using the Past-Future task described earlier. If we consider that future projection first involves rehearsing past memories and then choosing certain elements to build new scenarios, it is perhaps not surprising that future projection is also impaired in AD (D. R. Addis et al., 2009; El Haj et al., 2015a, 2015b; M. Irish et al., 2012a; M. Irish et al., 2012b; M. Irish et al., 2016; M. Irish et al., 2013). However, these studies have not consistently shown a difference in performance between future and past projections.

Neuroanatomical evidence

The neuroanatomical signature of temporal processing deficits observed in AD has not been formally established, though the hippocampus is an obvious candidate (El Haj & Kapogiannis, 2016), given its primary role in the temporal encoding of events (Eichenbaum, 2014). The hippocampus has also been implicated in future episodic thinking, although the associations was determined across a combined cohort of AD, bvFTD and svPPA patients (M. Irish et al., 2016).

Although the hippocampus is relatively spared in lvPPA, it can be atrophied, especially in later stages (Migliaccio et al., 2009). Temporal processing difficulties in lvPPA are therefore also likely. In addition, while mental time travel has not been studied in lvPPA, its associated atrophy profile (including the precuneus and the posterior cingulate cortex, both previously implicated in episodic memory recall (Poppenk et al., 2010; Spreng et al., 2008)) suggests that lvPPA patients would experience mental time travel difficulties that are similar to those observed in patients with typical AD.

1.6.4.2. FTD

Behavioural evidence

- **Clinical observations**

Temporal processing abilities have not traditionally been the focus of diagnosis in FTD. However, abnormal behaviours related to the perception of time form an integral part of the symptom profile in bvFTD and svPPA (H. Sivasathiaseelan et al., 2019; J. D. Warren, Rohrer, & Rossor, 2013). Those manifest as clockwatching, which refers to patients becoming fixated with time and punctuality, manifesting as anxiety about missed appointments and/or asking for the time frequently; and timing rigidity, which refers to patients being very strict about any appointment times and routines (Nonaka et al., 2014b; Nyatsanza et al., 2003; Snowden et al., 2001).

- **Motor timing**

Although not strictly relevant to this thesis, motor timing has also been assessed in bvFTD. In the previous single case study, the patient produced shorter estimates compared to healthy controls but did not differ from healthy controls on the reproduction task (M Wiener & Coslett, 2008), which is still consistent with a faster internal clock or a disrupted reference memory. A second study compared performance of FTD and AD patients on both externally paced and self-triggered finger-tapping tasks (Henley et al., 2014). bvFTD patients performed similarly but with a significantly higher variability compared to healthy controls on both tasks, replicating the finding from the single case study. However, svPPA and nfvPPA patients were unimpaired. Higher variability on the externally paced finger-tapping task was correlated with performance on the Stroop task, a neuropsychological test measuring executive function, for both bvFTD and healthy controls, suggesting that the pattern of performance in the bvFTD group may not have been solely due to timing deficits per se.

- **Interval timing**

To date, only one study has looked at interval timing in bvFTD (**Table** 1-2). It is a single-case study of a patient diagnosed with probable bvFTD, whose abilities in perceptual timing at the sub second and supra second scales were assessed using a verbal estimation and a duration discrimination task (M Wiener & Coslett, 2008). Compared to

healthy aged-matched controls, the patient perceived the duration of intervals as longer, which the authors attributed to either a faster "internal clock" or impaired memory processes. Indeed, following the internal clock model (**section 1.2.2**), a pacemaker that produces beats at a faster rate would result in an increased number of accumulated beats, which would lead to overestimation of the time interval. On the other hand, if the reference interval corresponding to the duration to be timed is shorter than its physical duration, the duration to be timed would also be overestimated (for example, consider an interval of one second during which 30 beats have been accumulated; if in reference memory, one second actually corresponds to 15 beats and not 30, the resulting estimate would be two seconds). The bvFTD patient's performance in duration discrimination at both sub and supra second scales did not differ from healthy controls, however, which would still be compatible with the two hypotheses put forward, as any disruption in pacemaker or memory processes would be applied for the two intervals to be compared, provided the decision-making processes are preserved.

Another study compared performance of the three PPA subtypes (svPPA, nfvPPA, and lvPPA) across different discrimination tasks of single intervals and rhythmic sequences (Grube et al., 2016). While the discrimination of several milliseconds long intervals was comparable to healthy controls on a group level for all PPA subtypes, the perceptual discrimination of rhythmic sequences was impaired in both nfvPPA and svPPA, with nfvPPA patients being particularly affected. This was evident even after taking into account differences in executive function. The authors suggested that the pattern of deficits observed in nfvPPA result from a more general impairment of the perception of auditory objects, probably due to a defective auditory working memory. They further proposed that these observations are compatible with their motor speech impairment, as auditory perceptual processing (particularly in regards to temporal structures of speech) has been shown to support normal speech production (Grube et al., 2013).

Finally, although discrimination sensitivity has not been assessed in FTD so far, it is possible that discrimination sensitivity is particularly lower for bvFTD patients compared to healthy participants considering their general cognitive impairment profile (deficits in attention, executive function, working memory) resulting from bilateral frontal lobe atrophy and that reduced working memory capacity and attentional resources have

been shown to correlate with lower discrimination sensitivity in healthy participants (Gagnon et al., 2018; Ogden et al., 2019).

- **Mental time travel**

The ability to project oneself in the past has also been assessed in FTD (mainly bvFTD and svPPA patients), often in conjunction with AD patients. Despite the use of different interview protocols, findings were quite consistent and revealed increased difficulties with past projection compared to healthy controls, irrespective of the temporal distance (e.g., of how far in the past they had to mentally travel) (Graham & Hodges, 1997; Hou et al., 2005; M. Irish et al., 2011a; Matuszewski et al., 2006; Nestor et al., 2002; P. Piolino et al., 2003).

The ability to project oneself in the future has been investigated more recently in FTD. Using the Past-future task, Irish et al found that both bvFTD and svPPA patients were impaired in future projection compared to healthy controls, and more so than they were for past projection (M. Irish et al., 2012a; M. Irish et al., 2012b; M. Irish et al., 2016; M. Irish et al., 2013).

Neuroanatomical evidence

There has been no formal assessment of the neuroanatomical substrates associated with interval timing deficits in FTD. However, given that the atrophy profiles of the different FTD syndromes overlap with the neural networks previously involved in timing (**section 1.2.4**), those different FTD syndromes are likely to exhibit temporal symptoms. Specifically, the bvFTD atrophy profile includes the fronto-striatal regions (Bertoux et al., 2015; Landin-Romero et al., 2017), which have been thought to orchestrate interval timing in the brain according to the Striatal Beat Frequency model (Buhusi & Meck, 2005). Another area of interest is the insular cortex: it has also been implicated in subjective time perception (Craig, 2009; Wittmann, Simmons, et al., 2010) and is atrophied to a varying degree in bvFTD and nfvPPA patients (Marshall, Hardy, Volkmer, et al., 2018; R. J. Perry et al., 2006). nfvPPA is also characterised by atrophy in the left inferior frontal gyrus, another region that has been consistently associated with timing, although more often on the right (M. Wiener et al., 2010). Finally, the characteristic atrophy profile of svPPA (damage of anterior temporal lobes and hippocampus with

relative spearing of subcortical structures such as the basal ganglia) likely explains the symptoms of impaired mental time travel described previously, and even suggests that timing abilities of short durations may be relatively spared in svPPA patients.

Neural substrates associated to past projection have not been separately assessed in the three FTD subgroups; rather they have been determined across a wider dementia cohort of AD, bvFTD and svPPA patients (M. Irish, Hornberger, et al., 2014). Those which were common across different past periods (recent and remote) were the hippocampus, the medial prefrontal and frontopolar cortices, while the posterior cingulate cortex was exclusively related to recent and the anterior temporal cortices to remote recollection of past personal events. The hippocampus (specifically the right) was additionally associated with episodic future thinking (M. Irish et al., 2016).

Table 1-2 Review of experimental studies looking at perceptual and motor aspects of temporal processing in AD and FTD patients

	Task type	Stimuli type	Timescale range	Performance					No. patients	Papers
				bvFTD	svPPA	nfvPPA	lvPPA	AD		
Perceptual	**Verbal estimation**	Read digits + finger-tapping at 1s pace	5, 10, 20, 40 **s**					*	15	Nichelli et al, 1993
		Empty intervals (baseline) Filled intervals (attentional task / digit span)	15, 50 **s**					>*	21	Papagno et al, 2004
		Moving object	< 10 **s**					>*	42	Barabassy et al, 2007
		250Hz pure tone 4x4 cm red square	2, 4, 6, 8, 10, 12 **s**	>					1	Wiener and Coslett, 2008
		Read digits	10, 25, 45, 60 **s**					*	17	Rueda & Schmitter-Edgecombe, 2009
		Verbal categorical tasks Filling connected squares Reading text/numbers	30, 60, 90, 120 **s**					<	16	El Haj et al, 2013
		Rotation time of virtual building	40 **s**					>*	10	Ranjbar Pouya et al, 2015
	Temporal bisection	Auditory onset/offset (900Hz tone) White square	100 - 600 **ms** 1 - 3 **s**						12	Caselli et al, 2009
	Interval discrimination	Red squares (standard vs comparison duration)	300 and 600 **ms** 2 and 8 **s**						1	Wiener and Coslett, 2008
		Auditory onset/offset (500 Hz tone)	300, 360, 420, 480, 560, 600 **ms**						8 / 6 / 4	Grube et al, 2016
	Rhythm discrimination	Pure tone sequences	180 - 220 **ms** or 300 - 600 **ms** (inter-onset-interval)						8 / 6 / 4	Grube et al, 2016

Motor	**Production**	Empty intervals	5, 10, 25 **s**					>	8	Carrasco et al, 2000
		250Hz pure tone 4x4 cm red square	2, 4, 6, 8, 10, 12 **s**	<					1	Wiener and Coslett, 2008
	Reproduction	Partly empty intervals	1 s					>*	15	Nichelli et al, 1993
		4x4 cm red square	2, 4, 6, 8, 10, 12 **s**	*					1	Wiener and Coslett, 2008
		Fixate cross Stroop task	15 **s**					<	17	El Haj et al, 2014
	Rhythm	Finger-tapping (self-paced; auditory and visual)	400 ms intervals	*					1	Wiener and Coslett, 2008
		Finger-tapping (externally triggered vs self-paced; auditory only)	1500 ms intervals	*					20 / 11 / 4 / 8	Henley et al, 2014

This table provides a summary of the paradigm characteristics and main findings for each experimental study identified. Results indicate statistically significant differences of average performance between the corresponding patient group and a healthy age-matched control group. For most experiments, performance was measured using accuracy (how close is the estimated/produced/reproduced interval compared to the physical time); except for the temporal bisection task, where performance was indicated by the temporal bisection point, and for the finger-tapping task, by the drift in inter-response interval (increase or decrease in tapping pace compared to experimentally defined pace). Colour code for performance: cyan, statistically non-significant difference in performance compared to controls; mustard, statistically significant difference in performance compared to controls; grey, group not tested. Symbol code for performance: <, shorter than target interval; >, longer than target interval; *, large variability. Abbreviations: cm, centimetres; Hz, Hertz; No., number; ms, milliseconds; s, seconds.

1.7. Rationale and hypotheses

1.7.1. Motivations for the present work

Time is ubiquitous and subserves a significant number of functions important to everyday living. Accumulated evidence demonstrates that the perception of time relies on several core cognitive functions, such as working memory, attention, executive function and decision-making, which are all susceptible to healthy ageing (Matthews & Meck, 2016; Turgeon et al., 2016). Time perception is therefore an ideal candidate for tracking cognitive dysfunction towards the end of life (Balci et al., 2009).

Notably, healthy ageing is accompanied by a sense of temporal acceleration (Friedman & Janssen, 2010; Wittmann & Lehnhoff, 2005a). Most studies also highlight differences in the magnitude and variability of temporal estimates between healthy older adults and healthy young adults, especially when cognitive demands are high (Block et al., 1998; Craik & Hay, 1999; Perbal et al., 2002; Pouthas & Perbal, 2004). Moreover, time disorientation has been established as a risk factor for dementia (Dumurgier et al., 2016), and is included in the Mini Mental State Examination (MMSE), a questionnaire used to evaluate disease severity in dementia (Folstein et al., 1975). As described earlier, evidence in major AD and FTD syndromes remains scarce, but suggests inaccurate and less sensitive internal timekeeping systems (El Haj & Kapogiannis, 2016; M Wiener & Coslett, 2008).

Considering time perception involves a distributed network of brain areas differentially affected in those neurodegenerative diseases, AD and FTD patients are likely to present with distinct temporal profiles. For example, the impact of emotion on duration estimation is a widely studied question in psychological time research (Droit-Volet & Gil, 2009; Droit-Volet & Meck, 2007). Given that emotional processing difficulties are particularly prominent in FTD (Fletcher, Downey, et al., 2015; Kumfor & Piguet, 2012; Marshall, Hardy, Allen, et al., 2018; Marshall, Hardy, Russell, et al., 2018), FTD patients are more likely than AD patients to show a difference in the emotional modulation of perceived duration compared to healthy older adults. Moreover, the effect of semantic characteristics on time perception, for example the difference in perceived duration between environmental and human sounds, has not yet been investigated in the healthy

population, but has particular resonance in semantic variant PPA given their physiological and cognitive deficits in the identification of nonverbal sounds (Fletcher et al., 2016; Golden et al., 2015; Muhammed et al., 2018).

Overall, examining subjective time perception in dementia would offer a novel window on disease neurobiology and improve understanding of clinical symptoms. Considering its importance in everyday living, it would further help inform adequate care strategies for patients, especially by designing experiments with a higher potential of translation to everyday living.

1.7.2. Key aims and experimental hypotheses

Motivated by the gap in our current understanding of how both healthy and pathological ageing may impact psychological time perception, the overarching rationale for this thesis is to explore and compare timing abilities relevant to everyday living between healthy young and older adults, as well as patients diagnosed with AD and FTD syndromes, using questionnaires and a classical interval timing paradigm, with the following core aims:

1. To determine the extent to which the emotional value and semantic characteristics of an auditory object may affect its perceived duration in healthy participants
2. To evaluate the impact of healthy and pathological ageing on subjective time perception
3. To identify the neuroanatomical correlates of subjective time perception to draw insights into the neural mechanisms underlying temporal dysfunction in AD and FTD

In the following pages, I will outline the aims and hypotheses motivating the experiments described in each thesis chapter.

Chapter 3: Subjective time perception in healthy ageing: effects of emotional valence and semantic characteristics

Overarching question

Does healthy ageing impact the modulation of perceived duration and discrimination sensitivity of short auditory intervals by their emotional valence and semantic characteristics?

Aims

1. Evaluate and compare the effects of emotional valence (pleasant vs unpleasant) and semantic characteristics (environmental vs human) on the perceived duration and discrimination sensitivity of short auditory intervals in healthy young adults
2. Compare performance of healthy young adults against healthy older adults
3. Explore the relation between performance and subjective perception of the speed of time's passing

Hypotheses

- The duration of unpleasant stimuli is overestimated compared to the duration of pleasant stimuli, irrespective of the semantic category
- Temporal sensitivity does not depend on the emotional valence of a stimuli but is influenced by the semantic category, with higher sensitivity for human sounds
- Healthy older adults time everyday life sounds similarly to young adults, but with a difference in timing sensitivity
- Across all participants and all sounds, underestimation of a time interval is correlated with an increase in perceived speed of time's passing

Chapter 4: Delivery of neuropsychology and neurolinguistic assessments to dementia patients in the COVID-19 era

Overarching question

Is remote assessment of healthy older participants as well as AD and FTD patients feasible during the COVID-19 pandemic?

Aims

1. Measure performance of healthy older adults as well as AD and FTD patients on several neuropsychological and neurolinguistic tests
2. Compare performance between testing modalities (remote vs face-to-face) in each participant group
3. Provide evidence for merging data collected before and during the pandemic

Hypotheses

- Across all participant groups, remote performance on tests of general intelligence, executive function and vocabulary is similar between testing modalities
- Across all participant groups, remote performance on certain tests of speech perception is decreased compared to face-to-face

Chapter 5: Subjective time perception in dementia: behavioural phenotypes and neuroanatomical correlates

Overarching question

Does pathological ageing in major dementias impact the modulation of perceived duration and discrimination sensitivity of short auditory intervals by their emotional valence and semantic characteristics?

Aims

1. Compare the performance of patients diagnosed with an AD or FTD syndrome against healthy older adults
2. Evaluate disease specific differences in duration estimation and discrimination sensitivity
3. Explore how general cognitive capacities affect timing performance in healthy older adults and dementia patients
4. Determine the neuroanatomical substrates of subjective time perception across all patient groups

Hypotheses

- Given their emotional processing difficulties, bvFTD and svPPA patients are differentially impacted by the emotional valence of sounds when making duration judgments compared to healthy age-matched control participants
- Due to their semantic deficits, svPPA patients are differentially impacted by the semantic characteristics of sounds when making duration judgments compared to healthy age-matched control participants
- AD and lvPPA patients generally perform differently from healthy participants (either by overestimating or underestimating the duration of all sounds).
- All dementia patients have a lower discrimination sensitivity for all sounds compared to healthy age-matched control participants
- Neuroanatomical substrates of duration estimation differences between patients and healthy control participants reflect the distinct intrinsic characteristics and functional significance of environmental and human sounds.

Chapter 6: Temporal phenotypes of daily life in dementia and neuroanatomical associations

Overarching question

Are AD and FTD syndromes behaviourally and neuroanatomically dissociable in respect to time perception of over longer time scale?

Aims

1. Determine and compare the prevalence of abnormal time behaviours over longer time scale in AD and FTD syndromes
2. Determine the neuroanatomical substrates of these temporal behaviours across all patient groups

Hypotheses

- AD and FTD syndromes can be characterised by distinct temporal phenotypes
- Neuroanatomical substrates of altered temporal behaviours in AD and FTD reflect current evidence on timing networks

2. General Methods

2.1. Participants

2.1.1. Healthy ageing study – recruitment

For the healthy ageing study, participants were recruited online from Prolific, a third-party recruitment platform, from November 2020 to April 2021. Prolific participants take part in research studies in return for financial compensation (set at a minimum rate of £7.50/hour; here it was set to £10/hour).

Importantly, Prolific participants remain anonymous during the entire study, as each participant is assigned an alphanumeric code which is the only means of identification accessible to researchers. When registering to Prolific, participants are asked several questions, ranging from demographics to personal hobbies, which are used by the platform to create screening filters. These allow researchers to narrow down their recruitment pool to their desired representative sample, since only those meeting the screening criteria will see the study advert. Study involvement is then on a first come first served basis (if ten participants are to be recruited, only the first ten who enter the study will be able to complete it till the end).

The study advert usually contains a brief description of the study (including duration, pay, and URL link), any specific requirements regarding the completion of the study, as well as any potential return and/or rejection criteria. Participants are allowed to return the study if they have encountered technical difficulties or if they simply do not wish to complete the entire study (they would then revoke their consent for their data to be used). Examples of rejection criteria include participants who did not answer certain questions that are critical to the study, produced low-effort responses, or were exceptionally fast (suggesting they did not complete the study appropriately).

Specificities regarding the recruitment of the healthy ageing study (including screening filters, study content, return and rejection criteria, as well as participants' demographics) will be detailed in **section 3.3.1**.

2.1.2. Dementia study – recruitment

Patients were recruited primarily from the tertiary specialist cognitive disorders clinic at the National Hospital for Neurology and Neurosurgery (NHNN). A minority of patients were recruited via direct referral to the research program from external clinicians or through our local rare dementia support groups. All patients recruited into the study had a diagnosis of one of the neurodegenerative diseases listed in the next section, with no prior stroke or major psychiatric illness, and were all able to comply with psychological testing.

Healthy control participants without any significant neurological or psychiatric disease were recruited both from the Joint Dementia Research and local databases of volunteers aged between 50 and 80. Additional details on participant recruitment into the dementia study during the COVID-19 pandemic will be given in **Chapter 4**.

2.1.3. Dementia study – diagnostic groupings

All participants underwent extensive clinical assessment in addition to volumetric T1 MR brain imaging to determine whether they met the consensus diagnostic criteria for Alzheimer's disease (**Appendix 1** (Dubois et al., 2014)), bvFTD (**Appendix 2** (Rascovsky et al., 2011)) or one of the three PPA subtypes (**Appendix 3** and **Appendix 4** (Dubois et al., 2014; M.L. Gorno-Tempini et al., 2011)) and were all of mild to moderate severity.

AD patients were included if they fulfilled the diagnostic criteria of "typical AD" (**Appendix 1**). They all had supportive brain imaging findings, 19 out of 43 had abnormal CSF biomarkers (i.e., a total tau/beta-amyloid 1-42 ratio higher than 0.8 based on local laboratory reference ranges), and 6 out of 43 had abnormal amyloid-PET imaging scans compatible with an AD diagnosis.

bvFTD patients were included if they fulfilled the "probable bvFTD" diagnostic criteria, while those with pathogenic genetic mutations (either a C9 open reading-frame 72 (C9orf72) mutation, a microtubule-associated protein tau (MAPT), or a progranulin (GRN) mutation) had "definite bvFTD pathology" (**Appendix 2**). The exact distribution of genetic cases will be specified in the relevant data chapters (**Chapters 5 and 6**).

Patients with a suspected diagnosis of PPA were included under the "imaging-supported PPA" diagnostic criteria, i.e., they had supportive brain imaging results (**Appendix 3**). In

addition, 7 out of 19 lvPPA patients had abnormal CSF biomarkers. Applying these criteria likely leads to most of the included patients having either AD or FTLD spectrum pathology at post-mortem (D. C. Perry et al., 2017; Spinelli et al., 2017).

2.1.4. Ethical approval and consent

Ethical approval for all studies in this thesis was obtained from the University College London and NHNN Research Ethics Committees, and all participants gave informed consent (either in-person or online) in accordance with the Declaration of Helsinki.

2.1.5. Basic participant characterisation

The following demographics information was collected from all participants involved in this thesis's work: age, sex, education, handedness, and hearing aids use.

2.2. Dementia study - clinical and behavioural assessments

2.2.1. Clinical assessment

When patients were seen for a face-to-face research visit, a clinical assessment was conducted by a neurologist from our research centre alongside the patient's primary caregiver (often their spouse or partner) who acted as their research informant to provide reliable collateral information. The main purpose of the clinical assessment was to substantiate the syndromic diagnosis by collecting a detailed inventory of the symptoms experienced by the patient, following a pre-defined structured format. Notably, the clinical assessment included questions pertaining to time perception, of which analysis will be covered in **Chapter 6**. The Mini Mental State Examination (MMSE; (Folstein et al., 1975)) was also performed as a widely used index of disease severity, although it is less predictive in FTD syndromes due to confounding linguistic demands. Age of disease onset (estimated based on caregiver timing of first symptom onset), as well as use of medication (antidepressants and neuroleptics) that could potentially affect time perception (Sysoeva et al., 2010; M. Wiener et al., 2011; Wittmann et al., 2007) were also recorded. Most participants also gave consent for their blood to be tested for pathogenic genetic mutations causing FTD and AD (Beck et al., 2014), and some underwent an additional lumbar puncture to look for biomarkers of Alzheimer's pathology (Ewers et al., 2015).

When patients were seen remotely, the full clinical assessment could not be conducted. Instead, a shortened version of the symptoms inventory was sent in the form of an online questionnaire to the caregiver for them to complete on their own time. Caregivers were also asked to provide a rough estimate of the age of disease onset. Because of the remote nature of the research visit, no neurological examination was performed, nor were any blood and CSF samples taken. A telephone version of the MMSE or T-MMSE (Kennedy et al., 2014; Newkirk et al., 2004) replaced the usual version of the MMSE and was delivered by a trained psychologist.

2.2.2. General neuropsychological and neurolinguistic assessments

General neuropsychological and neurolinguistic assessments were conducted by a trained psychologist with all healthy control participants and patients enrolled in the dementia study, except AD and bvFTD patients who did not undergo the neurolinguistic assessment. The aim of these assessments was to support the syndromic diagnosis, as well as provide covariates for analysis of experimental measures. They comprised standardised tests of general intellectual level and domain-specific tests. **Table** 2-1 and **Table** 2-2 list all the tests delivered face-to-face in the right column and those that were retained for remote testing in the left column. The selection for remote testing was based on whether the test could be delivered remotely and whether cognitive domains were representatively sampled, as neuropsychological and neurolinguistic test results were used to corroborate clinical, and neuroimaging based diagnostic grouping. Differences in testing procedures between face-to-face and remote settings will be detailed in **Chapter 4**.

When preserved ability in a specific domain was hypothesized to contribute to better performance on the experimental task, performance scores on the corresponding test were used as covariates during analysis (for example, digit span forward scores measure auditory working memory, a critical building block in interval timing– see **section 1.2.2**).

Table 2-1 List of neuropsychological tests performed with participants recruited into the dementia study

Tests by cognitive domain	Reference	Remote battery
General intellect		
WASI performance IQ	Wechsler (1981)	-
WASI verbal IQ	Wechsler (1981)	-
National Adult Reading Test (NART)	Nelson (1982)	X
Schonell Graded Word Reading Test	Schonell (1942)	X
Executive skills		
WASI Block Design	Wechsler (1997)	NF
WASI Matrices	Wechsler (1997)	X
WMS-R Digit Span Reverse (DS-R)	Wechsler (1987)	X
Fluency tests – Letter and Category	In-house test	X
Trails Making Test (TMT) A & B	Tombaugh (2004)	NF
D-KEFS Colour-Word interference test	Delis, Kaplan and Kramer (2001)	NF
WAIS-R Digit Symbol	Wechsler (1997)	NF
Working memory		
WMS-R Digit Span Forward (DS-F)	Wechsler (1987)	X
Episodic memory		
Recognition Memory Test (RMT) – Words (W) and Faces (F)	Warrington (1984)	F: short W: -
Camden Paired Associates Learning	Warrington (1996)	-
Language skills		
WASI Vocabulary	Wechsler (1997)	-
WASI Similarities	Wechsler (1997)	-
British Picture Vocabulary Scale (BPVS)	Dunn and Whetton (1982)	X
Graded Naming Test (GNT)	Mckenna and Warrington (1980)	X
Posterior Cortical skills		
Graded Difficulty Arithmetic (GDA)	Jackson and Warrington (1986)	X
Visual Object and Space Perception (VOSP) Object Decision test	Warrington and James (1981)	X
Usual/Unusual views	Warrington and Taylor (1973)	-

The right column lists all the neuropsychology tests delivered face-to-face. In the remote battery column, "X" indicates the test was retained in the remote battery; "-" indicates the test was not retained because other tests from the same domain were available; "NF" means the test was not feasible remotely online. For the Faces subtest of the recognition memory test, the short version was performed. D-KEFS, Delis Kaplan Executive System; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WASI, Wechsler Abbreviated Scale of Intelligence; WMS-R, Wechsler Memory Scale-Revised.

Table 2-2 List of neurolinguistic tests performed with participants recruited into the dementia study

Tests by linguistic domain	Reference	Remote battery
Auditory Input Processing		
PALPA-3	Kay et al (1992)	X
Word retrieval		
Boston Naming Test (BNT)	Kaplan et al (1983)	X
Language comprehension		
Synonyms test (Concrete and Abstract)	Warrington et al (1998)	X
PALPA-55	Kay et al (1992)	X
Modified Camel and Cactus	Bozeat et al (2000) Moore et al (2020)	X
Modified Kissing and Dancing	Bak and Hodges (2003)	-
Reading		
Grandfather passage	Darley, Aronson and Brown (1975)	X
Non-words	In-house test	X
Regular words	In-house test	X
Irregular words	In-house test	X
Spelling		
Graded Difficulty Spelling Test	Baxter and Warrington (1994)	NF
Speech Repetition		
Monosyllabic single word	Mccarthy and Warrington (1984)	X
Bisyllabic single word	Mccarthy and Warrington (1984)	X
Trisyllabic single word	Mccarthy and Warrington (1984)	X
Graded Difficulty Sentence repetition test	Mccarthy and Warrington (1984)	X
Spontaneous speech		
Holiday	In-house test	X
Cookie Jar Theft	Goodglass and Kaplan (1972)	X
Sentence construction		
Written (Wr) and spoken (Sp)	In-house test	Wr: NF Sp: X
Visuospatial working memory		
Spatial Span Forwards and Backwards	Corsi (1972)	NF

The right column lists all the neurolinguistic tests delivered face-to-face. In the remote battery column, "X" indicates the test was retained in the remote battery; "-" indicates the test was not retained because other tests from the same domain were available; "NF" means the test was not feasible remotely online. PALPA, Psycholinguistic Assessment of Language Processing in Aphasia.

2.2.3. Pure tone audiometry

Considering all timing experiments in this thesis rely on auditory processing, participants with a history of significant peripheral hearing loss (uncorrected with hearing aids) were excluded.

For participants seen face-to-face for the dementia study, pure tone audiometry was carried out using a dual-channel GSI Audiostar Pro audiometer and following protocol outlined by the British Society of Audiology (https://www.thebsa.org.uk/wp-content/uploads/2018/11/Recommended-Procedure-Pure-Tone-Audiometry-August-2018-FINAL.pdf).

Participants sat in a quiet room and were tested on each ear separately, starting with their better ear. To determine their hearing thresholds, they listened to pure tones of varying frequencies (starting at 1000Hz, then 2000Hz, 4000Hz, 8000Hz, then 500Hz, 250Hz, and finally 1000Hz) over descending intensity levels. Specifically, at each frequency, they were asked to indicate (verbally or using a gesture) if they could hear the sound, starting at a clearly audible level (usually 50 dB HL (decibel hearing level)). If they could, the level was decreased in steps of 10 dB until they could not, at which point the level was increased by steps of 5 dB, until they could hear it again. This procedure was repeated three times to establish the mean threshold at that frequency. For each participant, a composite hearing threshold was then created by calculating the mean threshold across all frequencies in the better ear.

Because participants who took part in the dementia study remotely could not complete pure tone audiometry, the composite hearing threshold was not used as a covariate in experimental analyses. Instead, correlations were conducted between the hearing score and timing performance measures (**section 2.8.2**), to assess between-group differences in peripheral hearing function as a potential confounder for between group differences in timing performance.

Participants enrolled in the healthy ageing study via Prolific did not undergo pure tone audiometry. However, participants who reported experiencing hearing difficulties were excluded from the recruitment pool (**section 3.3.1**). As such, peripheral hearing dysfunction is unlikely to have significantly impacted performance on the timing experiment.

2.3. Generation and validation of auditory stimuli for temporal bisection paradigm

Most studies looking at time perception using a temporal bisection paradigm in the visual domain have used a range of complex stimuli, from faces (Fayolle & Droit-Volet, 2014), pictures (Tipples, 2015), to films (Droit-Volet et al., 2011). However, studies in the auditory domain are limited and have either used music (Droit-Volet et al., 2010) or single words (Fallow & Voyer, 2013), and as such the breadth of sounds experienced on an everyday basis has not yet been experimentally covered. Here I aimed at filling this gap by choosing a variety of sounds which I thought would make suitable emotional carriers for the study of subjective time perception.

Specifically, recordings of environmental sounds and emotional vocalisations were obtained from online databases (freesound.org and soundsnap.com) or selected from a stimuli set generated by the Speech Communications Lab at University College London (Lavan et al., 2015). The raw sound recordings were then edited in Audacity (v2.3.3) to extract segments of duration 2, 2.5, 3, 3.5, 4, 4.5 or 5 seconds, with a sampling rate of at least 44.1 kHz and fixed root-mean-square (rms) intensity level. Extracted segments of different duration were windowed on and off to prevent click artefacts. Each individual sound file was processed following this procedure to minimise effects of variability in recording method and was then exported as a wav file.

The auditory stimuli were chosen to represent four different auditory source category – valence combinations (i.e., four experimental conditions), with several sound types for each combination: pleasant environmental noises (brook, river, blackbird); unpleasant environmental noises (angle grinder, car horn, bees); pleasant human vocal sounds (female laughter, male laughter, baby cooing); and unpleasant vocal sounds (female crying and scream, male crying and scream). The sound types presented for the healthy ageing study are not entirely the same as the ones for the dementia study; they will therefore be made explicit in **sections 3.3.2** and **5.3.2** respectively. Examples of stimuli are provided in **Appendix 5**.

This design employed sounds whose pleasantness has previously been validated (Fletcher, Nicholas, et al., 2015a) while at the same time allowing acoustic variation

across the stimulus set to reduce the potential for idiosyncratic stimulus effects on perceived duration. However, all participants were asked to rate the sounds for pleasantness to establish that their valence ratings on the experimental stimuli were in line with those predicted for each sound category.

The rating procedure was conducted as follows. A selection of stimuli from the main experiment representing all experimental conditions were administered in randomised order and the task on each trial was to rate the valence of the sound on a sliding scale. The scale was shown on the screen as a black horizontal line bounded by "extremely unpleasant" and "extremely pleasant" accompanied by icons of a sad face and a happy face, respectively; the participant rated the sound stimulus on the scale using the mouse and the mouse position was automatically converted into a percentage between 0 ("extremely unpleasant") and 100 ("extremely pleasant"). More details will be given in **sections 3.3.2** and **5.3.2** about the stimuli set used for each respective study and how the individual ratings were incorporated into the analysis. In a pilot cohort of healthy young and older adults, stimuli were also rated for arousal following a similar procedure, based on icons of a face with eyes closed and a face with eyes wide open with a sliding scale ranging from "extremely calm" to "extremely excited" (**Appendix 11**).

2.4. Temporal bisection paradigm

The temporal bisection paradigm is a classic timing paradigm that measures prospective timing abilities (**section 1.1.4**). In essence, on each trial, participants were asked to attend to a stimulus (here a sound) of varying duration and were asked to categorise each stimulus as a "short" interval or a "long" interval by responding with a keypress. Inspired by previously published protocols (Droit-Volet et al., 2010; Tipples, 2015), I chose 7 different durations spanning the range of 2 to 5 seconds (2, 2.5, 3, 3.5, 4, 4.5, 5 seconds), as that range is most pertinent for the study of the subjective experience of time with relevance to everyday living. As mentioned in **section 2.3**, four different sound categories were tested (environment/human x pleasant/unpleasant). Therefore, each experimental block represented all 28 experimental conditions (7 durations x 4 sound categories), which were presented in pseudo-randomised order (such that no two sounds from the same experimental condition were presented consecutively) and with

a varying inter-trial interval (between 1 and 3 seconds) to reduce expectancy effects. The order of the blocks was further randomised across participants. The number of blocks as well as the administration method were different between the healthy ageing study and the dementia study and will be made explicit in **sections 3.3.3** and **5.3.3** respectively. Importantly, participants were not told that the temporal bisection task examined the effect of emotion on time perception prior to taking part in the experiment.

2.5. Mood questionnaire

To make sure participants' performance was not specifically affected by poor mental health due to the COVID-19 pandemic, all participants tested during that period (patients and healthy young and older adults) were asked to fill in a mood questionnaire prior to completing any experimental session. The questionnaire was adapted from the Immediate Mood Scaler (Nahum et al., 2017) and included 4 questions asked on a 5-point Likert scale covering the following dimensions: Happy-Sad, Energetic-Tired, Interested-Bored, and Peaceful-Anxious. A composite score (sum of ratings on all four dimensions; out of 20) was calculated and exploratory correlations with temporal performance scores were conducted to investigate mood as a potential confounding factor.

2.6. Presentation of experiments

2.6.1. Healthy ageing study and dementia study (remote)

For the online healthy ageing study and the remote dementia study, all experiments were built using an online experiment builder known as Labvanced (Finger et al., 2016). This allowed participants to access experiments via a URL link. Web browser use was restricted to Chrome as the Labvanced support team recommended this as the most suitable browser for automatic delivery of sounds, otherwise known as the auto-play function, which allows participants to hear the sound without having to initiate the trial using a button click.

Because of the remote nature of these two studies, the hardware used to deliver the experiments (e.g., desktop computer/laptop/tablet and speakers/headphones) could

not be kept identical across all participants unlike for face-to-face testing. Details on which equipment participants used will be specified in corresponding chapters.

2.6.2. Dementia study (face-to-face)

For face-to-face testing, stimuli were presented using the Eyelink Experiment Builder software (SR Research, Ottawa, Canada). Participants listened to stimuli over ATH-M50X Audio Technica® headphones through a Mac laptop at a comfortable listening level (at least 70 dB).

2.7. Structural brain imaging and voxel-based morphometry

2.7.1. Structural image acquisition

When it was deemed safe for the patient to go into the scanner (absence of pacemaker and/or minimal risk of COVID-19 infection), a volumetric T1 MR brain image was acquired on a Siemens Prisma 3T MRI scanner using a 32-channel phased array head-coil and following a sagittal 3D magnetization-prepared rapid-gradient echo T1-weighted volumetric brain MR sequence (echo time/repetition time/inversion time respectively 2.9/2200/900ms, dimensions 256 × 256 × 208, voxel volume of 1.1 × 1.1 × 1.1mm). Prior to pre-processing, each scan was examined for quality control.

2.7.2. Structural image pre-processing

Pre-processing of brain images was performed using the New Segment and DARTEL toolboxes in SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/), following an optimized protocol (Ridgway et al, 2008). Normalization, segmentation, and modulation of grey and white matter images were carried out using default parameter settings. Grey matter images were subsequently smoothed using a 6mm full width-at-half-maximum Gaussian kernel. For each patient, total intracranial volume was calculated by summing grey matter, white matter, cerebrospinal fluid volumes after segmentation of these tissue types. A study-specific template brain image was created by warping all bias-corrected native space brain images to the final DARTEL template and calculating the average of the warped brain images.

2.7.3. VBM analysis

Following additional quality control, pre-processed brain MR images were entered into VBM analyses of the patient groups. MR images from healthy control participants were not incorporated in the VBM analyses. This was to avoid identifying spurious anatomical associations in brain areas with disease related grey matter atrophy, since, in the absence of neurodegeneration, factors other than regional brain volume changes is likely to drive the variance in experimental performance.

Full factorial models were used to assess associations of regional grey matter volume (indexed as voxel intensity) with each parameter of interest across the entire patient cohort. This type of model was chosen to reduce the effect of anatomical heterogeneity between groups and to ensure that grey matter associations identified would not correspond to atrophy pattern of a group specifically impaired compared to other diagnostic groups.

In all models, the following covariates of no interest were included: age, total intracranial volume, in addition to the MMSE score for **Chapter 6**. Currently, there is no single good measure of disease severity that would be equally valid for the different dementia types studied here. As previously mentioned, the MMSE score is typically used to evaluate disease severity for Alzheimer's disease patients, but it does not pick up on the impairment typically observed in behavioural variant FTD patients. In this regard, the WASI Matrices score is a more suitable one to use. However, for the dataset analysed in **chapter 6**, there were numerous missing datapoints which led me to choose the MMSE score instead.

Statistical parametric maps were generated using an initial threshold $p < 0.001$ and evaluated at peak voxel statistical significance level $p < 0.05$, after family-wise error (FWE) correction for multiple voxel-wise comparisons within individual pre-specified neuroanatomical regions of interest. These regions were selected a priori based on functional neuroanatomical substrates in the healthy brain (enumerated specifically in each chapter) and were defined using the Harvard-Oxford Brain Atlas (http://fsl.fmrib.ox.ax.uk/ fsl/fslwiki/Atlases).

2.8. Statistical analysis

All statistical analysis of behavioural data was performed using Stata (StataCorp, College Station, TX, USA). Brain imaging analysis was carried out using the SPM12 toolbox (http://www.fil.ion.ucl.ac.uk/spm/) in MATLAB 2019b.

2.8.1. Demographic and general neuropsychological data

For the analysis of continuous variables, independent samples t-tests were used to compare the two age groups in the healthy ageing study where the assumption of normality was validated. When more than two participant groups were compared, a one-way ANOVA was used if assumptions of homoscedasticity and normality, verified using Levene's test and Q-Q plot of residuals, were satisfied. If assumptions were not met, the non-parametric equivalents (Mann-Whitney rank-sum test and Kruskal-Wallis H test respectively) were performed instead. To correct for multiple comparisons, a Bonferroni correction was applied in case of parametric testing, while the Dunn's test was used as a non-parametric post-hoc test. For comparison of categorical variables (e.g., gender, handedness), a chi-square test was used, unless the expected counts were small, in which case a Fisher's exact test was used instead. A statistical threshold of $p<0.05$ was accepted for all tests.

2.8.2. Temporal bisection task data

For each participant, the number of long responses and the number of available trials (number of blocks minus any missed or unwanted trials – see **sections 3.3.6.2** or **5.3.7** for more details) was computed at each experimental condition (duration x sound category). These numbers were then used to plot the probability of a long response for each sound category as a function of duration. A psychometric curve was then estimated for each sound category and each participant using Psignifit (version 4.0), a MATLAB operated toolbox (Schütt et al., 2016). Briefly, the standard model assumes that each trial results from a Bernoulli process such that the probability of responding long on a given trial is independent of all other trials. As such, the number of long responses at the same stimulus level (here duration) is binomially distributed.

The psychometric function ψ then describes the relationship between the probability of responding long and the duration d, as follows:

$$\psi(d;\alpha,w,\gamma,\lambda) = \gamma + (1-\gamma-\lambda)S(d;\alpha,w)$$

where S is a sigmoid function chosen among a family of sigmoid functions (here logistic function) of which the precise shape is determined by the parameters α, the threshold and w, the width. The threshold α corresponds to the duration at which the sigmoid function S reached the probability of 0.5, and the width w is the difference between the durations at which the function reaches 0.05 and 0.95. The psychometric function ψ is further described by the parameters γ, also known as the guess rate, and λ, also known as the lapse rate. They respectively define the lower and upper asymptotes of ψ, i.e., the probability of responding long at infinitely short and long durations respectively. Here, γ and λ were estimated from the data, together with the threshold and width parameters. **Figure** 2-1below illustrates how Psignifit fits a psychometric curve function to hypothetical data.

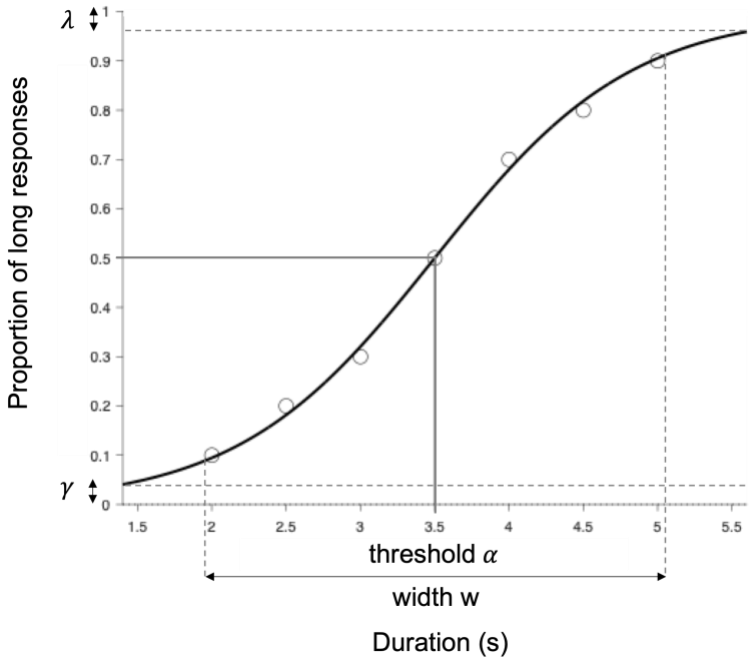


Figure 2-1 Example of psychometric curve fitting in Psignifit

Psignifit plots the proportion of long responses as a function of duration (white circles) then fits a psychometric curve (shown in black here) based on the equation written above, where the sigmoid function S is determined by the threshold α and the width w (see text for a description of how these are mathematically defined), with the additional parameters γ and λ corresponding to the lower and upper asymptotes respectively.

Following previous analysis methods (Droit-Volet et al., 2010; Fayolle & Droit-Volet, 2014; Tipples, 2015), two parameters were then extracted from each psychometric curve for further statistical analyses. The first is the temporal bisection point, which corresponds to the duration at which the curve reaches 50% probability and is equal to the threshold α. A lower bisection point would reflect underestimation of the corresponding sound category compared to others, and vice versa. The second parameter is known as the Weber's ratio or the coefficient of variation and can be easily calculated using the following formula:

$$Weber's\ ratio = \frac{Duration\ (at\ Plong = 0.75) - Duration\ (at\ Plong = 0.25)}{Bisection\ point}$$

The Weber's ratio gives an indication of the discrimination sensitivity, i.e., a higher value, obtained from a shallower slope, would indicate a lower discrimination sensitivity.

These parameters were averaged across participants from the same group and group averages were statistically compared according to the following analysis method. To perform between-group comparisons (healthy young adults vs healthy older adults or healthy older adults vs FTD vs AD patients) and within-group comparisons (across the 2 emotional valence x 2 semantic categories), as well as examine interaction effects on the bisection point and the Weber's ratio separately, I favoured linear mixed modelling over repeated measures ANOVA. Indeed, linear mixed modelling is less susceptible to outliers (by attenuating the impact of participants with missing data), and it incorporates both fixed and random effects (while ANOVA only models fixed effects). Here, I specifically used participant identity as a random effect to allow modelling of the difference between each participant's score and their corresponding group average following a normal distribution. Fixed effects included group (age group or diagnosis group depending on the study), semantic category (environmental vs human) and emotional valence category (pleasant vs unpleasant). Covariates are specified in each chapter when added.

Each model was validated by verifying the following key assumptions:

- normality of residuals, using Q-Q plots and the Shapiro-Wilk test of normality
- absence of significant outliers, defined as datapoints standing outside of three times the interquartile range below the first or above the third quartile

- absence of datapoints of high influence, defined as datapoints for which the Cook's distance is above the conventional cut-off of $4/n$, or for which the absolute value of DFITS is above $2/\sqrt{k/n}$ where k is the number of parameters and n is the sample size
- homoscedasticity, using the White's test
- absence of multicollinearity, by checking that variance inflation factors are inferior to 10
- model specification, using the link test and the Ramsey regression specification error test for omitted variables

When the normality assumption was violated, a transformation of the dependent variable was applied (either a logarithmic or a square root transformation). When this did not help, bootstrapping was performed, using 1000 replications and sampling with replacement, to calculate 95% confidence intervals. When present, significant outliers were also removed. If an effect was found, post-hoc comparisons were performed using Bonferroni corrections where appropriate.

I further explored the link between the bisection task performance measures (bisection point and Weber's ratio) and other relevant participant characteristics using either Pearson or Spearman correlations. These are made explicit in each data chapter.

3. Subjective time perception in healthy ageing: effects of emotional valence and semantic characteristics

3.1. Chapter summary

Aims

- Evaluate and compare the effects of emotional valence (pleasant vs unpleasant) and semantic characteristics (environmental vs human) on the perceived duration and discrimination sensitivity of short auditory intervals in healthy young adults
- Compare performance of healthy young adults against healthy older adults
- Explore the relation between performance and subjective perception of the speed of time's passing

Methods

- A total of 123 healthy young adults and 108 healthy older adults were recruited online on Prolific (a third-party recruitment platform)
- Interval timing abilities were assessed using a temporal bisection task with sounds of everyday life lasting several seconds and varying in emotional valence and semantic characteristics in a 2x2 factorial design
- Subjective perception of the speed of time's passing was assessed using the Subjective Time Questionnaire

Results

- All participants perceived the duration of unpleasant environmental sounds as longer than pleasant ones, and human sounds as shorter than environmental sounds. All participants also found human sounds less discriminable than environmental sounds
- Healthy older adults overestimated the duration of environmental sounds and had a higher duration discrimination sensitivity compared to healthy young adults
- Healthy young adults who underestimated the duration of all sounds and healthy older adults who had a lower discrimination sensitivity across all sounds rated time as passing more quickly

Conclusion

- This study replicates previous findings of emotion-induced lengthening of perceived duration and uncovers new effects of semantic characteristics on the subjective perception of time
- The impact of healthy ageing on interval timing abilities may reflect general changes in emotional processing and cognition as well as suggests the use of different timing strategies between healthy young and older adults
- Overall, these results further our understanding of temporal encoding mechanisms of complex sounds and how these may be affected in healthy ageing

3.2. Introduction

In this first data chapter, I aim at elucidating two main experimental questions. The first revolves around the effect of emotion and semantic characteristics on duration judgments of time intervals on the order of seconds (2-5s) using an auditory temporal bisection task with everyday life sounds selected to represent two opposing emotional (pleasant vs unpleasant) and semantic (environmental vs human) categories. The second question revolves around the impact of healthy ageing on interval timing using this same task.

What do we know about the influence of emotion on duration judgements of time intervals lasting seconds?

As laid out in the introduction, the literature on the effects of emotion on interval timing is extensive, particularly in the visual domain (Droit-Volet & Gil, 2009; Droit-Volet & Meck, 2007).

Using a temporal bisection task, previous research has shown that the duration of facial expressions of anger, fear, threat, or happiness is overestimated compared to neutral faces, and more specifically, that the duration of angry faces is consistently overestimated compared to happy or fearful faces (Droit-Volet et al., 2004; Effron et al., 2006; Tipples, 2008, 2011). The finding of duration overestimation of angry faces compared to neutral ones was replicated in a study using both static and dynamic facial expressions (Fayolle & Droit-Volet, 2014). Fear has been shown to have an effect on duration judgments similar to anger using different types of visual stimuli: faces (Tipples, 2011), whole bodily expressions (Droit-Volet & Gil, 2016), pictures of animals (Tipples, 2015), and films (Droit-Volet et al., 2011).

Findings in the auditory domain are minimal. For example, the duration of pleasant musical melodies (played in major mode) is overestimated compared to unpleasant ones (played in minor mode) (Droit-Volet et al., 2010). Similarly, the duration of single words expressed in a joyful tone is overestimated compared to an angry tone (Fallow & Voyer, 2013; Voyer & Reuangrith, 2015).

Emotional differences in temporal discrimination sensitivity, as indexed by the Weber's ratio, have also been investigated. While some studies found no differences (Droit-Volet et al., 2011; Droit-Volet & Gil, 2016; Fayolle & Droit-Volet, 2014; Tipples, 2008, 2011), others revealed a lower sensitivity for vocal expressions of anger (Fallow & Voyer, 2013), highly arousing negative pictures (S. D. Smith et al., 2011), and vocal expressions of happiness (Voyer & Reuangrith, 2015) compared to neutral stimuli, while a more recent study revealed increased sensitivity to threat compared to neutral stimuli (Tipples, 2019). Two studies further showed higher sensitivity for negative compared to positive stimuli, one in the visual domain (S. D. Smith et al., 2011) and the other in the auditory domain (Voyer & Reuangrith, 2015). The picture of the emotional impact on the Weber's ratio is therefore mixed.

Emotion-induced changes in perceived duration have mostly been explained in the context of pacemaker-accumulator models where the pacemaker acting as the "internal clock" can accelerate or decelerate its pace, thereby lengthening or shortening the duration of an interval, often as a result of changes in physiological arousal (Angrilli et al., 1997; Treisman, 1963). Attention has also been identified as a strong modulator in interval timing, with less attention paid to time leading to a reduction in perceived duration (Zakay & Block, 1996).

What do we know about the influence of semantic characteristics on duration judgements of time intervals lasting seconds?

Determining the impact of semantic characteristics on duration judgements (by comparing environmental sounds against human sounds for example) addresses the wider question of whether embodiment can modulate our experience of time. Indeed, human vocalisations are embodied and therefore likely engage neural circuits supporting the self/non-self interface more strongly than non-human sounds (Owens et al., 2018; J. E. Warren et al., 2006). Accordingly, semantic information is likely to influence temporal perception, together with emotional valence, especially given the participation of the insular cortex in integrating different types of interoceptive signals to shape a dynamic representation of psychological time (Craig, 2009; Wittmann, Simmons, et al., 2010).

However, this has received little focus up until now. In the previously mentioned study comparing static and dynamic presentation of faces, Fayolle and Droit-Volet have shown an increase in perceived duration for sad faces compared to neutral faces only for the dynamic condition, suggesting that embodiment exacerbates the influence of emotion on duration judgements (Fayolle & Droit-Volet, 2014). Another study evaluated emotional effects using both faces and animal pictures representing four emotions: neutral, anger, happiness, and fear (Jones et al., 2017). For both faces and animal pictures, the duration of stimuli associated with happiness is overestimated compared to neutral stimuli. However, only fearful faces and pictures of angry animals are perceived as lasting longer than neutral stimuli. Moreover, the bisection points corresponding to fearful and angry animals are higher than equivalent emotional facial expressions (although no formal statistical comparison has been performed). Overall, both studies were not designed to evaluate the impact of semantic characteristics on duration judgements per se, and it is therefore not possible to conclude on the existence and direction of such effects.

What do we know about the impact of healthy ageing on subjective time perception?

As described in the introduction, accumulated neuroanatomical (Bäckman et al., 2010; Bauer et al., 2015; Fama & Sullivan, 2015; Klostermann et al., 2012) and psychological (McDowd & Shaw, 2000; Zacks et al., 2000) evidence suggests that healthy older adults experience time differently from healthy young adults. However, it is not yet clear in which direction these changes occur (e.g., do healthy older adults underestimate or overestimate the duration of seconds-long intervals?) and how these changes may interact with other modulators of interval timing (e.g., if healthy ageing impacts duration judgements at all, does this happen only for intervals of certain emotional or semantic content?).

Previous research suggests that age-related differences in timing are task-dependent, since these are absent when using a temporal bisection task paradigm (Lamotte & Droit-Volet, 2017; McCormack et al., 1999; Wearden et al., 1997), and may only be observed when the task is complex or requires high attentional load (Craik & Hay, 1999; Perbal et al., 2002; Pouthas & Perbal, 2004). To date, only one study has explicitly compared healthy young and older adults on a temporal bisection task using different emotional

faces (Nicol et al., 2013). The findings revealed that healthy older adults overestimate the duration of all facial expressions compared to healthy young adults. In addition, while both healthy young and older adults overestimate the duration of angry faces against neutral faces and judge the duration of sad faces similarly to neutral faces, only healthy older adults overestimate the duration of happy faces against neutral faces. Age differences in duration discrimination sensitivity were not evaluated. However, other studies have found that healthy older adults produce more variable estimates compared to healthy young adults (Block et al., 1998; McCormack et al., 1999; Wearden et al., 1997). In addition, a lower discrimination sensitivity has been found to correlate with reduced working memory and attentional capacities (Gagnon et al., 2018; Ogden et al., 2019). Given these diminish in healthy ageing (Balci et al., 2009), it is likely that healthy older adults have a lower duration discrimination sensitivity.

What did I do here?

To assess the effect of both emotion and semantic information of auditory intervals on their perceived duration, I chose a temporal bisection task and used different sounds of everyday life fitting one of the following four experimental conditions: environmental unpleasant, environmental pleasant, human unpleasant, and human pleasant. I validated the emotional valence of these sounds by asking all participants to rate them for pleasantness and by taking into account individual ratings when attributing sounds to each experimental condition. I then compared performance of both healthy young and healthy older adults by representing psychometric functions for each experimental condition and each participant to extract corresponding bisection point and Weber's ratio values (indexing duration perception and discrimination sensitivity respectively). I then built linear mixed models for both timing performance measures including age group and both semantic and valence categories as fixed effects, and participant identity as random effect. I further assessed the effect of internal counting on the present findings. Finally, I correlated individual timing performance measures with perceived speed of time's passing as evaluated by the Subjective Time Questionnaire (Wittmann & Lehnhoff, 2005a).

What are my hypotheses?

First, based on previous research assessing emotional effects on interval timing, I hypothesise that heathy young adults will overestimate the duration of unpleasant stimuli compared to pleasant stimuli, irrespective of the semantic category. However, I expect emotional valence to have no influence on the Weber's ratio, though it is possible that healthy young adults will discriminate the duration of human sounds better than environmental sounds since the former can be embodied.

Regarding age differences, I hypothesise that healthy older adults will overestimate the duration of all sounds compared to healthy young adults but will be impacted by emotional and semantic characteristics of sounds similarly to healthy young adults when making duration judgements. Based on previous literature, it is further plausible that healthy older adults will have a lower discrimination sensitivity compared to healthy young adults.

Following previous accounts on the impact of counting on timing (Rattat & Droit-Volet, 2012), I also expect mental counting to specifically improve duration discrimination sensitivity.

Finally, I expect a positive correlation between the perceived speed of time's passing and overall bisection point across all participants (in other words, a participant who feels time passes more quickly is likely to underestimate the duration of a time interval).

3.3. Methods

3.3.1. Participant recruitment and study set-up

For the healthy ageing study, both young and older adults (aged between 18 to 30 or between 50 to 75 respectively) were recruited from December 2020 to April 2021 via Prolific using ten different screening filters (**Table** 3-1), to allow for proportionate gender representation and to exclude those with neurological and/or neuropsychiatric illnesses, those taking medication which may affect cognitive performance (antidepressants or anxiolytics), and those experiencing hearing difficulties. UK nationals were specifically recruited into this study to be consistent with the recruitment for the dementia study (**Chapter 5**).

Only Prolific participants who passed the screening filters were able to access the study which was advertised as a multi-part study (**Appendix 6**). Participants were asked to complete three rating experiments lasting about 30 minutes each and one time study lasting an hour on four separate occasions. The rating experiments consisted in rating the sounds from the main time experiment for pleasantness (**section 3.3.2**). In the final time study, participants had to complete the temporal bisection task (**section 3.3.3**) as well as questionnaires (**sections 3.3.4 and 3.3.5**).

A total of 231 participants (70 younger female, 53 younger male, 57 older female, 51 older male) expressed interest in the study, and 153 of those completed the full study (40 younger female, 41 younger male, 36 older female, 36 older male). From those 153 participants, several were removed from the final statistical analysis following criteria specified in **section 3.3.6.2**. The proportion of included versus excluded participants, as well as reasons for exclusion are shown in **Figure 3-1** for each participant group. As evident from **Figure 3-1**, most excluded participants did not provide any data. A few did not complete the entire study or produced unusable ratings data (majority of neutral ratings, inconsistent ratings, high proportion of missed trials) or time data (random responses). A minority of participants experienced technical difficulties which prevented them from completing the time task on their first attempt, and therefore produced a complete time dataset only at the second or third attempt. Those were excluded from further analysis to remove undesirable practice effects. Finally, a minority of participants were rejected because they gave inconsistent demographic information and failed data quality checks as reported by Prolific. None of them reported wearing hearing aids. Demographic details of participants included in the final statistical analysis are summarised in **Table** 3-2.

As mentioned in **section 2.6.1**, participants were allowed to use whatever audio equipment they preferred (headphones/speakers). Because the temporal bisection task was implemented as a reaction time task, participants were not allowed to use either tablets or smartphones and were restricted to Mac or Windows computers (either desktops or laptops were allowed). Details of the equipment used by participants for this study are given in **Appendix 7**.

Table 3-1. Prolific screening filters used for recruitment

Screening item	Question asked to Prolific participants	Their selected answer
Age	What is your date of birth?	YOUNG: 18 to 30 years OLDER: 50 to 75 years
Sex	What sex were you assigned at birth?	Male or Female
Nationality	What is your nationality?	United Kingdom
Medication use	Are you currently taking any medication to treat symptoms of depression, anxiety, or low mood (e.g., SSRIs)?	No
Mild cognitive impairment / dementia	Have you ever been diagnosis with mild cognitive impairment or dementia?	No
Multiple sclerosis	Have you ever been diagnosed with multiple sclerosis (MS)?	No
Autism spectrum disorder	Have you received a formal clinical diagnosis of autism spectrum disorder, made by a psychiatrist, psychologist, or other qualified medical specialist? This includes Asperger's syndrome, Autism Disorder, High Functioning Autism or Pervasive Developmental Disorder	No
Mental health / illness / condition ongoing	Do you have – or have you had a diagnosed, on-going mental health/illness/condition?	No
Mental illness daily impact	Do you have any diagnosed mental health condition that is uncontrolled (by medication or intervention) and which has a significant impact on your daily life / activities?	No
Hearing difficulties	Do you have any hearing loss or hearing difficulties?	No

Prolific offers researchers the possibility of narrowing down their recruitment pool by using their screening filters. Here are listed those that I used for recruiting participants into my healthy ageing study. On the left is indicated how the filter was labelled on both participants' and researchers' sides, in the middle, the corresponding question that participants were asked, and on the right, the answer they needed to have selected to qualify as a participant for my study. For age, participants are asked to indicate their date of birth when registering, however researchers do not have access to those data as they are classified as personal identifiable information. Instead, Prolific automatically calculates their age from their date of birth and if their age matches the researcher's recruitment criteria, participants can enter the study. Sex was also used as a screening filter, since, at the time of recruitment for this study, Prolific recommended this method to recruit an equal number of male and female participants.

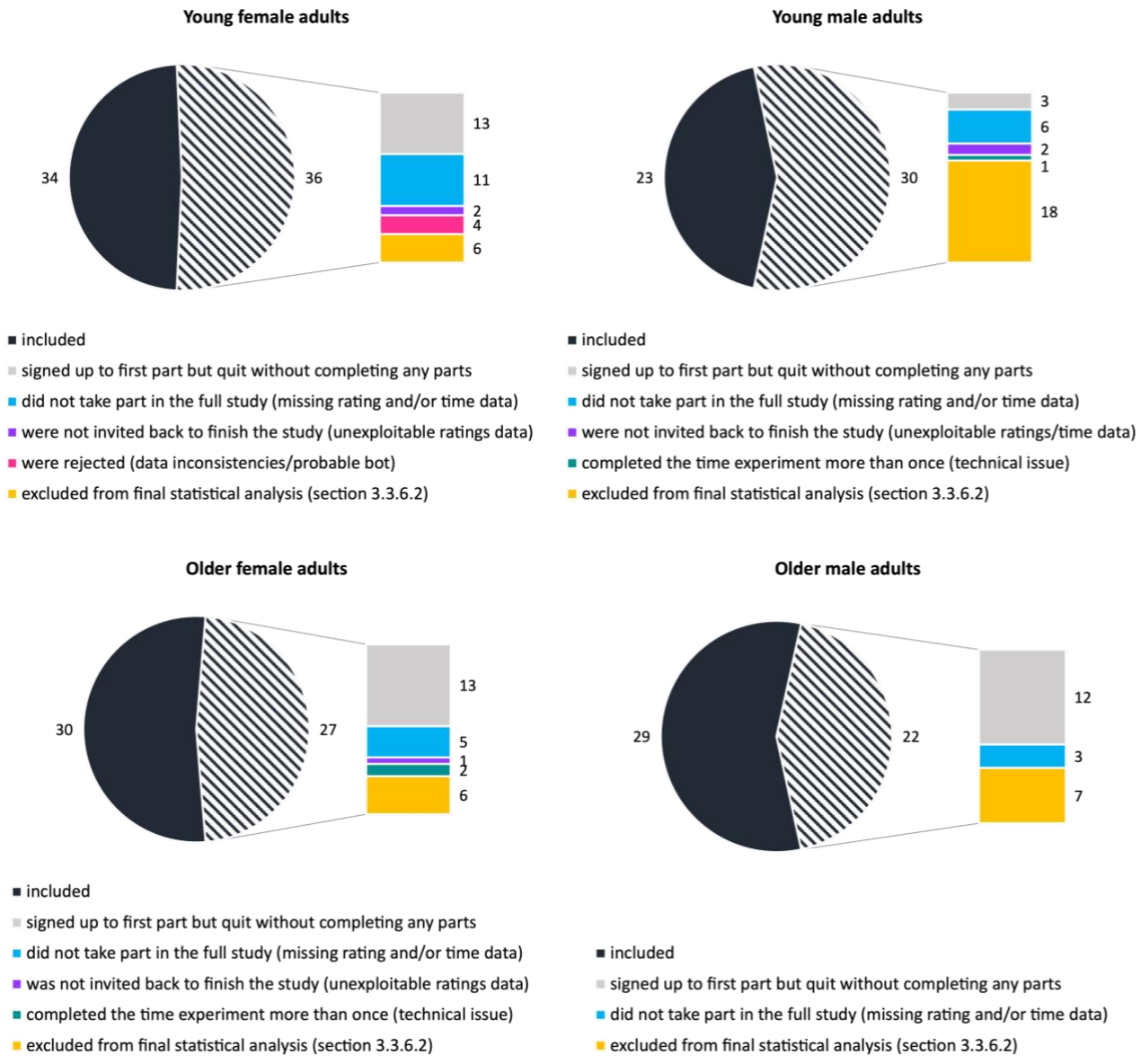


Figure 3-1. Prolific participants recruitment

For each group, the proportion of participants who have complete datasets (three rating datasets and one time dataset) is displayed as a dark-coloured slice, while the proportion of excluded participants is displayed as a striped slice. This proportion is further split by reason for exclusion on the side bar graph, with a different colour for each reason as indicated in the legend. Numbers of participants for each corresponding slice of each pie chart and side bar graph are also shown.

Table 3-2. Demographic details of Prolific participants who were entered in the final statistical analysis

Age group	Young adults	Older adults
Gender distribution	34 F / 23 M	30 F / 29 M
Age (years)	22.8 (3.6)	58.8 (6.2)
Handedness (R / L / A)	49 / 7 / 1	51 / 7 / 1
Education (years)	15.8 (1.9)	15.3 (2.4)

For each age group, gender and handedness distributions are reported, as well as mean age and education (standard deviations in parentheses). The two age groups were significantly different in mean age ($X^2(1) = 86.231$, $p = 0.0001$) but not gender distribution, handedness, or years of formal education. A, ambidextrous; F, female; L, left-handed; M, male; R, right-handed.

3.3.2. Experimental stimuli

As explained in the introduction, the present study aimed at determining the potential impact of healthy ageing on subjective time perception, i.e., on the emotional and semantic modulations of interval timing. Therefore, several sounds of everyday life were chosen to fit four experimental conditions (2 auditory source categories x 2 valence categories) with several sound types for each: pleasant environmental noises (brook, river, blackbird); unpleasant environmental noises (angle grinder, car horn, bees); pleasant human vocal sounds (female laughter, male laughter, baby cooing); and unpleasant vocal sounds (female crying, male crying, female scream, and male scream). All sound files used in this experiment, including the reference sound used for the partition method (pure tone of 600Hz set at a duration of 3.5 seconds), were edited in Audacity following the procedure detailed in **section 2.3**, and were exported as wav files. The resulting sounds corresponded to one of the following seven durations: 2, 2.5, 3, 3.5, 4, 4.5, 5 seconds.

To check my general assumptions about individual appreciation of these sounds, Prolific participants were asked to rate the full sound battery prior to completing the timing experiment (see **section 2.3** for rating procedure). The stimulus battery was divided into three sets of sounds, each set containing an equal proportion of environmental and human sounds as well as pre-defined pleasant and unpleasant sounds, as follows: set A (brook, bees, baby cooing, female and male screams); set B (river, angle grinder, female and male laughter, female and male crying); set C (blackbird, car horn, female and male

laughter, female and male crying). Importantly, all trials from one set were presented in randomised order and the order of these sets was counterbalanced across participants within each group. In addition, the rating experiments were completed on separate days to avoid saturation, and an additional week separated the last rating experiment from the time experiment to avoid strong memory effects. For each participant and each sound, an average rating score was then calculated and used to assign the sound to the appropriate valence category: an average score of 50% or higher was considered as pleasant, the rest as unpleasant. 59 participants (26 young adults, 33 older adults) had at least one sound that needed to be assigned to the opposite valence category. On average, however, sounds fit pre-defined valence category well for both age groups (**Figure** 3-3).

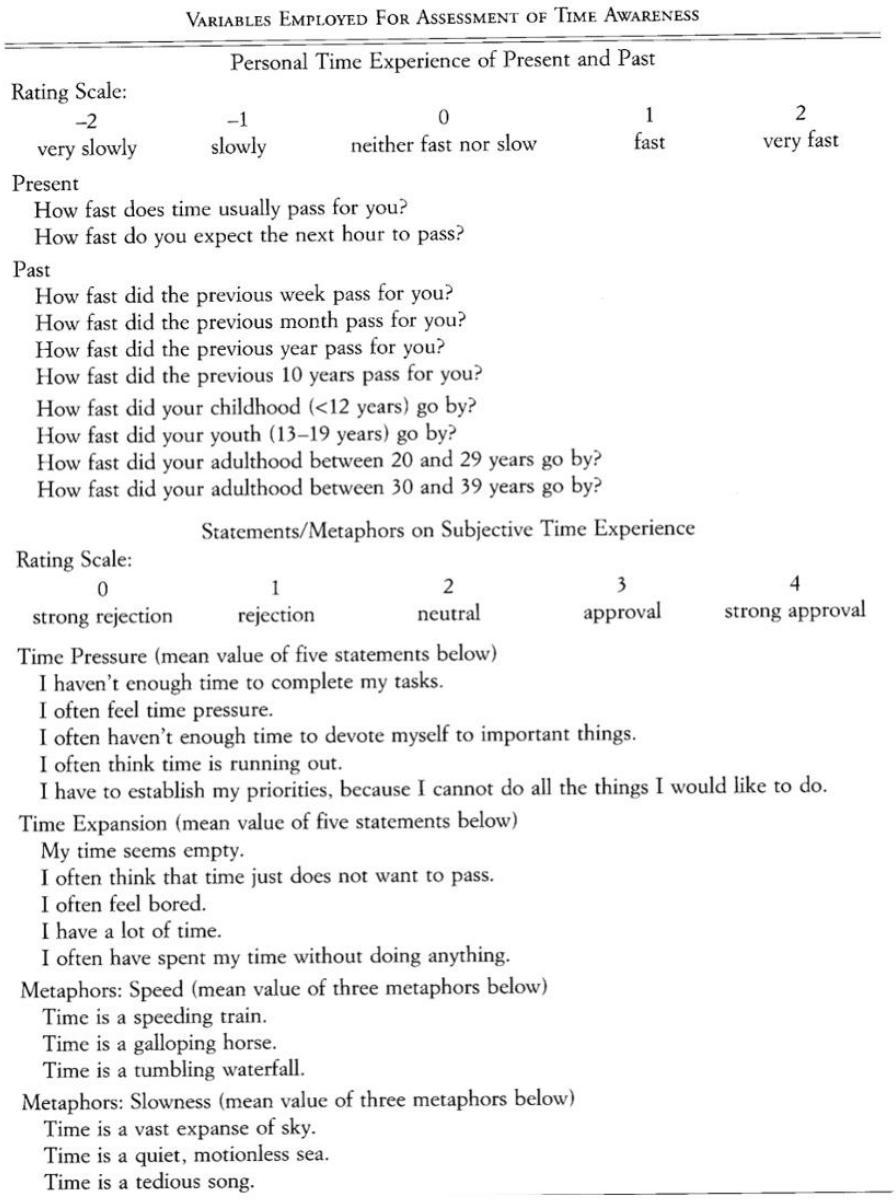
3.3.3. Temporal bisection task procedure

The principle of the temporal bisection task is detailed in **section 2.4**. I used the partition method, in which participants are asked to judge the duration of the current sound based on all previous trials. To time the first sounds, they were therefore presented with three successive pure tones set at the mean duration of the studied range (here 3.5 seconds) and instructed to use those as a reference for the first few trials. Participants were further asked to respond as fast and as accurately as they could using a keypress, and reaction times were collected. Participants completed a total of 420 trials, which were presented as fifteen blocks. They were allowed to take short breaks in between each block.

3.3.4. Subjective Time Questionnaire (STQ)

At the end of the temporal bisection task, participants completed the Subjective Time Questionnaire (Wittmann & Lehnhoff, 2005a), which consists of two distinct parts (**Figure** 3-2). The first looks at the subjective speed of time passing for the present and different periods of the past. The question relative to the decade between 30 to 39 years old was not included in the questionnaire delivered to participants as it was not applicable to the young cohort. The second part of the questionnaire proposes several statements also related to the subjective speed of time passing and with which participants may or may not agree. For the current study, this questionnaire was

delivered with the aim to anchor the lab-based seconds scale time experiment within everyday life perception of time. Therefore, we focused on the questions pertaining to the speed at which the present time passes (first two questions of part 1) and the metaphors on speed and slowness from part 2. Individual ratings from these questions were correlated with timing performance as described in **section 3.3.6.4**. Group ratings obtained for the other questions of the STQ are presented separately in **Appendix 8**.



VARIABLES EMPLOYED FOR ASSESSMENT OF TIME AWARENESS

Personal Time Experience of Present and Past

Rating Scale:

–2	–1	0	1	2
very slowly	slowly	neither fast nor slow	fast	very fast

Present

How fast does time usually pass for you?
How fast do you expect the next hour to pass?

Past

How fast did the previous week pass for you?
How fast did the previous month pass for you?
How fast did the previous year pass for you?
How fast did the previous 10 years pass for you?
How fast did your childhood (<12 years) go by?
How fast did your youth (13–19 years) go by?
How fast did your adulthood between 20 and 29 years go by?
How fast did your adulthood between 30 and 39 years go by?

Statements/Metaphors on Subjective Time Experience

Rating Scale:

0	1	2	3	4
strong rejection	rejection	neutral	approval	strong approval

Time Pressure (mean value of five statements below)

I haven't enough time to complete my tasks.
I often feel time pressure.
I often haven't enough time to devote myself to important things.
I often think time is running out.
I have to establish my priorities, because I cannot do all the things I would like to do.

Time Expansion (mean value of five statements below)

My time seems empty.
I often think that time just does not want to pass.
I often feel bored.
I have a lot of time.
I often have spent my time without doing anything.

Metaphors: Speed (mean value of three metaphors below)

Time is a speeding train.
Time is a galloping horse.
Time is a tumbling waterfall.

Metaphors: Slowness (mean value of three metaphors below)

Time is a vast expanse of sky.
Time is a quiet, motionless sea.
Time is a tedious song.

Figure 3-2. Subjective time questionnaire (Wittmann and Lehnhoff, 2005)

The subjective time questionnaire measures an individual's perception of the speed of time's passage using several Likert-scaled questions as shown. The question related to the adulthood period between 30-39 years old was omitted as it was not applicable to the entire cohort.

3.3.5. Other questionnaires

Participants completed other questionnaires to provide complementary information that could aid interpretation of their results. The first questionnaire covered questions about their basic demographic details (age, gender, handedness, highest qualification obtained, hearing aids use) and their environment (where they completed the study, how quiet that space was, and how distracted they felt in that environment). **Appendix 9** shows where both young and older adult participants completed the time experiment. All participants reported sitting in a quiet space and feeling little to no distractions during the study.

Considering participants were recruited during the emotionally challenging COVID-19 pandemic, they further filled in a mood questionnaire (**section 2.5**) before completing each study to evaluate the impact of mood on their performance (rating values and timing performance measures). This analysis will be further described in the statistical analysis section.

Finally, participants were provided with the opportunity to fill in a feedback questionnaire which covered general aspects of online testing (issues which could not be addressed by the experimenter due to their absence, such as technical issues, unclear written instructions, potential sources of distractions, wrong key presses), as well as specific aspects to the time experiment (counting or other timing strategies). No participants included in the current analysis reported any technical issues or difficulties in understanding the instructions. However, timing performance of participants who reported counting or using any other form of timing strategies was compared against those from the same age group who did not report such behaviour to explore whether active timekeeping strategies improved timing performance on this specific task.

3.3.6. Analysis of behavioural data

3.3.6.1. Valence ratings

To evaluate the impact of mood and age group on valence ratings, overall mood scores for each participant were averaged across the three rating sessions and a linear regression model was performed, with rating as the dependent variable, and the following three independent variables: sound identity (one of the ten sounds), age group (young vs older adults), and average mood score. Residuals were not normal even after attempting transformation (logarithmic, square root, and inverse). Bootstrapping was therefore carried out with 1000 replications and sampling with replacement.

3.3.6.2. Temporal bisection task data

Here, I looked at the effect of valence (pleasant/unpleasant) and semantic category (environmental/human) on subjective time perception, as measured by the bisection point and the Weber's ratio (see **section 2.8.2** for definitions) and compared the magnitude of both effects between the two age groups (healthy young adults vs healthy older adults).

As mentioned in **section 3.3.2**, sounds were reassigned to the correct valence category based on individual ratings. As a result, four participants had missing trials for one sound category (three for the human pleasant category and one for the environmental unpleasant category) and were removed from the final sample. All trials for which the reaction time was less than 100 ms and more than 2 s long were also discarded (for 75% of the participant pool, these trials represented less than 10% of the total number of trials available). A resulting 25 participants had less than four trials available for an experimental condition (sound category x duration) and were discarded from the analysis.

For each participant and each sound category, a psychometric curve was then generated following the procedure described in **section 2.8.2**. Two participants had one psychometric curve which plateaued before reaching a probability of responding 'long' of 0.75 (meaning the Weber's ratio could not be calculated) and were therefore discarded from the final sample. Six further participants were removed based on

malformed psychometric curves likely due to inattention, which can be expected in the context of prolonged and unmonitored online testing (see **Appendix 10**).

To assess experimental effects on the bisection point, a linear mixed model incorporating age group, semantic category and valence as fixed effects and participant identity as the only random effect was computed. Assumption of normality of residuals was violated and this was corrected by removing data from a single participant who was identified as a datapoint of high influence based on its Cook's distance and DFITS values (**section 2.8.2**). Further statistical testing revealed that the specified model omitted a variable. Individual mood score obtained for each participant prior to testing on the temporal bisection task was therefore incorporated into the model. When comparing bisection point averages across groups and/or experimental conditions, a higher value indicates underestimation of sound duration (while a lower value indicates overestimation).

To assess experimental effects on the Weber's ratio, a similar linear mixed model was computed, with age group, semantic category and valence as fixed effects and participant identity as the only random effect. Residuals were not normal and as there was no obvious outliers or datapoints of high influence in the dataset, a square root transformation of the dependent variable was applied instead (a logarithmic transformation was ineffective). Statistical testing revealed that the model was correctly specified, and no additional covariates were therefore added into the model. When comparing Weber's ratio averages across groups and/or experimental conditions, a higher value indicates a shallower slope and therefore lower discrimination sensitivity for the corresponding experimental condition (while a lower value indicates higher discrimination sensitivity).

3.3.6.3. Counting effects on temporal bisection task performance

Comments from the feedback questionnaire were further analysed, specifically to identify participants who reported mental counting. Age and gender distributions were then statistically compared between those who counted and those who did not using a chi-square test. To evaluate counting effects on timing performance, the bisection point and the Weber's ratio were averaged across the four sound conditions for each participant. Averages were then compared between those who reported counting and those who did not using an independent samples t-test or the non-parametric equivalent (Mann-Whitney rank-sum test) when the assumption of normality was violated. When this revealed a significant difference, an additional linear mixed model (with the same fixed and random effects specified earlier) was performed, including only those who did not report counting during the experiment to evaluate the specific impact of timekeeping strategies on the experiment. When the assumption of normality of residuals did not hold, a logarithmic transformation was applied.

3.3.6.4. Subjective Time Questionnaire (STQ) data

For the first two questions taken from part 1, the individual ratings were fed directly into the analysis. For the metaphors on slowness and speed from part 2, the individual ratings were first averaged across the statements corresponding to slowness and speed separately; those averages were then incorporated into the analysis

Age differences were first assessed using a Student's t test or the non-parametric equivalent (Mann Whitney rank test) for each questionnaire item of interest.

To explore links between perceived speed of time's passing and timing performance, bisection point and Weber's ratio values were averaged across experimental conditions for each participant. Pearson's or Spearman's correlation values were calculated separately for each age group to determine associations between individual average bisection point or Weber's ratio and perceived speed of time's passing in the present, as well as individual experience of speed and slowness.

3.4. Results

3.4.1. Validating the sound valence categories

As shown in **Figure** 3-3, valence ratings averaged across participants from each age group show that all stimuli fit pre-defined valence category. Specifically, sounds that were pre-defined as unpleasant (screaming, crying, bees, angle grinder, and car horn) were generally found unpleasant by both healthy young and older adults, and those pre-defined as pleasant (laughing, baby cooing, blackbird singing, brook and river) were also found pleasant by all participants. Importantly, the linear regression evaluating the impact of sound category, age group, and average mood score on rating values revealed that both mood and age group did not impact valence ratings (p=0.984 and p=0.101 respectively), while sound category did ($p < 0.001$).

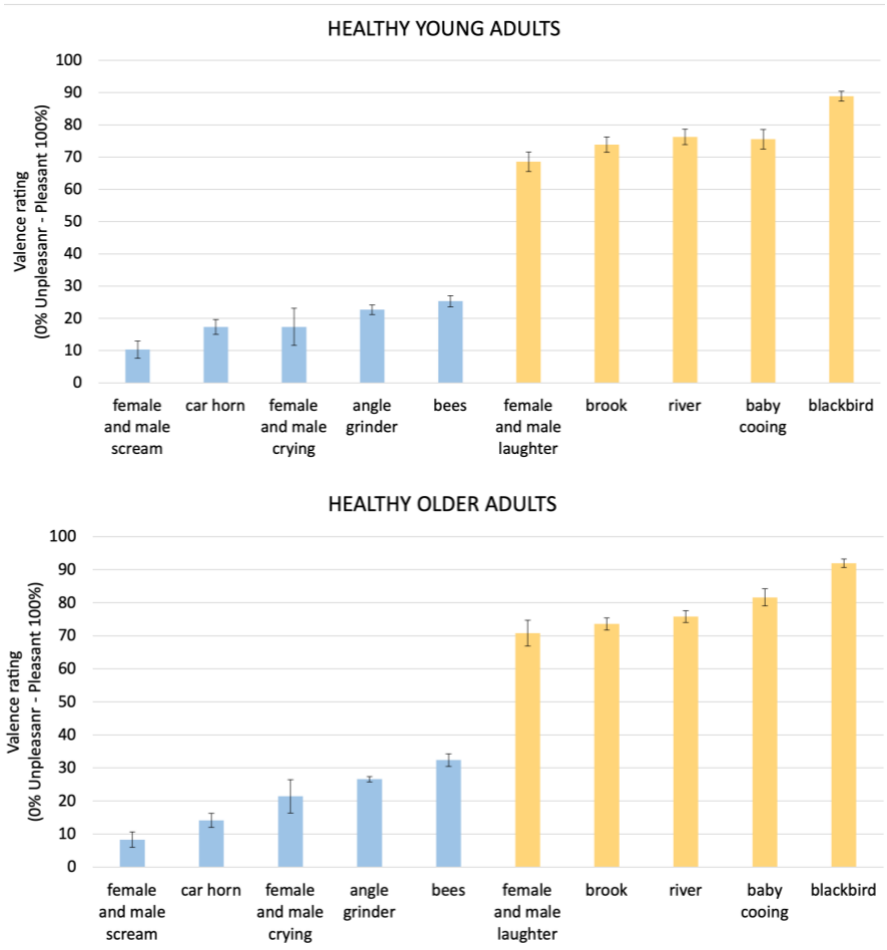


Figure 3-3. Average valence ratings for each sound presented in the time experiment

Ratings were given as percentages (0-49% corresponding here to unpleasant, 50-100% corresponding to pleasant). Standard deviations are shown as vertical bars.

Table 3-3. Average bisection point for each age group and each experimental condition

	Young adults		Older adults	
Number of participants	57		59	
Condition	**Environmental**	**Human**	**Environmental**	**Human**
Unpleasant	3.42 (0.37)	3.82 (0.34)	3.25 (0.37)	3.93 (0.44)
Pleasant	3.67 (0.35)	3.79 (0.39)	3.50 (0.42)	3.88 (0.50)

Average bisection point values in seconds (standard deviations) are shown for the four experimental conditions, for healthy young adults on the left and healthy older adults on the right. A higher bisection point value indicates underestimation of the sound duration for the corresponding experimental condition.

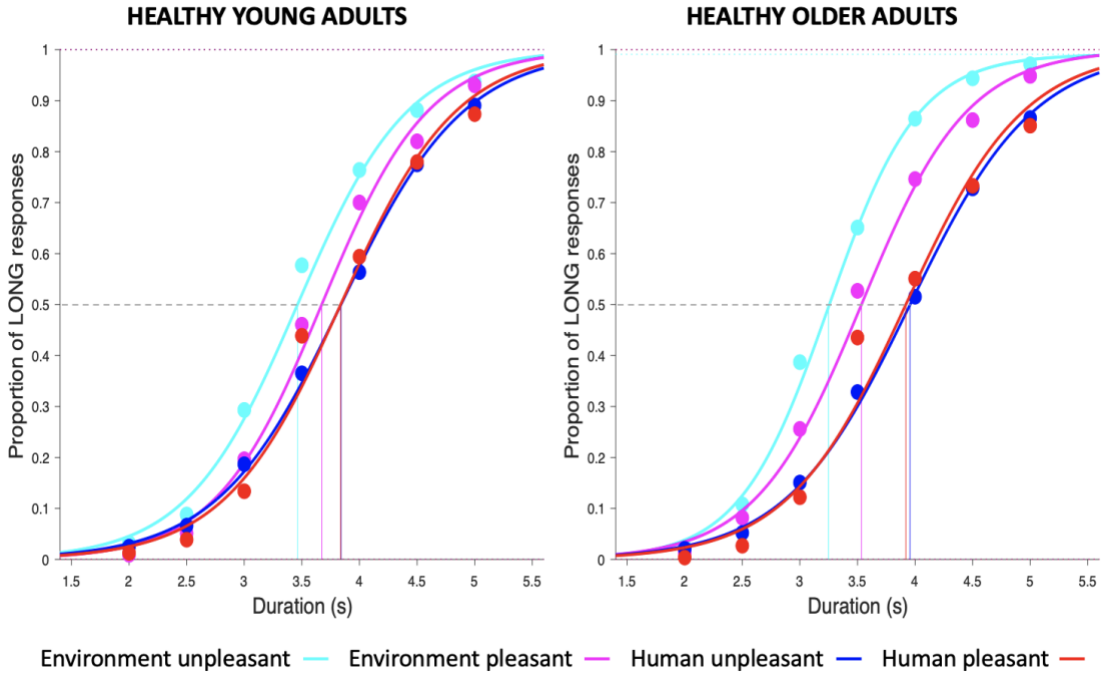


Figure 3-4. Average psychometric curve for each sound condition and each age group

The number of long responses and the number of total trials available at each duration and for each sound condition was averaged across participants from the same group and used to estimate psychometric curves for the corresponding group. Each psychometric curve corresponds to a different sound condition and is displayed in a different colour as indicated in legend.

3.4.2. Experimental effects on the bisection point

Average bisection point values are summarised in **Table** 3-3 and psychometric curves corresponding to each age group and experimental condition are shown in **Figure** 3-4.

The linear mixed model for the bisection point revealed significant main effects of age group ($z=-2.65$, $p=0.0008$), semantic category ($z=8.07$, $p<0.001$), and emotional valence ($z=5.03$, $p<0.001$), as well as significant interactions between age group and semantic category ($p<0.001$), and between valence and semantic category ($p<0.001$). The main effect of mood was not significant ($p<0.185$).

The main effect of age group indicated that across all sounds, the average bisection point of healthy older adults was lower than that of the healthy young adults such that the former group overestimated the duration of sounds compared to the latter group. The main effect of semantic category indicated that, irrespective of the emotional valence, the duration of environmental sounds seemed longer than that of the human sounds for all participants. When performing post-hoc comparisons, the age group and semantic category interaction revealed that healthy older adults overestimated the duration of environmental sounds compared to healthy young adults, irrespective of the emotional valence of the sounds ($z=-2.90$, $p=0.0004$), while there was no age group difference in the perceived duration of human sounds ($p=0.350$). In addition, the discrepancy in perceived duration between human and environmental sounds was more marked for healthy older adults compared to healthy young adults ($z=15.33$ for healthy older adults and $z=7.36$ for healthy young adults, both $p<0.001$).

Finally, the main effect of valence category indicated that, irrespective of the semantic category, the duration of unpleasant sounds seemed longer than that of the pleasant sounds for all participants. Post-hoc comparisons of the valence and semantic category interaction further indicated that for both age groups, environmental unpleasant sounds seemed to last longer than the environmental pleasant sounds ($z=7.26$, $p<0.001$). However, for both age groups, there was no statistically significant differences in bisection point between pleasant and unpleasant human sounds, although human pleasant sounds tended to be perceived as longer than human unpleasant sounds ($z=-1.28$, $p=0.199$). In addition, for all participants, the discrepancy in perceived duration

between human and environmental sounds was more marked for unpleasant than for pleasant sounds ($z=15.63$ for unpleasant and $z=7.09$ for pleasant, both $p<0.001$).

3.4.3. Experimental effects on the Weber's ratio

Average Weber's ratio values are summarised in **Table** 3-4 and psychometric curves corresponding to each age group and experimental condition are shown in **Figure** 3-4.

The linear mixed model for the Weber's ratio revealed significant main effects of age group ($z=-2.44$, $p=0.015$) and semantic category ($z=2.51$, $p=0.012$), while the main effect of emotional valence and all interactions were non-significant (all $p>0.05$).

The main effect of age group indicated that across all sounds, the average Weber's ratio of healthy older adults was lower than that of the healthy young adults such that healthy older adults had a higher discrimination sensitivity compared to healthy young adults for all sounds. The main effect of semantic category indicated that, irrespective of the emotional valence, environmental sounds were more discriminable than human sounds for all participants.

Table 3-4. Average Weber's ratio for each age group and each experimental condition.

	Young adults		**Older adults**	
Number of participants	57		59	
Condition	**Environmental**	**Human**	**Environmental**	**Human**
Unpleasant	0.25 (0.09)	0.28 (0.09)	0.22 (0.08)	0.27 (0.09)
Pleasant	0.24 (0.07)	0.25 (0.08)	0.23 (0.08)	0.23 (0.07)

Average Weber's ratio values (standard deviations) are shown for the four experimental conditions, for healthy young adults on the left and healthy older adults on the right. A higher Weber's ratio value indicates a lower temporal discrimination sensitivity for the corresponding experimental condition.

3.4.4. Counting effects on timing performance

Out of the 116 participants included in this analysis, 26 reported counting at some point during the experiment (no single participant reported counting during the entire experiment). There were no statistically significant differences in age nor gender distribution (all $p>0.05$). The average bisection point of those who reported counting was not significantly different from those who did not ($t=-0.0486$, $df = 114$, $p=0.9614$). However, there was a statistically significant difference in average Weber's ratio between those who reported counting and those who did not ($z = 3.146$, $p=0.0017$), those who counted having a higher discrimination sensitivity compared to those who did not.

Excluding those who reported counting for the linear mixed modelling analysis of the Weber's ratio did not reveal a main effect of age group, although there was a trend in the same direction ($z=-1.34$, $p=0.182$). There was still a main effect of semantic category, in the same direction ($z=2.37$, $p=0.018$), and still no main effect of emotional valence ($p=0.746$). There was also a significant interaction of valence and semantic category ($p=0.0001$). Post-hoc comparisons further revealed that unpleasant human sounds were less discriminable compared to pleasant human sounds ($z=-3.85$, $p<0.001$) and unpleasant environmental sounds ($z=4.32$, $p<0.001$). There was also a significant three-way interaction and corresponding post-hoc comparisons with Bonferroni correction revealed that the previous differences were only present in the healthy older adults' group ($z=3.99$, $p=0.002$ for the unpleasant human vs environmental sounds; $z=-3.43$, $p=0.017$ for the human pleasant vs unpleasant sounds).

3.4.5. Subjective Time Questionnaire – age differences and correlations with timing performance

Group ratings are shown in **Table** 3-5. Between group differences in subjective speed of time's passing for the present and the upcoming hour, as well as in metaphors of speed were non statistically significant (both $p>0.05$). However, healthy older adults agreed to metaphors of slowness significantly more than healthy young adults ($t = 3.6346$, $df = 114$, $p=0.0004$), although absolute values indicate rejection for both groups according to the rating scale used.

There was a significant correlation between the average bisection point and the usual speed of time's passing in the present for healthy young adults ($rho = 0.3262$, $p=0.0133$), suggesting that healthy young adults who underestimated the duration of all sounds also felt that time passes more quickly. There was also a significant correlation between the average Weber's ratio and the usual speed of time's passing in the present for healthy older adults ($r = 0.2604$, $p=0.0464$), suggesting that healthy older adults who had a lower discrimination sensitivity for all sounds also felt time passes more quickly. There were no other significant correlations between the bisection point or Weber's ratio and other scores of interest from the STQ.

Table 3-5. Group ratings from the Subjective Time Questionnaire

	Young adults	Older adults
Subjective speed of time's passing for the present -2 very slowly / -1 slowly / 0 neither fast nor slow / +1 fast / +2 very fast		
Present usually	0.53 (0.71)	0.69 (0.73)
Next hour	0.65 (0.97)	0.44 (0.65)
Metaphors 0 strong rejection / 1 rejection / 2 neutral / 3 approval / 4 strong approval		
Slow	**1.43 (0.72)**	**1.88 (0.63)**
Speed	2.10 (0.78)	1.83 (0.79)

Group averages are shown with standard deviations in parenthesis. Significant age differences are highlighted in bold.

3.5. Discussion

The present findings shed a new light on emotional and semantic category effects on interval timing. Specifically, using a validated battery of everyday life sounds, I showed that all participants overestimated the duration of unpleasant environmental sounds compared to pleasant environmental sounds, while there was a trend in the opposite direction for human sounds. In addition, all participants overestimated the duration of environmental sounds compared to human sounds across both valence categories. Environmental sounds were also more discriminable than human sounds, irrespective of emotional valence and age group.

These findings complement previous findings of emotion-induced lengthening of perceived duration in the visual domain by revealing pleasantness differences in timing for environmental sounds. Previously, this effect has been attributed to changes in physiological arousal, such that highly arousing stimuli (such as anger) lasted longer in comparison to low arousing stimuli (such as happiness) (Droit-Volet et al., 2004; Effron et al., 2006; Tipples, 2008). Arousal ratings from a pilot study (**Appendix 11**) indicates that environmental unpleasant sounds used here were found significantly more arousing than environmental pleasant sounds for both age groups. Provided that these ratings hold in the Prolific cohort, it is therefore possible that arousal strongly contributed to the observed increase in perceived duration of environmental unpleasant sounds compared to unpleasant ones.

The semantic difference in perceived duration is unlikely due to differences in arousal between environmental and human sounds (**Appendix 11**). Instead, it may be driven by differences in attention, such that human sounds attract more attention and are therefore perceived as lasting less time compared to environmental sounds. It may also be due to differences in their spectrotemporal characteristics. Indeed, a previous study showed that intervals filled with anisochronous sequences (i.e., with irregularly spaced tones) are perceived as shorter than intervals containing isochronous sequences as well as continuous intervals (N. K. Horr & M. Di Luca, 2015). Here, the chosen environmental sounds (angle grinder, car horn, water, bees) are akin to continuous tones because they are uninterrupted, while the human sounds (especially crying and laughter) include

intervals of silence (breaths) and are therefore akin to anisochronous sequences. These distinct perceptual characteristics may also explain why all participants found human sounds less discriminable than environmental sounds, since the same study showed that the duration discrimination sensitivity of anisochronous sequences is lower than that of continuous tones (N. K. Horr & M. Di Luca, 2015).

A few age differences on the temporal bisection task were further identified. Healthy older adults overestimated the duration of environmental sounds compared to healthy young adults, consistently with a previous study showing duration overestimation of happy faces by healthy older adults compared to healthy young adults (Nicol et al., 2013). However, unlike the previous study, healthy ageing did not impact duration judgements of human pleasant sounds nor of unpleasant ones. Nicol et al previously attributed the overestimation of durations by healthy older adults to the positivity effect of aging, whereby older adults raise their arousal responses to positive stimuli and diminish those to negative stimuli. It is possible that a similar effect operated here, e.g., that the significantly higher arousal response to environmental pleasant sounds and the apparent lower arousal response to environmental unpleasant sounds by healthy older adults compared to healthy young adults (**Appendix 11**) may have been sufficient to drive the age difference in perceived duration of environmental sounds. Finally, healthy young adults had a lower temporal discrimination sensitivity compared to healthy older adults across all experimental conditions. Although this result is surprising in regard to prior literature (Block et al., 1998; Gagnon et al., 2018; McCormack et al., 1999; Ogden et al., 2019; Wearden et al., 1997), it may reflect the higher dependence of the current task on crystallised intelligence (ability to use previously stored information accumulated through experience) as opposed to fluid intelligence (ability to think flexibly), thereby providing an advantage to healthy older adults whose crystallised cognitive ability has previously been shown to outperform that of healthy young adults (Samanez-Larkin & Knutson, 2015).

The correlation between perceived speed of time's passing and bisection point averaged across experimental conditions revealed that healthy young adults who underestimated the duration of all sounds also felt that time passes more quickly. While it is not clear why a similar correlation was not observed in healthy older adults, these results could

generally be attributed to a faster “internal clock”, or reduced attention oriented to time in healthy young adults when considering pacemaker-accumulator models. In addition, healthy older adults who have a lower discrimination sensitivity across all sounds were found to perceive time as passing more quickly, suggesting that difficulties with keeping track of time may result from noisier timing mechanisms in this age group (Turgeon et al., 2016).

Previous studies have shown that mental counting leads to violations of the scalar property (e.g., a constant Weber’s ratio across a wide range of durations), and that the most effective way to counteract this (e.g., with minimal impact on duration judgments) is to ask participants not to count (Rattat & Droit-Volet, 2012). Despite this, about a third of the participants tested here reported counting, with a similar distribution across age and gender groups. Unsurprisingly, counting only impacted Weber’s ratio averages across experimental conditions, with those who counted having a higher discrimination sensitivity compared to those who did not. In addition, excluding those who counted modified experimental effects on the Weber’s ratio in the following aspects: (1) the main effect of age group did not hold (although there was a trend in the same direction); (2) unpleasant environmental sounds were more discriminable than unpleasant human sounds specifically for healthy older adults; (3) human unpleasant sounds were less discriminable compared to human pleasant sounds specifically for healthy older adults as well. Considering there were more healthy older adults than healthy young adults who reported counting (almost twice as much), the first change suggests that healthy older adults adopted counting strategies to compensate for their deficits in attention. It may therefore be unsurprising that, when focusing on participants who did not count, the duration discrimination sensitivity was more strongly influenced by emotional and semantic sound characteristics specifically in healthy older adults.

The present findings need to be treated with caution, however. Unlike previous studies on subjective time perception, I did not recruit and test participants face-to-face in a controlled laboratory setting. Instead, I recruited participants remotely through the third-party recruitment platform Prolific. An increasing number of psychological research studies are performed on Prolific, since it has provided excellent means to continue research in the COVID-19 era, even for longitudinal assessments (Agley et al.,

2021; Nikolaidis et al., 2022; Stanton et al., 2022). However, testing participants remotely comes with several caveats which may have impacted performance on the current temporal bisection task: (1) participants may have been paying less attention without an experimenter monitoring their behaviour in the same room, which may explain the high number of participants who were excluded from final statistical analysis due to noisy data; (2) participants were not using the same auditory equipment, such that although they reported completing the study in a quiet room with minimal distractions, it is likely that they listened to sounds with a differing audio quality, which may further have impacted time judgements. Despite these issues, the present study replicated the previous finding of overestimation of unpleasant sounds compared to pleasant sounds, partially validating the current study settings.

Undoubtedly, the present study should be replicated in larger cohorts, perhaps restricting participants to the use of good quality headphones. It would also be interesting to conduct a similar experiment when the Covid pandemic has resolved (or at least when participants have accepted the "new normal") to determine whether the psychological impact of the pandemic has had a wider influence on the present results. Physiological measures of arousal using pupillometry or skin conductance could be collected, especially to implement arousal as an experimental factor (with low and high arousing categories) to properly dissect its impact on perceived duration and its interaction with emotional valence within the current sound battery. The study could also be expanded into a more diverse range of sounds, for example by using a 2x2 factorial design with either continuous or dynamic environmental and human sounds to test the hypothesis of perceptual characteristics driving differences in perceived duration between environmental and human sounds. Finally, the healthy older group tested here may have still been relatively young (Turgeon et al., 2016) and testing much older participants (above the age of 75) may reveal stronger age differences in timing.

In the next chapter, I will consider the effect of remote testing (using Zoom) on neuropsychological performance of healthy older adults and patients with diverse dementia syndromes to assess the impact of different neurodegenerative diseases on subjective time perception and compare with current findings on healthy ageing.

4. Delivery of neuropsychology and neurolinguistic assessments to dementia patients in the COVID-19 era

4.1. Chapter summary

Aims

- Measure performance of healthy older adults as well as AD and FTD patients on several neuropsychological and neurolinguistic tests
- Compare performance between testing modalities (remote vs face-to-face) in each participant group
- Provide evidence for merging data collected before and during the pandemic

Methods

- A total of 25 patients (13 typical and logopenic AD, 12 FTD) were recruited for remote testing and 64 patients (31 typical and logopenic AD, 33 FTD) tested face-to-face before the pandemic were selected from a historical database. Ten healthy older participants took part in both face-to-face and remote testing
- Face-to-face testing was carried out at our research centre in a dedicated testing room, while remote testing was carried out over Zoom from the comfort of participants' homes
- General neuropsychological and neurolinguistic assessments included tests of general intellect, episodic and working memory, arithmetic, visuospatial and executive function skills, as well as tests of phoneme perception, reading, single word and sentence comprehension, speech repetition and sentence construction

Results

- Remote delivery of neuropsychological and neurolinguistic assessments to dementia patients during the COVID-19 pandemic was technically feasible
- Testing modality (face-to-face vs remote) did not affect performance of healthy participants or dementia patients on neuropsychological tests measuring working memory, executive function and arithmetic skills, as well as general semantic knowledge

Conclusion

- Collecting new neuropsychological datasets remotely is feasible
- Remote performance is largely comparable to face-to-face performance, providing evidence for merging timing data collected face-to-face pre-pandemic with timing data collected remotely during the pandemic

4.2. Introduction

This chapter describes work conducted as part of my research team's response to the COVID-19 pandemic in relation to the neuropsychological and neurolinguistic testing of dementia patients, who were particularly at risk of experiencing severe symptoms from infection by the COVID-19 virus. The pandemic strongly impacted my PhD project by interrupting data collection for almost a full year (from March 2020 to February 2021) due to several periods of national lockdown. Given the uncertainty around vaccine development that prevailed at the time, my research team anticipated that a return to a 'normal' pre-pandemic research environment would be difficult, if not impossible. General anxiety directly related to the global pandemic meant that even if we implemented ways to make face-to-face research safer for participants, they would not necessarily feel safe enough to be willing to come to the Dementia Research Centre (DRC). Hearing from the rare dementia support groups connected to the DRC that patients and their families were still eager to contribute to research despite the pandemic, my research team decided to restart research efforts by moving online.

Here I present general neuropsychological and neurolinguistic data collected both face-to-face (pre-pandemic) and remotely from patients diagnosed with major FTD and AD syndromes, as well as healthy older participants. I evaluate the impact of delivering general neuropsychology and neurolinguistic tests remotely as opposed to face-to-face with the view to justifying the merging of both datasets for the time perception analysis developed in **Chapter 6**.

What do we know?

Development and implementation of online cognitive assessments for dementia patients, particularly within communities who experience difficulties in accessing clinical care (for diagnosis and treatment) is not new (Poon et al., 2005). However, with the COVID-19 pandemic, there has been a clear shift towards the use of online methods to meet clinical needs and resume research activities. This is particularly well illustrated by the increase in publications related to online cognitive assessments of dementia patients since the start of the pandemic. A quick PubMed search using the following keywords (videoconference, online

assessment, face-to-face assessment, cognitive, neuropsychology, dementia) resulted in 13 papers published in 2021 alone (only two dated from the year before).

Of particular relevance is a review published in 2021 (Hunter et al., 2021), summarising 20 years of research comparing face-to-face and online administration of cognitive tests to healthy older adults and participants diagnosed with mild cognitive impairment (MCI), Alzheimer's disease (AD), or other types of dementia (often unspecified; one study mentioned testing one FTD participant but results were merged across all dementia types). The authors identified 12 studies where video conferencing methods were used, four of which included patients who were tested directly from their homes, except for one. Overall, the findings demonstrate that remote testing is feasible and that online performance remains stable across testing modalities (with a maximum delay of 3 months between assessments), especially in the following cognitive domains: executive function (measured using the letter and category fluency tests), working memory (with digit span forward slightly better preserved across modalities compared to the reverse version), verbal episodic memory, and language (in particular naming using the Boston Naming Test). Minimal evidence was available for visuospatial tasks, tests of single word and sentence comprehension (only one study evaluated this and found preserved online performance), and another test of executive function (WASI Matrix reasoning for which healthy older adults scored comparably across testing modalities while no data on dementia patients are currently available).

Despite these promising findings, more research needs to be done to further validate remote neuropsychological testing in patients. Specifically, it would be important to further assess the feasibility of remote cognitive testing: (1) in a non-controlled environment where low or unstable internet connection speed and use of equipment not designed for research purposes is likely to impact the delivery of both auditory and visual stimuli; (2) with patients diagnosed with different types of dementia (beyond AD); notably, patients with language-led dementias such as the Primary Progressive Aphasias (svPPA, nfvPPA, lvPPA) are likely to be impacted more than patients with AD by the testing modality due to their prominent communication difficulties, an aspect that has not been evaluated before; and (3) using tests measuring diverse cognitive functions, especially those which have not been delivered to dementia cohorts before (WASI Matrix reasoning, visuospatial tasks). There is also a need to more consistently report the recruitment and remote testing protocols used to evaluate the

inevitable selection bias that ensues from remote testing due to the technological requirements or possible visual/auditory difficulties that cannot be accommodated for in a remote testing setting.

What did I do here?

Based largely on the face-to-face protocol for general neuropsychological and neurolinguistic testing used at the DRC, I built a protocol for remote testing of patients diagnosed with major AD and FTD syndromes directly from their homes via a widely used video conferencing software (Zoom). I also recruited healthy older adults who had physically taken part in our research at the Dementia Research Centre 3-4 years before the pandemic. I first compared healthy controls' performance on several neuropsychological and neurolinguistic tests between the two testing modalities (face-to-face vs remote). I also compared performance of AD and FTD patients tested remotely with performance from a historical cohort of patients chosen to represent the same syndromes and to match the remote cohort based on age, education, and symptom duration. Critically, I compared performance on each individual neuropsychological and neurolinguistic test between the two testing modalities separately for each group, using a Bayesian approach that assesses the amount of evidence in favour of the null hypothesis relative to the alternative hypothesis (significant difference between face-to-face and remote). I did not perform between group comparisons of neuropsychological and neurolinguistic performance as these profiles have been reviewed and published elsewhere (Marshall, Hardy, Volkmer, et al., 2018; H. Sivasathiaseelan et al., 2019).

What are my hypotheses?

Based on previous research on neuropsychological testing in dementia patients (Hunter et al., 2021), I did not expect any differences in performance between healthy and dementia participants tested face-to-face and those assessed remotely on most neuropsychological and neurolinguistic tests, especially those measuring general intelligence and cognitive functions such as executive function and vocabulary. However, worse remote performance on tests of speech perception is possible, considering it is more difficult to control the auditory environment outside of the laboratory.

4.3. Methods

4.3.1. Participant remote recruitment and group matching

By October 2020, our research ethics was updated (through the NHS and UCL Ethics committees) to accommodate for online testing of dementia patients and healthy older adults. Participants were recruited via means listed in **section 2.1.2** during the Covid-19 pandemic between February and August 2021. All participants took part in a trial run to establish they had access to the necessary equipment (tablet or desktop/laptop computer), a stable broadband internet connection and a quiet testing space to support the remote assessment. They further completed the T-MMSE (**section 2.2.1**) to assess their disease severity. A cut-off score of 12 on the T-MMSE, which corresponds to a converted MMSE score of 16 (Newkirk et al., 2004), was used as an inclusion criterion. Six participants were excluded due to technological requirements associated with remote testing (e.g., they were not comfortable with video assessments, or had visual/hearing limitations).

A resulting twenty-five patients (eight typical AD, three bvFTD, four svPPA, five nfvPPA, and five lvPPA) were enrolled into the study. A historical cohort of 64 patients (25 AD, 12 bvFTD, nine svPPA, 12 nfvPPA, six lvPPA) who had previously taken part in face-to-face testing at the Dementia Research Centre were selected to match the cohort assessed remotely as closely as possible for syndromic composition, age, years of education and symptom duration. They will be respectively referred to as the 'remote' and 'face-to-face' patient cohorts hereafter. All patients fulfilled consensus criteria for the relevant syndromic diagnosis (Dubois et al., 2014; M.L. Gorno-Tempini et al., 2011; Rascovsky et al., 2011) and had a disease of mild to moderate severity. Brain MRI was consistent with the syndromic diagnosis in all patients, without evidence of significant cerebrovascular burden.

Ten healthy older individuals with no history of neurological or psychiatric illness and who had been previously seen for face-to-face testing between three and four years previously were also invited for remote testing.

Demographic details for all participants are summarised in **Table** 4-1.

Table 4-1. General demographic and clinical characteristics for all participant groups

Group	CTL	AD		bvFTD		svPPA		nfvPPA		lvPPA	
Setting	**Remote**	**F2F**	**Remote**	**F2F**	**Remote**	**F2F**	**Remote**	**F2F**	**Remote**	**F2F**	**Remote**
No.	10	25	8	12	3	9	4	12	5	6	5
Gender (M/F)	7/3	15/10	5/3	8/4	3/0	7/2	2/2	6/6	2/3	4/2	4/1
Age (yrs)	74 (4.1)*	69.5 (4.1)	69.8 (5.9)	70.3 (2.9)	72.0 (5.6)	60.3 (5.2)	58.3 (9.3)	67.1 (5.2)	68.2 (6.4)	69.5 (3.6)	71.6 (4.7)
Education (yrs)	17.6 (0.7)	14.8 (2.5)	16.0 (3.7)	14.9 (2.7)	14.7 (3.1)	16.0 (1.9)	15.5 (3.1)	15.3 (2.3)	14.8 (2.8)	16.0 (1.7)	16.0 (3.3)
Handedness (R/L/A)	9/1/0	23/1/1	8/0/0	11/1/0	3/0/0	9/0/0	3/1/0	10/2/0	5/0/0	5/1/0	5/0/0
Symptom duration (yrs)	N/A	6.8 (2.3)	7.3 (3.7)	4.7 (2.1)	3.7 (3.8)	4.1 (1.9)	3.5 (1.9)	3.4 (1.7)	3.2 (0.8)	4.2 (1.9)	3.8 (1.9)

Mean (standard deviation) values are shown for age, education, symptom duration for each group. No significant differences were found between remote and face-to-face cohorts. *on average healthy controls were 3.5 years younger when tested face-to-face; A, ambidextrous; F, female; F2F, face-to-face; L, left M, male; N/A, not applicable; R, right.

4.3.2. Testing procedure face-to-face

All face-to-face neuropsychological and neurolinguistic tests were separately administered in dedicated quiet testing rooms at the Dementia Research Centre, with the participant sitting opposite the experimenter and following standard administration methods (see **section 2.2.2** for a list of both batteries). Patients with bvFTD and AD did not receive the neurolinguistic battery.

The neuropsychological battery typically required around two hours and the neurolinguistic battery around an hour and a half to administer, allowing for short breaks. Participants were predominantly tested on their own, unless a patient's carer requested to be present, in which case they were explicitly asked not to intervene during testing. No feedback was given about performance and no time limits were imposed unless timing was intrinsic to the test. The procedure put in place for face-to-face delivery of neuropsychological tests at the Dementia Research Centre between 2013 and 2020 served as a basis for developing the remote testing protocol.

4.3.3. Testing procedure – remote

An initial session was conducted on Zoom to accustom participants with the remote testing format, check the screen and sound sharing options on Zoom, and make sure the quality of their internet connection was acceptable.

Participants were permitted to use their preferred technology interface (tablet, laptop, or desktop computer). To ensure screen visibility, we did not accept the use of smartphones for remote testing. Only six participants used headphones; most participants (90%) used speakers. In all cases, device volume was set to a comfortable level by each participant or their caregiver. Remote assessments were planned to ensure testing could be carried out in a quiet environment with minimal distractions. Each patient's primary caregiver was asked to be available during each research session in case of any problem using the remote testing technology; in practice, no major technological issues arose during the remote testing sessions.

Before beginning remote testing, participants listened to a set of 10 sentences from the Bamford-Kowal-Bench list to check basic audibility in the remote testing environment. These sentences have previously been validated in hearing-impaired children (Bench et al., 1979). Spoken sentences were delivered online using Labvanced (**section 2.6.1**) and

shown to the participant via screen and sound share on Zoom. A perfect score on the final 3 items of the test was required to go on to the remote testing session proper (this allowed each participant and/or caregiver to manually adjust the volume to a comfortable level to make sure the participant could hear all the words in the sentence). Most participants (95%) performed at ceiling, and no one was rejected based on their performance on this screening test. Detailed results from the BKB sentences test are displayed in **Table** 4-2.

A reduced version of the neuropsychological and neurolinguistic face-to-face batteries was delivered remotely (**section 2.2.2**), such that each battery would take about an hour to administer. The remote neuropsychological battery comprised tests of general intellect, episodic and working memory, language, as well as arithmetic, visuospatial and executive function skills. The remote neurolinguistic battery assessed phoneme perception, reading, single word and sentence comprehension, speech repetition and sentence construction.

To further minimise 'Zoom fatigue', each battery was delivered on separate sessions typically within the same week (and never more than two weeks apart). At the end of each testing session, each participant was debriefed by the experimenter to provide them with the opportunity to raise any technical difficulties with and give their impressions of remote testing. No technical difficulties were reported, and all participants said they felt comfortable with remote testing.

4.3.4. Statistical analysis

All statistical analysis was performed in JASP (version 0.16).

The remote and face-to-face patient cohorts were compared on demographic characteristics using independent samples t-tests and Wilcoxon rank-sum tests. Healthy controls' scores in remote and face-to-face testing modalities were compared using paired samples t-tests or (where the assumption of normality was not met) Wilcoxon signed rank tests. To reduce Type I error, no corrections for multiple comparisons were applied.

I did not perform between group comparisons of neuropsychological and neurolinguistic performance as these syndromic profiles of the neuropsychological and neurolinguistics tests have been reviewed and published previously (Marshall, Hardy, Volkmer, et al., 2018; H. Sivasathiaseelan et al., 2019).

Our null hypothesis was that there would be no effect of testing modality on neuropsychological performance – i.e., no differences in performance between remote and face-to-face assessment settings – for any participant group. To critically assess the magnitude of evidence in favour of this null hypothesis versus the alternative hypothesis (i.e., that there was in fact an effect of testing modality), we employed a Bayesian approach (Dienes, 2014). Bayesian independent samples t-tests (and non-parametric equivalents) were performed for each general neuropsychological and neurolinguistic test in each patient group separately. Given the small sample size of some patient groups, I also compared testing modalities across the combined patient cohort. Healthy control performance was compared using Bayesian paired samples t-tests (or non-parametric equivalents). A Bayes factor, which is the ratio of evidence supporting the null hypothesis over the alternative hypothesis (hereafter BF_{01}) was calculated for each comparison using JASP. A BF_{01} value > 3 indicates strong evidence in favour of the null hypothesis while a value < 0.33 supports the alternative hypothesis; BF_{01} value between 0.33 and 3 are classified as 'anecdotal' evidence. Results from the Bayesian analysis are presented in **Table** 4-4 and **Table** 4-6.

Table 4-2. Results from the BKB test for remote testing participants

	Controls	AD	bvFTD	svPPA	nfvPPA	lvPPA
BKB test before general neuropsychology testing						
Average number of incorrect items (/10)	0.0 (0.0)	0.1 (0.4)	0.0 (0.0)	0.0 (0.0)	0.2 (0.4)	0.0 (0.0)
BKB test before neurolinguistic testing						
Average number of incorrect items (/10)	0.0 (0.0)	N/A	N/A	0.0 (0.0)	0.4 (0.9)	0.0 (0.0)

The data indicate that there were no major background listening environmental confounds nor any significant differences between participant groups (all p>0.05). Mean number of incorrect items out of 10 for each group are shown.

4.4. Results

4.4.1. General participant characteristics

No significant differences in age, years of education or symptom duration were found between the face-to-face and remote testing patient cohorts.

4.4.2. General neuropsychological assessment

Healthy individuals scored equally well on the digit span reverse, the British Picture Vocabulary Scale (BPVS), the Graded Difficulty Arithmetic (GDA), and on both letter and category fluency tests (all BF_{01} > 3 indicating strong evidence in favour of the null hypothesis for all tests). However, they performed less well on the Visual Object and Spatial Perception Object Decision task (VOSP) in remote testing compared to face-to-face testing (BF_{01} = 0.0404, indicating strong evidence in favour of the alternative hypothesis), though absolute performance differences were relatively small (face-to-face average score = 19.5 vs remote average score = 18.4; **Table** 4-3 and **Table** 4-4, **Figure** 4-1 and **Figure** 4-2).

When comparing the combined face-to-face patient cohort against the combined remote patient cohort, I found strong evidence supporting the null hypothesis for all neuropsychological tests (all BF_{01} > 3), except for the NART and both fluency tests, for which the evidence was only anecdotal (**Table** 4-3 and **Table** 4-4).

Regarding individual patient groups (**Table** 4-3 and **Table** 4-4, **Figure** 4-1), the AD group tested remotely performed similarly to the AD group seen face-to-face in most tests spanning all cognitive domains except episodic memory, namely: the WASI matrix reasoning, digit span forward, graded naming test (GNT), BPVS, GDA, and category fluency test (all BF_{01} > 3). However, the remote AD cohort performed less well on the VOSP compared to the face-to-face AD cohort (face-to-face average score = 16.1 vs remote average score = 13.0; BF01 = 0.171, strong evidence). On the other hand, the remote lvPPA group performed better on the letter fluency test compared to the face-to-face lvPPA group (face-to-face average score = 2.6 vs remote average score = 11.3; BF01 = 0.188, strong evidence).

There was only anecdotal evidence in favour of the null hypothesis for all other comparisons (**Table** 4-4).

Table 4-3. Performance on the general neuropsychological battery of the face-to-face cohort compared to the remote cohort

	Controls		AD		bvFTD		svPPA		nfvPPA		lvPPA	
	F2F	Remote	F2F	Remote	F2F	Remote	F2F	Remote	F2F	Remote	F2F	Remote
No. tested	10	10	25	8	12	3	9	4	12	5	6	5
General intellect												
WASI Matrix (/32)	26.9 (2.4)	26.3 (3.5)	14.5 (7.5)	13.7 (11.5)[b]	14.6 (9.5)[a]	7.7 (2.5)	25.8 (4.9)	23.3 (3.4)	18.6 (8.3)[a]	24.0 (2.6)	10.0 (9.2)	17.6 (10.3)
Episodic memory												
RMT faces Short (/25)	N/A	23.3 (2.5)	18.9 (3.7)[k]	15.3 (2.1)	N/A	20.3 (4.0)	N/A	19.3 (3.7)	N/A	22.4 (3.7)	N/A	21.6 (3.8)
RMT faces Long (/50)	42.7 (4.72)	N/A	30.44 (6.56)[i]	N/A	28.56 (6.29)[c]	N/A	31.5 (4.47)[a]	N/A	40.3 (5.79)[t]	N/A	33.17 (8.93)	N/A
Working memory												
DS(Forward) (/12)	9.8 (2.0)	9.2 (2.0)	6.5 (2.1)[a]	6.6 (2.3)	7.8 (2.9)	6.3 (0.6)	9.4 (2.2)	7.3 (0.5)	5.1 (2.6)[b]	6.0 (4.4)	3.0 (3.1)[a]	5.0 (2.5)
Language												
BPVS (/150)	149.0 (1.1)	148.9 (1.1)	135.1 (24.0)[a]	133.9 (21.4)	118.7 (28.9)[a]	148.0 (1.0)	61.9 (44.1)	98.0 (46.3)	136.3 (30.4)	142.8 (8.4)	120.2 (39.6)	145.2 (4.4)
GNT (/30)	27.3 (2.1)	26.8 (1.8)	13.7 (8.5)[a]	12.4 (6.3)	11.5 (11.0)[a]	20.0 (4.4)	0.2 (0.4)	0.5 (1.0)	15.8 (6.8)	20.2 (7.6)	6.2 (7.7)	12.4 (7.0)
NART (/50)	45.2 (3.4)	44.6 (3.0)	28.3 (11.9)[a]	37.1 (4.6)	30.7 (13.1)	40.0 (2.0)	16.1 (10.2)	16.3 (13.6)	28.3 (15.0)[f]	30.8 (14.9)	20.4 (18.5)[a]	29.8 (16.9)
Arithmetic												
GDA (/24)	16.6 (6.4)	16.1 (4.0)	4.9 (5.0)[e]	4.8 (5.4)	8.2 (7.4)[a]	8.3 (7.2)	13.3 (5.5)	7.3 (4.0)	5 (3.6)[d]	6.4 (7.2)	1.7 (1.5)	7 (5.8)
Visuospatial												
VOSP (/20)	19.5 (0.7)	18.4 (1.2)	16.1 (2.6)[a]	13.0 (3.0)	14.0 (4.2)	17.0 (1.0)	15.3 (6.3)[a]	14.5 (5.9)	16.8 (3.6)[b]	17.6 (2.1)	15.8 (3.1)	15.8 (2.7)
Executive												
DS (Reverse) (/12)	8.0 (2.6)	8.2 (2.2)	4.6 (1.9)[c]	4.0 (1.9)	5.0 (3.1)[a]	4.0 (0.0)	6.9 (2.7)	5.5 (2.7)	4.4 (1.7)[d]	5.2 (4.2)	2.4 (1.1)[a]	4.8 (1.8)
Letter fluency	19.7 (6.0)	20.8 (4.2)	10.3 (5.2)	11.9 (7.4)	6.8 (3.9)[a]	7.3 (2.3)	7.0 (3.6)[b]	10.8 (7.0)	4.8 (5.8)[d]	14.0 (8.2)[a]	2.6 (3.8)[a]	11.3 (3.9)
Category fluency	25.0 (6.6)	24.7 (5.4)	10.0 (5.6)	10.4 (6.7)	8.0 (6.1)	10.3 (6.0)	6.1 (5.3)[a]	9.8 (6.2)	8.6 (5.8)[d]	18.6 (11.5)	5.7 (5.8)	11.6 (8.1)

Mean (standard deviation) values of performance on neuropsychology tests are shown (maximum scores are indicated in parentheses) for each testing modality (face-to-face vs remote research setting) in each participant group. Green cells indicated strong evidence for the null hypothesis (H0); blue cells indicate strong evidence for the alternative hypothesis (H1). Exact values for the Bayes factor comparing H0 against H1 (BF_{01}) are presented in **Table** 4-4. A reduced number of participants completed certain tests, as follows: [a]n-1, [b]n-2, [c]n-3, [d]n-4, [e]n-5, [f]n-6, [g]n-7, [h]n-8, [i]n-9. [j]n-11, [k]n-16, [l]n-20. F2F, face-to-face; N/A, not available.

Table 4-4. Bayes factor values for general neuropsychological performance comparisons between remote and face-to-face testing modalities

	Controls	All patients	AD	bvFTD	svPPA	nfvPPA	lvPPA
General intellect							
WASI Matrix	2.56^{t} (Anecdotal)	5.403 (Strong)	3.134^{t} (Strong)	1.477^{t} (Anecdotal)	1.911^{t} (Anecdotal)	1.356^{t} (Anecdotal)	1.441^{t} (Anecdotal)
Episodic memory							
RMT Faces short	N/A	3.46 (Strong)	0.411^{t} (Anecdotal)	N/A	N/A	N/A	N/A
Working memory							
DS (Forward)	2.663^{t} (Anecdotal)	4.54 (Strong)	3.467^{t} (Strong)	1.948^{t} (Anecdotal)	0.799^{t} (Anecdotal)	2.528^{t} (Anecdotal)	1.598^{t} (Anecdotal)
Language							
BPVS	4.304^{t} (Strong)	4.05 (Strong)	3.363 (Strong)	1.836 (Anecdotal)	1.382^{t} (Anecdotal)	2.754 (Anecdotal)	1.261 (Anecdotal)
GNT	2.923^{t} (Anecdotal)	4.16 (Strong)	3.542 (Strong)	1.407^{t} (Anecdotal)	2.331 (Anecdotal)	1.68^{t} (Anecdotal)	1.325^{t} (Anecdotal)
NART	2.83^{t} (Anecdotal)	1.99 (Anecdotal)	1.552 (Anecdotal)	1.511^{t} (Anecdotal)	2.606^{t} (Anecdotal)	2.52^{t} (Anecdotal)	1.948^{t} (Anecdotal)
Arithmetic							
GDA	3.671 (Strong)	5.30 (Strong)	3.33 (Strong)	2.467^{t} (Anecdotal)	0.943^{t} (Anecdotal)	2.483^{t} (Anecdotal)	1.123^{t} (Anecdotal)
Visuospatial							
VOSP	0.0404 (Strong)	4.76 (Strong)	0.171^{t} (Strong)	2.215 (Anecdotal)	2.478 (Anecdotal)	2.553 (Anecdotal)	2.592^{t} (Anecdotal)
Executive							
DS (Reverse)	4.304^{t} (Strong)	5.28 (Strong)	2.746^{t} (Anecdotal)	Variance at 0	1.991^{t} (Anecdotal)	2.659 (Anecdotal)	0.417^{t} (Anecdotal)
Letter fluency	3.159^{t} (Strong)	0.59 (Anecdotal)	2.86^{t} (Anecdotal)	2.426^{t} (Anecdotal)	1.519^{t} (Anecdotal)	0.511^{t} (Anecdotal)	0.188^{t} (Strong)
Category fluency	3.767^{t} (Strong)	1.08 (Anecdotal)	3.532 (Strong)	2.186^{t} (Anecdotal)	1.715^{t} (Anecdotal)	1.027 (Anecdotal)	1.29^{t} (Anecdotal)

The table shows the values for the Bayes factor BF_{01} indicating the amount of evidence in favour of the null hypothesis H0 against the alternative hypothesis H1 comparing performance between testing modalities for each test in each group (e.g., a BF_{01} value of 4 means that the obtained data are 4 times more likely under the null hypothesis than under the alternative hypothesis). For $BF_{01} > 3$ or $<1/3$, it is considered that there is strong evidence supporting either of the alternative hypotheses. Any values in between are categorised as 'anecdotal' evidence. Results are influenced by the prior (more specifically the shape of the prior influences the strength of the evidence), which can be specified be default using a Cauchy distribution, as here; the Cauchy scale set here is 1.00. The superscript ^{t} indicates that a parametric Bayesian test was used; else, the non-parametric equivalent Mann Whitney (with 1000 iterative samples) was used. Colour coding is identical to **Table** 4-3.

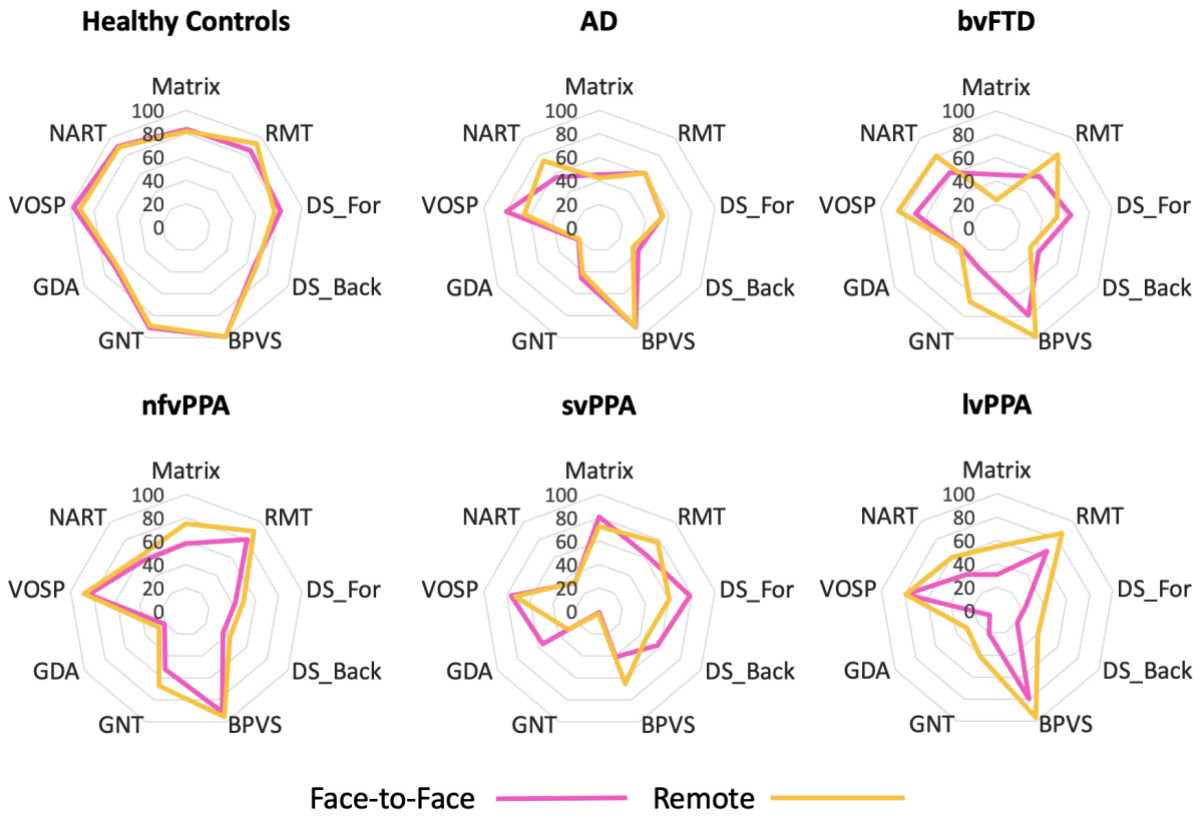


Figure 4-1. Radar plots of performance on the general neuropsychology battery for all participant groups.

Average percentage correct score (plotted on concentric lines) was calculated for each test on the neuropsychology battery, each testing modality, and each participant group. Scores for the fluency tasks were not included here as responses on these tasks cannot be evaluated as correct/incorrect. BPVS, British Picture Vocabulary Scale; DS_For/Back, Digit Span Forwards/Backwards; GDA, Graded Difficulty Arithmetic test; GNT, Graded Naming Test; Matrix, WASI Matrix Reasoning; NART, National Adult Reading Test; RMT, Recognition Memory Test; VOSP, Visual Object Space Perception Object Decision test.

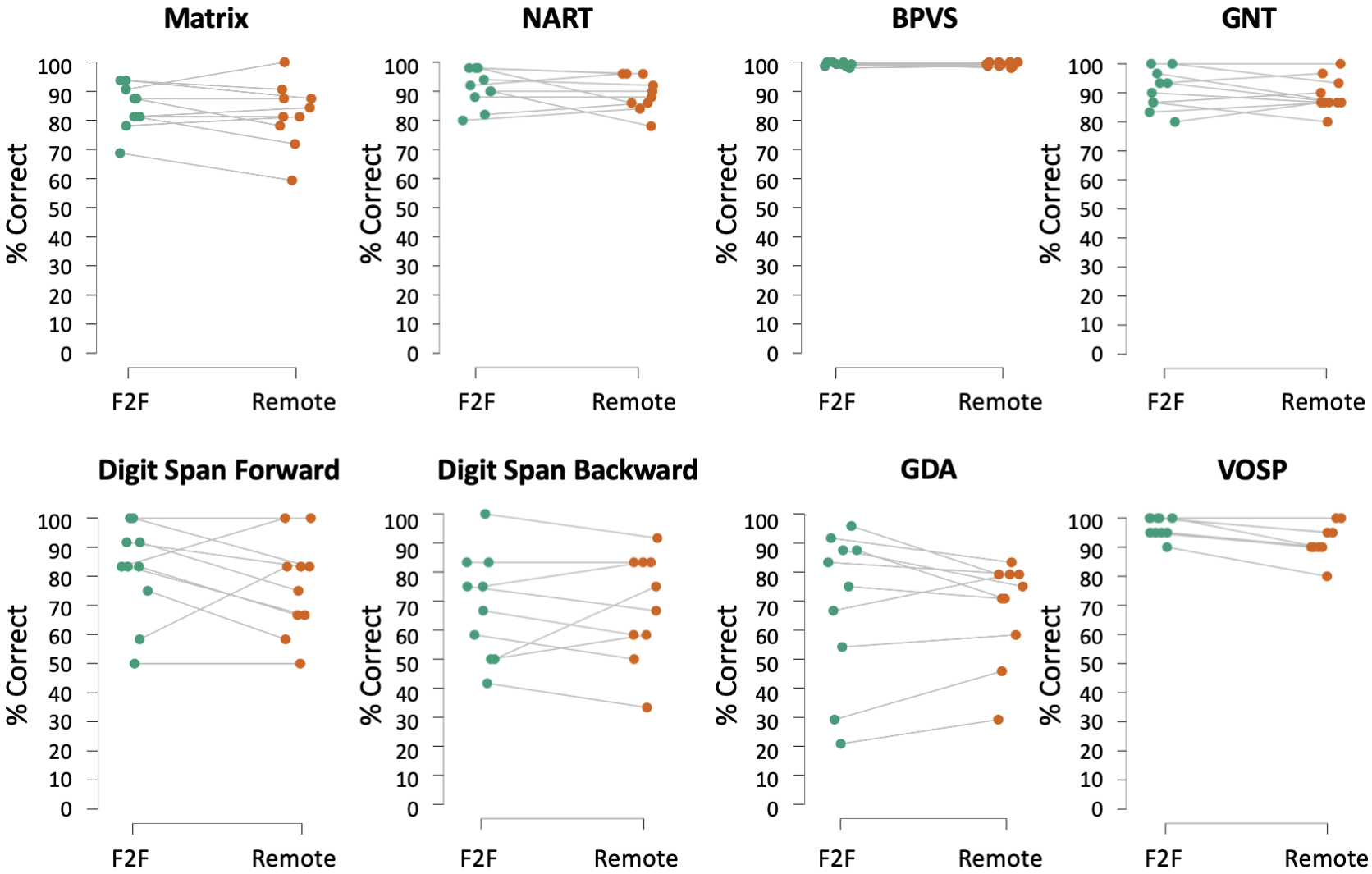


Figure 4-2. Performance profiles of healthy control participants on the general neuropsychological battery

Line plots indicating percentage scores for each healthy control participant on representative tests from the neuropsychological battery administered face-to-face and remotely.

4.4.3. Neurolinguistic assessment

Healthy individuals scored equally well on the Boston Naming Test (BNT), the camel and cactus test, and the bisyllabic single word repetition test (all $BF_{01} > 3$ indicating strong evidence in favour of the null hypothesis for all tests). However, they performed less well on the monosyllabic word repetition test in remote testing than in face-to-face testing, though the absolute performance difference was quite small (face-to-face average score = 14.6 vs remote average score = 12.7; BF01 = 0.0487, strong evidence; **Table** 4-5 and **Table** 4-6, **Figure 4-3** and **Figure** 4-4).

When comparing the combined face-to-face patient cohort against the combined remote patient cohort, I found strong evidence supporting the null hypothesis for the non-word reading, concrete synonyms, PALPA-55, as well as bisyllabic and trisyllabic single word repetition tests (all $BF_{01} > 3$; **Table** 4-5 and **Table** 4-6).

There was only anecdotal evidence in favour of the null hypothesis for all other comparisons (**Table** 4-6).

Table 4-5. Performance on the neurolinguistic battery of the face-to-face cohort compared to the remote cohort

	Controls		svPPA		nfvPPA		lvPPA	
	F2F	Remote	F2F	Remote	F2F	Remote	F2F	Remote
No. tested	10	10	9	4	12	5	6	5
Phoneme perception								
PALPA 3 (/36)	34.9 (1.6)	33.8 (2.0)	35.3 (1.3)	33.5 (2.6)	31.9 (5.7)	34.0 (1.6)	33.8 (2.4)[a]	32.0 (4.0)
Reading								
Non-word reading (/25)	24.4 (0.8)	24.9 (0.3)	19.6 (4.9)	16.0 (9.8)	19.3 (5.7)[d]	15.8 (8.7)	14.5 (5.4)	16.4 (9.6)
Regular reading (/25)	25.0 (0.0)	25.0 (0.0)	22.8 (3.9)[d]	21.3 (6.2)	23.3 (2.2)[g]	22.2 (4.2)	24.5 (0.7)[d]	21.8 (6.1)
Irregular reading (/25)	24.7 (0.7)	25.0 (0.0)	18.8 (5.8)[d]	18.3 (8.9)	19.8 (6.4)[g]	21.6 (4.4)	21.5 (3.5)[d]	22.6 (2.1)
Naming								
BNT (/30)	29.2 (0.8)	29.0 (1.0)	3.3 (3.4)	9.5 (7.1)	24.7 (4.4)[b]	24.4 (7.6)	9.7 (8.0)	16.8 (8.8)
Semantic association								
Camel and cactus (/32)	31.0 (1.0)	30.9 (1.1)	22.3 (5.1)[e]	25.5 (2.6)	28.3 (5.5)[h]	30.0 (1.4)	29.0 (0.0)[e]	29.0 (2.1)
Word comprehension								
Concrete synonyms (/25)	24.5 (0.5)	24.3 (0.5)	15.5 (2.9)[c]	17.0 (4.0)[a]	22.2 (3.2)[b]	21.0 (4.2)	15.6 (9.4)[a]	21.4 (3.5)
Abstract synonyms (/25)	24.8 (0.4)	24.3 (0.8)	14.4 (1.5)[d]	17.3 (1.2)[a]	21.4 (3.7)[b]	21.2 (3.4)	16.5 (11.2)[b]	22.3 (2.1)[a]
Sentence comprehension								
PALPA 55 (/24)	23.8 (0.4)	23.1 (1.3)	22.6 (1.6)[a]	21.8 (2.2)	19.6 (4.8)[a]	21.0 (2.6)	18.8 (2.6)[a]	20.0 (2.1)
Speech repetition								
Monosyllabic word repetition (/15)	14.6 (0.5)	12.7 (1.6)	14.8 (0.4)	10.8 (3.2)	12.8 (2.6)[c]	10.0 (4.2)	14.0 (1.2)[b]	11.2 (3.3)
Bisyllabic word repetition (/15)	14.7 (0.5)	14.7 (0.7)	14.8 (0.7)	13.0 (1.6)	12.8 (3.3)[c]	12.4 (4.7)	12.0 (2.9)[b]	14.8 (0.4)
Trisyllabic word repetition (/15)	15.0 (0.0)	15.0 (0.0)	14.8 (0.4)	12.8 (3.2)	11.1 (5.9)[c]	12.0 (6.2)	12.3 (2.9)[b]	14.0 (1.0)
Graded difficulty sentence repetition (/10)	9.8 (0.4)	9.3 (0.9)	8.3 (1.2)	7.3 (1.7)	4.6 (3.0)[e]	5.2 (3.2)	4.7 (2.9)[c]	5.2 (1.6)
Sentence construction								
Spoken (/25)	25.0 (0.0)	24.9 (0.3)	19.1 (7.5)	23.5 (1.3)	18.0 (7.4)[d]	21.6 (5.1)	18.0 (5.3)[c]	22.8 (2.7)

Mean (standard deviation) values of performance on neurolinguistic tests are shown (maximum scores are indicated in parentheses) for each testing modality (face-to-face vs remote research setting) in each participant group. Green cells indicated strong evidence for the null hypothesis (H0); blue cells indicate strong evidence for the alternative hypothesis (H1). Exact values for the Bayes factor comparing H0 against H1 (BF_{01}) are presented in **Table** 4-6. A reduced number of participants completed certain tests, as follows: [a]n-1, [b]n-2, [c]n-3, [d]n-4, [e]n-5, [f]n-6, [g]n-8, [h]n-9.

Table 4-6. Bayes factor values for neurolinguistic performance comparisons between remote and face-to-face testing modalities

	Controls	All patients	svPPA	nfvPPA	lvPPA
Phoneme perception					
PALPA 3	1.003 (Anecdotal)	2.918 (Anecdotal)	1.594 (Anecdotal)	2.731 (Anecdotal)	2.079 (Anecdotal)
Reading					
Non-word reading	1.544 (Anecdotal)	3.239 (Strong)	1.940[t] (Anecdotal)	2.033[t] (Anecdotal)	2.428[t] (Anecdotal)
Regular reading	Variance at 0	2.989 (Anecdotal)	1.975 (Anecdotal)	2.305 (Anecdotal)	1.923 (Anecdotal)
Irregular reading	Variance at 0	2.996 (Anecdotal)	2.256 (Anecdotal)	2.194[t] (Anecdotal)	2.005 (Anecdotal)
Naming					
BNT	3.612[t] (Strong)	1.995 (Anecdotal)	0.584[t] (Anecdotal)	2.580 (Anecdotal)	1.490 (Anecdotal)
Semantic association					
Camel and cactus	4.039[t] (Strong)	1.067[t] (Anecdotal)	1.524[t] (Anecdotal)	2.102 (Anecdotal)	N<2 for F2F
Word comprehension					
Concrete synonyms	2.739[t] (Anecdotal)	3.622 (Strong)	2.009[t] (Anecdotal)	2.400[t] (Anecdotal)	1.413[t] (Anecdotal)
Abstract synonyms	1.726[t] (Anecdotal)	2.718 (Anecdotal)	0.782 (Anecdotal)	2.741 (Anecdotal)	1. 941 (Anecdotal)
Sentence comprehension					
PALPA 55	0.944 (Anecdotal)	3.954 (Strong)	2.246 (Anecdotal)	2.603 (Anecdotal)	2.110 (Anecdotal)
Speech repetition					
Monosyllabic word repetition	0.0487[t] (Strong)	0.117 (Anecdotal)	0.477[t] (Anecdotal)	1.167[t] (Anecdotal)	1.055[t] (Anecdotal)
Bisyllabic word repetition	4.304[t] (Strong)	3.744 (Strong)	1.086 (Anecdotal)	2.639 (Anecdotal)	0.650[t] (Anecdotal)
Trisyllabic word repetition	Variance at 0	3.701 (Strong)	1.339 (Anecdotal)	2.400 (Anecdotal)	1.677 (Anecdotal)
Graded difficulty sentence repetition	1.779 (Anecdotal)	2.983 (Anecdotal)	1.420[t] (Anecdotal)	2.535[t] (Anecdotal)	1.996 (Anecdotal)
Sentence construction					
Spoken	Variance at 0	1.525 (Anecdotal)	2.270 (Anecdotal)	1.960. (Anecdotal)	0.930[t] (Anecdotal)

Bayes factor (BF_{01}) values are shown for each remote vs face-to-face testing comparison for each participant group. Colour coding is identical to **Table** 4-5. F2F, face-to-face.

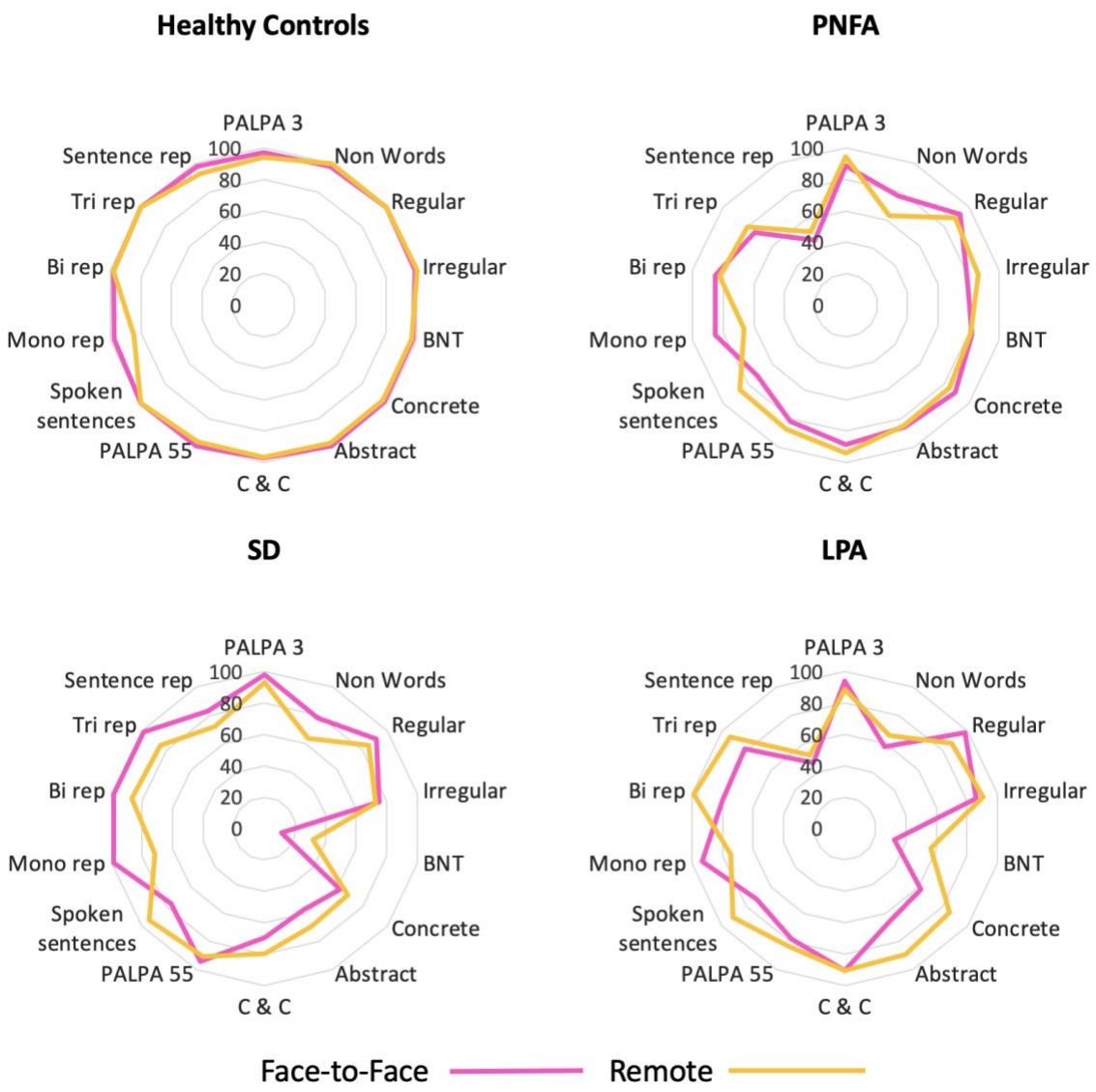


Figure 4-3. Radar plots of performance on the neurolinguistic battery for all participant groups.

Average percentage correct score (plotted on concentric lines) was calculated for each test of the neurolinguistic battery, each testing modality, and for both healthy controls and language-led patient groups. Abstract, abstract synonyms test; bi rep, bisyllabic single word repetition; BNT, Boston Naming Test; C & C, camel and cactus test; concrete, concrete synonyms test; F2F, face-to-face; irregular, irregular word reading test; mono rep, monosyllabic single word repetition test; non-word, non-word reading test; PALPA, Psycholinguistic Assessment of Language Processing in Aphasia subtests; regular, regular word reading test; sentence rep, graded difficulty sentence repetition test; spoken sentences, spoken sentences test; tri rep, trisyllabic single word repetition test.

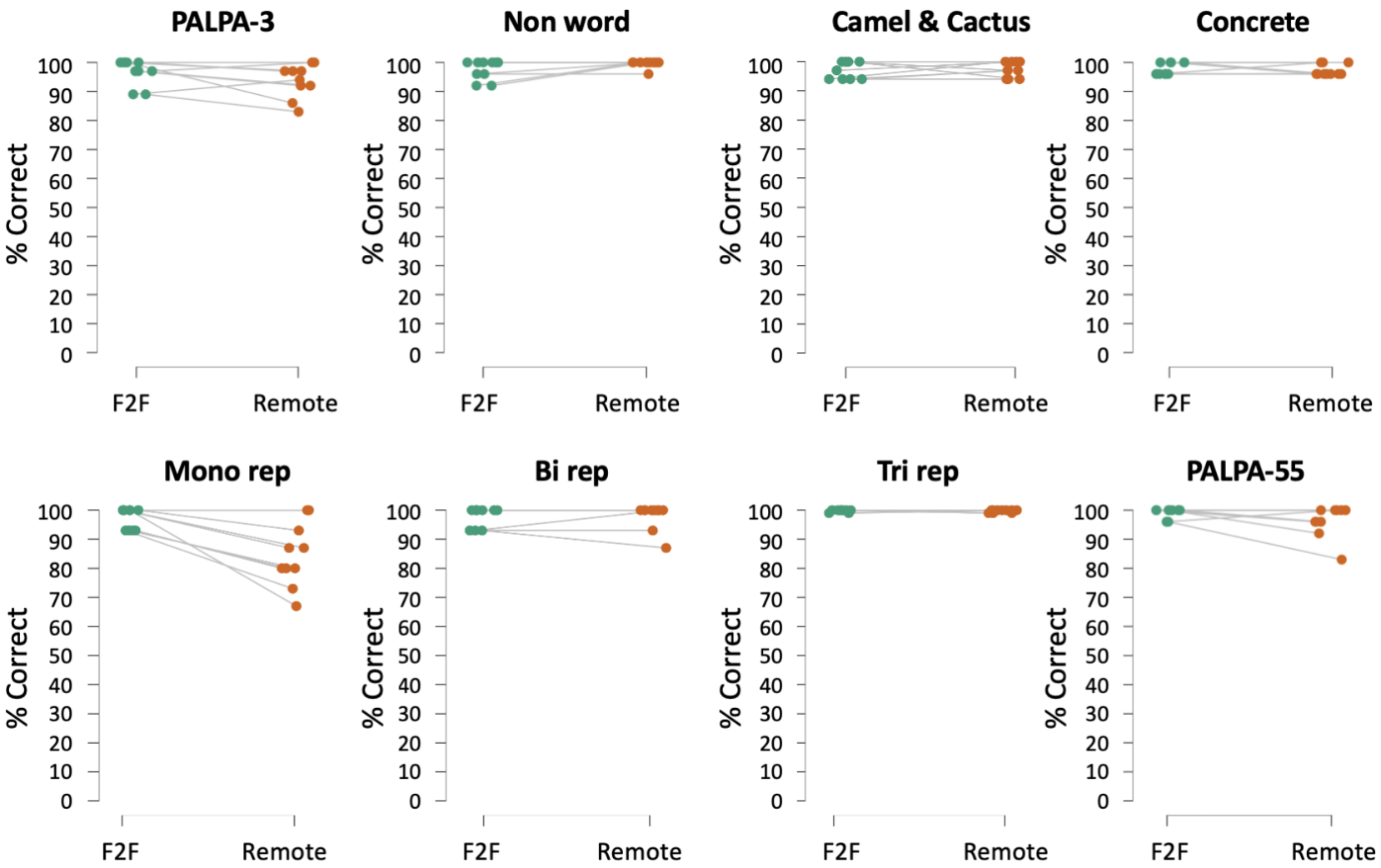


Figure 4-4. Performance profiles of healthy control participants on the general neurolinguistic battery

Line plots indicating percentage scores for each healthy control participant on representative tests from the neurolinguistic battery administered face-to-face and remotely. Scores on the trisyllabic single word repetition task were jittered slightly on the x-axis to allow for plotting as participants were uniformly at ceiling in both modalities. Mono, monosyllabic; Bi, bisyllabic single word repetition test; Tri, trisyllabic; rep, single word repetition test.

4.5. Discussion

The present findings indicate that the delivery of cognitive assessments remotely over the internet to healthy older adults and patients diagnosed with diverse types of dementia is feasible. Indeed, only a few potential participants were precluded due to technological limitations. Using a Bayesian statistical approach, I further demonstrated that there was strong evidence supporting comparable performance across testing modalities of healthy participants and AD patients on a range of general neuropsychological and neurolinguistic tests, specifically those targeting working memory (digit span forward), executive functioning (digit span reverse, letter and category fluency tests, WASI matrix reasoning), arithmetic skills (GDA), and general semantic knowledge (BNT, BPVS, Camel and Cactus, GNT). These findings corroborate previous reports of preserved neuropsychological performance on executive function, working memory, and language tests across testing modalities in both healthy individuals and AD patients (Hunter et al., 2021).

These findings also corroborate recent research suggesting the feasibility of remote assessments with patients diagnosed with PPA (L. A. Rao et al., 2022). Given the ongoing COVID-19 pandemic, remote testing protocols allow neuropsychological research efforts to continue. In this context, the present study successfully demonstrates the feasibility of assessing not only AD patients (who have been the primary focus of previous studies), but also PPA patients whose language difficulties may have discouraged remote testing, and most surprisingly bvFTD patients whose prominent behavioural disturbances impose specific challenges to remote assessments. Undoubtedly, remote assessment of those patients was possible thanks to the caregivers' presence who gave their time to technologically assist participants.

The way the neuropsychology and neurolinguistic testing protocol was adapted for remote delivery may have favoured these null differences. The testing sessions were made shorter and were spread out within a week, which may have helped counteract the effect of anxiety related to the unfamiliarity of the remote testing setting, as well as potential 'Zoom' fatigue (Bailenson, 2021). The increased flexibility of scheduling compared to face-to-face testing in addition to the absence of potentially stressful factors associated to a face-to-face visit (travelling, sleeping in a hotel room) may have led to more relaxed testing setting. Certain tests selected for remote delivery may also be intrinsically less susceptible to changes in

testing protocol (e.g., BPVS), and we made conscious decisions on excluding tests that would not be practical for remote delivery (e.g., WASI Block design, Baxter spelling test, Trails). Anecdotally, all participants reported satisfaction with the remote testing protocol.

Nevertheless, I found strong evidence suggesting both healthy control participants and AD patients performed worse remotely on the VOSP object decision task assessing visuospatial skills. Given their associated brain atrophy profile involving the postero-occipital cortices, it is perhaps not surprising that AD patients were particularly susceptible to a change in administration method on this test (although no testing modality differences in performance for other tasks using visual stimuli were found in AD). Regarding the healthy control participants, it is worth noting that the absolute performance difference across modalities was small. However, this decrease could be attributed to a wider ageing effect, a plausible hypothesis given they were tested remotely 3-4 years after they were tested face-to-face.

There was also strong evidence supporting a lower remote performance of healthy individuals on the monosyllabic single word repetition test. This could be partly explained by the remote delivery, i.e., the video-conferencing software impacting the quality of the auditory signal (Weerathunge et al., 2021). This hypothesis is further substantiated by the healthy controls' preserved performance on the bisyllabic single word repetition test where top-down information can be used to complement the bottom-up auditory information partially degraded by the videoconferencing software (Jiang et al., 2021). Alternatively, this worse performance could also be due to age-related hearing loss, making healthy older adults particularly vulnerable to communication via videoconferencing (Goodwin et al., 2021; Helfer et al., 2021; Naylor et al., 2020).

The finding of better performance on the verbal fluency test in lvPPA patients tested remotely compared to those tested face-to-face is surprising. It may be either due to the remote cohort being less severely affected than the face-to-face cohort (although, on average, they did not differ significantly in symptom duration), or to the remote setting being less anxiety-provoking compared to face-to-face testing in an unfamiliar environment.

The current study presents several limitations which can inform future work. First, while most statistical comparisons indicated similar performance between testing modalities for healthy and dementia participants, they were not all supported by strong evidence and certain comparisons even led to the opposite conclusion. Second, the present study was not ideally designed to compare the two testing modalities, as the patient cohorts were different and

the healthy control participants were not tested simultaneously in both modalities within the same year. These findings would therefore need to be replicated in larger cohorts to rule out the possibility of small differences observed in favour of face-to-face testing. Patients of equivalent disease severity would also need to be tested to compare the differential impact of diagnosis on remote performance. Third, here we did not control for potential deficits in peripheral hearing as these are difficult to measure remotely without adequate equipment. However, they likely explain the worse remote performance on certain neurolinguistic tests and should therefore be taken into account for future experimental designs.

Overall, the present findings demonstrate that, despite challenges in setting up remote testing protocols (specifically due to technological requirements), these produce similar results to face-to-face testing protocols. They are encouraging given the current climate, since research participants may favour remote over face-to-face assessments for safety reasons or other (e.g., not having to travel) even outside of lockdown periods. Importantly for the work presented in this thesis, no major differences were noted on cognitive domains that crucially support temporal estimation tasks, e.g., executive function and working memory skills, as well as higher order linguistic abilities, despite an uncontrolled auditory environment. In **Chapter 5**, I therefore combined timing data from healthy older adults and patients collected before and during the pandemic to assess between group differences in the perception of short intervals varying in semantic characteristics and emotional valence.

5. Subjective time perception in dementia: behavioural phenotypes and neuroanatomical correlates

5.1. Chapter summary

Aims

- Compare the performance of patients diagnosed with an AD or FTD syndrome against healthy older adults
- Evaluate disease specific differences in duration estimation and discrimination sensitivity
- Explore how general cognitive capacities affect timing performance in healthy older adults and dementia patients
- Determine the neuroanatomical substrates of subjective time perception across all patient groups

Methods

- A total of 60 patients (24 typical and logopenic AD, 36 FTD) were recruited into this study, along with 25 healthy control participants
- Interval timing abilities were assessed using the same temporal bisection task described in Chapter 3 with a reduced sound battery
- All participants completed two additional tasks to measure basic auditory categorisation and sound recognition abilities
- Cognitive abilities were assessed using general neuropsychological tests following procedure detailed in Chapters 2 and 4
- Neuroanatomical correlates of subjective time perception across all patients were determined using voxel-based morphometry

Results

- Both healthy older adults and dementia patients (irrespective of their diagnosis) perceived the duration of unpleasant environmental sounds as longer than pleasant ones and unpleasant human sounds as shorter than pleasant ones, thereby replicating findings from Chapter 3. All participants also perceived the duration of

human sounds as shorter than environmental sounds and discrimination sensitivity was higher for unpleasant than for pleasant sounds

- Compared to healthy older adults, lvPPA patients underestimated the duration of human sounds, while nfvPPA patients overestimated the duration of environmental sounds. bvFTD and AD patients also had a lower discrimination sensitivity across all sounds.
- Environmental and human sounds were experienced as shorter in duration for bvFTD patients compared to svPPA and nfvPPA patients respectively. Discrimination sensitivity across all sounds in svPPA patients was higher compared to bvFTD, AD and lvPPA patients.
- Across all patients a reduction in auditory working memory and executive function skills was correlated with duration underestimation, while a reduction in executive function skills was correlated with lower discrimination sensitivity. No significant correlations were found between these cognitive abilities and timing performance measures across healthy control participants.
- For environmental pleasant sounds, increasing difference in duration estimation versus healthy older adults in a cohort of dementia patients was associated with grey matter atrophy in the right precuneus. For human unpleasant sounds, this was associated with grey matter atrophy in the right insular cortex. For human pleasant sounds, this was associated with grey matter atrophy in the right inferior parietal lobule.

Conclusion

- Overall, this study provides initial evidence towards distinct profiles of interval timing abilities in dementia, in line with the clinico-anatomical characteristics defining each dementia type

5.2. Introduction

The healthy ageing study presented earlier in this thesis revealed that across all ages, participants perceived environmental unpleasant sounds as lasting longer than environmental pleasant sounds and tended to perceive human unpleasant sounds as briefer than human pleasant sounds. Environmental sounds were also more discriminable than human sounds for all participants. I further identified a few age-related differences in timing performance: healthy older adults overestimated the duration of environmental sounds and had higher discrimination sensitivity for all sounds compared to healthy young adults.

In this chapter, I measured the impact of pathological ageing on subjective time perception. Specifically, I tested patients representing canonical syndromes of FTD (bvFTD, svPPA, nfvPPA) and AD (typical amnestic AD and language-led lvPPA) on the same psychophysical experiment as in the healthy ageing study, and I compared patients' performance against healthy age-matched control participants. In the previous chapter, I demonstrated that patients and healthy older participants performed similarly between face-to-face and remote testing settings on several neuropsychological and neurolinguistic tasks. Based on this, I merged the timing dataset that I collected face-to-face before the COVID-19 pandemic, with the one that I collected remotely during the COVID-19 pandemic following a remote testing protocol described in **Chapter 4**. The findings presented in this chapter result from the analysis of this combined dataset.

What do we know about interval timing in AD and FTD?

As described in **section 1.6.4**, interval timing is a relatively unexplored topic in AD and FTD. The majority of studies have been conducted in AD, but findings are inconsistent, with some identifying poorer timing performance compared to healthy age-matched control participants (Barabassy et al., 2007; El Haj et al., 2013; Papagno et al., 2004; Ranjbar Pouya et al., 2015) and others showing similar performance between the two groups (Caselli et al., 2009; Rueda & Schmitter-Edgecombe, 2009). This mixed picture may be largely attributed to the diversity of tasks and stimuli used. Among the studies previously cited, the one most relevant to the present chapter is the study conducted by Caselli and colleagues (Caselli et al., 2009). They used a temporal bisection task to assess duration estimation of intervals lasting several seconds of which onset and offset

were defined by an auditory pure tone, with a white square presented during the entire duration of the interval. They found no statistically significant differences between mild AD patients and healthy age-matched participants on the bisection point and the Weber's ratio, which are measures of estimation and discrimination sensitivity respectively. Regarding the language variant of AD known as logopenic PPA, no studies have evaluated interval timing in the supra-second range. However, one study did look at this in the sub-second range and showed that the lvPPA group performs similarly to controls on an interval discrimination task (with empty intervals defined by an auditory onset and offset) as well as on several rhythmic discrimination tasks (Grube et al., 2016). This study also assessed svPPA and nfvPPA patients and showed that while both are unimpaired on duration discrimination of intervals lasting several hundreds of milliseconds, they perform worse than healthy age-matched participants on the perceptual discrimination of rhythmic sequences, particularly nfvPPA patients. However, the sample sizes in this study were relatively small (4 lvPPA, 8 svPPA, 6 nfvPPA), thereby calling for additional studies to confirm these findings. So far, there has been only study focusing on interval timing in bvFTD (M Wiener & Coslett, 2008). This single-case study found an overestimation of the duration of intervals lasting several seconds by the bvFTD patient compared to a group of healthy control participants but a similar performance on a duration discrimination task.

Although evidence demonstrating interval timing deficits in these neurodegenerative diseases is scarce, impairment in general cognitive domains previously implicated in time perception (namely attention, working memory, and executive function) suggest time perception may indeed be an issue. Those particularly affected in this regard may be the bvFTD, typical AD and lvPPA patients considering: (a) the frontal lobe atrophy characterising bvFTD is associated with executive dysfunction (which would lead to impairment in decision-making processes, such as deciding whether an interval is short or long), as well as reduced working memory and higher impulsivity; (b) AD patients have reduced attentional resources compared to healthy controls which would lead them to generally underestimate time intervals; (c) similarly, lvPPA patients have a reduced auditory verbal working memory span, which suggest they might also underestimate the duration of intervals.

However, deficits in timing resulting from neurodegeneration may only be identified using certain tasks. Indeed, age-related changes in timing have not previously been identified for duration discrimination and temporal bisection tasks (**section 1.5.3**), and the single case study of a bvFTD patient mentioned earlier noted differences on the verbal estimation task but not on the duration discrimination task. This has been explained in the context of information processing models of timing: for example in a temporal bisection task, a faster internal clock would affect encoding of all stimuli such that their internal representation would correspond to shorter intervals; however, this would not affect the decision outcome since it is the duration ratio of the current stimuli and the reference stimuli that informs the decision.

However, the study presented in this current chapter aims not only at uncovering potential timing differences in several dementia cohorts compared to controls, but it also aims at evaluating whether these different neurodegenerative diseases may be impacted differently by manipulation of emotional and semantic characteristics of time intervals when making duration judgements. In other words, while I have previously shown that healthy older adults perceive environmental unpleasant sounds as lasting longer than environmental pleasant sounds and tend to perceive human unpleasant sounds as briefer than human pleasant sounds, the results may not be the same for AD and FTD patients. In fact, impaired emotional processing is particularly salient in FTD syndromes (Balconi et al., 2015; Fletcher, Downey, et al., 2015; Hazelton et al., 2016; Kumfor et al., 2019; Kumfor & Piguet, 2012; Marshall, Hardy, Allen, et al., 2018; Marshall, Hardy, Russell, et al., 2018), and abnormalities of affective and emotional processing are increasingly recognised in AD as well (Balconi et al., 2015; Fletcher et al., 2016; Fletcher, Nicholas, et al., 2015b; Klein-Koerkamp et al., 2012; Torres Mendonça De Melo Fádel et al., 2019), suggesting that both AD and FTD patients could be affected by the current experimental manipulations.

In the previous healthy ageing study, I showed that healthy older adults found environmental sounds more discriminable than human sounds, but that their discrimination sensitivity was not affected by emotional valence. Due to the lack of experimental findings, it is difficult to predict a priori whether discrimination sensitivity changes resulting from manipulations of emotional valence and semantic characteristics of sounds will be different in the current dementia cohorts. However, AD and FTD patients are likely to have reduced discrimination sensitivity compared to healthy control participants when considering previous studies associating lower discrimination sensitivity with diminished working memory and attentional resources (Gagnon et al., 2018; Ogden et al., 2019).

What did I do here?

To assess the impact of pathological ageing on subjective time perception and later discuss differences between healthy and pathological ageing, I used the same experimental design described in **Chapter 4**. Specifically, I used a temporal bisection task and included sounds of everyday life fitting one of the following four experimental conditions: environmental unpleasant, environmental pleasant, human unpleasant, and human pleasant. I tested patients diagnosed with typical amnestic AD, language-led AD variant lvPPA, and canonical syndromes of FTD (bvFTD, svPPA and nfvPPA) against a cohort of healthy aged-matched participants. I evaluated between-group differences in timing performance using the same analysis method described in **section 2.8.2**, i.e., I first represented psychometric functions for each experimental condition and each participant to extract corresponding bisection point and Weber's ratio values, and then built linear mixed models for both timing performance measures including diagnosis and both semantic and valence categories as fixed effects, and participant identity as a random effect. I further determined the influence of general cognitive abilities (executive function, working memory, digit span) across healthy and dementia participants separately by correlating bisection point and Weber's ratio values averaged across experimental conditions with performance on corresponding neuropsychological tasks. Finally, I determined neuroanatomical substrates of differences in duration estimation within the combined patient cohort for each sound condition using voxel-based morphometry.

What are my hypotheses?

Although the literature on subjective interval timing in AD and FTD is minimal, especially regarding the impact of emotional valence and semantic characteristics, I propose the following hypotheses for this study based on deficits in timing related factors (working memory, attention, executive function) and impairment in emotional processing known to be differentially associated with these diseases. First, I expect bvFTD and svPPA patients to be differentially impacted by the emotional valence of sounds when making duration judgments compared to healthy age-matched control participants, and svPPA patients to be differentially impacted by the semantic characteristics of sounds when making duration judgments compared to healthy age-matched control participants. I further hypothesise that AD and lvPPA patients generally perform differently from healthy participants (either by overestimating or underestimating the duration of all sounds). I also expect that all dementia patients will have a lower discrimination sensitivity for all sounds compared to healthy age-matched control participants. Based on previous literature on the neuroanatomy of interval timing in the supra second range described in **section 1.2.4** (Harrington et al., 2004; Hayashi et al., 2014; Lewis & Miall, 2006a; Livesey et al., 2007; Van Wassenhove et al., 2011; Wittmann, Simmons, et al., 2010), I further hypothesise that neuroanatomical substrates of duration estimation differences between patients and healthy control participants will differentially implicate the dorsolateral prefrontal cortex (dlPFC), the insular cortex, the intraparietal lobule (IPL) and the precuneus, reflecting the distinct intrinsic characteristics and functional significance of environmental and human sounds.

5.3. Methods

5.3.1. Participants

A total of 60 patients were recruited for this study from September 2019 to March 2020, and from February 2021 to December 2021. 15 of those had a diagnosis of typical AD (10 took part remotely), 15 (four remote) had bvFTD, 11 (four remote) had svPPA, 10 (six remote) had nfvPPA, and nine (seven remote) had lvPPA. Remote recruitment was carried out following the procedure detailed in **Chapter 4**. All patients fulfilled consensus criteria for the relevant syndromic diagnosis (Dubois et al., 2014; M.L. Gorno-Tempini et al., 2011; Rascovsky et al., 2011) and were of mild to moderate disease severity. Brain MRI was consistent with the syndromic diagnosis in all patients, without evidence of significant cerebrovascular burden. All participants underwent general neuropsychological assessment following procedure detailed in **section 2.2.2**.

Several participants were removed from the final analysis sample for reasons specified in **section 5.3.7**. Focusing on the participants who completed the full timing experiment, six AD patients and one lvPPA patient had CSF biomarker support for underlying AD pathology, with a total CSF tau/beta-amyloid 1-42 ratio higher than 0.8 based on local reference ranges, and three out of 11 AD patients also had abnormal brain amyloid PET imaging. Genetic screening further revealed four bvFTD patients with C9orf72 mutations, and one bvFTD patient with a MAPT mutation.

Twenty-five healthy older individuals with no history of neurological or psychiatric illness were also invited to this study, 11 of whom took part remotely. All (except one who was removed; see **section 5.3.7**) presented no history of clinically significant peripheral hearing impairment.

Clinical, demographic, and general neuropsychological characteristics of the final participant cohort are summarised in **Table** 5-1.

Table 5-1. Demographic, clinical and neuropsychological characteristics of participant groups

Characteristics	Controls	AD	lvPPA	nfvPPA	svPPA	bvFTD
Demographic and clinical						
N (M/F)	12/12	7/4	6/2	5/3	7/4	5/3
Age (years)	69.4 (6.5)	71.3 (5.4)	70.4 (5.4)	69.4 (5.7)	66.0 (9.3)	67.9 (7.2)
Handedness (R/L/A)	20/3/1	11/0	8/0	8/0	9/1	8/0
Education (years)	16.1 (2.6)	14.4 (3.7)	15.8 (3.0)	14.3 (3.1)	15.5 (1.8)	13.6 (2.0)
Symptom duration (years)	N/A	6.3 (3.3)	5.8 (5.3)	3.1 (1.1) bv	5.5 (3.1) bv	13.0 (9.3) nf; sv
T-MMSE (/27)	26.0 (1.3)	**18.7 (3.8)**	**17.5 (6.1)** nf	23.4 (2.9) lv	**21.8 (3.9)**	**20.9 (5.4)**
General neuropsychological assessment						
General intellect						
Performance IQ	123.6 (11.1) n-10	85.0 (1.4) n-9	101.3 (35.4) n-5	94.0 (21.7) n-5	114.3 (21.8) n-5	100.1 (24.4) n-1
Verbal IQ	123.3 (8.4) n-10	95.0 (14.1) n-9	***55.0** n-6	***74.0** n-7	**74.8 (21.0)** n-5	**81.2 (24.0)** n-2
NART	41.5 (6.3)	32.7 (10.8) n-1	28.4 (14.1)	28.7 (13.8) n-1	**17.8 (14.5)** n-2	30.6 (17.4)
Executive function						
WASI Block Design (/71)	47.1 (12.5) n-10	**5.0 (1.4)** n-9	22.3 (31.8) n-5	21.0 (11.5) n-5	40.3 (20.0) n-5	22.1 (19.7) n-1
WASI Matrices (/32)	26.1 (3.0)	**12.4 (9.6)** sv n-2	**17.1 (8.2)**	22.0 (7.2)	22.5 (6.8) ad	**17.3 (9.1)**
Letter fluency	18.8 (4.7)	**9.9 (6.8)** n-2	**8.1 (5.2)**	**9.3 (8.4)** n-1	**9.1 (6.5)** n-2	**7.9 (6.8)**
Category fluency	24.6 (4.9)	**10.6 (6.4)** n-2	**10.1 (7.1)** n-1	18.3 (9.4) sv n-1	**7.7 (6.3)** nf n-2	**11.3 (6.8)**
TMT A (s)	31.1 (10.2) n-10	68.0 (9.9) n-9	63.7 (37.4) n-5	40.5 (7.8) n-6	61.0 (33.3) n-6	62.4 (41.1) n-1
TMT B (s)	60.4 (20.3) n-10	**253.0 (66.5)** n-9	183.0 (165.5) n-6	129.0 (80.6) n-6	148.8 (101.4) n-6	162.7 (109.6) n-1
D-KEFS Stroop colour (s)	30.9 (5.9)	56.5 (20.0) n-5	**71.3 (25.4)** n-1	**76.2 (37.6)**	48.8 (21.7) n-3	52.8 (21.6)
D-KEFS Stroop word (s)	23.0 (4.0)	39.4 (16.9) n-5	**43.6 (13.6)** n-1	**57.8 (18.8)** sv; bv	29.4 (11.8) nf n-3	32.7 (16.5) nf

Characteristics	Controls	AD	lvPPA	nfvPPA	svPPA	bvFTD
D-KEFS Stroop interference (s)	56.2 (11.5)	**118.4 (45.9)** n-5	**157.0 (73.3)** n-2	**112.9 (34.9)**	94.0 (39.6) n-3	**115.8 (56.7)**
Working memory						
DS-F (max)	6.8 (0.9)	**5.2 (1.5)** sv n-1	**4.5 (1.2)**	5.1 (1.9)	6.5 (0.9) lv	5.8 (2.3)
DS-R (max)	5.6 (1.2)	**3.3 (1.2)** n-1	**3.1 (1.8)**	3.9 (1.5)	4.9 (1.4)	4.1 (2.0)
Episodic memory						
RMT Words (/50)	48.1 (2.5) n-10	39.5 (2.1) n-9	**31.0 (10.4)** n-5	***46.0** n-7	**35.2 (8.3)** n-6	40.1 (10.1) n-1
RMT Faces (/50)	40.7 (4.7) n-10	**28.0 (4.2)** n-9	**25.7 (1.2)** n-5	***34.0** n-7	**31.3 (3.7)** n-5	34.3 (7.6) n-2
RMT Faces short (/25)	23.4 (2.5) n-14	**15.9 (3.4)** nf	21.6 (3.8) n-3	22.8 (3.5) ad n-2	19.3 (3.7) n-7	23.0 (1.4) n-6
Camden PAL (/24)	21.1 (3.6) n-10	5.5 (2.1) n-9	**5.3 (9.8)** n-4	16.7 (5.8) n-5	**8.8 (8.8)** n-6	**8.3 (9.1)**
Language						
GNT (/30)	25.7 (2.3) n-1	**12.5 (6.7)** sv	**8.1 (8.0)**	**16.3 (9.9)** sv	**1.5 (4.5)**	**15.1 (9.6)** sv
BPVS (/150)	147.9 (2.0) n-1	136.7 (18.8) sv	133.0 (23.8) sv	137.8 (15.6) sv	**86.4 (51.6)** n-2	122.5 (50.8)
Arithmetic						
GDA (/24)	15.6 (5.0) n-1	**5.0 (5.1)** n-2	**4.8 (5.6)** n-2	**6.5 (5.8)**	10.1 (6.8) n-2	11.0 (8.5)
Visuospatial						
VOSP (/20)	18.7 (1.7)	**14.3 (3.4)** n-1	**14.8 (2.9)**	17.6 (1.9)	**15.6 (4.0)** n-2	17.6 (1.5)

Mean (standard deviation) scores are shown unless otherwise indicated (standard deviations not shown when sample size equals 1). Maximum scores are shown in parentheses after tests where relevant. A reduced number of participants took part in certain tests and missing numbers are indicated following this scheme: n-1 1 missing datapoint. Statistically significant differences between patient group averages and healthy controls ($p < 0.05$) are indicated in bold. Between patient group differences are indicated as follows: ad significantly different from AD; lv significantly different from lvPPA; nf significantly different from nfvPPA group; sv significantly different from svPPA group; bv significantly different from bvFTD group. *Performance from only one participant was available and was therefore compared to healthy controls group using a one sample t-test.

5.3.2. Experimental stimuli

Similarly to the heathy ageing study (**Chapter 3**), the auditory stimuli for the temporal bisection task were chosen to represent four different auditory source category – valence combinations, and the sounds chosen for each combination were as follows: pleasant environmental noises (brook, river); unpleasant environmental noises (angle grinder, car horn); pleasant human vocal sounds (female laughter, male laughter); and unpleasant vocal sounds (female crying, male crying). All sound files used in this experiment were edited in Audacity following the procedure detailed in **section 2.3** and were exported as wav files.

A valence verification task was designed to establish that participants' valence ratings were in line with those predicated for each sound category. Thirty-six stimuli from the main experiment representing the four experimental conditions and lasting 3.5 seconds were administered in randomised order and the task on each trial was to say how pleasant each sound was using following the rating procedure explained in **section 2.3**. For each participant and each one of the eight sounds, an average rating score was then calculated. An average score of 50% or higher was considered as pleasant, a score below 50% as unpleasant. For seven healthy control participants, the mean valence assigned to at least one sound did not fit the pre-defined valence category (5 for laughter, one for river, and one for angle grinder) and the corresponding trials were therefore reassigned to the appropriate valence category before analysis of time data. For patients, average valence ratings were also calculated but were only considered in a secondary analysis to evaluate how sound category adjustments influence the results, as ratings of this kind are not always reliable given the emotional disturbances experienced in this patient cohort (Fletcher, Downey, et al., 2015; Kumfor & Piguet, 2012; Marshall, Hardy, Allen, et al., 2018; Marshall, Hardy, Russell, et al., 2018). This analysis will be presented in more detail in **Appendix 12**, but the results were largely similar. However, the majority of individuals gave ratings that matched the initial valence categories (**Figure** 5-3).

For the auditory categorisation task (see **section 5.3.4**), pure tones were created using the Generate module in Audacity, by specifying the following characteristics: sine waveform, frequency (in Hz, as listed in **section 5.3.4**), amplitude of 0.8, and duration of

2 or 5 seconds. All sound files were then rms fixed at the same intensity level as the sound files for the temporal bisection task and exported as wav files.

5.3.3. Temporal bisection task procedure

Please refer to **section 2.4** for a general description of the temporal bisection paradigm. Regarding the procedure, I used the non-partition method, which divides the experiment into a practice phase and an experimental phase.

In the initial training phase, participants learned the duration of the short (2 seconds) and long (5 seconds) reference sounds. For this, they first heard four example sounds (two short references and two long ones, in interleaved order, i.e., short, long, short, long) while viewing a text descriptor on the screen ('short' or 'long'). The sounds used here (gibbon call and rain) were not subsequently used in the experiment and only served for the participant to familiarise themselves with the experimental paradigm. Participants then completed 16 practice trials (representing the eight different sounds, at both reference durations, in pseudo-randomised order). On each trial, participants were instructed to decide whether the sound was 'short' or 'long'. If seen in-person, participants were asked to respond with a keypress and in some cases, were allowed to verbally indicate or point to their response; if seen remotely, participants were asked to verbally indicate their answer. Visual feedback about the participant's performance was given on every practice trial. A minimum score of 80% correct responses (13 out of 16 trials correct) was required to enter the experimental phase. Participants were allowed to repeat the practice trials (with the same sounds) if they failed the first time but were not invited to complete the experimental phase if they failed a second time.

In the experimental phase, participants were presented with sound stimuli representing the five intermediate durations (2.5, 3, 3.5, 4, 4.5, 5 seconds) as well as the two reference durations (2 and 5 seconds). The task on each trial was to categorise the duration of the sound as closer to either the short or the long reference durations, and participants provided their answers in the same way as for the practice trials. Here, there were a total of 224 experimental trials, which were divided into eight blocks of 28 trials each (7 durations x 4 sounds categories). Participants were allowed to take short breaks (about 2 min) between blocks.

5.3.4. Additional tasks

Two additional tasks were administered after the temporal bisection task. These tasks were designed to evaluate the influence of potential confounding factors.

The first one was a simple duration categorisation task. It was designed to assess whether participants could make basic temporal decisions. Similarly to the temporal bisection task, participants were instructed to categorise a sound (here a pure tone) into a "short" or "long" interval. First, they were asked to complete eight practice trials (four different frequencies – 200, 300, 1000, 1100 Hz – lasting either 2 or 5 seconds) presented in randomised order. A minimum score of 75% (6 out of 8 correct responses) was required to complete the experimental phase. The experimental phase consisted of twelve or eight trials (tones chosen among the following frequencies - 400, 500, 600, 700, 800, 900 Hz – lasting either 2 or 5 seconds) where participants categorised the sounds as "short" or "long" without any feedback. Participants provided their answers in the same way as for the temporal bisection task.

To account for potential differences in auditory semantic knowledge as another confounding factor, patients were further asked to complete a sound recognition task (**Figure** 5-1). In this task, patients had to choose the picture that matched the sound among a choice of four different pictures, each representing one of the four sound categories. The task comprised a total of 16 trials (two examples for each of the 8 sound types), and all sound files were taken from the main timing experiment.

The percentage of correct trials on each of these two tasks was calculated for all participants. Statistical analysis of these scores will be detailed in **section 5.3.7**.

5.3.5. Pure tone audiometry

When participants were seen face-to-face, pure tone audiometry was conducted following the procedure detailed in **section 2.2.3**. Statistical analysis of these hearing scores will be described in **section 5.3.7**.

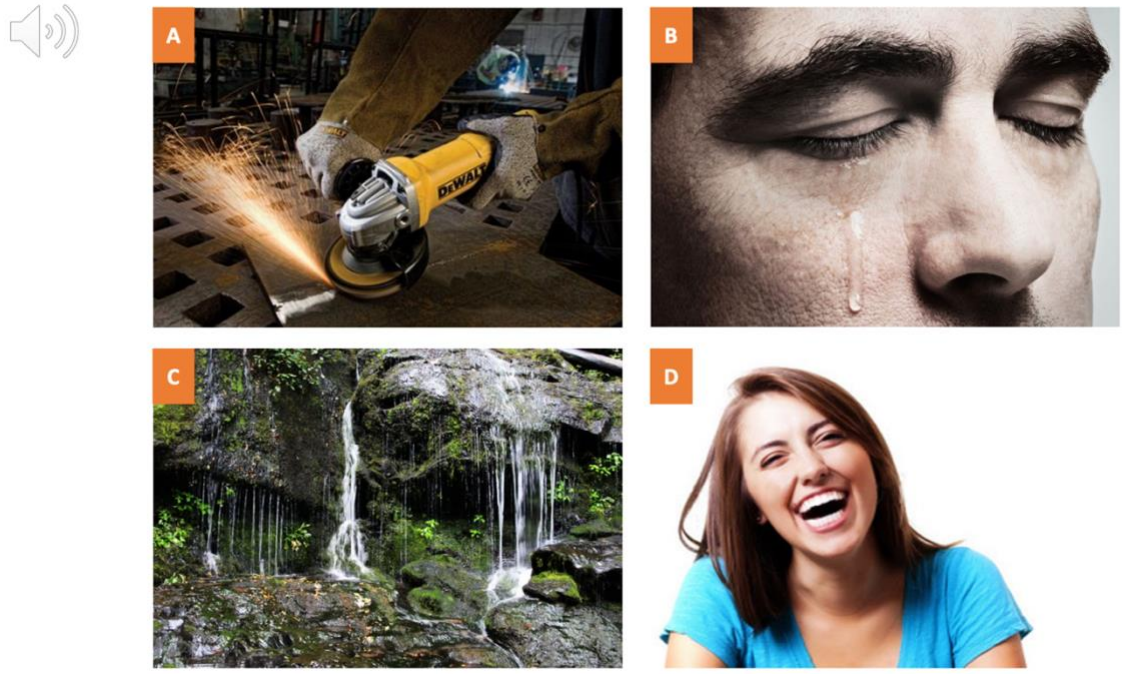


Figure 5-1. Recognition task: trial example.

On each trial, participants listened to a sound file taken from the experiment and were asked to choose the picture that matched the sound among a choice of four, each picture representing one experimental condition (for example here: A, environmental unpleasant; B, human unpleasant; C, environmental pleasant; D, human pleasant). The location of each experimental condition on the screen was counterbalanced across trials so that each condition would be equally displayed among the four locations. The order of presentation of each sound was also pseudo-randomised to avoid two examples of the same kind of sound being played consecutively.

5.3.6. Questionnaires

Extensive musical experience may significantly improve timing performance (Ehrle & Samson, 2005; Rammsayer & Altenmüller, 2006) and as such, participants enrolled in the dementia study were asked to complete a music questionnaire that covered previous and current musical practice. Based on participants' answers, the following scoring procedure was adopted:

- Score 0: they never played an instrument nor engaged in singing, neither formally nor informally
- Score 1: they played an instrument or engaged in singing for less than a year either formally and/or informally
- Score 2: they have more than 2 years of instrument/singing practice but did not obtain any grades

- Score 3: they obtained a grade 3 or 4 in a particular instrument/singing or have reached at least 10 years of practice without obtaining grades
- Score 4: they learned to play an instrument/sing and have reached grade 7 or 8

Participants who were recruited during the emotionally challenging COVID-19 pandemic also filled in a mood questionnaire (section 2.5) before completing the temporal bisection point to evaluate the impact of mood on their timing performance.

5.3.7. Analysis of behavioural data

5.3.7.1. Valence ratings

To evaluate any potential between-group differences in valence ratings, a linear regression model was performed, with rating as the dependent variable and both sound identity (one of the eight sounds) and group as the independent variables. Residuals were not normal even after removing one outlier participant and attempting transformation (logarithmic, square root, and inverse). Bootstrapping was therefore carried out with 1000 replications and sampling with replacement.

5.3.7.2. Temporal bisection task data

Here, I evaluated the effect of valence (pleasant/unpleasant) and semantic category (environmental/human) on subjective time perception, as measured by the temporal bisection point and the Weber's ratio (**section 2.8.2**) and compared the magnitude of both effects across groups.

As mentioned in **section 5.3.1**, not all participants could be included in the analysis of the temporal bisection task. One healthy participant was excluded on the basis that they had significant hearing loss (uncorrected by hearing aids) and produced aberrant valence ratings (they found all the unpleasant sounds of angle grinder, car horn, and crying pleasant). A substantial number of participants (7 bvFTD, 2 nfvPPA, 1 lvPPA, 4 AD) failed the practice phase and were likewise not included. A certain number of those also failed the simple duration categorisation task. Their timing abilities will be discussed separately in **Appendix 13**.

For each participant and each sound category, a psychometric curve was then generated, and corresponding bisection point and Weber's ratio values were extracted following procedure described in **section 2.8.2**.

To explore the impact of general cognitive abilities on timing performance in healthy older adults (**Chapter 3**), I performed correlations between bisection point and Weber's ratio individual values averaged across the four experimental conditions and scores on the digit span forward test (measuring auditory verbal working memory), as well as WASI matrices and digit-span reverse test, both indexing executive function skills. The same correlations were explored in the patient cohort.

The following variables were considered as potentially having a confounding influence on between group differences in timing performance:

- Participant's average mood score before completing the temporal bisection task
- Participant's hearing score
- Participant's past musical experience
- Participant's correct percentage score in the temporal bisection task's practice phase
- Participant's correct percentage score on the recognition task
- Participant's correct percentage score on the control task

To determine whether these should be included as potential nuisance covariates, I first statistically compared participant group averages using one-way ANOVAs. I further explored correlations between participant scores on the tasks listed above and performance measures from the temporal bisection task (bisection point and Weber's ratio) using Pearson's or Spearman's correlation measures.

To assess experimental effects on the bisection point, a linear mixed model incorporating age group, semantic category and valence as fixed effects and participant identity as the only random effect was computed. Assumptions of normality of residuals and heteroscedasticity were not violated, and further statistical testing confirmed that the current model was correctly specified (**section 2.8.2**). When comparing bisection point averages across groups and/or experimental conditions, a higher value indicates underestimation of sound duration (while a lower value indicates overestimation).

To assess experimental effects on the Weber's ratio, a similar linear mixed model was computed, with age group, semantic category and valence as fixed effects and participant identity as the only random effect. Residuals were not normal, and one participant (diagnosed with bvFTD) was identified as an outlier and therefore removed. However, this did not restore normality and therefore a logarithmic transformation of

the dependent variable was applied instead. Assumption of heteroscedasticity was valid and further statistical testing confirmed that the model was correctly specified. When comparing Weber's ratio averages across groups and/or experimental conditions, a higher value indicates a shallower slope and therefore lower discrimination sensitivity for the corresponding experimental condition (while a lower value indicates higher discrimination sensitivity).

5.3.8. Analysis of neuroanatomical data

T1-weighted volumetric brain MRI data from 27 patients were entered into the VBM analysis (scans were not available for all patients due to remote testing). All scans were acquired, and pre-processed following methodology described in **section 2.7**.

Across the combined patient cohort, I ran a full factorial model to assess associations of regional grey matter volume with duration estimation differences between controls and patients for each sound condition (environmental unpleasant, environmental pleasant, human unpleasant, human pleasant). Specifically, the model incorporated the difference between the bisection point averaged across all control participants for a specific sound condition and the patient's individual bisection point for that same sound condition, diagnosis as a five-level factor, and two nuisance covariates (age and total intracranial volume). For every sound condition, negative associations with regional grey matter were evaluated (to determine correlations between increased difference in duration estimation between patients and healthy controls and grey matter atrophy).

Statistical parametric maps were generated using an initial cluster-forming threshold $p < 0.001$ and evaluated at peak voxel statistical significance level $p < 0.05$, after family-wise error (FWE) correction for multiple voxel-wise comparisons, separately within individual pre-specified neuroanatomical regions of interest. The selection of these regions was informed by previous studies on the neuroanatomy of interval timing in the healthy brain (**section 1.2.4**). They were defined for both the right and left hemispheres and included: the dorsolateral prefrontal cortex (Lewis & Miall, 2006a), the insular cortex (Van Wassenhove et al., 2011; Wittmann, Simmons, et al., 2010), the inferior parietal lobule (Hayashi et al., 2014; Livesey et al., 2007) and the precuneus (Harrington et al., 2010). See **Figure** 5-2 for a visual representation of these regions.

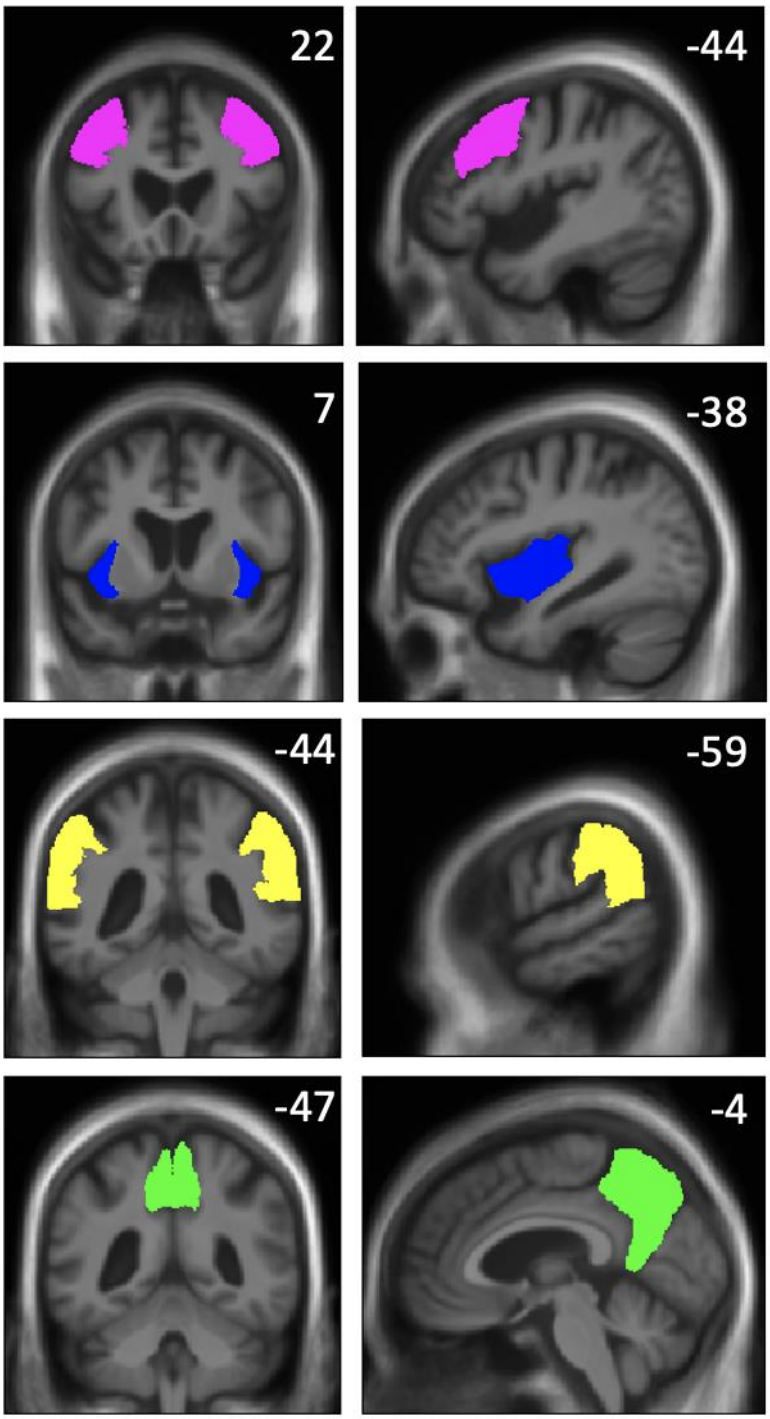


Figure 5-2. Pre-specified anatomical regions of interest for the present VBM analysis

Coronal (left) and sagittal (right) views of the regions of interest used in the present VBM analysis during small volume correction for multiple voxel-wise comparisons (see text for details). Regions have been overlaid on the group mean structural brain image in MNI space, coordinates (mm) of the plane of each section are indicated. Magenta: middle frontal gyrus; blue: insular cortex; yellow: inferior and superior parietal lobule; green: precuneus.

5.4. Results

5.4.1. General participant characteristics

Participant groups did not significantly differ in age, education, sex or handedness distributions (all p>0.05, Table 1). However, the AD, lvPPA, svPPA, and bvFTD groups all had an average T-MMSE score that was significantly lower than the healthy control group (Kruskal-Wallis, X^2 = 33.981, p < 0.001). bvFTD patients had also a significantly longer symptom duration compared to nfvPPA and svPPA patients (ANOVA, F = 3.961, p = 0.021).

5.4.2. Validating the current sound battery

Figure 5-3 presents the average valence ratings for each sound and each participant group. Overall, the results show that all stimuli fit pre-defined valence category. Specifically, sounds that were pre-defined as unpleasant (female and male crying, angle grinder, and car horn) were found unpleasant by all participants on average, and those pre-defined as pleasant (female and male laughing, brook and river) were also found pleasant by all participants. This was confirmed by the linear regression yielding a significant main effect of sound (X^2 = 856.76, df = 7, p<0.0001). There was also a significant main effect of group (X^2 = 12.17, df = 5, p=0.0325) and post-hoc comparisons revealed that svPPA patients produced higher valence ratings compared to healthy control participants across all sounds (z=3.01, p = 0.039). A significant interaction between sound identity and group was also found (X^2 = 54.63, df = 35, p=0.0184). Corresponding post-hoc comparisons revealed that svPPA patients found angle grinder and car horn sounds more pleasant compared to healthy controls (z=4.29, p<0.001 and 3.27, p=0.016 respectively) and nfvPPA patients (z=-3.34, p=0.012 and -2.96, p=0.046 respectively). bvFTD patients also found car horn sounds more pleasant compared to healthy controls (z=3.04, p=.035) and nfvPPA patients (z=-2.94, p=0.049).

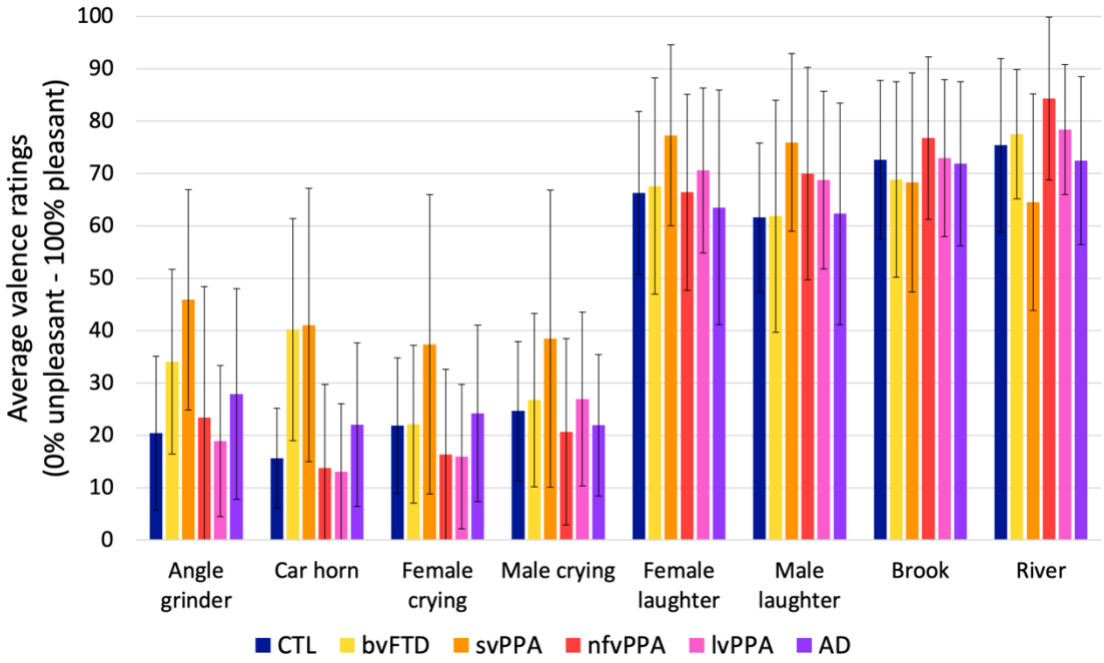


Figure 5-3. Average valence ratings across all participant groups for the eight different sounds used in the dementia study.

Ratings were given as percentages (0-49% being unpleasant, 50-100% being pleasant) and averages across participants were calculated for each sound. Error bars correspond to standard deviations.

5.4.3. Correlating timing performance of the current healthy control cohort with cognitive abilities

No statistically significant correlations were identified between timing performance (indexed by the bisection point and the Weber's ratio averaged across all four experimental conditions) and performance on the digit span forward and reverse tests as well as the WASI Matrix reasoning test.

5.4.4. Determining covariates for statistical analysis of pathological ageing effect on timing performance

There were no statistically significant between group differences in hearing threshold, mood score, musical background, as well as percentage correct scores on the practice phase of the temporal bisection task, the auditory control task, and the recognition task ($p>0.05$; **Table** 5-2). None of these measures were therefore included in the linear mixed models presented hereafter.

Table 5-2. Average performance on complementary tasks

	Controls	AD	lvPPA	nfvPPA	svPPA	bvFTD
Number of participants	24	11	8	8	11	8
Hearing threshold	26.3 (11.5) n-14	43.5 (3.5) n-9	27.7 (9.5) n-5	31.3 (15.0) n-5	25.4 (10.0) n-6	33.0 (7.8) n-1
Mood score (/20)	7.7 (2.5) n-10	8.8 (3.7) n-3	5.8 (1.8) n-2	6.7 (4.5) n-2	6.2 (2.3) n-6	7.0 (1.4) n-6
Musical background (/4)	1.4 (1.4) n-2	1.4 (1.0) n-2	2.2 (1.8) n-2	1.0 (1.3) n-1	1.8 (1.6) n-2	1.6 (0.9)
Practice correct score (%)	94.2 (6.2)	88.0 (6.7)	91.6 (6.6)	90.9 (5.8)	94.5 (5.9)	89.0 (9.4)
Control correct score (%)	97.8 (4.1)	94.1 (9.7) n-1	95.7 (4.8)	94.4 (9.1)	98.9 (3.6)	96.9 (6.2)
Recognition correct score (%)	N/A	98.9 (3.6)	100.0 (0.0)	100.0 (0.0)	96.0 (13.3)	97.8 (4.5)

Group averages (standard deviation) are shown here. Maximum scores are shown in parentheses for relevant variables. A higher mood score indicates worse mood; a high score on the musical background questionnaire indicates extensive musical experience. A reduced number of participants completed certain tasks (audiometry was only performed with participants tested face-to-face; the mood questionnaire was only administered to the remote cohort; other missing datapoints due to lack of time). Missing numbers are indicated following this scheme: $^{n-1}$ 1 missing datapoint. There were no statistically significant differences between participant group averages on any of the variables listed here.

Table 5-3. Average bisection point for each experimental condition and participant group.

	Controls		AD		lvPPA		nfvPPA		svPPA		bvFTD	
Condition	**Env**	**Hum**	**Env**	**Hum**	**Env**	**Hum**	**Env**	**Hum**	**Env**	**Hum**	**Env**	**Hum**
Unpleasant	3.3 (0.4)	4.3 (0.5)	3.1 (0.6)	4.5 (0.5)	3.3 (0.5)	4.7 (0.4)	2.9 (0.6)	4.7 (0.6)	3.4 (0.4)	4.3 (0.5)	3.4 (0.4)	4.5 (0.5)
Pleasant	3.6 (0.4)	4.1 (0.4)	3.3 (0.5)	4.4 (0.6)	3.3 (0.5)	4.4 (0.5)	3.3 (0.7)	4.3 (0.7)	3.3 (0.3)	3.9 (0.3)	3.6 (0.5)	4.5 (0.6)

Average bisection point values in seconds (standard deviations) are shown for the four experimental conditions. A higher bisection point value indicates underestimation of the sound duration for the corresponding experimental condition.

Table 5-4. Average Weber's ratio for each experimental condition and participant group.

	Controls		AD		lvPPA		nfvPPA		svPPA		bvFTD	
Condition	**Env**	**Hum**	**Env**	**Hum**	**Env**	**Hum**	**Env**	**Hum**	**Env**	**Hum**	**Env**	**Hum**
Unpleasant	0.20 (0.07)	0.18 (0.06)	0.27 (0.07)	0.20 (0.12)	0.25 (0.08)	0.24 (0.08)	0.22 (0.10)	0.21 (0.08)	0.17 (0.04)	0.20 (0.05)	0.29 (0.17)	0.21 (0.04)
Pleasant	0.23 (0.08)	0.22 (0.07)	0.28 (0.11)	0.27 (0.12)	0.25 (0.07)	0.24 (0.10)	0.3 (0.11)	0.27 (0.09)	0.19 (0.09)	0.24 (0.08)	0.31 (0.15)	0.26 (0.09)

Average Weber's ratio values are shown for the four experimental conditions with standard deviations in parentheses. A higher Weber's ratio value indicates a lower temporal discrimination sensitivity for the corresponding experimental condition.

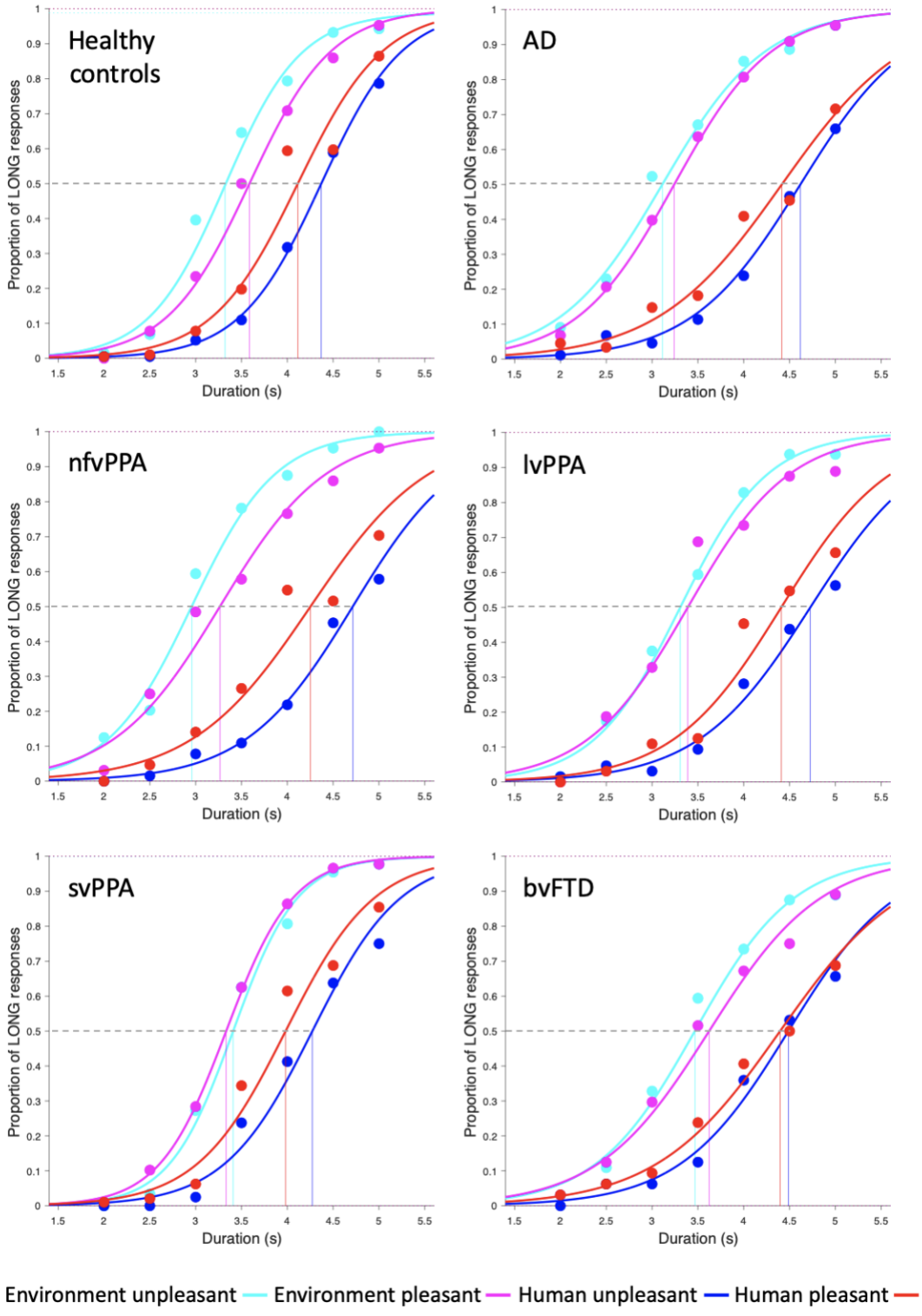


Figure 5-4. Average psychometric curves for each experimental condition and each participant group.

The number of long responses and the number of total trials available at each duration and for each experimental condition was averaged across participants from the same group and used to estimate psychometric curves for the corresponding group. Each experimental condition is displayed in a different colour as indicated in the legend.

5.4.5. Impact of pathological ageing on the bisection point

Average bisection point values are summarised in **Table** 5-3 and average psychometric curves corresponding to each age group and experimental condition are shown in **Figure** 5-4.

The linear mixed model corresponding to the bisection point revealed a main effect of semantic ($z=8.86$, $p<0.0001$) and valence categories ($z=2.27$, $p=0.023$), and significant interactions between semantic category and diagnosis as well as valence (all $p<0.001$). No other main effects or significant interactions were identified.

The main effect of semantic category indicates that overall, participants underestimated the duration of human sounds compared to environmental sounds. Post-hoc comparisons of the interaction between diagnosis and semantic category indicated that nfvPPA patients overestimated the duration of environmental sounds compared to healthy controls ($z=-2.03$, $p=0.043$) and bvFTD patients ($z=-2.08$, $p=0.038$). In addition, lvPPA patients underestimated the duration of human sounds compared to healthy controls ($z=2.28$, $p=0.023$), while svPPA patients overestimated the duration of human sounds compared to bvFTD patients ($z=-2.04$, $p=0.041$). However, none of these differences survive Bonferroni correction.

The main effect of valence category indicates that all participants underestimated the duration of pleasant sounds compared to unpleasant sounds. Post-hoc comparisons of the interaction between valence and semantic categories indicated that all participants overestimated the duration of environmental unpleasant sounds compared to environmental pleasant sounds ($z=2.34$, $p=0.019$), while they underestimated the duration of human unpleasant sounds compared to human pleasant sounds ($z=-3.69$, $p<0.001$).

5.4.6. Impact of pathological ageing on the Weber's ratio

Average Weber's ratio values are summarised in **Table** 5-4 and psychometric curves corresponding to each age group and experimental condition are shown in **Figure** 5-4.

The linear mixed model corresponding to the Weber's ratio revealed main effects of diagnosis and valence category ($z=4.11$, $p<0.001$), as well as a significant interaction

between diagnosis and semantic category (p=0.0427). No other main effects or significant interactions were identified.

The main effect of valence indicates that across all participants, discrimination sensitivity is higher for unpleasant sounds compared to pleasant sounds.

Post-hoc comparisons for the main effect of diagnosis showed that healthy control participants have a higher discrimination sensitivity compared to patients diagnosed with bvFTD (z=2.45, p=0.014) and AD (z=2.07, p=0.039). In addition, svPPA patients have a higher discrimination sensitivity compared to bvFTD patients (z=-2.63, p=0.009), AD (z=2.29, p=0.022) and lvPPA patients (z=2.01, p=0.045). None of these differences survive Bonferroni correction.

Post-hoc comparisons of the interaction between diagnosis and semantic category revealed that svPPA patients had a higher discrimination sensitivity compared to bvFTD patients (z=-3.5, p=0.007, Bonferroni corrected) and AD patients (z=3.66, p=0.004, Bonferroni corrected). There were also statistically significant differences in semantic category for svPPA and AD patients, but not for the other groups. Specifically, human sounds were less discriminable than environmental sounds for svPPA patients (z=2.13, p=0.033), while the opposite was true for AD patients (z=-2.37, p=0.018).

5.4.7. Correlations between patient performance and cognitive abilities

Bisection point and Weber's ratio values were first averaged across the four experimental conditions for each patient. Across the entire patient cohort, there were no statistically significant correlations between these performance measures and average hearing thresholds, mood score, musical background, as well as percentage correct scores on the practice phase of the temporal bisection task, the control task, and the recognition task. However, there was a statistically significant correlation between average bisection point values and forward digit span scores (Spearman's rho = - 0.438, p=0.003) as well as reverse digit span scores (Spearman's rho = - 0.305, p=0.042), meaning that reduced auditory verbal working memory and executive function skills are associated with duration underestimation. There was also a statistically significant correlation between average Weber's ratio values and WASI matrices scores (Spearman's rho = - 0.313, p=0.038), meaning that reduced executive function skills is associated with lower discrimination sensitivity. There were no other statistically

significant correlations between neuropsychological task performance (WASI Matrices, Camden PAL, digit span forward and reverse) and bisection point or Weber's ratio values.

5.4.8. Neuroanatomical results

Significant grey matter associations of duration estimation differences from healthy controls across the entire patient cohort for each sound condition are summarised in **Table** 5-5, all thresholded at $p_{FWE}<0.05$ within pre-specified anatomical regions of interest. The corresponding statistical parametric maps are shown in **Figure** 5-5. Across all patient groups, increased differences from the healthy control group in duration estimation of environmental pleasant sounds were correlated with reduced grey matter in the right precuneus. The same association was found for environmental unpleasant sounds but did not survive correction for multiple comparisons within the pre-specified anatomical region of interest and is therefore not shown here. In addition, across all patient groups, increased differences in duration estimation of human unpleasant sounds were correlated with reduced grey matter in the right insular cortex, while increased differences in duration estimation of human pleasant sounds was correlated with reduced grey matter in the right inferior parietal lobule. No other neuroanatomical associations were found.

Table 5-5. Neuroanatomical associations of duration estimation differences in the patient cohort

Sound	Region	Side	Cluster (voxels)	Peak (mm)			T score	P_{FWE}
				x	y	z		
Environmental pleasant	Precuneus	R	34	14	-44	48	5.21	0.019
Human unpleasant	Insula	R	22	32	14	4	4.43	0.041
Human pleasant	Inferior parietal lobule	R	171	62	-22	24	6.1	0.005

The table presents the regions where local grey matter volume is negatively associated with a difference in duration estimation between healthy participants and patients for the sound condition shown on the left. Coordinates of local maxima are in standard MNI space. P values were all significant ($p<0.05$) after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-specified anatomical regions of interest.

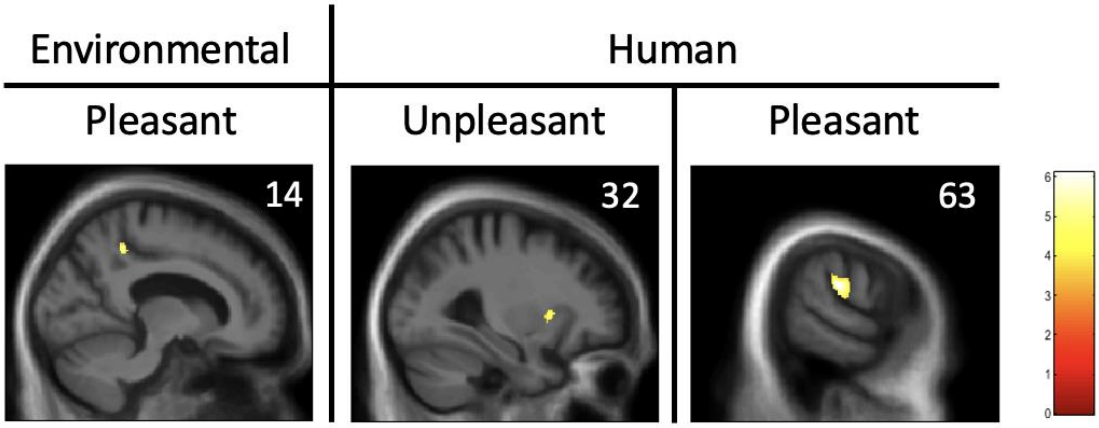


Figure 5-5. Statistical parametric maps showing neuroanatomical correlates of duration estimation differences from healthy participants across the entire patient cohort.

Across all patient groups, increasing differences in duration estimation from healthy participants were negatively correlated with regional grey matter volume. Corresponding statistical parametric maps show the right precuneus for environment pleasant sounds, the right insula for human unpleasant sounds, and the right inferior parietal lobule for human pleasant sounds. For display purposes, maps are displayed on coronal sections of the group mean T1-weighted MR brain image in MNI space, thresholded at $p<0.001$ uncorrected for multiple voxel-wise comparisons over the whole brain (areas significant at $p_{FWE} < 0.05$ after correction for multiple comparisons within pre-specified neuroanatomical regions of interest are specified in **Table** 5-5). The colour bar indicates voxel-wise T scores, and the plane of each section is given by the y-coordinate (mm) in MNI space shown on the top right-hand corner of the corresponding image.

5.5. Discussion

The present findings confirm observations from the healthy ageing study presented in **Chapter 3**, since both healthy and dementia participants tested here perceived human sounds as being shorter than environmental sounds, and all participants perceived environmental unpleasant sounds as being longer than environmental pleasant sounds, while the effect of pleasantness on perceived duration was in the opposite direction for human sounds. However, a few between-group differences were also found: lvPPA patients underestimated the duration of human sounds compared to healthy controls; bvFTD patients underestimated the duration of human sounds compared to svPPA patients; nfvPPA patients overestimated the duration of environmental sounds compared to healthy controls and bvFTD patients.

Patient group differences in performance compared to the control group are surprising given the lvPPA and nfvPPA groups were not the primary targets of the current experimental manipulation. Based on information-processing models of interval timing, underestimation may be attributed to either diminished attentional resources (less attention paid to time would lead to less pulses being accumulated for lvPPA compared to controls for the same time interval), or to reduced working memory capacity (which would affect storage of long intervals relative to short intervals and could therefore induce a shift of the corresponding psychometric curve to the right). Given previous literature in lvPPA (Giannini et al., 2017; Marshall, Hardy, Volkmer, et al., 2018), the second explanation is likely, especially given that underestimation of time intervals was associated with reduced auditory verbal working memory across all patients. However, it is unclear why this would affect human sounds specifically in lvPPA. Arguably, the human sounds presented here (laughter and crying) have a more complex spectrotemporal signature compared to the environmental sounds (angle grinder, car horn, water), which may have driven the effect. On the other hand, overestimation may be caused by a faster internal clock due to increased physiological arousal in nfvPPA compared to controls. The present finding may be interpreted in the light of the difference in functional significance between the environmental and human sounds: environmental sounds may be generally more salient than human sounds because they more likely require an immediate action (a car horn can be a warning signal, an angle

grinder may express danger and water sounds, while they may be relaxing to listen to, may also signal danger – flood for example). As such, overestimation of the duration of environmental sounds in nfvPPA may result from a generalised state of increased alertness upon hearing environmental sounds (irrespective of their pleasantness) and echoes previous studies of reduced predictive flexibility in dynamic auditory environments in nfvPPA (Benhamou et al., 2021; Cope et al., 2017).

While I had no prior hypotheses about between-patient-group differences in duration estimation, the fact that bvFTD patients underestimated the duration of environmental sounds compared to nfvPPA patients and human sounds compared to svPPA patients may be generally understood in light of their associated frontal lobe atrophy resulting in reduced working memory capacity and executive function skills. Duration underestimation across all sound categories is associated with reduced executive function skills across the entire patient cohort, and there was a particularly high number of bvFTD patients who failed to categorise sounds as either short or long in the practise phase of the temporal bisection task, suggesting that the bvFTD group is particularly impaired in temporal decision-making.

Discrimination sensitivity as indexed by the Weber's ratio was negatively correlated with executive function skills across the combined patient cohort, echoing previous associations between lower discrimination sensitivity and reduced working memory capacity as well as attentional resources (Gagnon et al., 2018; Ogden et al., 2019). This finding further suggest that discrimination sensitivity may index general cognitive abilities (such as processing speed, executive function skills, or working memory). Moreover, all participants found unpleasant sounds more discriminable than pleasant sounds, confirming previous account of increased sensitivity for negatively valenced sounds (S. D. Smith et al., 2011; Tipples, 2019; Voyer & Reuangrith, 2015). In addition, healthy control participants had a higher discrimination sensitivity compared to patients diagnosed with bvFTD and AD patients, which contradicts a previous temporal bisection task study showing AD patients have a reduced discrimination sensitivity for durations in the sub second but not the supra second range compared to healthy controls (Caselli et al., 2009). However, they corroborate previous findings of lower discrimination sensitivity in Parkinson's disease and Huntington's disease patients (Righi et al., 2016; J.

Zhang et al., 2016) since both diseases primarily target the basal ganglia, which is also affected in bvFTD (Bertoux et al., 2015; Landin-Romero et al., 2017).

Again, I formulated no specific hypotheses about between-patient group differences in discrimination sensitivity. However, the finding of an overall higher discrimination sensitivity in svPPA compared to bvFTD, AD, and lvPPA, is in line with the clinical observation of increased timing rigidity in svPPA (Nonaka et al., 2014b; Nyatsanza et al., 2003; Snowden et al., 2001) but may also reflect their retained ability to keep track of time through mental counting. Although I did not attempt to assess which patients actively counted during the temporal bisection task, svPPA patients are known to have preserved numerical abilities (Papagno et al., 2013; H. Sivasathiaseelan et al., 2021) and I previously showed in Chapter 3 that Prolific participants who reported counting had a higher discrimination sensitivity compared to those who did not. In addition, similarly to healthy older adults, svPPA patients found human sounds less discriminable than environmental sounds, suggesting preserved modulation of timing sensitivity by semantic characteristics. However, the results were opposite in AD (environmental sounds were less discriminable than human sounds), perhaps reflecting impaired sustained attention that would particularly affect duration judgements of environmental sounds since they are less spectrotemporally dynamic and are therefore less salient than human sounds.

Results of between-group differences in both duration estimation and discrimination sensitivity should be interpreted with caution, however, since most do not survive Bonferroni correction for multiple comparisons. This probably reflects the large variability in temporal estimates within each individual group. Indeed, for most sound conditions, there was roughly an equal number of patients who overestimated or underestimated the duration of those sounds compared to controls. It would therefore be valuable to replicate the present findings in larger cohorts with comparable degrees of disease severity within and across groups. The experimental design could also be modified to implement more intermediate durations in the higher range, which may help refine the estimation of the psychometric curve functions (especially for the human sounds where many participants did not produce many “long” responses even at the longest duration) and would therefore impact the corresponding bisection point and Weber’s ratio values. A simpler design with less experimental conditions may also be

chosen for testing dementia patients as fatigue effects may have impacted the present results by adding noise in the memory representations of the experimental durations.

Subjective time perception is a highly complex process resulting from the interaction of several higher order cognitive functions (namely working memory, attention, and decision-making) with more basic internal bodily signals (interoception, emotion, physiological arousal), as instantiated in information-processing models. It is therefore difficult to dissociate the influence of those different components on the current behavioural findings without additional information about how patients perform regarding those components. Here, for example, duration underestimation was associated with reduced auditory verbal working memory across all patients, however lvPPA patients (who are known to present with impaired working memory) underestimated only human sounds compared to healthy controls, suggesting deficits in cognition do not fully account for changes in subjective time perception identified here. To further tease apart the different effects, different other experimental designs could be envisaged: evaluating the effect of task difficulty (Livesey et al., 2007), directly manipulating levels of attention (El Haj et al., 2014) or working memory, or explicitly modulating physiological arousal (Van Wassenhove et al., 2011).

The neuroanatomical correlates identified here based on structural imaging provide an initial perspective on the neural mechanisms underlying modulation of sound duration by their emotional valence and semantic characteristics. Indeed, grey matter atrophy in the right precuneus was associated with increased difference between healthy controls and patients in duration estimation of environmental pleasant sounds (as well as for environmental unpleasant sounds although this did not survive correction for multiple comparisons). The precuneus is known as an important node of the “default-mode” network implicated in self-referential processes and memory retrieval (Spreng et al., 2008). Previous timing studies have suggested that the precuneus may play a role in the encoding and retrieval of duration information in healthy participants (Ferrandez et al., 2003; Harrington et al., 2004) and Parkinson’s disease patients (Dusek et al., 2012), especially given its implication in working memory (Ustun et al., 2017). The fact that this correlate is only found for environmental sounds is further interesting in the light of a previous fMRI study (Van Wassenhove et al., 2011). In this study, the authors compared duration judgements of looming and receding stimuli and found a stronger activation in

the posterior cingulate cortex and precuneus for looming compared to receding stimuli, a finding that has been interpreted under the light of self-referential processes recruited for the retrieval of temporal information related to the looming stimuli.

Different neuroanatomical correlates were found for human sounds: grey matter atrophy in the right anterior insular cortex was associated with increased difference between healthy controls and patients in duration estimation of human unpleasant sounds, and the right inferior parietal lobule was associated with increased difference between healthy controls and patients in duration estimation of human pleasant sounds. While both results are supported by previous neuroanatomical literature in the healthy brain (Hayashi et al., 2014; Wittmann, Van Wassenhove, et al., 2010), they also shed an interesting light on how the brain may specifically encode temporal information associated to human sounds. Indeed, listening to positive nonverbal vocalisations has been previously shown to engage an auditory-motor "mirror" network (J. E. Warren et al., 2006). Particularly relevant to the present study is the activation of the inferior parietal lobule during orofacial movements, suggesting here that mental rehearsal of human laughter may facilitate retrieval of timing information. In contrast, the retrieval of duration information associated with unpleasant human sounds may not require rehearsal and would instead rely on internal introspection since the anterior insular has been previously described as the potential neuroanatomical locus for subjective time awareness in humans by integrating interoceptive and emotional signals based on internal bodily signals (Craig, 2009). Considering the perceptual nature of crying sounds (which are filled with breaths and are therefore comparable to irregular sequences, i.e. intervals filled with irregularly spaced stimuli), this finding is in line with recent studies demonstrating that interoceptive awareness predicts accuracy in duration reproduction only for irregular sequences and that timing performance in this condition is modulated by the connectivity of the right posterior insula (Teghil, Boccia, et al., 2020; Teghil, Di Vita, et al., 2020).

It is further interesting to note that all neuroanatomical substrates found here are in the right hemisphere, consistent with the apparent right dominance in the timing literature (Harrington et al., 2004; Hayashi & Ivry, 2020; Lewis & Miall, 2006a; M. Wiener et al., 2010). However, many of the core timing networks have not been identified here, for example the dorsolateral prefrontal cortex, the inferior frontal gyrus, and the

supplementary motor area. This may be due to the neuroanatomical substrates being largely constrained by the atrophy profiles of the current dementia cohort. It would therefore be particularly valuable to perform a functional neuroimaging experiment, either using functional magnetic resonance imaging (fMRI) or magnetoencephalography (MEG) to deepen our understanding on subjective time perception in FTD and AD.

Overall, the present study provides initial evidence on how AD and FTD patients may time the duration of everyday life sounds varying in emotional valence and semantic characteristics differently from healthy participants as well as inform our understanding on how subjective time perception is encoded in the brain, as will be discussed further in the general discussion chapter.

6. Temporal phenotypes of daily life in dementia and neuroanatomical associations

6.1. Chapter summary

Aims

- Determine and compare the prevalence of abnormal time behaviours over longer time scale in AD and FTD syndromes
- Determine the neuroanatomical substrates of these temporal behaviours across all patient groups

Methods

- A total of 108 patients (37 typical and logopenic AD, 71 FTD) and 32 healthy participants completed this study
- A customised questionnaire was used to estimate the proportion of individual experiencing altered temporal behaviours in their everyday lives within each group
- Neuroanatomical correlates of altered temporal awareness across all patients were determined using voxel-based morphometry

Results

- Disruptions of temporal awareness are common in AD and FTD syndromes
- AD and FTD syndromes are dissociable based on their temporal behaviours. Specifically, difficulties in estimating temporal distance between the present and events from the past and/or the future as well as confusion when ordering past events were most frequently experienced by patients diagnosed with typical AD or lvPPA. On the other hand, svPPA patients primarily presented with timing rigidity and clockwatching, while bvFTD patients experienced all these four temporal symptoms with similar frequency in addition to an increased tendency to relive past event
- Increased tendency to relive past events in dementia patients was associated with relative preservation of grey matter in a distributed left-sided network encompassing the hippocampus as well as temporal and parietal cortices

Conclusion

- Overall, these findings demonstrate distinct temporal phenotypes of altered temporal awareness in AD and FTD

6.2. Introduction

The previous **Chapter 5** evaluated the impact of semantic and emotional information on the estimation of intervals of short duration (on the order of several seconds) in patients diagnosed with major syndromes of AD and FTD. While AD and FTD patients were impacted similarly to healthy controls by the experimental manipulations, a few differences were identified, with nfvPPA patients overestimating the duration of environmental sounds and lvPPA patients underestimating the duration of human sounds compared to controls. In addition, both AD and bvFTD patients were found to have a lower discrimination sensitivity across all sounds compared to controls.

In this present chapter, I looked at the awareness of longer time scales across canonical syndromes of AD and FTD, using a customised questionnaire designed to capture temporal behaviours indicative of a distorted temporal awareness. I additionally sought to determine the neuroanatomical correlates associated with these temporal symptoms across the entire patient cohort, focusing on regions that are key to well-functioning temporal processes. This is an area of utmost clinical importance as impaired perception of time likely contributes to significant care burden and patients' psychological distress.

What do we know about altered temporal awareness over long time scales in AD and FTD?

While it is easier to experimentally manipulate short intervals on the order of seconds and milliseconds, which are consequently extensively studied in time perception research (Teki, 2016), most of our psychologically relevant experiences unfold over longer timescales. To study those phenomena, several questionnaires and interview protocols have been created for both healthy and clinical populations (Crisci et al., 2016; Wallace, 1956; Wittmann & Lehnhoff, 2005b; Zimbardo & Boyd, 1999). As extensively described in **Chapter 1**, previous research has shown that temporal disturbances related to both past and future mental time travel are widely recognised in AD, while temporal processing had received little attention in FTD up until now (Liu et al., 2021). Specifically, future prospection has been found to be particularly impaired in FTD; obsessional and inflexible behaviours around time form also part of the repertoire of frequently observed symptoms, although no associated validated questionnaires are currently available.

Importantly, the present work relies on the assumption that, considering each neurodegenerative disease is characterised by a specific atrophy profile and that all of them target brain regions that have been previously implicated with timing in the healthy brain (Seeley et al., 2009; J. D. Warren et al., 2012; J. D. Warren, Rohrer, & Rossor, 2013; J. D. Warren, Rohrer, Schott, et al., 2013; Zhou et al., 2012), each one of them is likely associated with a unique phenotype of altered temporal awareness (although it may overlap with the other diseases). Directly comparing different neurodegenerative diseases, such as FTD and AD, on aspects of temporal processing may therefore lead to further understanding of their underlying pathophysiology and clinical symptomatology.

What did I do here?

I used a customised questionnaire completed by patients' primary caregivers to compare subjective temporal awareness in canonical syndromes of FTD (bvFTD, svPPA, nfvPPA) against typical amnestic AD and its language-led variant (lvPPA), as well as healthy older individuals. The temporal behaviours assessed here were selected based on clinical observations of the targeted diseases and on their relevance for the study of temporal awareness in everyday living. However, this first study was not meant to characterise these temporal symptoms in detail. Instead, the aims were to first, survey the types of altered time awareness that can arise in FTD, and second, to evaluate the proportion of patients with different FTD diagnoses reporting those behaviours relative to typical AD and lvPPA. I further performed a voxel-based morphometry analysis to determine the common structural neuroanatomical substrates of temporal symptoms across all patients.

What are my hypotheses?

Hypotheses for this study are directly informed by previous clinical observations. I expect patients diagnosed with typical AD and lvPPA to mainly report difficulties with temporal distance estimation and event ordering, while patients diagnosed with FTD syndromes (especially bvFTD and svPPA) would be particularly prone to timing rigidity (manifesting as intolerance to delays and insistence on doing things at a specific time) and clockwatching (e.g. tendency to 'watch the clock' or increased attention to time). Based on previous studies of timing in the healthy brain detailed in **Chapter 1** (Coull et al., 2004; Craig, 2009; Franklin & Jonides, 2009; M. J. Hayashi, R. Kanai, et al., 2013; Jin et al., 2009; Kanayet et al., 2018; Lewis & Miall, 2006b; Lisman et al., 2017; Macar et al.,

2006; Mita et al., 2009; Paton & Buonomano, 2018; M. Wiener et al., 2010; Wittmann, 2009; Wittmann, Simmons, et al., 2010), I also hypothesise that the neural substrates associated with each temporal symptom would differentially involve the posterior temporo-parietal cortices and hippocampus (implicated in temporal ordering) and the prefrontal and antero-mesial temporal cortex (participating in the appraisal and valuation of time intervals).

6.3. Methods

6.3.1. Participants

A total of 71 patients diagnosed with FTD (34 bvFTD, 17 svPPA, 20 nfvPPA), twenty-eight patients with a typical amnestic AD and nine patients with lvPPA were recruited for this study following methodology detailed in **section 2.1.2**. All patients fulfilled consensus diagnostic criteria for the relevant syndromic diagnosis (Dubois et al., 2014; M.L. Gorno-Tempini et al., 2011; Rascovsky et al., 2011) and had disease of mild to moderate severity. 12 patients with typical AD and six patients with lvPPA had additional CSF biomarkers indicative of an underlying AD pathology, based on local reference ranges (total tau/beta-amyloid1−42 ratio >0.8). Genetic screening revealed eight mutations with C9orf72 (all diagnosed with bvFTD), seven MAPT (six bvFTD and one svPPA), seven GRN (four bvFTD and three nfvPPA). Thirty-two age-matched healthy individuals with no history of neurological or active psychiatric illness were also recruited. Anticipating the potential impact of antidepressants and neuroleptics on time perception (Ho et al., 2002; Tomassini et al., 2016), information on medication use for all participant groups was also recorded. Participant characteristics are summarised in **Table** 6-1.

Table 6-1. Demographic, clinical and neuropsychological characteristics of participant groups

Characteristics	Controls	bvFTD	svPPA	nfvPPA	lvPPA	AD
General demographic and clinical						
No. (Male/Female)	32 (16/16)	34 (26/8)	17 (10/7)	20 (10/10)	9 (8/1)	28 (13/15)
Age (years)	68.2 (6.9)	65.8 (6.9)	66.5 (7.5)	68.5 (8.4)	69.2 (9.6)	70.4 (7.8)
Handedness (R/L)	29/2	32/1	17/0	18/1	8/1	25/2
Education (years)	16.1 (2.4)	13.8 (4.0)	15.0 (2.9)	13.6 (2.5)	16.2 (2.1)	14.9 (2.0)
MMSE (/30)	29.8 (0.4)	22.4 (6.4)	21.8 (8.0)	18.4 (9.5)	13.1 (7.8)	18.1 (6.6)
Symptom duration (years)	N/A	7.2 (5.0)	6.1 (2.4)	4.3 (2.4)	5.2 (1.9)	6.9 (3.6)
Medication use**: no (%)	2 (6)	16 (47)	6 (35)	8 (40)	2 (22)	13 (46)
Neuropsychological						
General intellect						
WASI Verbal IQ	123.7 (8.2)[a]	82.4 (27.6)[c]	67.9 (18.3)[a]	72.3 (18.9)[b]	61.3 (19.1)	93.1 (20.2)[a]
WASI Performance IQ	125.2 (12.9)[a]	92.8 (22.9)[c]	114.5 (17.5)[a]	88.8 (22.4)[b]	81.7 (12.9)	82.6 (16.7)[a]
Episodic memory						
RMT Words (/50)	48.8 (1.2)[a]	28.4 (18.8)[g]	26.3 (16.3)[d]	31.1 (18.4)[b]	20.2 (20.3)	25.4 (11.5)[e]
RMT Words (/25)*	24.7 (0.8)	N/A	N/A	N/A	N/A	15.3 (3.5)
RMT Faces (/50)	43.9 (5.0)[a]	23.7 (15.8)[f]	26.9 (11.7)[b]	30.5 (15.8)[b]	19.9 (19.7)	26.7 (11.7)[e]
RMT Faces (/25)*	24.6 (0.7)	N/A	N/A	N/A	N/A	17.8 (2.8)
Working memory						
DS-F (max)	7.2 (1.1)[a]	5.7 (1.4)[a]	6.6 (0.9)[a]	3.8 (2.2)[c]	3.0 (2.4)	5.9 (1.4)[a]
Executive function						
DS-R (max)	5.5 (1.3)[a]	3.6 (1.8)[a]	5.0 (1.5)[a]	1.9 (1.6)[c]	1.8 (1.4)	3.3 (1.8)[b]

See other tests on the next page

Characteristics	Controls	bvFTD	svPPA	nfvPPA	lvPPA	AD
D-KEFS Stroop						
colour (s)	30.1 (4.9)[b]	53.8 (22.0)[a]	52.6 (23.2)[a]	77.3 (19.8)[d]	81.9 (13.7)	57.4 (17.1)[d]
word (s)	23.3 (5.0)[b]	35.5 (19.0)[a]	32.0 (18.4)[a]	70.3 (25.5)[d]	60.8 (22.8)	44.4 (22.5)[d]
interference (s)	54.8 (13.2)[b]	119.9 (54.8)[a]	96.9 (45.9)[a]	155.9 (44.8)[d]	180.0 (0.0)	145.6 (40.5)[d]
Fluency						
Letter (total)	17.7 (5.7)[a]	6.6 (5.4)[a]	6.9 (5.4)[a]	4.1 (4.4)[d]	2.0 (2.9)	8.9 (4.9)[b]
Category (total)	24.6 (5.4)[a]	10.0 (6.9)[a]	5.3 (4.4)[a]	9.4 (7.2)[d]	2.2 (2.9)	8.0 (5.0)[a]
TMT A (s)	31.1 (9.2)[a]	75.7 (46.4)[a]	53.5 (27.7)[a]	82.1 (45.4)[d]	116.9 (37.6)	99.3 (42.4)[a]
TMT B (s)	60.2 (24.1)[a]	202.2 (93.5)[a]	147.3 (88.4)[a]	229.2 (94.4)[c]	300.0 (0.0)	269.7 (69.0)[c]
Language skills						
BPVS (/150)	148.0 (1.4)[a]	110.7 (45.5)[e]	62.1 (39.8)[b]	117.6 (44.4)[b]	92.6 (55.0)	124.1 (36.7)[a]
GNT (/30)	26.6 (2.7)[a]	12.1 (9.3)[d]	1.0 (4.0)[a]	10.7 (7.2)[c]	7.0 (8.5)[a]	12.5 (8.3)[b]
Visuospatial skills						
VOSP (/20)	18.9 (1.2)[a]	14.2 (5.2)[d]	14.1 (4.7)[a]	15.1 (4.7)[b]	13.6 (3.7)	15.4 (2.6)[a]

Mean (standard deviation) values are shown unless otherwise indicated (maximum scores on neuropsychological tests are in parentheses); significant differences in performance between healthy controls and patient groups ($p<0.05$) are coded in bold. *based on data from an historical cohort of 24 healthy older controls and six patients with AD from the present cohort. **includes medications with a potentially relevant impact on time perception (see text). A reduced number of participants completed certain tests, as follows: [a]n-1, [b]n-2, [c]n-3, [d]n-4, [e]n-7, [f]n-9, [g]n-11. N/A, not applicable.

6.3.2. Assessing temporal phenotypes of daily life

Time-related behaviours that participants may be experiencing in their everyday living and that could suggest an altered temporal awareness over longer time scales were selected based on accumulated clinical experience of the diseases targeted in this study (**section 1.6.4**). They are shown in **Table** 6-2 and included: apparent confusion about the order in which experienced past personal events have taken place, difficulty estimating the temporal distance between the present and an event situated in the past or in the future, increased timing rigidity, clockwatching, and heightened tendency to re-live past personal events.

These behaviours were assessed in the form of a questionnaire where participants were asked to indicate whether they experienced any of the temporal symptoms in their current day-to-day living. Specifically, participants were asked to record any changes in their current behaviour compared to their behaviour 10 years previously, a time frame that reflects the typical duration of clinical symptoms in the target diseases, including any prodromal differences. While healthy control participants completed the questionnaire by themselves, each patient was aided by their primary caregiver (either their spouse or child). This was necessary as participants with dementia (particularly FTD) do not retain full insight into their disease (**section 1.6.3**) and may therefore not fully understand or accurately report their symptoms, while patients with AD often have significant difficulties with autobiographical recall. Participants were also invited to supply free text entries with further details about their temporal behavioural changes.

Table 6-2. Survey used to identify alterations in temporal awareness

	Questions
Temporal symptom	Thinking about [her / his / your] activities most days, please indicate whether you feel there has been a clear increase in any of the following
Ordering past events	Confusion about the order in which personal events have happened
Estimating intervals between events	Difficulty estimating how long ago personal events occurred / how far in the future events will occur
Temporal rigidity	Intolerant of delays, anxiety or irritation about missing appointments or late arrivals, insistence on doing things at a particular time
Clockwatching	Tendency to 'watch the clock' or preoccupation with the time
Re-living past events	Tendency to re-live personal events or episodes from the past

Survey symptom items were chosen based on clinical observations of the disease groups targeted in this study. The questionnaire was completed by healthy control participants themselves and by patients' primary caregivers. If the respondent was a healthy control participant, they indicated whether they were experiencing changes in their time-related behaviour compared to their behaviour over the past 10 years; if the respondent was a caregiver, they compared the patient's time-related behaviour with their premorbid behaviour.

6.3.3. Analysis of clinical and behavioural data

Statistical analysis of clinical and behavioural data was carried out using Stata (version 14.0) following methodology detailed in **section 2.8.1**.

The analysis of the questionnaire data consisted in evaluating the prevalence of changes in long scale time behaviours in each participant group and comparing the prevalence of each behaviour across all groups. First, each symptom was coded as 1 (present) or 0 (absent). For each symptom, I then compared its prevalence in the healthy control group against its prevalence in all patient groups combined using a two-tailed Fisher's exact test and corrected for multiple comparisons using the Benjamini-Yekutieli procedure (Benjamini & Yekutieli, 2001). Although logistic regression models were then used for a detailed patient group comparison, I did not build one here because, for three of the five surveyed items, no healthy control participant exhibited the symptom.

Once an overall disease effect was established for each temporal behaviour, I built a logistic regression model to compare the log odds of exhibiting that symptom (as the dependent variable) between patient groups. I coded a dummy variable for diagnosis, specifying the AD group as the reference, and included three covariates (age, gender and MMSE score) to take into account potentially confounding effects. Although not ideal for reasons explained in **section 2.7.3**, the MMSE score was incorporated as a widely used index of overall disease severity. I further explored associations between each individual symptom and additional covariates not addressed by the logistic regression models (years of education, relevant medication use) using the Student t-test or the Wilcoxon rank sum test for the first, and the chi-square test for the second. Finally, additional logistic regression models were built to determine potential correlations between temporal symptoms grouped along three domains (confusion ordering past events together with estimation difficulties of past and future temporal distance; timing rigidity together with clockwatching; reliving past events) across all participants. A statistical significance threshold $p < 0.05$ was accepted for all tests.

6.4. Brain Image acquisition and analysis

T1-weighted volumetric brain MRI data from 91 patients were entered into the VBM analysis; scans were unavailable for 14 patients (three bvFTD, one nfvPPA, two lvPPA, eight AD) and a further three (two bvFTD, one nfvPPA) were inadequate on technical grounds. All scans were acquired, and pre-processed following methodology described in **section 2.7**.

Across the combined patient cohort, we ran a full factorial model to assess associations of regional grey matter volume with each temporal symptom. The model incorporated the five temporal symptom items (respectively coded as 0/1 for absence/presence of that symptom), diagnosis as a five-level factor, and the following nuisance covariates: age, total intracranial volume, and MMSE score. For every item, negative (inverse) associations with regional grey matter (i.e., associations with grey matter atrophy) were evaluated. Positive grey matter associations were additionally assessed for symptoms of temporal rigidity, clockwatching, and re-living the past, since these are likely to require at least partially preserved temporal processing mechanisms (Nonaka et al., 2014a).

Statistical parametric maps were generated using an initial threshold $p < 0.001$ and evaluated at peak voxel statistical significance level $p < 0.05$, after family-wise error (FWE) correction for multiple voxel-wise comparisons, separately within individual pre-specified neuroanatomical regions of interest. The selection of these regions was informed by previous studies on the neuroanatomy of time perception in the healthy brain (**sections 1.2.4 and 1.4.2**). They were defined for both the right and left hemispheres and included: the anterior temporal lobe (the anterior parts of the superior, middle, inferior temporal, and fusiform gyri, and the temporal pole) (Ballotta et al., 2018; Bueti et al., 2008; Stevens et al., 2007; Tracy et al., 2000), insular cortex (Apaydin et al., 2018; Craig, 2009; Wittmann, 2009; Wittmann, Simmons, et al., 2010), parietal cortex (inferior and superior parietal lobules, precuneus and posterior cingulate cortex) (Franklin & Jonides, 2009; Gonneaud et al., 2014; Hayashi et al., 2015; M. J. Hayashi, R. Kanai, et al., 2013; Kanayet et al., 2018) and hippocampus (Eichenbaum, 2014, 2017a; Lisman et al., 2017). See **Figure** 6-1 for a visual representation of these regions.

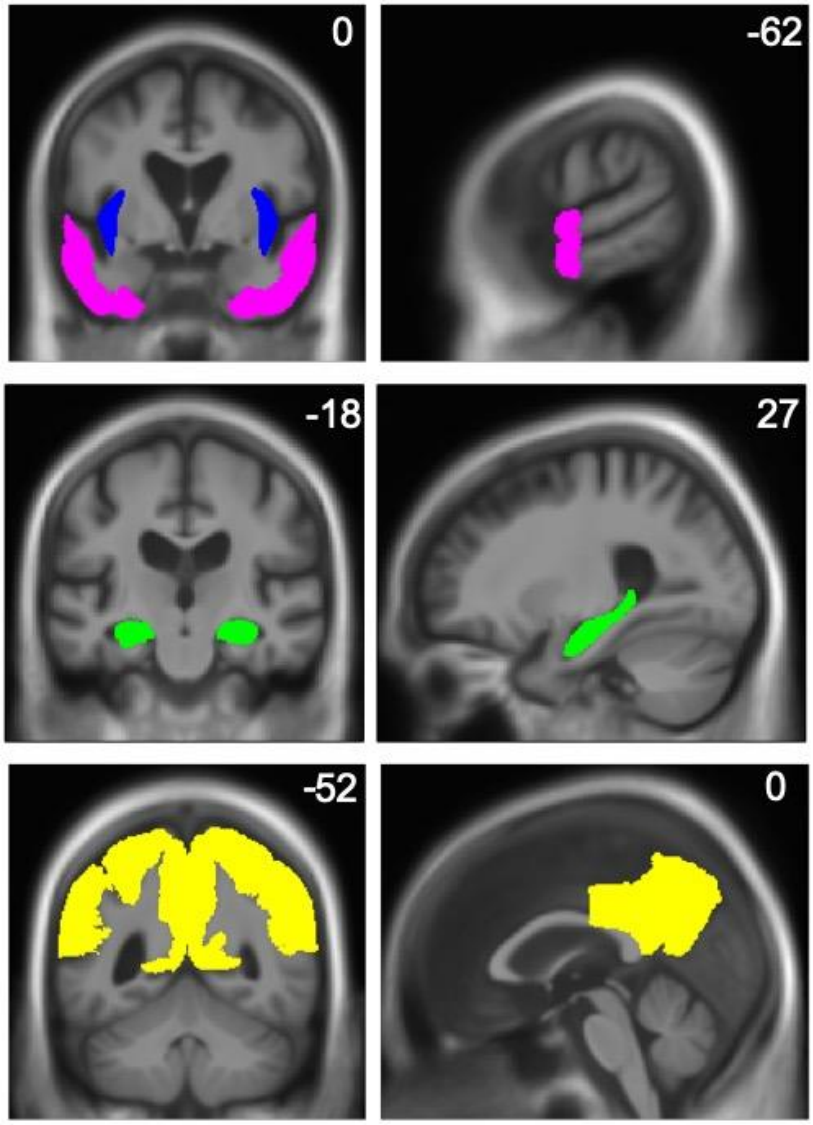


Figure 6-1. Pre-specified anatomical regions of interest for the present VBM analysis

Coronal (left) and sagittal (right) views of the regions of interest used in the present VBM analysis during small volume correction for multiple voxel-wise comparisons (see text for details). Regions have been overlaid on the group mean structural brain image in MNI space, coordinates (mm) of the plane of each section are indicated. Blue: insular cortex; magenta: anterior temporal lobe; green: hippocampus; yellow: parietal region (inferior and superior parietal lobules, precuneus, and posterior cingulate cortex).

6.5. Results

6.5.1. General demographic, clinical and neuropsychological data

Table 6-1 presents the general demographic, clinical and neuropsychological characteristics of the entire study cohort. Participant groups did not significantly differ in age ($F(5,134) = 1.31$; $p = 0.2619$), nor handedness ($p = 0.885$). Sex distribution was unequal across groups ($X^2(5,140) = 11.204$; $p = 0.047$). There was a significant difference in education too, although the absolute difference was only about two years ($H(5) = 15.212$; $p = 0.0095$). Importantly, patient groups did not differ significantly in symptom duration ($H(4) = 8.43$; $p = 0.077$). However, there was a significant difference in MMSE scores ($F(4,103) = 3.66$; $p = 0.0078$), with bvFTD patients scoring significantly higher than lvPPA patients ($p = 0.012$). Finally, no significant differences in medication use were found across patient groups ($X^2(4,108) = 2.4$; $p = 0.667$).

6.5.2. Temporal awareness symptom data

Data on the prevalence of temporal awareness alterations for all participant groups are summarised in **Table** 6-3 below. The logistic regression analysis comparing patient groups is presented in **Table** 6-4. The Logistic regression analysis evaluating temporal symptom correlations is also presented in **Table** 6-5. The proportions of individual patients with genetic mutations causing FTD who experienced time symptoms are shown in **Table** 6-6.

Table 6-3. Prevalence of symptoms indicating altered time awareness in study cohort

	Controls	bvFTD	SD	PNFA	LPA	AD
Temporal symptom	n = 32	n = 34	n = 17	n = 20	n = 9	n = 28
Ordering past events	0%	62%	12%	15%	56%	68%
Estimating intervals between events	0%	59%	18%	35%	67%	79%
Temporal rigidity	0%	41%	65%	35%	11%	11%
Clockwatching	3%	44%	59%	35%	22%	18%
Re-living past events	9%	59%	47%	25%	22%	21%

The present data was derived from the customised questionnaire to determine the prevalence of time perception changes in each participant group, evaluated as the proportion (percentage) of participants presenting with a symptom for that group (total group sizes shown above). All patient groups combined were significantly different from the healthy control group ($p<0.001$ after correction for multiple comparison).

An initial look at the raw percentages in **Table** 6-3 reveals that changes in time perception over longer time scales were frequent in all patient groups and were only reported by a minority of healthy controls. Notably, confusion ordering past events and difficulty estimating intervals between events were the two most frequently reported symptoms in patients with a probable AD pathology (AD and lvPPA), whereas the three other symptoms (temporal rigidity, clockwatching, tendency to relive past events) were most often experienced by patients with an FTD pathology (bvFTD, svPPA, nfvPPA). Certain behaviours were especially prominent in specific groups (i.e., present in more than half of cases in that group): confusion about past event ordering and difficulty estimating temporal distance between events in bvFTD, lvPPA and AD; temporal rigidity and clockwatching in svPPA; and a tendency to relive past events in bvFTD.

Compared to the healthy control group, the combined patient cohort had a significantly higher proportion of participants presenting with confusion about ordering events in time and difficulty estimating intervals between events (both $p<0.0001$). Regarding patient group differences in prevalence, the corresponding logistic regression model showed a main effect of diagnosis for both confusion of temporal order ($X^2(4, 103) = 20.70$, $p = 0.0004$) and interval estimation difficulties ($X^2(4, 103) = 16.29$, $p = 0.0026$). More specifically, AD patients were more likely to display such behaviours compared to svPPA patients (temporal ordering: odds ratio (OR) = 0.06, 95% confidence interval (CI) 0.01 – 0.35; temporal estimation: OR = 0.06, CI 0.01 – 0.31) and nfvPPA patients (temporal ordering: OR = 0.06, CI 0.01 – 0.30; temporal estimation: OR = 0.12, CI 0.03 – 0.49).

The combined patient cohort also had a significantly higher proportion of patients engaging in timing rigidity and clockwatching compared to healthy controls (both $p<0.001$). The associated logistic regression models revealed a main effect of diagnosis for both symptoms (temporal rigidity: $X^2(4, 103) = 12.98$, $p = 0.0114$; clockwatching: $X^2(4, 103) = 10.57$, $p = 0.0318$). More precisely, timing rigidity was more frequently reported by patients diagnosed with bvFTD, svPPA or nfvPPA than AD (bvFTD: OR = 5.50, CI 1.24 – 24.40; svPPA: OR = 17.33, CI 3.30 – 91.09; nfvPPA: OR = 5.29, CI 1.11 – 25.14). Additionally, patients diagnosed with bvFTD and svPPA were more prone to clockwatching than AD patients (bvFTD: OR = 4.44, CI 1.21 – 16.35; svPPA: OR = 8.98, CI 2.09 – 38.58).

Finally, all patient groups were significantly more likely to re-live past events in comparison to healthy controls ($p<0.001$). However, the corresponding logistic regression model revealed no significant main effect of diagnosis ($X^2(4,108) = 5.78$, $p = 0.22$), preventing individual between-patient group comparisons.

The logistic regression analysis evaluating patient group differences in prevalence for each temporal symptom also showed a significant association between the MMSE score and symptoms related to ordering of past events and estimation of temporal distance between events across the entire patient cohort (OR = 0.92, CI 0.86 – 0.98 and OR = 0.91, 95% CI 0.86 – 0.97, respectively). No other significant associations were found between temporal symptoms and the two other demographic characteristics (age and gender) incorporated in the logistic regression models.

As shown in **Table** 6-5, difficulties with temporal distance estimation and confusion in ordering past events together were significantly correlated with symptoms of temporal rigidity and clockwatching, whereas no significant associations were found between these symptoms and a tendency to relive past events.

Considering the small number of patients with genetic mutations, no formal statistical between-group comparison has been performed. However, it is clear that symptoms of altered time perception were generally common with all major mutations causing FTD (**Table** 6-6). Numbers further suggests that temporal rigidity as well as clockwatching were particularly associated with *MAPT* mutations, given its comparatively low prevalence in *C9orf72* cases and its absence in *GRN* cases.

Further associations between temporal awareness symptoms and general patient characteristics (medication use or education) were investigated but none were statistically significant.

Table 6-4. Results of the logistic regression analysis over the patient cohort

Temporal symptom	Variable	OR	95% CI	P value
Ordering past events	Diagnosis			
	bvFTD	0.94	0.28-3.12	0.926
	SD	0.06	0.01-0.35	**0.002**
	PNFA	0.06	0.01-0.30	**0.001**
	LPA	0.34	0.06-1.91	0.219
	Gender (F)	0.91	0.33-2.50	0.852
	Age	0.97	0.92-1.04	0.407
	MMSE	0.92	0.86-0.98	**0.010**
	Constant	71.55	0.77-6633.90	0.065
Estimating intervals between events	Diagnosis			
	bvFTD	0.51	0.14-1.82	0.302
	SD	0.06	0.01-0.31	**0.001**
	PNFA	0.12	0.03-0.49	**0.003**
	LPA	0.33	0.05-2.02	0.232
	Gender (F)	1.03	0.39-2.71	0.948
	Age	0.99	0.93-1.05	0.666
	MMSE	0.91	0.86-0.97	**0.005**
	Constant	51.48	0.62-4292.08	0.081
Temporal rigidity	Diagnosis			
	bvFTD	5.50	1.24-24.40	**0.025**
	SD	17.33	3.30-91.09	**0.001**
	PNFA	5.29	1.11-25.14	**0.036**
	LPA	1.04	0.09-12.41	0.975
	Gender (F)	0.52	0.19-1.41	0.197
	Age	1.05	0.99-1.11	0.132
	MMSE	1.04	0.98-1.11	0.203
	Constant	0.00	0.00-0.29	**0.013**
Clockwatching	Diagnosis			
	bvFTD	4.44	1.21-16.35	**0.025**
	SD	8.98	2.09-38.58	**0.003**
	PNFA	2.80	0.70-11.12	0.146
	LPA	0.90	0.13-6.41	0.919
	Gender (F)	0.48	0.18-1.24	0.130
	Age	1.06	1.00-1.12	0.054
	MMSE	10.98	0.92-1.04	0.450
	Constant	0.01	0.00-0.57	**0.026**

See results related to the last temporal symptom
on the next page

Temporal symptom	Variable	OR	95% CI	P value
Re-living past events	Diagnosis			
	bvFTD	3.49	1.05-11.63	**0.042**
	SD	2.40	0.61-9.47	0.212
	PNFA	1.12	0.28-4.47	0.875
	LPA	1.06	0.16-6.93	0.951
	Gender (F)	0.66	0.26-1.66	0.378
	Age	0.97	0.91-1.02	0.256
	MMSE	1.04	0.98-1.11	0.154
	Constant	1.56	0.03-96.61	0.832

For each logistic regression model, the AD group acts as the reference group for between-patient group comparisons. Significant associations with individual variables ($p<0.05$) are coded in bold. CI, confidence interval; F, female; OR, odds ratio.

Table 6-5. Results of the logistic regression analysis evaluating correlations between temporal symptoms across the patient cohort

Temporal symptom	Variable	OR	95% CI	P value
Temporal distance estimation + Ordering past events	Temporal rigidity + Clockwatching	0.23	0.10-0.55	**0.001**
	Re-living past events	1.08	0.47-2.48	0.851
	Constant	1.83	1.04-3.22	**0.037**
Temporal rigidity + Clockwatching	Temporal distance estimation + ordering past events	0.23	0.10-0.55	**0.001**
	Re-living past events	1.30	0.55-3.10	0.555
	Constant	0.91	0.47-1.73	0.763
Re-living past events	Temporal distance estimation + ordering past events	1.84	0.88-3.87	0.106
	Temporal rigidity + Clockwatching	2.05	0.91-4.61	0.082
	Constant	0.29	0.15-0.80	**< 0.001**

Time symptoms were grouped as shown to simplify analysis. Each time domain was chosen in turn as the reference to determine correlations between symptoms in different time domains across the whole patient cohort; significant associations are coded in bold ($p<0.05$). CI, confidence interval; OR, odds ratio.

Table 6-6. Prevalence of altered time awareness in FTD patients with genetic mutations

	C9orf72	***MAPT***	***GRN***
Number of cases	n = 8	n = 7	n = 7
Confusion ordering events	63%	57%	57%
Difficulty estimating intervals between events	63%	71%	57%
Temporal rigidity	25%	71%	0%
Clockwatching	50%	71%	0%
Re-living past events	75%	57%	57%

The proportion (percentage) of genetic cases presenting with a temporal symptom is shown for each reported genetic mutation (total group sizes shown above). Mutation carriers are coded by site of mutation as follows: ***C9orf72*****,** mutation in open reading frame 72 on chromosome 9; ***GRN***, progranulin; ***MAPT***, microtubule associated protein tau.

6.5.3. Neuroanatomical associations of altered time perception

Significant grey matter associations of altered time perception across the entire patient cohort are summarised in **Table** 6-7, all thresholded at $p_{FWE}<0.05$ within pre-specified anatomical regions of interest. The corresponding statistical parametric maps are shown in **Figure** 6-2. Across all patient groups, an increased tendency to re-live past events was correlated with relatively preserved grey matter in a distributed left-sided network involving the anterior middle temporal gyrus and superior temporal sulcus, the hippocampus, as well as the posterior cingulate and superior parietal cortices. No other neuroanatomical associations were found.

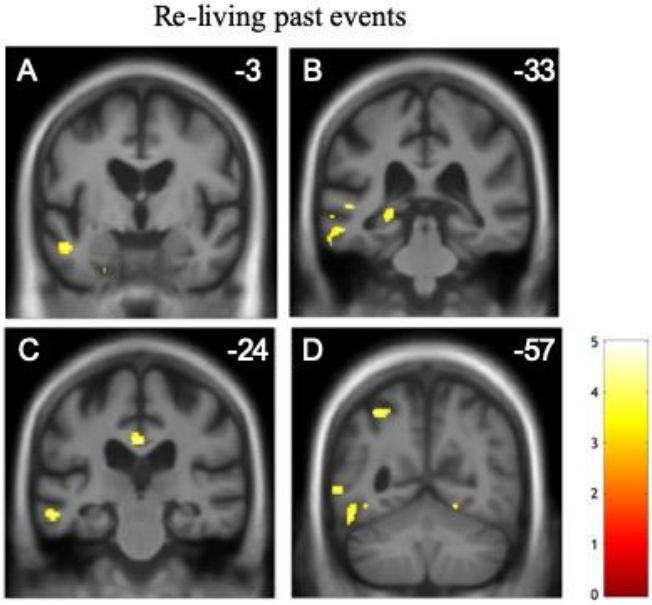


Figure 6-2. Statistical parametric maps showing neuroanatomical correlates of altered time perception across the entire patient cohort.

Across all patient groups, the tendency to re-live past events was positively correlated with regional grey matter volume. Corresponding statistical parametric maps show a left-sided distributed network of regions including the anterior middle temporal gyrus and superior temporal sulcus (A), the hippocampus (B), the posterior cingulate cortex (C) and the superior parietal cortex (D). For display purposes, maps are displayed on coronal sections of the group mean T1-weighted MR brain image in MNI space, thresholded at $p<0.001$ uncorrected for multiple voxel-wise comparisons over the whole brain (areas significant at $p_{FWE} < 0.05$ after correction for multiple comparisons within pre-specified neuroanatomical regions of interest are specified in **Table** 6-7). The colour bar indicates voxel-wise T scores, and the plane of each section is given by the y-coordinate (mm) in MNI space shown on the top right-hand corner of the corresponding image.

Table 6-7. Neuroanatomical associations of altered time perception in the patient cohort

Region	**Side**	**Cluster** (voxels)	**Peak** (mm)			**T score**	**P_{FWE}**
			x	y	z		
Middle temporal gyrus / superior temporal sulcus	L	118	-50	-3	-26	3.95	0.038
Hippocampus	L	31	-22	-33	-4	3.74	0.019
Posterior cingulate	L	184	-2	-24	33	4.52	0.015
Superior parietal lobule	L	75	-32	-57	51	4.23	0.038

The table presents the regions where of local grey matter volume is positively associated with the tendency to re-live past events (the only temporal symptom for which a significant neuroanatomical association was found) over the combined patient cohort. Coordinates of local maxima are in standard MNI space. P values were all significant ($p<0.05$) after family-wise error (FWE) correction for multiple voxel-wise comparisons within pre-specified anatomical regions of interest.

6.6. Discussion

The present study highlights the predominance of several temporal symptoms within FTD and AD syndromes, indicating a disrupted perception of long durations in comparison to healthy older adults. Specifically, those symptoms were reported by more than half of the patients diagnosed with bvFTD, svPPA, typical AD, and lvPPA, and by about a third of nfvPPA patients, while a negligeable number (or none) of healthy individuals had similar experiences. The study further endorses previous clinical observations of FTD and AD syndromes by establishing distinct profiles of altered time perception (though these do overlap). Specifically, difficulties in estimating temporal distance between the present and events from the past and/or the future as well as confusion when ordering past events were most frequently experienced by patients diagnosed with typical AD or lvPPA. On the other hand, svPPA patients primarily presented with timing rigidity and clockwatching, while bvFTD patients experienced all these four temporal symptoms with similar frequency in addition to an increased tendency to relive past events. Importantly, those profiles were identified even when taking into account basic demographic and clinical characteristics (age, gender, and MMSE score).

The temporal symptoms surveyed in this work can be further synthesised according to previous research on time perception in the healthy brain (D. Bernsten & A. S. Jacobsen, 2008; Bonato et al., 2012a; Brunec et al., 2015; Pathman et al., 2018). Difficulties with temporal distance estimation and past event ordering may suggest general temporal disorientation resulting from an impaired mental timeline. Separately, symptoms of temporal rigidity and clockwatching could both indicate disrupted mechanisms of mental timekeeping. This proposed perspective is further substantiated by the finding that a patient who experienced temporal distance estimation difficulties and/or confusion ordering past events was less likely to experience timing rigidity and clockwatching (and vice versa; see **Table** 6-5).

Neither of these two temporal domains was associated with the tendency to relive past events, further strengthening the idea that this temporal behaviour may manifest in compensation of a disordered mental timeline, similarly to the normal phenomenon of ‘nostalgia’ (Ismail et al., 2018). Across all diagnoses, neuroanatomical correlates of this

phenomenon were expressed as relative preservation of grey matter in a distributed left-sided network encompassing the hippocampus as well as temporal and parietal cortices. These findings are supported by current evidence on the neuroanatomy of time perception and episodic memory in the healthy brain. Specifically, the hippocampus plays a pivotal role in encoding events together with their emotional context (Çalışkan G, 2018; Eichenbaum, 2014, 2017a; Lisman et al., 2017). The middle temporal gyrus has also been involved in the encoding as well as retrieval of memories, particularly using recollection processes (Dahlgren et al., 2020; Quamme et al., 2010; Risius et al., 2019; Thakral et al., 2017). Finally, the implication of the posterior cingulate cortex as a core region of the default-mode network reflects the importance of self-referential processes when recollecting autobiographical memories as opposed to imagined scenarios (Gardini et al., 2006; Hassabis et al., 2007; Spreng et al., 2008; Thakral et al., 2017), a process that may even require reflected self-appraisal, e.g., taking a third-person perspective (Delahoy et al., 2022). It is therefore plausible that these regions together participate in mental time travel. Considering representation and access to events would need to be maintained in order for those events to be relived, at least some participation of these grey matter regions would be necessary for patients to relive past personal events, in line with previous work in AD and FTD (M. Irish, Piguet, et al., 2014; Serra et al., 2018; Yamashita et al., 2019).

Absence of neuroanatomical correlates for the other temporal symptoms may be potentially accounted for by numerous factors. Firstly, those symptoms may be more directly related to the distinct atrophy profiles associated with the syndromes studied here and therefore are not necessarily supported by brain substrates that are shared by all patients irrespective of diagnosis, unlike the increased tendency to relive past events of which correlates should reflect the neuroanatomy of 'normal' temporal processing for reasons specified above. Second, it is possible that the statistical model used here for the VBM analysis could not reliably identify those additional neural substrates because those were widely distributed across the brain, or perhaps because they highly varied between individuals, or even converged between symptoms. Third, those symptoms may arise from functional and not structural changes in the brain, which VBM is not designed to identify.

The present findings provide initial evidence that should encourage the development of questionnaires examining temporal symptoms across different types of neurodegenerative diseases in a more detailed fashion. Specifically, while the temporal profiles described here were relatively separable based on syndromes (i.e., FTD or AD), they were also overlapping, thereby calling for future studies building on previous work on molecular factors of time perception (M. Wiener et al., 2011) to define the functional links between pathology, brain network, and behaviour in neurodegenerative diseases. This is especially relevant for bvFTD given its heterogeneity. In that regard, the outlined temporal profiles of the major FTD mutations presented here (e.g., symptoms of mental timekeeping not being reported by GRN mutations though prominent amongst MAPT mutations) are of interest despite the small numbers. The atrophy profile of MAPT mutations is distinct from that of the GRN mutations, with the former predominantly involving antero-mesial temporal lobes (J.D. Rohrer et al., 2011) and the latter more extensively the parietal cortex (J.D. Rohrer et al., 2010). These shed light on a potential neuroanatomical basis for mental timekeeping abilities. To further meet the need for a biological basis of these temporal symptoms, it would be highly valuable to validate the current findings in larger patient cohorts where additional background histopathological and molecular information is available, and to directly compare temporal phenotypes of FTD and AD patients with other neurodegenerative diseases targeting brain areas previously associated with time perception in the healthy brain, such as Lewy body dementia. Additionally, considering the limiting scope of VBM, using functional imaging techniques such as magnetoencephalography may capture the precise neural dynamics supporting temporal processing and underpinning the temporal phenotypes studied here.

While this initial study presents a qualitative view of diverse temporal symptoms, it would be interesting in future investigations to take a quantitative approach by measuring the frequency and severity of these symptoms. Describing more precisely their difficulties may help pin down a potential cognitive mechanism for their symptoms. For example, patients who experience “difficulty” estimating the temporal distance between events may either truly not be able to compute elapsed time as a quantity or they may produce incorrect values for this quantity. Such mental timeline disturbances should be further unpacked as it is not yet clear, for example, how they relate to the

strength and salience of those events when initially encoded. In this regard, it would be important to collect more information directly from patients in parallel with caregivers, with the caveat that self-reporting of temporal symptoms may not be reliable particularly in bvFTD.

A longitudinal perspective on the altered temporal behaviours studied here would also be pertinent considering the potential impact of crucial life events (e.g. retirement) on the sense of time of both patients and healthy older adults, as well as the dynamic and multiphasic nature of neurodegenerative diseases. Here, the finding of an association between mental timeline disturbances and increased disease severity as indexed by the MMSE score across the combined cohort echoes previous proposal of clockwatching behaviour as a potential marker of earlier disease stage in FTD (Nonaka et al., 2014b; Nyatsanza et al., 2003). Evaluating the present symptoms in a detailed longitudinal approach could therefore contribute to the development of novel functional biomarkers tracking the normal functioning of temporal processes to assess integrity of neural networks in neurodegenerative diseases.

The present findings also bear clinical relevance. Generally, they corroborate previous work describing obsessional clockwatching and temporal rigidity as part of a wider repertoire of complex stereotypical behaviours in bvFTD and svPPA (Nonaka et al., 2014b; Nyatsanza et al., 2003; H. Sivasathiaseelan et al., 2019; Snowden et al., 2001), as well as time estimation difficulties in AD (El Haj & Kapogiannis, 2016). Considering the prevalence of these time symptoms across different dementia types, a more detailed account of these changes would be highly valuable for the development of innovative behavioural interventions that may help patients and their caregivers better cope with these symptoms that have an undeniable impact on their everyday living.

Overall, the present work highlights the importance and relevance of symptoms of altered time perception and their associated neuroanatomical correlates across major dementia syndromes, thereby motivating a more systematic evaluation of time perception changes in neurodegenerative diseases. It should further inform future research efforts into the design and validation of tools developed to diagnose or track disease progression, as well as the elaboration of management interventions to better support patients living with dementia.

7. General Discussion

7.1. Summary of experimental findings

This thesis focused on three overarching questions: how both healthy and pathological ageing may differentially impact the subjective perception of time, and how distinct neuroanatomical substrates may subtend temporal dysfunction in canonical syndromes of dementia. Subjective time perception was assessed using a classic interval timing paradigm known as the temporal bisection task, which was adapted to examine the modulation of the perceived duration of everyday life sounds by their emotional valence (pleasant vs unpleasant) and semantic characteristics (environmental vs human). Timing performance of healthy young adults was compared with that of healthy older adults based on duration estimation and discrimination sensitivity. Healthy older adults were similarly compared to patients representing major AD and FTD syndromes. Timing performance of dementia patients was further correlated with measures of working memory and executive function taken from performance on neuropsychological tests. Complementary information on the perceived speed of time's passing was collected in healthy young and older adults using a standardised questionnaire and was correlated with timing performance. A second customised questionnaire was used in AD and FTD patients to draw out abnormal phenotypes of subjective time awareness evident from their everyday living. Neuroanatomical substrates associated with altered temporal perception dysfunctions in AD and FTD were further assessed using voxel-based morphometry. The main findings from each experimental chapter are recapitulated hereafter.

7.1.1. Chapter 3: Subjective time perception in healthy ageing

- For both healthy young and older adults, unpleasant environmental sounds were experienced as longer in duration than pleasant environmental sounds, while human sounds were experienced as shorter in duration and were less discriminable compared to environmental sounds.
- The duration of environmental sounds was experienced as longer for healthy older adults compared to healthy young adults.
- Healthy young adults had a lower discrimination sensitivity compared to healthy older adults.
- Healthy young adults who underestimated the duration of all sounds and healthy older adults who had a lower discrimination sensitivity across all sounds rated time as passing more quickly on a standardised questionnaire.

7.1.2. Chapter 4: Neuropsychology and neurolinguistic assessments to dementia patients in the COVID-19 era

- Remote delivery of neuropsychological and neurolinguistic assessments to dementia patients during the COVID-19 pandemic was technically feasible.
- Testing modality (face-to-face vs remote) did not affect performance of healthy participants or dementia patients on neuropsychological tests measuring working memory, executive function and arithmetic skills, as well as general semantic knowledge.
- Overall, these results suggest it is acceptable to collect new neuropsychological datasets remotely and to merge data collected face-to-face pre-pandemic with data collected remotely during the pandemic.

7.1.3. Chapter 5: Subjective time perception in dementia

- For both healthy older adults and dementia patients (irrespective of their diagnosis), unpleasant environmental sounds were experienced as longer in duration compared to pleasant environmental sounds, while unpleasant human sounds were experienced as shorter in duration compared to pleasant human sounds, thereby replicating findings from Chapter 3. Human sounds were also experienced as shorter in duration compared to environmental sounds.
- Human sounds were experienced as shorter in duration for lvPPA patients compared to healthy older adults, while environmental sounds were experienced as longer in duration of nfvPPA patients compared to healthy older adults.
- Environmental and human sounds were experienced as shorter in duration for bvFTD patients compared to svPPA and nfvPPA patients respectively.
- For both healthy older adults and dementia patients (irrespective of their diagnosis), discrimination sensitivity was higher for unpleasant compared to pleasant sounds.
- bvFTD and AD patients had a lower discrimination sensitivity across all sounds compared to healthy older adults.
- Discrimination sensitivity across all sounds in svPPA patients was higher compared to bvFTD, AD and lvPPA patients.
- Across all patients a reduction in auditory working memory and executive function skills was correlated with duration underestimation, while a reduction in executive function skills was correlated with lower discrimination sensitivity.
- For environmental pleasant sounds, increasing difference in duration estimation versus healthy older adults in a cohort of dementia patients was associated with grey matter atrophy in the right precuneus. For human unpleasant sounds, this was associated with grey matter atrophy in the right insular cortex. For human pleasant sounds, this was associated with grey matter atrophy in the right inferior parietal lobule.

7.1.4. Chapter 6: Temporal phenotypes of daily life in dementia

- Disruptions of temporal awareness are common in AD and FTD syndromes.
- AD and FTD syndromes are dissociable based on their temporal behaviours. Specifically, difficulties in estimating temporal distance between the present and events from the past and/or the future as well as confusion when ordering past events were most frequently experienced by patients diagnosed with typical AD or lvPPA. On the other hand, svPPA patients primarily presented with timing rigidity and clockwatching, while bvFTD patients experienced all these four temporal symptoms with similar frequency in addition to an increased tendency to relive past event.
- Increased tendency to relive past events in dementia patients was associated with relative preservation of grey matter in a distributed left-sided network encompassing the hippocampus as well as temporal and parietal cortices.

7.2. Impact of healthy ageing and dementia on interval timing

7.2.1. Hedonic and semantic modulation of perceived duration

As outlined in the introduction, several factors could potentially impact the subjective perception of time over the scale of several seconds. Here I will draw an overview of how some of these factors may help clarify the present findings.

7.2.1.1. Arousal

Arousal is one of the most frequently evoked factors when discussing the influence of emotional valence on perceived duration (Angrilli et al., 1997; Droit-Volet & Meck, 2007). As described in the pacemaker-accumulator models of interval timing, arousal is thought to influence the pulsing rate of a pacemaker acting as an internal clock, such that a highly arousing stimuli increases the number of pulses accumulated during a time interval and therefore its perceived duration (Treisman, 1963). Here, physiological measures of arousal were not taken. However, arousal ratings collected in a pilot cohort of healthy young and older adults before the pandemic (**Appendix 11**) reveal that environmental unpleasant sounds were significantly more arousing than environmental pleasant sounds for both cohorts, while pleasant and unpleasant human sounds were equally arousing. Provided the ratings hold in the larger Prolific cohort, these ratings would fit well with the present findings since environmental unpleasant sounds were perceived as lasting longer than environmental pleasant sounds and pleasant and unpleasant human sounds were perceived as lasting equally long.

Age differences in physiological reactivity may also explain why healthy older adults perceived the duration of environmental sounds as being longer than did healthy young adults. This hypothesis is further corroborated by the finding that healthy older adults perceived that time passed more slowly compared to healthy young adults, suggesting a faster internal clock, which would lead to overestimation of durations. In addition, Nicol and colleagues previously found an age difference in perceived duration of happy faces for which the age difference in physiological arousal was the highest (Nicol et al., 2013). However, my pilot data indicated no age-difference in arousal ratings for environmental sounds, suggesting that other factors may be in play.

Diminished physiological reactivity is a plausible factor for the overall duration underestimation of bvFTD patients compared to svPPA and nfvPPA patients. Indeed, bvFTD patients have been previously shown to display reduced physiological responses to emotional stimuli as measured by pupillometry and skin conductance levels, providing a physiological basis to their symptoms of socioemotional dysfunction (Fletcher, Nicholas, et al., 2015a; Hua et al., 2019; Joshi et al., 2014; Kumfor et al., 2019; Mendez, Carr, et al., 2019). These deficits have been further attributed to atrophy in the insular cortex (Kumfor et al., 2019; Marshall et al., 2019), a brain area critical for subjective time perception (Craig, 2009; Wittmann, Simmons, et al., 2010).

Separately, while unpleasant and pleasant human sounds were perceived to last the same duration in the healthy ageing study, a result which is consistent with a previous study on the impact of emotional body postures on time perception (Droit-Volet & Gil, 2016), unpleasant human sounds (crying) were perceived as shorter than pleasant human sounds (laughter) in the dementia study. This discrepancy is likely to be influenced by patients' own perception of the valence of these emotional sounds, such that certain patient groups may have experienced laughter as more pleasant and/or crying as more unpleasant compared to healthy participants, as suggested by **Figure** 5-3 (although no statistically significant group differences were found for these sounds). Additionally, a recent study demonstrated lower valence rating scores for sadness in AD compared to healthy participants (Fernandez-Aguilar et al., 2021). Valence ratings from my patient cohort may have translated into a higher difference in arousal between the two sound conditions, which in turn may have contributed to the observed difference in the perceived duration of human sounds.

7.2.1.2. Attention

Here, I have demonstrated that human sounds are perceived as lasting shorter than environmental sounds, an effect that could be attributed to human sounds being more salient than environmental sounds, thereby attracting more attention. Indeed, attention is another factor frequently referred to in studies assessing emotional modulations of interval timing (Droit-Volet & Meck, 2007). Its influence is based on the idea that our attentional resources are limited and are therefore divided across different simultaneously incoming signals for processing. As such, stimuli that attract particular

attention would divert some of these resources away from time, which, in the context of pacemaker-accumulator models, would lead to missing pulses and shortening of corresponding duration (Treisman, 1963). This effect has been contextualised by the addition of an attentional gate that controls the extent and/or frequency of the switch's closing (the switch controlling the number of pulses collected by the accumulator) (Zakay & Block, 1996). While the contribution of attention to the semantic modulation of perceived duration is interesting from the perspective of evolutionary adaptation (attending in priority to social signals over environmental ones may present an evolutionary advantage such as reinforcing social bonds), it does not exclude a possible contribution from other factors (see next sections).

Age differences in attention may still be a plausible explanation for the duration overestimation of environmental sounds by healthy older adults compared to healthy young adults. Indeed, healthy older adults may be recruiting additional attentional resources to compensate for impairment in encoding the duration of those sounds (Turgeon et al., 2016). This may be akin to the observed increase in recruitment of frontal regions and attentional networks in the face of deteriorated processing of visual signals (Ansado et al., 2012; Kurth et al., 2016; Sciberras-Lim & Lambert, 2017), and more recently hearing loss (Fitzhugh et al., 2019) in healthy ageing.

Moreover, bvFTD patients who did not pass the practice phase of the temporal bisection task failed to report long reference intervals (lasting 5 seconds) as long. In addition, both bvFTD and lvPPA have been shown to underestimate the duration of human sounds compared to nfvPPA patients and healthy participants respectively. Notably, diminished capacity for sustained attention has been demonstrated in both bvFTD and lvPPA patients (Manuel et al., 2019) and general attentional resources have been shown to rapidly decline in both groups (Foxe et al., 2021; Smits et al., 2015). Overall, these results suggest that attention deficits may also play a role in subjective time perception in dementia.

7.2.1.3. Working memory

Considering the importance of memory processes in interval timing (Buhusi & Meck, 2005; Gibbon & Church, 1984; Treisman, 1963), it is not surprising that duration underestimation correlates with reduced working-memory capacity across all patients.

The previously mentioned result of duration underestimation by lvPPA patients may therefore also be due to deficits in working memory, which form part of their general neuropsychological profile (Giannini et al., 2017; Mendez, Monserratt, et al., 2019).

7.2.1.4. Intrinsic stimulus characteristics

An aspect that has been less examined in the literature is the impact of intrinsic stimulus characteristics on perceived duration. A striking example of this is the filled-duration illusion, whereby an 'empty' interval (marked by an auditory onset and offset tone) is perceived as lasting shorter than an interval 'filled' with a continuous tone, a difference that has been attributed to an increased pacemaker pulsing rate for filled compared to empty intervals (Wearden et al., 2007). Later studies confirmed this effect and further showed that intervals filled with anisochronous sequences (i.e., with irregularly spaced tones) were perceived as shorter than intervals containing isochronous sequences as well as continuous intervals (N. K. Horr & M. Di Luca, 2015). This phenomenon would nicely explain the difference in perceived duration between environmental and human sounds observed here. Indeed, while the chosen environmental sounds (angle grinder, car horn, water) were uninterrupted (and were therefore akin to continuous tones), the human sounds (especially crying and laughter) included intervals of silence (breaths) and were therefore comparable to anisochronous sequences and highly dynamic in nature. Put more simply, it is also possible that human sounds were experienced as shorter in duration compared to environmental sounds because, for the same time interval, they effectively represented less acoustic signal. This is further corroborated by previous studies demonstrating that temporal information can be extracted directly from specific sensory areas, although this has only been demonstrated for sub-second durations (Bendixen et al., 2005; Kanai et al., 2006; Karmakar & Buonomano, 2007; Van Wassenhove et al., 2008). This perspective of local temporal encoding may further explain why lvPPA patients had particular difficulties with timing human sounds compared to healthy controls, since they previously showed impairment in recognition of vocal emotional expressions (J. D. Rohrer et al., 2012).

7.2.2. Hedonic and semantic modulation of duration discrimination sensitivity

Modulations of duration discrimination sensitivity have not been studied as closely as modulations of perceived duration. Here, I will attempt to explain the different findings from this thesis based on the limited number of papers on emotional time perception which have addressed this performance measure as well as general studies on executive function and decision-making.

7.2.2.1. Emotion

Across both healthy participants and dementia patients, unpleasant sounds were more discriminable than pleasant sounds. Although this result must be interpreted with caution since it also takes into account valence ratings from FTD patients who have prominent difficulties in socioemotional processing (Fletcher, Downey, et al., 2015; Kumfor & Piguet, 2012; Marshall, Hardy, Allen, et al., 2018; Marshall, Hardy, Russell, et al., 2018), it is nevertheless consistent with previous studies in healthy participants showing increased sensitivity for negatively valenced sounds (S. D. Smith et al., 2011; Tipples, 2019; Voyer & Reuangrith, 2015). This finding may further reflect an evolutionary advantage since a perceived expansion of time would offer additional time to prepare for an appropriate reaction in the face of threat.

7.2.2.2. Intrinsic stimuli characteristics

As described earlier, the filled-duration illusion provided an explanation for the difference in perceived duration between human and environmental sounds and could further explain why human sounds were less discriminable than environmental sounds in the present study. Indeed, as previously explained, human sounds are comparable to anisochronous sequences, while environmental sounds may be more akin to continuous intervals due to their respective spectrotemporal characteristics Anisochronous sequences have previously been associated with a shallower psychometric function slope compared to continuous intervals, indicating that they are less discriminable (N. K. Horr & M. Di Luca, 2015). Duration discrimination sensitivity therefore likely depends on the complexity of the stimuli themselves.

7.2.2.3. Executive function and decision-making

In the heathy ageing study, healthy young adults displayed a lower discrimination sensitivity compared to healthy older adults. This result is surprising in the context of progressively declining cognition in healthy ageing (Turgeon et al., 2016) and increased neural noise leading to impairment in sensory processing (Tran et al., 2020). Instead, this counterintuitive result may reflect the involvement of crystallised intelligence in the temporal bisection task where healthy older adults would therefore be favoured because they would have had more opportunities to time different events during their lives (Samanez-Larkin & Knutson, 2015).

In addition, a lower discrimination sensitivity was associated with reduced executive function skills across all dementia patients. Interestingly, AD and bvFTD patients, who have previously been characterised by prominent executive dysfunction, particularly in the domains of attention and working memory (Possin et al., 2013), were found here to have a lower discrimination sensitivity compared to healthy older adults. However, the sources of this underperformance are likely to be different between these groups.

On one hand, AD is characterised by the gradual loss of cholinergic neurons resulting in progressive cholinergic deficiency (Hampel et al., 2018; Mesulam, 2013; Whitehouse et al., 1981). Previous pharmacological experiments showed reduced temporal estimates and duration discrimination sensitivity when cholinergic inputs were limited (Meck & Church, 1987). Therefore, the lower discrimination sensitivity observed in AD is likely caused by cholinergic deficiency affecting the encoding of learned durations in reference memory (Buhusi & Meck, 2005). Their performance on the temporal bisection task further echoes a more recent study revealing impairment in dealing with uncertainty in a decision-making task (Korthauer et al., 2019) and makes sense in the context of my task where I included sounds corresponding to the mean duration for which the short and long responses would be equally valid.

On the other hand, the lower discrimination sensitivity of bvFTD patients may reflect broader difficulties in decision-making and goal-directed behaviours (Piguet et al., 2011; Wong et al., 2018), as well as impaired learning mechanisms. Indeed, bvFTD patients have been shown to have reduced physiological responses to errors (Scherling et al., 2017), a diminished tendency to self-correct (Plutino et al., 2020), and an inability to

apply rule-based learning (Clark et al., 2018; Wong et al., 2019). These deficits may be the result of grey matter atrophy in the basal ganglia characterising bvFTD (Bertoux et al., 2015; Landin-Romero et al., 2017).

7.2.3. Dissociating non-temporal processes from interval timing

In the previous sections 7.2.1 and 7.2.2, I discussed my results in the light of factors that are most frequently evoked in the interval timing literature, namely arousal, attention, working-memory and decision-making processes. This is largely due to information-processing models, which incorporate these different factors either as modules or external components (see **Figure** 1-1), still dominating the body of work examining the effects of emotion on perceived duration (Droit-Volet & Gil, 2009). The question of whether these factors fully account for my results (and therefore whether any timing deficits would be solely caused by issues in these higher-order cognitive functions) is challenging to answer, however. The extent to which these supporting functions contributed to timing performance of healthy older adults and patients likely depends on what "time" is being measured. Arguably, the temporal bisection task is not a pure timing task since it includes a major decision-making component. In addition, I incorporated sounds lasting several seconds long, thereby putting higher demands on working-memory, and the entire task took about 40 to 45 minutes to complete depending on the participant, therefore requiring long periods of sustained attention. Considering the neuropsychological profile of the dementia patients tested here, it is probable that deficits in non-temporal processes have had a substantial impact on their timing performance. However, as highlighted in the discussion of the corresponding chapter, the five dementia groups tested (AD, lvPPA, bvFTD, svPPA and nfvPPA) performed, on average, differently, suggesting the existence of true timing deficits and therefore of temporal phenotypes, as will be discussed in the next section.

The research presented in this thesis, especially in regard to subjective time perception changes in a diverse dementia cohort, is, to my knowledge, the first of its kind. Therefore, much work remains to be done to properly evaluate the contribution of higher-order cognitive functions (such as attention, working-memory, decision-making) on timing performance in these patients. A few potential directions of future work related to this aspect are proposed in **section 7.5**.

7.3. Linking interval timing with everyday life behaviour

In **Chapter 6** I showed that different dementia types could be distinguished based on their abnormal time related behaviours manifesting in their everyday lives. Specifically, while typical amnestic AD patients and language-led lvPPA patients most frequently exhibited difficulties with estimating temporal distance in the past and the future as well as confusion ordering past events, svPPA and nfvPPA patients most frequently exhibited timing rigidity and clockwatching, and bvFTD patients presented with all four temporal symptoms in addition to an increased tendency to relive past events.

The results from the temporal bisection task seem to further dissociate these disease groups. Indeed, compared to healthy controls, AD patients had a lower duration discrimination sensitivity, while lvPPA patients did not but experienced human sounds as being shorter in duration. Moreover, nfvPPA patients experienced environmental sounds as being longer in duration compared to healthy controls, while svPPA had an increased duration discrimination sensitivity compared to AD, lvPPA and bvFTD patients. Finally, bvFTD patients experienced the duration of environmental and human sounds as shorter in duration compared to svPPA and nfvPPA patients respectively and had a lower duration discrimination sensitivity compared to healthy controls.

Findings on the temporal bisection task may further explain the altered temporal behaviours of dementia patients manifesting in their everyday living. Notably, the increased timing rigidity of svPPA patients may be understood as an increased sensitivity to temporal information (as revealed by the temporal bisection task results). The increased duration discrimination sensitivity in svPPA may further reflect the increased use of counting strategies by these patients (though I did not formally assess this), since in the healthy ageing study, participants who reported using counting strategies had a higher discrimination sensitivity. This would also be corroborated by studies revealing intact numerical processing in svPPA (Green & Patterson, 2009; Midorikawa et al., 2017; Papagno et al., 2013; H. Sivasathiaseelan et al., 2021), as well as studies demonstrating that timing and counting share psychophysical similarities (Cavdaroglu & Balci, 2016; Meck & Church, 1983) and neural substrates (Hinton et al., 2004). These findings would further support a common magnitude system in the parietal cortex (Walsh, 2003),

especially given that this brain area is spared in svPPA (although see (Rammsayer & Verner, 2015) and (Gauthier & Van Wassenhove, 2016)).

While typical AD and lvPPA patients presented as frequently with behaviours suggestive of a disturbed mental timeline, they were not impacted in the same way by the hedonic and semantic modulation of interval timing. This likely reflects the distinct neural substrates underlying these two temporal processes as well as the distinct brain atrophy profiles characterising AD and lvPPA, specifically the more left-sided nature of neurodegeneration in lvPPA. In addition, the lower duration discrimination sensitivity in AD suggests that deficits of the mental timeline may be caused by impaired temporal processing in this dementia type. It is further interesting to note that both AD and bvFTD groups had a high proportion of patients experiencing difficulties in estimating temporal distance in the light of the present finding of lower duration discrimination sensitivity in both groups compared to the control group, as well as previous finding of reduced sensitivity to temporal delay information in delay-discounting tasks where both AD and bvFTD patients tended to choose immediate small rewards as opposed to later larger rewards (Beagle et al., 2019). The fact that deficits in temporal processing are particularly prominent in these two groups also speaks to their brain atrophy profiles involving the right hemisphere. Indeed, Coull and colleagues previously demonstrated a right-sided network of brain regions subserving reproduction of time intervals, while a left-sided network was recruited for a temporal orienting task where external temporal cues were used to inform the timing of motor responses (Coull et al., 2013). This is somewhat in line with my present findings of the association of grey matter atrophy in a right lateralised brain network with duration estimation differences between patients and healthy controls and the association of relative preservation of grey matter in a left lateralised network with increased tendency to relive past events, since prospective timing relies on internally generated representations of durations while reliving past events supposes preserved ability to orientate oneself to specific moments in time.

7.4. Limitations

Several general limitations shared across the different experiments described in this thesis will be outlined here to inform future work. Limitations that are specific to each data chapter are described in their respective discussion section.

Most of the data presented here were collected remotely. This was a direct consequence of the COVID-19 pandemic that started halfway through my PhD when I had already begun collecting data for the dementia study. This presented several challenges which may have impacted the work presented in this this thesis in the following ways:

- Recruitment bias

To take part in remote research, participants needed to have access to a stable internet connection as well as own a computer. The impact of remote testing on recruitment of dementia patients was more overt compared to using Prolific for which there may have been an inherent bias (since it is oriented specifically for online research). Indeed, upon the realisation that not all dementia patients owned computers or owned well-functioning ones, the equipment criterion was broadened to include tablets. In addition, some patients expressed interest in the study but decided to wait until face-to-face testing at our research centre was possible again because they did not meet the technological eligibility criteria. Finally, while a trial run was conducted with participants enrolled in the dementia study to verify the strength and stability of their broadband connection, it was difficult to implement a similar procedure for Prolific participants. Perhaps unsurprisingly, three participants encountered disruption of their internet connection while performing the timing study. However, considering the large sample size for this study, this issue is unlikely to have substantially affected the results.

- Inconsistent hardware use

Participants were allowed to use whatever hardware they had at home (desktop or laptop computer with Windows or MacOS application software). While tablets were also allowed to accommodate a larger number of dementia patients, they were not allowed for the study on Prolific since participants using tablets were considered more distractible. Although participants seen face-to-face at our research centre were tested

on the same Mac computer, Windows machines were also allowed to minimise recruitment bias (healthy older adults were more likely to own Windows machines compared MacOS), and inconsistent hardware use was not expected to have a strong impact on performance on the temporal bisection task.

- Inconsistent audio equipment use

In a face-to-face laboratory testing setting, auditory stimuli are delivered through the same pair of high-quality headphones. However, this was not possible in a remote testing setting and participants were allowed to use whatever audio equipment they had (headphones or speakers of no specific brand) as long as it was of good quality. Restricting participants to use only headphones would have significantly impacted recruitment (most dementia patients and healthy older adults did not own any). Moreover, using headphones over speakers was deemed less crucial for the present timing experiment, especially in comparison to a dichotic digit experiment where different inputs need to be delivered to the right and left ears.

- Inability to control the remote testing environment

All participants recruited remotely took part in my experiments from the comfort of their homes. They were asked to choose a quiet space with minimal distractions to ensure they could hear the sounds well and would maintain high levels of attention on the experiment throughout testing. However, this was obviously difficult to verify. While the experimenter could constantly monitor participants' attention levels for the dementia study, the temporal bisection task for the healthy ageing study was implemented as a reaction time task with timed breaks, to encourage constant engagement with the experiment.

- Inability to control for peripheral hearing function

Audiometry measures could not be collected remotely, and it was therefore not possible to determine whether potentially impaired peripheral hearing function would impact performance on the timing task for remotely tested participants. However, potential participants with hearing difficulties were excluded from recruitment on Prolific, and participants taking part in the dementia study remotely completed a sentence comprehension test which enabled me to verify that they set their volume at a sufficiently high level for them to hear the audio files reliably. Reassuringly, hearing

thresholds, which were available for healthy older adults and dementia patients tested face-to-face, did not correlate with timing performance, suggesting minimal impact.

- Impact of the Covid-19 pandemic on sustained attention and fatigue

'Zoom fatigue' is a now widely recognised phenomenon whereby people experience fatigue and diminished ability to sustain attention after many hours spent on the video conferencing software Zoom. A similar phenomenon has been highlighted for people generally spending long hours in front of the screen as a direct consequence of the pandemic. This has been demonstrated for students at all levels of education attending online classes (Coiado et al., 2020; Idris et al., 2021; Scarpellini et al., 2021). While the remote testing procedure for the dementia study was developed to mitigate these issues (by including breaks, reducing length of testing sessions and spreading those testing sessions over several days), it is possible that Prolific participants may have had more difficulties with sustained attention (as suggested by the number of participants who were excluded due to poor performance on the temporal bisection task based on the shape of their psychometric curves).

- Impact of the Covid-19 pandemic on mood

Although recruitment of healthy participants via Prolific allowed the exclusion of potential participants with mental health issues (e.g., depression, anxiety), it is possible that recruited participants may have been psychologically impacted by the pandemic in a way that could not be captured by screening filters. It may therefore be possible that a certain proportion of participants experienced some form of psychological distress which may have in turn impacted their performance on the temporal bisection task. Similarly, while I showed that mood ratings did not affect timing performance in healthy controls or dementia patients tested remotely, it is possible that (1) such a questionnaire was unable to capture the extent of the experienced psychological impact of the COVID-19 pandemic; (2) ratings provided by patients are unreliable given their diminished insight into their internal emotional states. Low mood may have had a general impact on valence ratings (although the correlation was non-significant for Prolific participants), as well as timing performance by reducing capacity for sustained attention, increasing decision uncertainty or impulsivity.

A study conducted by Droit-Volet et al showed that conscious awareness of experimental manipulations reduced the emotional impact on perceived duration (Droit-Volet, Lamotte, et al., 2015). Although here participants were not explicitly told the temporal bisection task examined the effect of emotion on time perception, they may have deduced this while taking part in the experiment and may therefore have been influenced by folk wisdom ("Time flies when you're having fun"). Participants may have similarly been influenced by knowledge of the impact of age on time perception when responding to the subjective time questionnaire although results on this questionnaire tend to suggest this is unlikely.

Further, the modulation of perceived duration by the emotional valence revealed here is highly dependent on the individual appreciation of the sound battery used. It is possible that the effect of emotion on human sounds was less pronounced than for environmental sounds in the healthy ageing study because participants perceived the chosen examples of laughter and crying as 'fake'. Indeed, it has been shown that healthy participants are able to discriminate spontaneous genuine laughter from volitional fake laughter (Lavan & McGettigan, 2017) and that spontaneous laughter is more positively valenced than fake laughter (Pinheiro et al., 2021). Further, sounds were grouped together based on four distinct categories (unpleasant and pleasant environmental sounds, unpleasant and pleasant human sounds) and the effects of each chosen sound on interval timing could not be investigated separately given the low number of trials available for each sound. However, there may have been more subtle differences not captured by the current design. For example, sounds of bees may be unpleasant to listen to because they signal threat (bees may sting), while sounds of a car horn may be unpleasant because of their intrinsic auditory properties (Kumar et al., 2008).

The sample study size for the dementia study was relatively small. This was both due to the pandemic which interrupted data collection and the difficulties in recruiting rare dementia patients in the case of FTD, as well as recruiting patients who must be shared across multiple simultaneous observational and clinical studies in the case of AD. Here, the sample size is especially an issue given the variability of results (not all patients of the same diagnosis overestimated or underestimated the duration of sounds from the same condition). While this inconsistency may be due to how the sounds were grouped

or how patients experienced those sounds, it may also be attributable to variability in disease severity within one patient group. This caveat poses a particular challenge in dementia since no disease stages have been defined as of today. The disease stages are further crucial given that neurodegenerative diseases become more and more similar as they progress, suggesting that at later disease stages, diagnostic boundaries are blurred. In that regard, obtaining information about neural function in the dementia groups studied here would have helped pinpoint the origin of their distinct temporal difficulties to specific brain regions. This was not possible here as the COVID-19 pandemic largely shifted data collection to remote.

7.5. Future directions

The experiments presented in this thesis suggest several directions for future work.

A natural extension of this work would be to replicate the current findings in face-to-face cohorts. Despite the many caveats of remote testing described earlier, it is unlikely that it has had a major impact on timing performance (for example by reversing the direction of estimation across pleasantness or semantic conditions). However, it would be highly valuable to confirm this, especially considering the difficulty in assessing this post-hoc with the currently available data. Embracing a face-to-face testing protocol would further allow for additional recording of physiological measurements of arousal (such as skin conductance levels or pupil dilation measures). This would help substantiate the impact of arousal on subjective duration estimation described in the corresponding data chapters by providing arousal metrics for both within-subject comparisons of sound conditions and between-group comparisons (healthy young adults against healthy older adults as well as across different dementia groups). The current paradigm could be further modified to properly examine the impact of arousal by implementing sounds fitting low and high arousing conditions, similarly to previous studies (Angrilli et al., 1997; Jones et al., 2017; S. D. Smith et al., 2011; Tipples, 2010). Moreover, the effect of attention could be measured by explicitly instructing participants to either pay attention to the duration or the emotion of the sound and assessing the impact of this experimental manipulation on the difference in perceived duration between sounds of varying pleasantness, similarly to a seminal study by Coull and colleagues (Coull et al., 2004).

The sound battery used here was relatively varied, especially compared to other studies of subjective time perception where at most three different emotions were compared against a neutral facial expression (Droit-Volet & Meck, 2007). However, it would be worth testing other sounds, especially to examine the impact of embodiment on time perception. Indeed, I have primarily ascribed the difference in perceived duration between environmental and human sounds to differences in their inherent spectrotemporal characteristics. However, it is also possible that the ability to embody

human sounds as opposed to environmental sounds may have had an influence on temporal estimates. As such, it would be interesting to explicitly compare the effect of animal sounds on perceived duration against that of human sounds. Based on a previous study of diminished emotional processing due to impoverished ability to mimic emotions in FTD (Marshall, Hardy, Russell, et al., 2018), performing EMG recordings of facial muscles during the timing experiment would further corroborate the embodiment hypothesis in dementia.

Other changes to the current paradigm could be explored with a view to design a more ecologically valid paradigm. For example, instead of using only sounds (or only visual stimuli), it would be possible to use movies (Droit-Volet et al., 2011), for example short clips of someone laughing or birds singing, which would have the additional advantage of facilitating sustained attention. Using different ranges of duration, especially longer ones to increase attentional and memory demands would be another option. When defining these new durations, it would also be preferable to use a logarithmic spacing to prevent counting strategies. Another possibility would be to use a retrospective timing task instead since retrospective duration judgments are more common in everyday living than prospective ones (Riemer et al., 2021). However, additional information on the cognitive mechanisms of temporal decision-making can also be obtained from prospective timing paradigms, for example by examining the influence of previous trials (M. Wiener et al., 2014) or building drift-diffusion models (Balci & Simen, 2014; Tipples, 2015; M. Wiener et al., 2018).

The neuroanatomical correlates of subjective time perception obtained from analysing structural imaging data provide a stimulating yet limited picture of the neural mechanisms underlying the hedonic and semantic modulations of perceived duration. The current experimental findings should therefore be complemented with a functional imaging experiment, either using functional magnetic resonance imaging (fMRI) to closely compare the brain areas involved in these modulations or ideally, using magnetoencephalography (MEG) to temporally dissect the underlying neural mechanisms. Notably, mapping the different stages of temporal processing (encoding, comparison, decision-making) onto the oscillatory brain dynamics and comparing those

dynamics across the different sound conditions and groups studied here would considerably further understanding of the neurobiological basis for the current experimental findings. Another related interesting avenue would be the comparison of neurodegenerative diseases essentially characterised by dopaminergic deficiency, such as Parkinson's disease or dementia with Lewy bodies, with neurodegenerative diseases primarily involving cholinergic depletion, such as Alzheimer's disease.

As mentioned previously, the present experimental findings on subjective time perception in dementia are somewhat clouded by the variability of individual profiles (clinical symptoms, brain atrophy pattern, disease stage, and more broadly the history of temporal experiences). A longitudinal perspective could help cope with this caveat by drawing a more fine-grained picture of how timing abilities may gradually change with age. Here, healthy ageing was separately studied from pathological ageing, however, in the early stages, both likely overlap. Evaluating older adults at a pre-symptomatic stage and later when they start to show the recognised signs of dementia would contribute to establishing an earlier diagnosis. In that regard, developing more ecological designs for the study of time perception is especially important to better understand the timing related difficulties faced by older individuals in their everyday living and develop appropriate support systems and treatments.

Appendix

Appendix 1. IWG-2 diagnostic criteria for typical AD (Dubois et al., 2014)

Level of diagnosis	Criteria
Typical AD	Must meet A plus B at any stage A Specific clinical phenotype • Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features: ▪ Gradual and progressive change in memory function reported by patient or informant over more than 6 months ▪ Objective evidence of an amnestic syndrome of the hippocampal type, based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test B In-vivo evidence of Alzheimer's pathology (one of the following) • Decreased amyloid beta 1-42 together with increased total tau or phosphorylated tau in CSF • Increased tracer retention on amyloid PET • AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP)
Exclusion criteria	History • Sudden onset • Early occurrence of the following symptoms: gait disturbances, seizures, major and prevalent behavioural changes Clinical features • Focal neurological features • Early extrapyramidal signs • Early hallucinations • Cognitive fluctuations Other medical conditions severe enough to account for memory and related symptoms • Non-AD dementia • Major depression • Cerebrovascular disease • Toxic, inflammatory, and metabolic disorders, all of which may require specific investigations • MRI FLAIR of T2 signal changes in the medial temporal love that are consistent with infections or vascular insults

Appendix 2. Rascovsky diagnostic criteria for bvFTD (Rascovsky et al., 2011)

Level of diagnosis	Criteria
Neurodegenerative disease	Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant)
Possible bvFTD	Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria A. Early behavioural disinhibition (one of the following must be present) A.1. Socially inappropriate behaviour A.2. Loss of manners or decorum A.3. Impulsive, rash, or careless actions B. Early apathy or inertia (one of the following must be present): B.1. Apathy B.2. Inertia C. Early loss of sympathy or empathy (one of the following must be present): C.1. Diminished response to other people's needs and feelings C.2. Diminished social interest, interrelatedness, or personal warmth D. Early perseverative, stereotyped or compulsive/ritualistic behaviour (one of the following must be present): D.1. Simple repetitive movements D.2. Complex, compulsive or ritualistic behaviours D.3. Stereotypy of speech E. Hyperorality and dietary changes (one of the following must be present): E.1. Altered food preferences E.2. Binge eating, increased consumption of alcohol or cigarettes E.3. Oral exploration or consumption of inedible objects F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following must be present): F.1. Deficits in executive tasks F.2. Relative sparing of episodic memory F.3. Relative sparing of visuospatial skills
Probable bvFTD	All of the following symptoms (A–C) must be present to meet criteria A. Meets criteria for possible bvFTD B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

	C. Imaging results consistent with bvFTD (one of the following must be present): C.1. Frontal and/or anterior temporal atrophy on MRI or CT C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT
Behavioural variant FTD with definite FTLD pathology	Criterion A and either criterion B or C must be present to meet criteria A. Meets criteria for possible or probable bvFTD B. Histopathological evidence of FTLD on biopsy or at post-mortem C. Presence of a known pathogenic mutation
Exclusionary criteria for bvFTD	Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders B. Behavioural disturbance is better accounted for by a psychiatric diagnosis C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

Appendix 3. Gorno-Tempini diagnostic criteria for PPA (M.L. Gorno-Tempini et al., 2011)

Level of diagnosis	nfvPPA	svPPA	lvPPA
Clinical diagnosis	At least one of the following core features 1. Agrammatism in language production 2. Effortful, halting speech with inconsistent speech sound error and distortions (apraxia of speech) At least 2 or 3 of the following other features must be present 1. Impaired comprehension of syntactically complex sentences 2. Spared single-word comprehension 3. Spared object knowledge	Both of the following core features must be present 1. Impaired confrontation naming 2. Impaired single-word comprehension At least 3 of the following other features must be present 1. Impaired object knowledge, particularly for low-frequency or low-familiarity items 2. Surface dyslexia or dysgraphia 3. Spared repetition 4. Spared speech production (grammar and motor speech)	Both of the following core features must be present 1. Impaired single-word retrieval in spontaneous speech and naming 2. Impaired repetition of sentences and phrases At least 3 of the following other features must be present 1. Speech (phonologic) errors in spontaneous speech and naming 2. Spared single-word comprehension and object knowledge 3. Spared motor speech 4. Absence of frank agrammatism
Imaging supported	Both of the following criteria must be present 1. Clinical diagnosis of nonfluent/agrammatic variant PPA 2. Imaging must show one or more of the following results: a. Predominant left posterior	Both of the following criteria must be present 1. Clinical diagnosis of semantic variant PPA 2. Imaging must show one or more of the following results	Both of the following criteria must be present 1. Clinical diagnosis of logopenic variant PPA 2. Imaging must show one or more of the following results:

	fronto-insular atrophy on MRI b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET	a. Predominant anterior temporal lobe atrophy b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET	a. Predominant left posterior perisylvian or parietal atrophy on MRI b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET
Pathologically definite	Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present 1. Clinical diagnosis of nonfluent/agrammatic variant PPA 2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other) 3. Presence of a known pathogenic mutation	Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present 1. Clinical diagnosis of semantic variant PPA 2. Histopathological evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, Ad, other) 3. Presence of a known pathogenic mutation	Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present 1. Clinical diagnosis of logopenic variant PPA 2. Histopathological evidence of a specific neurodegenerative pathology (e.g. AD, FTLD-tau, FTLD-TDP, other) 3. Presence of a known pathogenic mutation

Appendix 4. IWG-2 diagnostic criteria for logopenic variant PPA as a form of atypical AD (Dubois et al., 2014)

Level of diagnosis	Criteria
Atypical AD	Must meet A plus B at any stage A Specific clinical phenotype (logopenic variant) • Defined by presence of early, predominant, and progressive impairment of single word retrieval and in repetition of sentences, in the context of spared semantic, syntactic, and motor speech abilities B In-vivo evidence of Alzheimer's pathology (one of the following) • Decreased amyloid beta 1-42 together with increased total tau or phosphorylated tau in CSF • Increased tracer retention on amyloid PET • AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP)
Exclusion criteria	History • Sudden onset • Early and prevalent episodic memory disorders Other medical conditions severe enough to account for related symptoms • Major depression • Cerebrovascular disease • Toxic, inflammatory, or metabolic disorders

Appendix 5. Example sounds for the temporal bisection task

Sound file number	Sound condition	Sound example
1	Environment unpleasant	Angle grinder
2		Car horn
3		Bees
4	Environment pleasant	Brook
5		River
6		Blackbird
7	Human unpleasant	Male crying
8		Female crying
9		Male screaming
10		Female screaming
11	Human pleasant	Male laughing
12		Female laughing
13		Baby cooing

All selected sound files are 3.5 seconds long and have been created following the methodology described in **section 2.3**.

Appendix 6. Example of a study advert on Prolific as viewed by participants

Subjective perception of emotional sounds

Hosted by *Maï-Carmen REQUENA-KOMURO*

£4.17 · 25 mins · £10.00/hr · 26 places remaining

THIS IS A MULTI-PART STUDY WITH SOUNDS.

Dementia can impact our lives in a number of different ways. We are hoping that our research will lead to the development of new tests that can be used with people with dementia in the future.

The **multi-part study** will run as follow:

Parts 1, 2 & 3: here we will focus on emotion. For each part, you will listen to a different set of sounds from everyday life, and we will ask you to rate how pleasant each sound is to you.
Part 4: here we will focus on time. You will listen to the sounds you heard in the previous parts, and you will be asked to say as quickly but as accurately as possible how long each sound lasts using keypresses.

Timepoints of testing, experiment duration and payment for each part:

Week 1:

day 1: part 1 - estimated completion time: 25 min - £4.17
a different day: part 2 - estimated completion time: 25 min - £4.17
another different day: part 3 - estimated completion time: 25 min - £4.17

Week 2:

day 1: part 4 - estimated completion time: 60 min - £10

Total possible gain: £22.51

BONUS: you will be awarded an extra **£0.49** if you use the SAME SET-UP (computer and headphones/speakers) FOR ALL 4 PARTS.

Who do we want: We are looking for participants who:

- have no known hearing problems

- do not have a current psychiatric (e.g. bipolar disorder, depression) or neurological diagnosis (e.g. traumatic brain injury, neurodegenerative disease)

- are not taking medication that may impact their cognitive performance.

PLEASE NOTE:

1. This is an experiment with sounds, **so please ensure you are sitting in a QUIET room with MINIMAL distractions.**

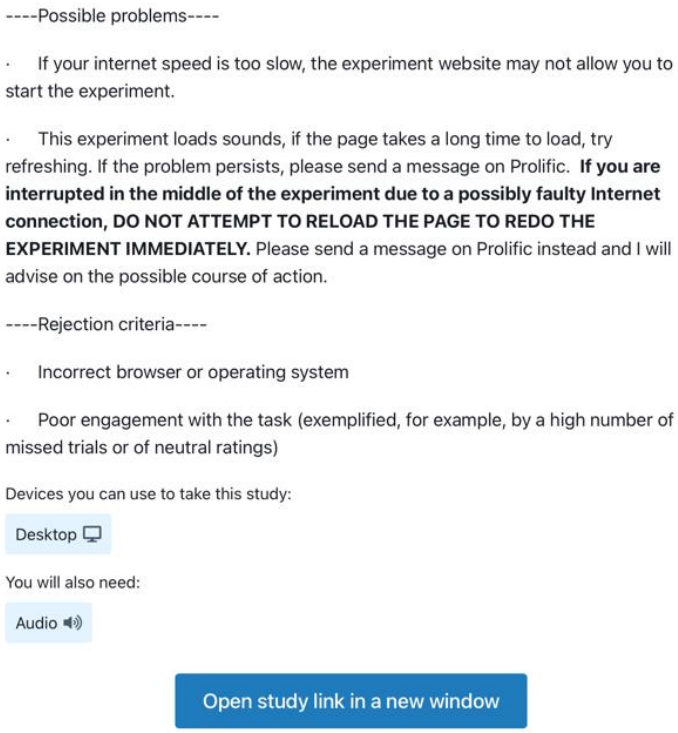
2. You should also be using **HEADPHONES.** If you do not own headphones, **you can still use speakers, provided they are of GOOD QUALITY.**

3. You are only allowed to use **a Windows** or a **Mac computer.**

4. Whatever set-up (computer and headphones/speakers) you use for this part, **PLEASE MAKE SURE YOU USE THE SAME ONE FOR ALL SUBSEQUENT PARTS.**

5. All experiments will only open on **Chrome. Please enable autoplay** if it is not already enabled.

6. Finally, **please be aware that payments will be delayed until completion of all parts.**



A study advert contains a brief description of the study (with duration, pay and number recruited at the very top), recruitment criteria and any additional requirements specific to the study (use of a computer and Chrome as a web browser for example), as well as rejection criteria. By clicking the button at the bottom of the study advert, Prolific participants are taken directly to the experiment which opens in a new window.

Appendix 7. Summary of equipment used by Prolific participants to complete the temporal bisection task

Participant group	Young adults	Older adults
Numbers	57	59
Desktop/Laptop	8 / 49	15 / 44
Mac/Windows	15 / 42	3 / 56
Headphones/Speakers	41 / 16	31 / 28

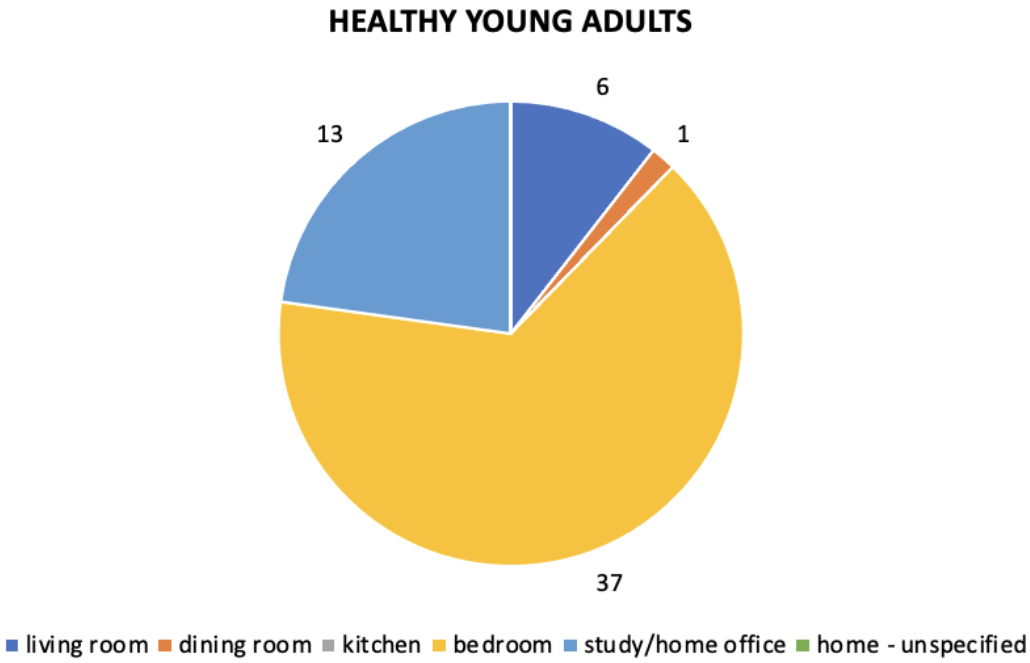
No significant difference in computer type was observed between age groups, but there was a significant difference in software type ($X^2(1) = 9.8685$, $p = 0.002$) and audio equipment ($X^2(1) = 4.6285$, $p = 0.031$), i.e. there were significantly less Mac users among older adults compared to young adults, and significantly more headphones users among young adults compared to older adults.

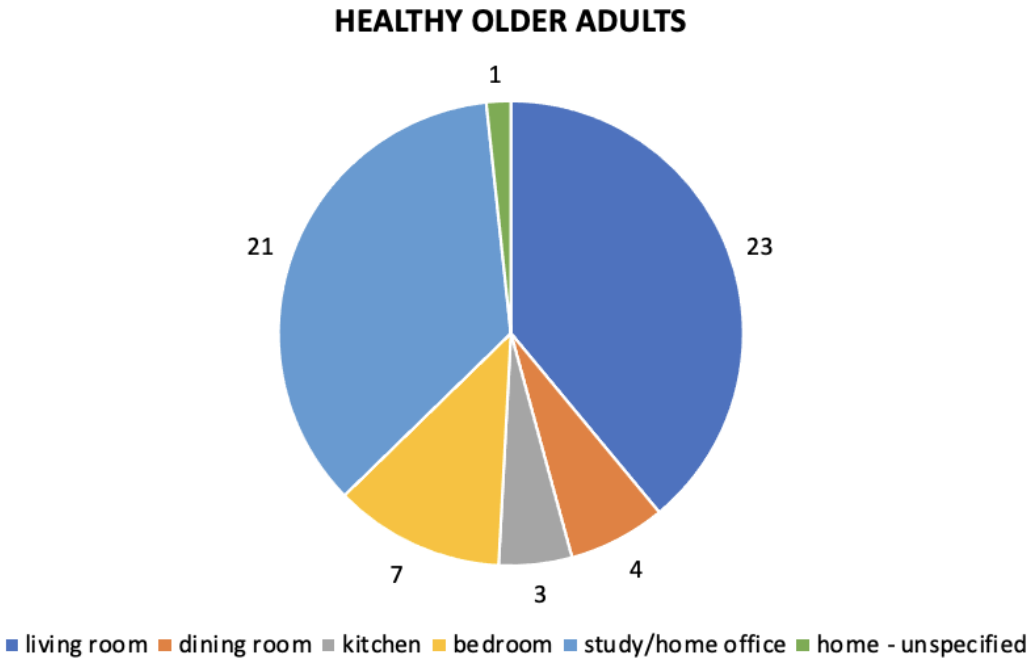
Appendix 8. Additional group ratings on the perceived speed of time's passing for different periods of the past and on metaphors indicating time pressure and expansion from the Subjective Time Questionnaire (Wittmann and Lehnhoff, 2005)

	Young adults	Older adults
Subjective speed of time's passing for several past periods -2 very slowly / -1 slowly / 0 neither fast nor slow / +1 fast / +2 very fast		
Previous week	1.02 (0.88)	0.73 (0.94)
Previous month	**1.09 (0.99)**	**0.73 (0.88)**
Previous year	0.77 (1.00)	0.58 (1.1)
Previous 10 years	**0.44 (1.07)**	**1.03 (0.85)**
Childhood (<12 years)	0.47 (1.17)	0.08 (1.16)
Youth (13-19 years)	0.53 (1.02)	0.22 (1.04)
Adulthood (20-29 years)	0.39 (0.87)	0.47 (0.75)
Metaphors 0 strong rejection / 1 rejection / 2 neutral / 3 approval / 4 strong approval		
Time Pressure	**2.34 (0.92)**	**1.70 (0.74)**
Time Expansion	**1.70 (0.69)**	**1.36 (0.64)**

Individual ratings for the above questions were analysed using the procedure described in **section 3.3.6.4**. Here, group averages are shown with standard deviations in parenthesis. Significant age differences are highlighted in bold. Similarly to previous studies (Friedman & Janssen, 2010; Wittmann & Lehnhoff, 2005a), the past 10 years passed significantly more quickly for healthy older adults compared to healthy young adults, and time pressure decreased with age. New results include healthy young adults perceiving the past month as passing significantly more quickly compared to healthy older adults, and healthy young adults agreeing significantly more to metaphors indicating time expansion (although the absolute difference was small). These results are likely spurious given previous studies were conducted in larger cohorts and failed to identify these differences. However, since participants completed this questionnaire during the UK national lockdown when most people were working from home, these results may also reflect the effect of the ongoing COVID-19 pandemic on the perceived speed of time's passing, which may have been particularly strong in healthy young adults.

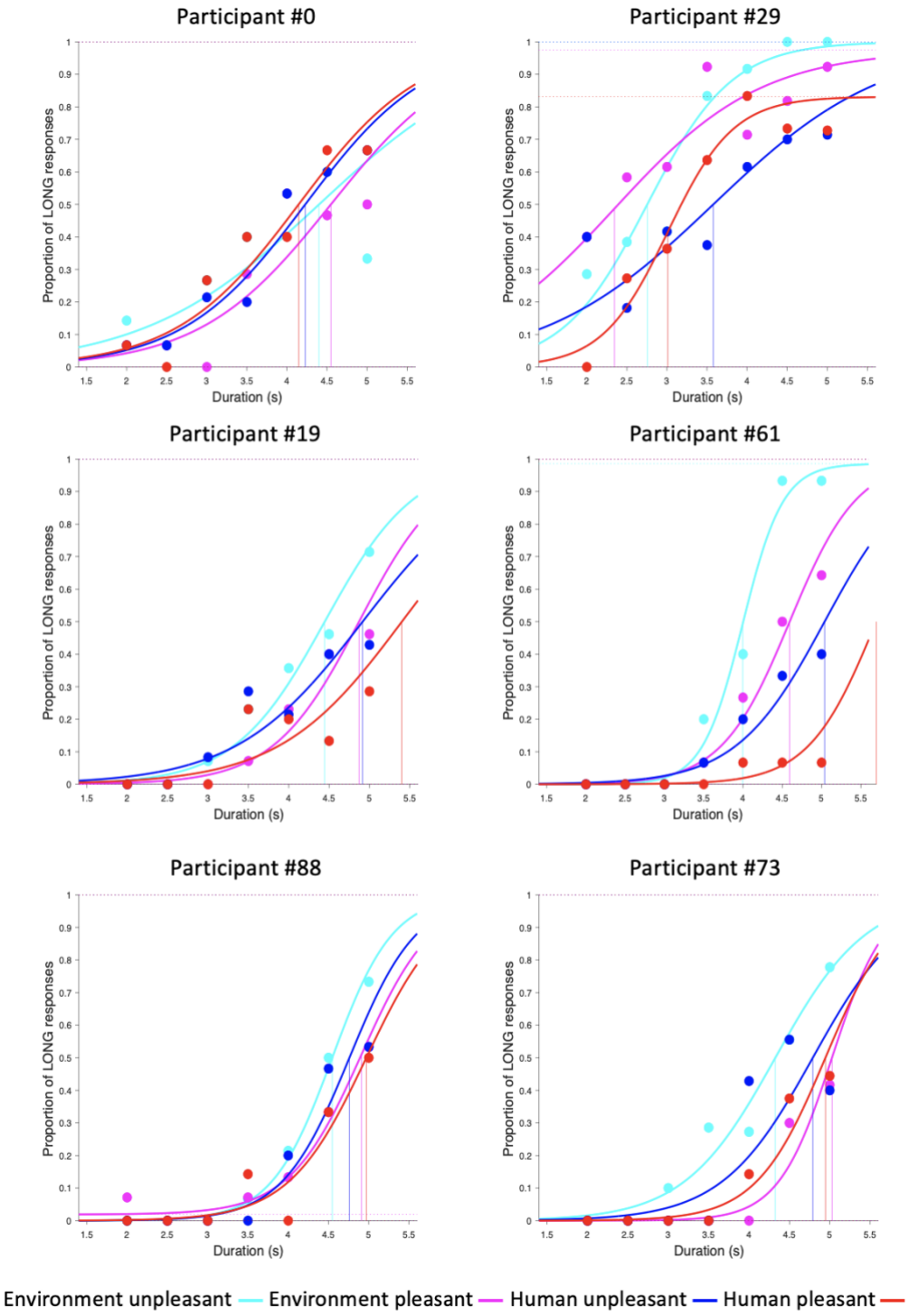
Appendix 9. Summary of where Prolific participants completed the time study





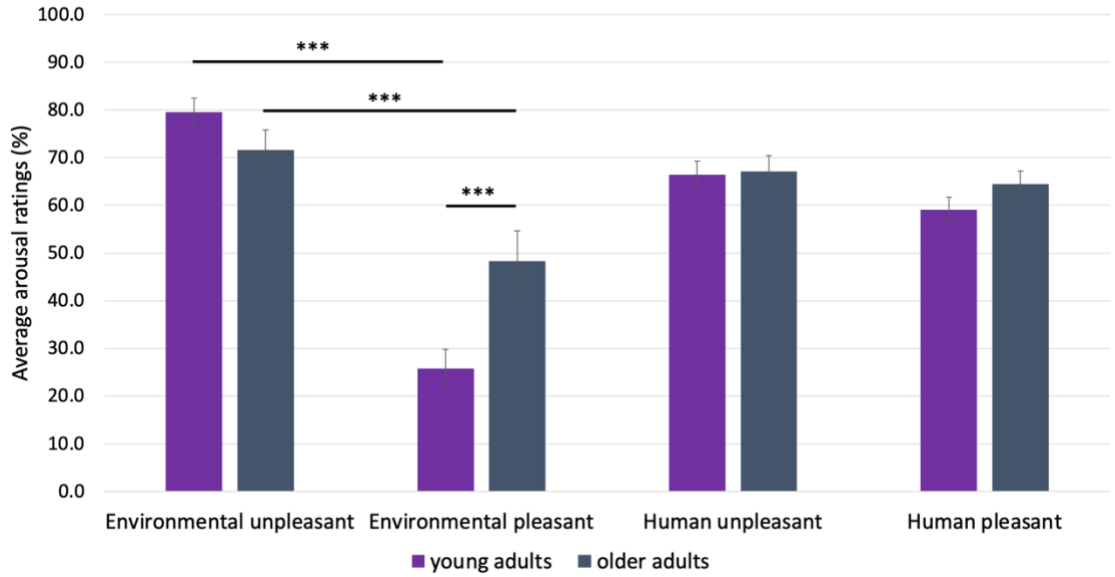
Participants were asked to indicate where they were when they completed the time experiment. All participants were at home, with most young adults completing the study from their bedroom, and most older adults from either their living room or their dedicated office space at home.

Appendix 10. Psychometric curves from excluded Prolific participants



The above six Prolific participants were removed from the final sample. The shape of their psychometric curves suggested high levels of inattention or poor engagement with the task, as can be expected from prolonged and unmonitored online testing. Participant #0 had a probability of responding long at 5 seconds lower than 0.5 for environmental sounds (while most participants were above 0.9); #29 had a probability of responding long at 2 seconds higher than 0.3; the other four answered short on 75% of trials. Each coloured psychometric curve corresponds to a separate sound condition as indicated in the legend.

Appendix 11. Arousal ratings from healthy ageing pilot study



As mentioned in **section 2.3**, arousal ratings were collected from a pilot cohort of healthy young adults (N=13, 6F; mean age=25.4, standard deviation=4.9) and healthy older adults (N=14, 8F; mean age=66.9, standard deviation=6.7). The two groups were statistically different in age ($t = -18.14$, $df = 25$, $p<0.001$) but not in gender distribution ($p>0.05$). Ratings were given as percentages (0-49% corresponding here to low arousing, 50-100% corresponding to high arousing). In the bar graph above, group averages are shown for each sound condition with standard errors as vertical bars. A repeated measures ANOVA was conducted with age group as a between-group factor and sound as a within-group factor. There was a significant main effect of sound ($F=6.98$, $df = 3$, $p< 0.001$), indicating that for both healthy young and older adults, environmental unpleasant sounds were significantly more arousing than environmental pleasant sounds. There was also a significant interaction between age group and sound. Post-hoc comparisons showed that environmental pleasant sounds were significantly less arousing for healthy young adults compared to healthy older adults ($t = 3.82$, $p< 0.001$).

Appendix 12. Temporal bisection task analysis for the dementia study with sound categories adjusted to reflect patients' valence ratings

Some patients produced valence ratings that did not fit pre-defined categories. In this secondary analysis, the corresponding sounds were reassigned to the correct category (for example, if the patient found angle grinder sounds pleasant, those sounds were assigned to the environmental pleasant category instead of the unpleasant one). The number of changes made is shown in the table below for each diagnostic group and each sound (sometimes more than one change was made for a participant).

	Angle grinder	Car horn	River	Brook	Male crying	Female crying	Male laughter	Female laughter
AD	1	0	0	0	0	1	4	2
lvPPA	0	0	0	0	0	0	0	0
nfvPPA	2	0	1	0	0	0	0	1
svPPA	5	3	2	3	2	2	0	0
bvFTD	2	3	1	0	1	0	2	1

As a result of these changes, one svPPA patient had to be excluded because they liked all sounds, and eight patients had one missing category (2 environmental pleasant, 2 environmental unpleasant , 3 human pleasant, 1 human unpleasant) but were maintained in the analysis sample. Psychometric curves were then estimated, corresponding bisection point and Weber's ratio vales were calculated and a statistical analysis was performed, all following the same procedure as for the first analysis (**section 5.3.7.2**). Averages values with standard deviations in parenthesis are shown in the tables on the next page, with changes written in orange and the number of missing participants as a result of sound reassignment coded as follows: $^{n-1}$, 1 missing participant.

Bisection point	Healthy controls		AD		lvPPA		nfvPPA		svPPA		bvFTD	
Condition	Env	Hum	Env	Hum	Env	Hum	Env	Hum	Env	Hum	Env	Hum
Unpleasant	3.3 (0.4)	4.3 (0.5)	3.1 (0.6)	4.5 (0.5)	3.3 (0.5)	4.7 (0.4)	3.0 (0.6)	4.7 (0.6)	3.4 (0.5) n-2	4.3 (0.5) n-2	3.4 (0.5) n-1	4.5 (0.5)
Pleasant	3.6 (0.4)	4.1 (0.4) n-3	3.3 (0.5)	4.2 (0.4) n-2	3.3 (0.5)	4.4 (0.5)	3.3 (0.8)	4.3 (0.7)	3.4 (0.3) n-3	4.0 (0.3) n-1	3.6 (0.5)	4.4 (0.7) n-1

As shown in the first analysis (**section 5.4.5**), the linear mixed model for the bisection point revealed a main effect of semantic category and significant interactions between semantic category and diagnosis as well as valence (all $p<0.001$). Post-hoc comparisons were also identical, except for svPPA patients who were found to overestimate the duration of human sounds compared to lvPPA patients instead of bvFTD patients ($z=2.20$, $p=0.028$). Another difference is that no significant main effect of valence was found in this second analysis.

Weber's ratio	Healthy controls		AD		lvPPA		nfvPPA		svPPA		bvFTD	
Condition	Env	Hum	Env	Hum	Env	Hum	Env	Hum	Env	Hum	Env	Hum
Unpleasant	0.20 (0.07)	0.18 (0.06)	0.28 (0.08)	0.22 (0.11)	0.25 (0.08)	0.24 (0.08)	0.22 (0.09)	0.22 (0.08)	0.19 (0.05) n-2	0.21 (0.05) n-2	0.22 (0.09) n-1	0.20 (0.06)
Pleasant	0.23 (0.08)	0.22 (0.07) n-3	0.28 (0.11)	0.28 (0.13) n-2	0.25 (0.07)	0.24 (0.10)	0.27 (0.11)	0.26 (0.10)	0.17 (0.08) n-3	0.22 (0.08) n-1	0.30 (0.19)	0.28 (0.10) n-1

The linear mixed model for the Weber's ratio revealed a significant main effect of diagnosis ($p=0.0219$) and valence ($p=0.030$), similarly to the first analysis (**section 5.4.6**), but no significant interaction between semantic category and diagnosis ($p>0.05$). Further changes include the loss of significant differences between the bvFTD group and both the control and SD groups for the post-hoc comparisons of the main effect of diagnosis.

Appendix 13 Demographic characteristics and performance on additional tasks of patients who did not complete the temporal bisection task

Diagnosis	AD	lvPPA	nfvPPA	bvFTD
Demographics				
N (M/F)	4 (3/1)	1 (1/0)	2 (2/0)	7 (7/0)
Age (years)	66.3 (7.8)	74.0 (N/A)	76.0 (4.2)	66.7 (6.0)
Handedness (R/L)	4/0	1/0	2/0	6/1
Education (years)	17.0 (2.2)	12.0 (N/A)	14.5 (3.5)	15.1 (3.0)
Symptom duration (years)	5.5 (2.1)	3.0 (N/A)	3.5 (0.7)	5.0 (2.7)
T-MMSE (/27)	11.3 (5.0)	22.0 (N/A)	15.5 (13.4)	17.8 (3.9)
Performance on additional tasks				
Auditory control task percentage correct score (%)	93.3 (6.1) n-1	100 (N/A)	N/A	83.3 (18.2) n-3
Recognition task percentage correct score (%)	81.3 (22.5) n-1	100 (N/A)	31.3 (N/A)	95.5 (6.9)

Averages (standard deviations) are shown unless specified otherwise. N/A is indicated in parenthesis where data correspond to a single participant and corresponding standard deviation cannot therefore be calculated. Numbers with missing data either because partipants failed the practice phase of the control task, or because participants did not understand task instructions for the recognition task are indicated as follows: n-x where x is the number of participants. There are no data available on the auditory control task for nfvPPA patients because both were too distressed to continue with the experimental testing.

Strikingly, the bvFTD group holds the highest number of participants who were unable to complete the temporal bisection task, with all seven being non-genetic cases. Three of them further failed the auditory control task, suggesting that they were particularly impaired. The remaining four had an average percentage correct score that seemed to be lower than those who completed the full temporal bisection task (96.9%; see **Table** 5-2). Four AD patients also failed the practice phase of the temporal bisection task, one of them also failing the auditory control task. They further had an average percentage score on the recognition task that seemed to be lower than those who completed the full temporal bisection task (98.9%; see **Table** 5-2).

Division of labour

The work in this thesis was conducted by MCRK with assistance from other researchers based at the Dementia Research Centre, University College London, and the Department of Psychology at George Mason University. Contributions are detailed below:

Chapter 3: Subjective time perception in healthy ageing: effects of emotional valence and semantic characteristics

Experimental design: MCRK, JDW in consultation with MW (temporal bisection task)

Construction of stimuli: MCRK

Data collection: MCRK

Data analysis: MCRK in consultation with MW and FB (Psignifit)

Chapter 4: Delivery of neuropsychology and neurolinguistic assessments to dementia patients in the COVID-19 era

Experimental design: MCRK, JJ, CH and JDW in consultation with SB (ethics)

Construction of stimuli: MCRK, JJ

Data collection: MCRK, JJ, EB, RLB, CH, LLR, CG

Data analysis: MCRK, JJ

Chapter 5: Subjective time perception in dementia: behavioural phenotypes and neuroanatomical correlates

Experimental design: MCRK, JDW

Construction of stimuli: MCRK

Data collection: MCRK, JJ, EB, CH, HS, JCSJ, AC, AN

Data analysis: MCRK in consultation with JMN (statistics)

Chapter 6: Temporal phenotypes of daily life in dementia and neuroanatomical associations

Experimental design: CM, JDW

Construction of stimuli: CM, JDW

Data collection: CM, HS, EB, RLB, CH, CG, KM, LLR

Data analysis: MCRK, CM

Publications

Publications arising as a direct result of the work conducted in this thesis

Altered time awareness in dementia: clinical features and brain substrates Front Neurol (2020) ***Requena-Komuro M-C****, Marshall CR, Bond RL, Russell LL, Greaves C, Moore KM, Agustus JL, Benhamou E, Sivasathiaseelan H, Hardy CJD, Rohrer JD, Warren JD.*

Neuropsychological assessments for dementia research in the COVID-19 era: a face-to-face vs remote comparative study, in preparation, ***Requena-Komuro M-C,*** *Jiang J, Benhamou E, Russell, LL, Bond RL, Brotherhood EV, Greaves C, Baker S, Crutch SJ, Hardy CJD, Warren JD.*

Subjective time perception in healthy ageing: effects of emotional valence and semantic characteristics, in preparation, ***Requena-Komuro M-C****, Jiang J, Hardy CJD, Wiener M, Warren JD.*

Subjective time perception in dementia: a behavioural and neuroanatomical analysis, in preparation, ***Requena-Komuro M-C****, Jiang J, Benhamou E, Johnson JCS, Sivasathiaseelan H, Chokesuwattanaskul A, Nelson A, Russell LL, Greaves C, Hardy CJD, Rohrer JD, Warren JD.*

Other substantial contributions

Phonemic restoration in neurodegenerative disease: a preliminary investigation, Brain Commun (2022) *Jiang J, Johnson JCS,* ***Requena-Komuro M-C****, Benhamou E, Sivasathiaseelan H, Sheppard DL, Volkmer AP, Rohrer JD, Crutch SJ, Warren JD, Hardy CJD.*

Decoding expectation and surprise in dementia: the paradigm of music, Brain Commun (2021) *Benhamou E, Zhao S, Sivasathiaseelan H, Johnson JCS,* ***Requena-Komuro M-C****, Bond RL, van Leeuwen JEP, Russell LL, Greaves C, Nelson A, Nicholas JM, Hardy CJD, Rohrer JD, Warren JD.*

Altered phobic reactions in frontotemporal dementia: A behavioural and neuroanatomical analysis, Cortex (2020) *Jimenez DA, Bond RL,* ***Requena-Komuro M-C****, Sivasathiaseelan H, Marshall CR, Russell LL, Greaves C, Moore KM, Woollacott IOC, Shafei R, Hardy CJD, Rohrer JD, Warren JD.*

Impaired phonemic discrimination in logopenic variant primary progressive aphasia, Ann Clin Transl Neurol (2020) *Johnson JCS, Jiang J, Bond RL, Benhamou E,* ***Requena-Komuro M-C****, Lucy LL, Greaves C, Nelson A, Sivasathiaseelan H, Marshall CR, Volkmer AP, Rohrer JD, Warren JD, Hardy CJD*.

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