Neurodevelopmental brain reserve in behavioural variant Frontotemporal Dementia

Harper, Luke Karl

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LUKE HARPER
DEPT OF CLINICAL SCIENCES MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

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Luke Harper

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 25th of April 2025 at 13.00 at Belfragesalen, Biomedical Centre, Sölvegatan 19, 223 62, Lund

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Abstract:
Background: Behavioural variant Frontotemporal Dementia (bvFTD) is an early-onset dementia characterised by early anterior cingulate (AC) neuropathological insult. The AC exhibits high morphological heterogeneity, which may be classified according to the presence of a paracingulate sulcus (PCS), a tertiary sulcus that, when present, develops during the third gestational trimester and thereafter remains stable throughout life. **Aim:** This thesis examines the role of the PCS in bvFTD, focusing on its prevalence and disease-specific associations with age at onset (AAO), disease progression, and survival. Furthermore, it aims to explore the impact of PCS presence on cerebral structural and functional connectivity. **Results**: Hemispheric PCS frequencies in both sporadic and genetic bvFTD were similar to those of healthy individuals. Presence of a right PCS was associated with a later AAO, an accelerated rate of disease progression and reduced survival following AAO in sporadic bvFTD. In genetic bvFTD, possession of a right PCS was associated with a later AAO in *GRN* but not *C9orf72* or *MAPT* mutation carriers. In a sub-group of *GRN* mutation carriers accelerated early disease progression after AAO was observed in individuals possessing a right PCS. In healthy individuals, we identified an association between left PCS presence and altered structural and functional connectivity. **Conclusion:** Whilst PCS presence is not a risk factor for the development of bvFTD, this thesis provides evidence that right PCS presence modifies disease expression, progression, and survival in this disease. As such, within the reserve framework, right PCS presence represents the first proxy of brain reserve in frontotemporal dementia. These findings establish a novel association between intrauterine neurodevelopment and the expression of a neurodegenerative disease – an insight with potential implications for future clinical trials in bvFTD. Finally, this thesis describes a novel link between structure and function and provides a plausible explanation of how cognitive advantages associated with paracingulate sulcal presence may be mediated by a highly connected local functional network reliant on short association fibres.

Key words: Frontotemporal dementia, behavioural variant frontotemporal dementia, paracingulate sulcus, gyrification, sulcation, reserve, brain reserve

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Luke Harper

LUND
UNIVERSITY

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Faculty of Medicine

Department of Clinical Sciences Malmö

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MADE IN SWEDEN

To my parents, Karl and Kay

Table of Contents

Abstract

Background: Behavioural variant Frontotemporal Dementia (bvFTD) is an early-onset dementia characterised by early anterior cingulate (AC) neuropathological insult. The AC exhibits high morphological heterogeneity, which may be classified according to the presence of a paracingulate sulcus (PCS), a tertiary sulcus that, where present, develops during the third gestational trimester and thereafter remains stable throughout life.

Aim: This thesis examines the role of the PCS in bvFTD, focusing on its prevalence and disease-specific associations with age at onset (AAO), disease progression, and survival. Furthermore, it aims to explore the impact of PCS presence on cerebral structural and functional connectivity.

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List of publications

Thesis publications

This thesis is based on the following articles, which in the text are referred to by their Roman numerals. Each article is published in full in the appendices.

I. **Harper L**, Lindberg O, Bocchetta M, Todd EG, Strandberg O, van Westen D, Stomrud E, Landqvist Waldö M, Wahlund LO, Hansson O, Rohrer JD, Alexander Santillo. Prenatal gyrification pattern affects age at onset in frontotemporal dementia *Cereb Cortex. 2022;*32(18):3937-3944.

II. **Harper L**, de Boer S, Lindberg O, Lätt J, Cullen N, Clark L, Irwin D, Massimo L, Grossman M, Hansson O, Pijnenburg Y, McMillan CT, Santillo AF. Anterior cingulate sulcation is associated with onset and survival in frontotemporal dementia. Brain Commun. 2023;5(5): fcad264.

III. **Harper L**, Strandberg O, Spotorno N, Nilsson M, Lindberg O, Hansson O, Santillo AF. Structural and functional connectivity associations with anterior cingulate sulcal variability. Brain Struct and Funct. 2024; 229(7):1561-1576.

IV. **Harper L**, Cash D, Lindberg O, Hansson O, Bouzigues A, Russell L, Foster PH, Ferry-Bolder E, van Swieten JC, Jiskoot LC, Seelaar H, Sanchez-Valle R, Laforce R, Graff C, Galimberti D, Vandenberghe R de Mendonça A, Tiraboschi P, Santana I, Gerhard A, Levin J, Sorbi S, Otto M, Pasquier F, Ducharme S, Butler CR, Le Ber I, Finger E Tartaglia MC, Masellis M, Rowe JB, Synofzik M, Moreno F, Borroni B, Rohrer J, Santillo AF on behalf of the GENFI consortium. Neurodevelopmental brain reserve in genetic frontotemporal dementia. (Unpublished Manuscript).

Publications not part of the present thesis

I. Santillo A.F, Leuzy A, Honer M, Landqvist Waldö M, Tideman P, **Harper L**, Ohlsson T, Moes S, Giannini L, Jögi J, Groot C, Ossenkoppele R, Strandberg O, van Swieten J, Smith R, Oskar Hansson. [^{18}F]RO948 tau positron emission tomography in genetic and sporadic frontotemporal dementia syndromes. Eur J Nucl Med Mol Imaging. 2023;50(5):1371–1383.

II. Lindberg O, Li T.Q, Lind C, Vestberg S, Almkvist O, Stiernstedt M, Ericson A, Bogdanovic N, Hansson O, **Harper L**, Westman E, Graff C, Tsevis T, Mannfolk P, Fischer H, Nilsonne G, Petrovic P, Nyberg L, Wahlund L.O, Santillo A.F on behalf of the Swedish FTD initiative. Altered empathy processing in frontotemporal dementia. JAMA Network Open. (In press).

Abbreviations

AAO	age at onset
AC	anterior cingulate
ACC	anterior cingulate cortex
AD	Alzheimer's disease
ALLFTD	ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration study
ALS	amyotrophic lateral sclerosis
BA	Brodmann area
BioFINDER	Swedish BioFINDER-2 study
bRGC	radial glial cells
bvFTD	behavioural variant FTD
CB	cingulate bundle
CBD	corticobasal degeneration
CBG	peri-genual cingulum
CBS	corticobasal syndrome
CDR	Clinical Dementia Rating scale
CDR® plus NACC FTLD	Clinical Dementia Rating Scale plus the National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration scale
CS	callosal sulcus
CSF	cerebrospinal fluid
CT	computerised tomography
DLB	dementia with Lewy bodies
DMN	default mode network
DSM	Diagnostic and Statistical Manual of mental disorders
FA	fractional anisotropy
fMRI	functional MRI
FTD	frontotemporal dementia
FTD@UCL/LIFTD	FTD at University College London/ Longitudinal Investigation of FTD

FTLD	frontotemporal lobar degeneration
GENFI	Genetic Frontotemporal Dementia Initiative
GRN	progranulin
GW	gestational weeks
HC	healthy control
LP	lumbar puncture
LUPROFS	Lund Prospective Frontotemporal Dementia study
lvPPA	logogenic variant PPA
MAPT	microtubule-associated protein tau
MCC	mid-cingulate cortex
MCI	mild cognitive impairment
MIR	Multidomain Impairment Rating scale
MRI	magnetic resonance imaging
MSA	multiple system atrophy
nfvPPA	non-fluent variant PPA
PCC	paracingulate cortex
PCG	paracingulate gyrus
PCS	paracingulate sulcus
PET	positron emission tomography
PoCC	posterior cingulate cortex
PPA	primary progressive aphasia
PSP	progressive supranuclear palsy
RD	radial diffusivity
ROI	region of interest
rsFC	resting-state functional connectivity
rsfMRI	resting-state fMRI
rtvFTD	right-temporal variant FTD
sACC	subgenual ACC
SLF	superior longitudinal fasciculus
SN	saliance netork
SPECT	single photon emission computed tomography
svPPA	semantic variant PPA
TDP-43	transactive response DNA-binding protein 43 kDa
UPS	ubiquitin-proteasome system
VENs	von Economo neurons

1. Background

> In recent times "dementia" has been replaced by the less stigmatising term, "Major Neurocognitive Disorder" in the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5). Eleven years after this publication however, the term dementia remains in common use amongst academics, physicians, and lay people. With consideration for this the terms, "dementia" and "Major Neurocognitive Disorder" are used interchangeably throughout this work.

A neurocognitive disorder describes an acquired syndrome characterized by impairment of one or more of six cognitive domain(s); learning and memory, language, executive function, complex attention, perceptual-motor function, and social cognition. Where this impairment is significant enough to interference with an individual's daily function and independence the term major neurocognitive disorder (formally dementia) is applied (Sachdev et al., 2014; American Psychiatric Association, 2013). A mild neurocognitive disorder meanwhile refers to Mild Cognitive Impairment (MCI) in which cognitive decline from a previous level of performance is apparent but insufficient to interfere with an individual's independence (Sachdev et al., 2014; American Psychiatric Association, 2013). Definitions of both disorders stipulate that cognitive deficits must be distinct from other mental disorders and persist outside of the context of a delirium. The diagnostic criteria for mild and major neurocognitive disorders according to the DSM-5 are reproduced in **Table 1.**

As of 2022 over 55 million people worldwide were estimated to be living with a major neurocognitive disorder. Without significant intervention, the combination of population growth, ageing, risk-factor exposure, educational attainment, and medical advancement outside of dementia, particularly in low- and middle-income countries, is expected to lead to a tripling of this number by 2050 (Nichols et al., 2022).

Neurocognitive disorders exert immense social and emotional pressures on individuals, families, and societies whilst also posing an unavoidable huge financial challenge. The global financial burden of neurocognitive disorders is substantial. Costs incurred are typically divided between direct medical costs, social sector costs (which includes informal caregiving expenses), and lost productivity. Lost productivity is the largest of these, accounting for 50% of the entire financial burden (Wimo et al., 2023). Whilst 61% of individuals with dementia live in low-and middle-income countries, 74% of the incurred costs of dementia occur in high-income countries (Wimo et al., 2023). The

financial weight of dementia accounts for a significant portion of the total healthcare expenditure and is straining healthcare systems and societies (Wimo et al., 2023).

Whilst major neurocognitive disorders are commonly associated with aging, they are not a normal part of the aging process. Instead, an underlying acquired aetiology causative of cognitive impairment is implicated, the most prevalent of which include Alzheimer's disease, cerebrovascular disease, Lewy body disease, frontotemporal dementia (FTD), traumatic brain injury (TBI), infections, and alcohol abuse.(Sachdev et al., 2014) These etiological sub-types of major neurocognitive disorders often exhibit significant overlap and with progression tend to converge on a global impairment of all cognitive domains. Differentiation of the etiological sub-types of dementia is complicated further by atypical presentations and comorbid pathology. Accurate subtyping of the neurocognitive disorders is crucial for improving diagnostic accuracy, facilitating meaningful research, and developing precise disease specific treatment strategies. At the time of writing, despite dementia being recognised as a global public health priority by the World Health Organisation in 2012, curative and effective treatments with the ability to halt or reverse disease progression remain elusive for the vast majority of the etiological sub-types of the neurocognitive disorders. Research endeavours focusing on further characterisation and understanding of these sub-types are essential in progression of the field towards the development of curative therapeutic interventions and addressing the immense human and societal affliction of dementia. This thesis aims to contribute to this effort by examining neurodevelopmentally derived brain reserve in one of the etiological sub-types of the neurocognitive disorders, Frontotemporal Dementia.

Table 1. Diagnostic Criteria for Neurocognitive Disorders

Diagnostic Criteria	Major Neurocognitive Disorder/Dementia	Mild Neurocognitive Disorder/MCI
A	Evidence of **significant** cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:	Evidence of **modest** cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
	1 Concern of the individual, a knowledgeable informant, or the clinician that there has been a **significant** decline in cognitive function; and	1 Concern of the individual, a knowledgeable informant, or the clinician that there has been a **mild** decline in cognitive function; and
	2 A **substantial** impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.	2 A **modest** impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B	The cognitive deficits **interfere** with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).	The cognitive deficits **do not interfere** with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
C	The cognitive deficits do not occur exclusively in the context of a delirium.	
D	The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).	
Specify whether due to: **Note:** Each subtype listed has specific diagnostic criteria and corresponding text, which follow the general discussion of major and mild neurocognitive disorders.		
Alzheimer's disease	Frontotemporal degeneration	
Lewy body disease	Vascular disease	
Traumatic brain injury	Substance/ medication use	
HIV infection	Prion disease	
Parkinson's disease	Huntington's disease	
Another medical condition	Multiple aetiologies	
Unspecified aetiology		

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (Copyright 2022). American Psychiatric Association. Coding notes and a complete list of specifiers for major and mild cognitive disorders can be found in **Appendices I** and **II**.

2. Introduction

2.1. Reserve

Individuals receiving the same neurological diagnosis, such as a dementia sub-type do not follow a uniform trajectory of cognitive or functional decline. Instead, the impact of a neurological disease upon an individual displays a degree of variability which is somewhat unique to the affected individual. A proportion of this variability may be accounted for by individual specific characterises capable of providing either resilience or vulnerability.

Reserve refers to individual differences in the capacity to withstand the burden of aging or a neurological disease (Katzman et al., 1988). Compared to individuals with low reserve, individuals with high reserve can cope with a greater pathological disease burden prior to the onset of symptoms. Characteristics and exposures associated with reserve are termed *reserve proxies.* In accordance with the Whitepaper developed by the Reserve, Resilience, and Protective factors professional interest area, under the auspices of the Alzheimer's Association, *resilience* meanwhile is used as an umbrella term, broadly referring to multiple reserve related processes. As such, resilience may be operationalised and consists of *cognitive reserve, brain reserve,* and *brain maintenance* (Stern et al., 2020).

2.1.1. Cognitive reserve

The concept of cognitive reserve derives from observations of discrepancies between the extent of brain pathology and the severity of clinical manifestations (Stern, 2012). Cognitive reserve is proposed as a protective factor, where enhanced adaptability of cognitive functional processing, reliant on neural networks and associated with task performance, modifies the susceptibility of cognitive function to brain aging, pathology, or insult (Stern et al., 2020). Cognitive reserve has been studied primarily in Alzheimer's disease (AD) where several proxies, including education, occupational complexity and engagement in leisure activities have been described and are associated with a delay in the onset of cognitive impairment (Lee et al., 2019; Stern, 2012; Groot et al., 2018; Stern et al., 2020; van Loenhoud et al., 2017). Neuroimaging techniques that permit visualisation of the accumulation of neuropathology and neurodegeneration enable the identification of individuals who, despite displaying significant markers of neuropathology (evidenced by reduced

cerebral perfusion and metabolism and increased cortical atrophy or tau aggregation), are able to maintain disproportionately high cognitive performance due to possession of cognitive reserve proxies. (Stern, 2012; Lee et al., 2019; Bosch et al., 2010; Kemppainen et al., 2008; Bocancea et al., 2023). There is therefore indication that individuals with greater cognitive reserve are capable of tolerating greater pathological insult prior to the development of cognitive impairment. Once cognitive impairment arises however, protective mechanisms credited to cognitive reserve proxies become overwhelmed and thereafter disease progression ensues more rapidly in individuals with greater than lesser cognitive reserve, reflecting the fact that the disease is more advanced at this point (Hall et al., 2007; Stern, 2012). A schematic of reserve is depicted in **Figure 1**.

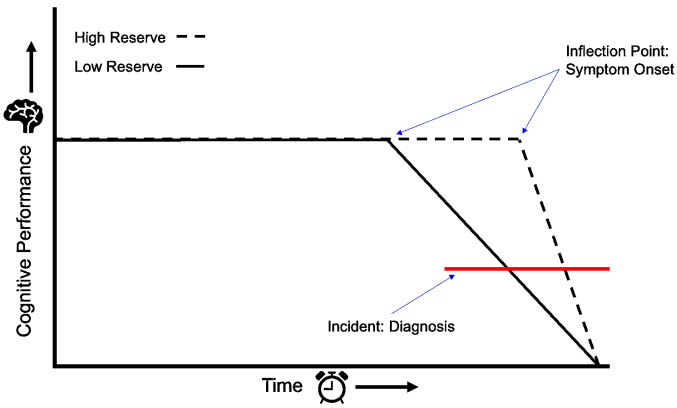

Figure 1. Schematic of cognitive reserve. This figure illustrates changes in cognitive performance over time in individuals with high and low reserve in the presence of a neurodegenerative disease according to the cognitive reserve principle. In the early stage of disease pathology advances prior to an observable change in cognitive performance. At a point, an inflection point is reached where performance begins to decline and symptom onset occurs. This point is later in individuals with higher reserve as they are able to tolerate more pathology before performance is compramised. Diagnosis typically occurs later, with further, notable decline in cognitive proformance. A point is hypothesized where pathology is so severe that cognitive performance is nil. This point is the same for individuals with both high and low reserve. Given this common endpoint, the figure hypothesizes that once decline begins, the rate of decline is accelerated in individuals with higher reserve compared to those with lower reserve.

Education has been associated with neuroimaging features of cognitive reserve in both FTD (Perneczky, Diehl-Schmid, Drzezga, & Kurz, 2007; Premi et al., 2012; Beyer et al., 2021; E. Premi et al., 2020) and behavioural variant Frontotemporal Dementia (bvFTD) (Borroni et al., 2009, Maiovis, Ioannidis, Gerasimou, Gotzamani-Psarrakou, & Karacostas, 2018). Similarly, one study has identified neuroimaging evidence of cognitive reserve using an index of education and working activity in bvFTD (Skeggs et al., 2023). An association between occupational attainment/complexity and cognitive reserve has been demonstrated in individuals with bvFTD in some studies (Borroni et al., 2009; Dodich et al., 2018),

whilst others do not identify such associations (Maiovis et al., 2018; S. H. Kim et al., 2022; Kinney et al., 2021). Similarly, conflicting evidence exists with regards to exposure to leisure activities in bvFTD (Borroni et al., 2009; Maiovis et al., 2018; Kinney et al., 2021). Lastly, female sex has been associated with greater behavioural and executive reserve than male sex in bvFTD in one, unreplicated study (Illán-Gala et al., 2021). For an extensive review of cognitive reserve in individuals with FTD the reader is refereed to Grebe et al 2024 (Grebe, Vonk, Galletta, & Goral). Importantly, to date no potential proxy of cognitive reserve in FTD or bvFTD has been associated with age at onset (AAO).

2.1.2. Brain reserve

Brain reserve refers to individual differences in the anatomical and structural characteristics of the brain referred to as neurobiological capital (numbers of neurons, synapses, etc.) that enable some individuals to preserve their cognitive or functional status in spite of aging or neuropathology. Importantly, at any point in time brain reserve is a fixed construct. Brain reserve provides passive protection, it does not protect against the accumulation of brain pathology but rather against the effects of the pathology (Stern et al., 2020). Brain and cognitive reserve are not mutually exclusive. Reserve theory suggests that greater brain reserve induces a functional adaptation thereby increasing cognitive reserve (van Loenhoud, Groot, Vogel, van der Flier, & Ossenkoppele, 2018).

There is significant support for the model of brain reserve in AD where gross anatomical measures such as head circumference and intracranial volume are identified proxies (Perneczky et al., 2010; van Loenhoud et al., 2018). To the best of our knowledge, prior to the work presented in this thesis, a Whitepaper definition of a brain reserve proxy, as defined by Stern et al 2020 (Stern et al., 2020) has not yet been established in FTD.

2.1.3. Brain maintenance

Whereas brain reserve refers to neurobiological capital at a fixed point in time, brain maintenance is defined by longitudinal preservation of neurobiological capital in spite of ageing or neurodegeneration, influenced by genetic or environmental exposures. In this context these exposures are otherwise referred to as brain maintenance proxies. There is some replicated evidence that greater physical activity may attenuate structural changes (atrophy and white matter microstructure integrity) associated with aging in healthy individuals. (Pettigrew & Soldan, 2019). Of the studied potential proxies of brain maintenance in disease however, there is inconsistency, with only weak evidence of a direct impact on the rate of change of brain structure and function, which is yet to be replicated. Notably, longitudinal studies of brain maintenance in disease are scarce and limited to relatively short

follow up periods. In FTD, one study has demonstrated greater grey matter density in right frontal cortical regions of individuals with higher education and occupation attainment after controlling for age and disease duration, aligning with the brain maintenance concept (Placek et al., 2016). In bvFTD, late-life lifetime exposure scores (but not education or occupational attainment) have been positively associated with both relatively preserved cortical thickness early in bvFTD and a slower rate of longitudinal cortical loss (Kinney et al., 2021).

Consideration of reserve proxies is relatively novel. Traditionally the medical field has focused more on the identification of disease risk factors than exploring reserve factors. The latter is however important for both clinical and academic practice. Clinically, establishment of reserve factors may inform policy, shape public health programs, and improve disease prognostication. In research, reserve factors are an important consideration in the development of study designs for therapeutic interventions, given trial endpoints are potentially impacted by the presence of reserve proxies. Finally, and somewhat more speculatively, the identification of reserve proxies may elucidate key mechanisms whose preservation are crucial in preventing symptom onset and disease progression and may even be targeted by future therapeutic interventions.

2.2. Frontotemporal dementia

Frontotemporal dementia (FTD) is a highly heterogeneous neurodegenerative disorder, characterized by a progressive disturbance of complex behaviour, predominantly effecting interpersonal conduct and/or language. This is accompanied by early focal degeneration of the frontal and/or temporal lobes. FTD is a major cause of dementia in individuals under the age of 65 and is therefore regarded as an early-onset dementia. In this age range FTD represents over 10% of dementia cases in Europe, Asia and North and South America, a proportion similar to that of Alzheimer's disease (Hogan et al., 2016). In individuals aged over 65 however, FTD accounts for a much smaller proportion of total dementia cases, approximately 3% (Hogan et al., 2016).

The AAO in FTD peaks at 40-70 years of age and the European incidence of FTD is estimated at 2.36 cases per 100 000 person-years, with a point prevalence ranging between 20-200 cases per 100 000 individuals (Logroscino et al., 2023; Onyike & Diehl-Schmid, 2013; Hogan et al., 2016; Coyle-Gilchrist et al., 2016). In Sweden, the mean age at diagnosis for FTD is 69.6 years and 70% of individuals are aged 65 years or older at the time of diagnosis (Nilsson, Landqvist Waldö, Nilsson, Santillo, & Vestberg, 2014). Importantly, the available epidemiological data are widely considered to underestimate the true presence of FTD (Grossman et al., 2023; Ratnavalli, Brayne, Dawson, & Hodges, 2002; Woolley, Khan, Murthy, Miller, & Rankin, 2011). These underestimates reflect the current diagnostic challenges and limitations in FTD, discussed further below.

2.2.1. Clinicoradiological syndromes

FTD is an umbrella term for several clinicoradiological syndromes, the most common of which is the behavioural variant of FTD (bvFTD), which accounts for approximately 60-70% of all cases (Sosa-Ortiz, Acosta-Castillo, & Prince, 2012). BvFTD is characterised by early alterations in personality and behaviour, cardinal features of which include; disinhibition, apathy/inertia, loss of sympathy/empathy, preservative/compulsive behaviour, hyperorality and a dysexecutive neuropsychological profile (Rascovsky et al., 2011). A loss of insight is characteristic but not part of the current diagnostic criteria. In addition to bvFTD there are three language variants of FTD, referred to collectively as the Primary Progressive Aphasias (PPA). These consist of a semantic variant (svPPA), a non-fluent variant (nfvPPA) and a logopenic variant (lvPPA). The latter is however typically associated with AD neuropathology (Teichmann et al., 2013) and is not further discussed in this work. The PPAs are characterised by an early and predominant disturbance of language leading to functional impairment with relative preservation of other cognitive domains (Ghosh, 2020; Gorno-Tempini et al., 2011).

Specific deficits attributed to svPPA include impairment of single-word comprehension and object naming whilst fluency, repetition, and grammar are preserved. NfvPPA is characterised by either or both, agrammatism and speech apraxia. More recently a right-temporal variant of FTD (rtvFTD) has been described (Ulugut Erkoyun et al., 2020; Younes et al., 2022), the clinical profile of which involves early behavioural alterations, widespread semantic deficits, and episodic memory impairment (Younes et al., 2022). Additionally, a number of motor syndromes are included within the FTD spectrum. These syndromes include amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and frontotemporal degeneration with Parkinsonism-17 (FTDP-17) (Moore et al., 2020; Warren, Rohrer, & Rossor, 2013).

An important complicating factor in characterising the clinical profiles of FTD syndromes in practice is the extensive clinical overlap observed both intrinsically, between FTD sub-types, and extrinsically with non-FTD diagnoses. Non-FTD diagnoses most commonly include other neurodegenerative diseases, primary psychiatric disorders and phenocopies. In this context a *phenocopy* refers to a clinical profile which mimics FTD but cannot be explaining by psychiatry and is not neurodegenerative.

Neuroimaging

FTD is associated with neuroimaging abnormalities of the frontal and/or temporal lobes, indicative of neurodegeneration, which may be detected using structural (Computerised Tomography [CT] and Magnetic Resonance Imaging [MRI]) and/or functional (Single Photon Emission Computed Tomography [SPECT] and Positron Emission Tomography [PET]) imaging modalities, represented as regions of atrophy, hypoperfusion or hypometabolism. Specific canonical epicentres of neurodegeneration have been attributed to each of the FTD clinical syndromes which are reflected by typical patterns of neuroimaging abnormalities. BvFTD is typically associated with bilateral abnormalities of the prefrontal cortices (specifically the anterior cingulate cortices [ACC]), the frontoinsula cortices and the temporal lobes (D. C. Perry et al., 2017; Seeley et al., 2008; Zhou, Gennatas, Kramer, Miller, & Seeley, 2012). NfvPPA is primarily associated with abnormalities of the left inferior frontal gyrus, corresponding with Broca's area and the left posterior frontoinsular cortex, although the left middle and superior premotor and homologous regions in the right hemisphere typically become involved with disease progression.

(Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2011; Josephs et al., 2006). SvPPA abnormalities are typically observed in the inferomesial temporal poles, usually asymmetrically with left hemisphere predominance, with spread to the orbitofrontal cortex with progression (Ghosh, 2020; Gorno-Tempini et al., 2004). As suggested by the nomenclature, rtvFTD imaging abnormalities occur most

prominently in the right anterior temporal lobe, broadly mirroring the pattern seen in the left hemispheres of individuals with svPPA (Younes et al., 2022). Typical patterns of neuroimaging abnormalities in bvFTD, svPPA and nfvPPA are depicted in **Figure 2.** Similarly, in genetic FTD, discussed below, there is an association between gene group and specific patterns of neuroimaging abnormalities (Cash et al., 2018; Sha et al., 2012; Simón-Sánchez et al., 2012; Whitwell et al., 2012; Yokoyama & Rosen, 2012).

There are a number of important caveats to consider regarding the neuroimaging of FTD. Early in the disease course, neuroimaging may appear normal (Piguet, Hornberger, Mioshi, & Hodges, 2011; R. J. Perry et al., 2006). In fact, even as the disease progresses, characteristic frontal and/or temporal neuroimaging abnormalities may only be detectable on MRI in 50-65% of cases (Knopman et al., 2005; Mendez, Shapira, McMurtray, Licht, & Miller, 2007; Pijnenburg et al., 2008). Notably, FDG-PET imaging offers higher sensitivity and is therefore recommended when MRI results are normal. Used together, MRI and FDG-PET have a reported sensitivity of 96% and a specificity of 73% (Vijverberg et al., 2016). Of further consideration, as with their clinical profiles, there is considerable neuroradiological overlap amongst FTD sub-types. Distinct patterns of neuroradiological abnormalities are most apparent in the early stages of disease and over time there is a tendency to convergence within the FTD spectrum and later on a global dementia phenotype.

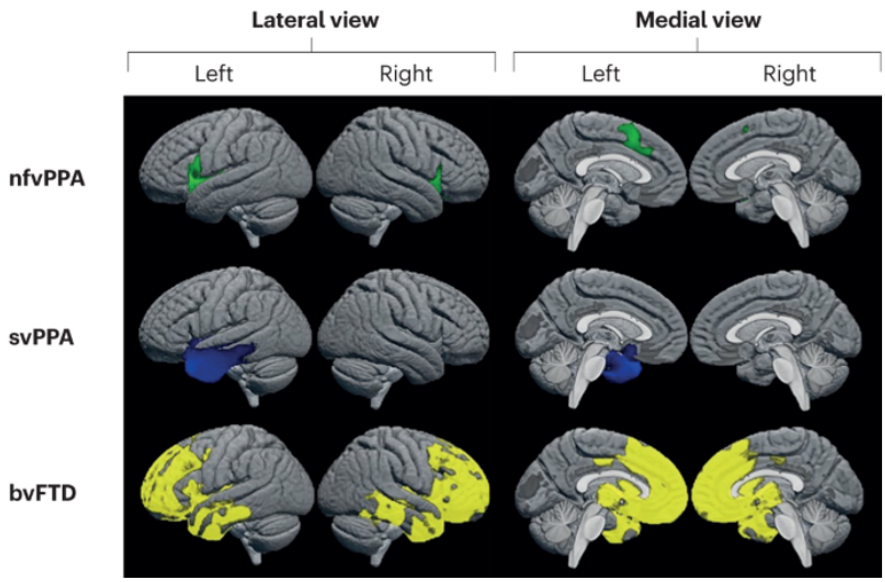

Figure 2. Characteristic patterns of neurodegeneration in different FTD syndromes. Group-level differences in brain volume loss for frontotemporal dementia (FTD) syndromes compared with healthy controls. Non-fluent variant primary progressive aphasia (nfvPPA) is typically associated with abnormalities in Broca's area in the left hemisphere, although left middle and superior premotor cortex and homologous regions in the right hemisphere can become involved with disease progression. Semantic variant PPA (svPPA) is typically associated with abnormalities in the left anteromedial temporal lobe, with spread into the right anteromedial temporal lobe and left orbitofrontal cortex with progression. Behavioural variant FTD (bvFTD) is typically associated with bilateral abnormalities in the prefrontal cortex, insula, and anterior temporal lobes. Adapted and reprinted with permission from Grossman 2023, Nat Rev Dis Primers.

2.2.2. Frontotemporal lobar degeneration

The term "Frontotemporal Lobar Degeneration (FTLD)" refers to the pathological diagnosis associated with the clinical FTD syndrome. The pathological entity of FTLD may be subdivided according to the nature of characteristic cytoplasmic or nuclear protein inclusions observed histopathologically. Such inclusions are broadly divided into four major molecular classes:

FTLD-TDP

Transactive response DNA-binding protein 43 (TDP-43) is a deoxyribonucleic acid (DNA)/ ribonucleic acid (RNA) binding protein expressed primarily in cell nuclei and involved in transcription regulation (Davidson et al., 2007). FTLD-TDP pathology is characterised by loss of normal nucleic TDP-43 and abnormal accumulation of phosphorylated and/or ubiquitinated TDP-43. The histological

hallmarks of which are the identification of neural cytoplasmic inclusions, neuronal intranuclear inclusions, dystrophic neurites, and glial cytoplasmic inclusions (Neumann & Mackenzie, 2019). FTLD-TDP represents approximately 50% of all FTLD cases (Neumann & Mackenzie, 2019). FTLD-TDP pathology is subtyped according to morphology, inclusion loci and distribution throughout the brain. Type A represents 40-50% of FTLD-TDP cases, Type B, approximately 30%, Type C, up to 25%, meanwhile Type D is considered rare (Davidson et al., 2007). In addition to FTD, TDP-43 accumulation and inclusion formation is also observed in most genetic and sporadic cases of ALS as well as ALS overlapping with FTD (Geser et al., 2009; Gijselinck et al., 2012). The mechanisms through which TDP-43 protein abnormalities are associated with neurodegeneration are not yet understood but are a focus of ongoing research.

FTLD-tau

Tau protein is encoded by the microtubule-associated protein tau (*MAPT*) gene on chromosome 17. In health, Tau stabilises microtubules, promotes microtubule assembly and regulates axonal transport. Tau is alternatively spliced at *MAPT* exon 10 into six isoforms, among which there is a three amino acid sequence repeat isoform (3R) and a four-repeat isoform (4R). Normal cells contain equal proportions of 3R and 4R tau. FTLD-tau subtypes are defined by the ratio and morphology of pathological hyperphosphorylated 3R and 4R tau inclusions. Pick's disease, previously synonymous with FTD but now regarded as a pathological subtype of FTLD (the hallmarks of which are described and depicted in **Figure 3**, below) is a 3R-predominant tauopathy. Conversely, Corticobasal degeneration (CBD), PSP, and less common pathologies including argyrophilic grain disease and globular glial tauopathy (GGT) predominantly feature 4R tau inclusions (Gorno-Tempini et al., 2011; Grossman et al., 2023). FTLD due to *MAPT* mutations, Alzheimer's disease, and chronic traumatic encephalopathy (CTE) meanwhile feature both 3R and 4R tau inclusions. FTLD-tau accounts for approximately 40% of FTLD pathology (Neumann & Mackenzie, 2019).

FTLD-FET

FTLD-FET inclusions are normally nucleic, composed of the FUS–Ewing sarcoma–TAF15 (FET) family of RNA-binding proteins which include atypical FTLD with ubiquitin-positive inclusions (aFTLD-U), basophilic inclusion body disease (BIBD) and neuronal intermediate filament inclusion disease (NIFID) FTLD (Andersson et al., 2008). These are typically sporadic and individuals with these subtypes have inclusions composed of all three FET family proteins (Neumann et al., 2011). Whereas Fused in Sarcoma (FUS) inclusions are genetic and are seen in genetic FTD as well as genetic ALS (Mackenzie & Neumann, 2017). FTLD-FET accounts for 5-10% of FTLD.

FTLD-UPS

Ubiquitin proteasome system (UPS) inclusions include ubiquitin- and p62-positive granular neurocytoplasmic inclusions that are negative for tau, TDP-43, and FUS proteins. These are rare and account for < 1% of FTLD. Most cases are associated with FTD linked to chromosome 3 caused by mutations in CHMP2B (Neumann & Mackenzie, 2019; Holm, Englund, Mackenzie, Johannsen, & Isaacs, 2007; Holm, Isaacs, & Mackenzie, 2009).

Predicting the underlying pathology of the clinicoradiological FTD syndromes is challenging, particularly in bvFTD. Approximately 47% of bvFTD is explained by FTLD-TDP pathology, 29% by FTLD-tau pathology and 7% FTLD-FUS pathology (D. C. Perry et al., 2017). The PPAs are more predictable, svPPA is highly associated with FTLD-TDP type C pathology and nfvPPA is most commonly associated with 4R tau and to a lesser extent TDP type A pathology (Montembeault, Brambati, Gorno-Tempini, & Migliaccio, 2018). **Figure 3** depicts the specific characteristic histology of the most common FTLD pathologies.

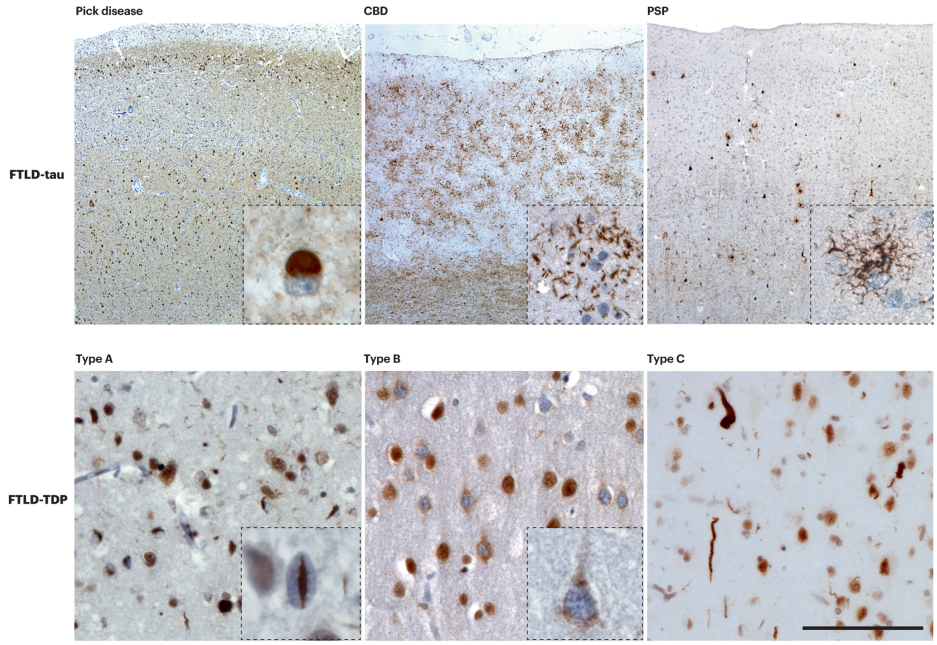

Figure 3. Frontotemporal lobar degeneration pathology.
Photomicrographs show the characteristic features of the six most common frontotemporal lobar degeneration (FTLD) subtypes: FTLD-tau (top row, CP-13 antibody to P-tau at S202) includes Pick disease, characterized by Pick bodies (inset) most prominent in cortical layers two, five and six; corticobasal degeneration (CBD), characterized by astrocytic plaques (inset) and copious white matter axonal and oligodendroglial tauopathy; and progressive supranuclear palsy (PSP), characterized by prominent tufted astrocytes (inset), neuronal cytoplasmic inclusions and oligodendroglia coiled bodies. FTLD–TAR DNA-binding protein (FTLD-TDP; bottom row, pan-TDP antibody) includes: type A, with rare neuronal nuclear inclusions (inset) and frequent compact or crescentic neuronal cytoplasmic inclusions and short neuropil threads, all most prominent in upper cortical layers; type B, featuring granular/stippled neuronal cytoplasmic inclusions (inset) without substantial neuropil threads; and type C, characterized by long, swollen dystrophic neurites. Note that normal nuclear TDP-43 immunoreactivity is absent in inclusion-bearing neurons. Insets are cropped to highlight a single characteristic feature of each disorder. Scale bar, 1,000 μm in top row panels and 100 μm in bottom row panels. Reprinted with permission from Grossman 2023, Nat Rev Dis Primers.

2.2.3. Genetics

FTD is highly heritable, approximately 20-30% is genetic, the vast majority of which is accounted for by autosomal dominant inheritance of chromosome 9 open reading frame 72 (*C9orf72*) repeat expansions and pathogenic mutations of progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*) (Gazzina et al., 2019; Greaves & Rohrer, 2019; Grossman et al., 2023). Other gene mutations associated with FTLD-TDP (TTLD-*VCP*, *SQSTM1*, *TBK1*, *TIA1*, *TARDBP* and *OPTN)* and FTLD-UPS (*CHMP2B)* have been described but are rare. Together mutations in these genes explain ~3-5% of total cases (Mol et al., 2021).

Individual gene mutations are associated with a spectrum of clinical syndromes and a major molecular class. In brief, *C9orf72* and *GRN* mutations are predominantly associated with FTLD-TDP43 pathology, whilst *MAPT* mutations are associated with FTLD-Tau pathology (Bang, Spina, & Miller, 2015). Similarly, as introduced previously there is an association between gene group and patterns of neuroimaging abnormalities. *C9orf72* expansion carriers typically exhibit a more diffuse pattern of atrophy than other genetic or sporadic forms of FTD with greater involvement of parietal, occipital, cerebellar and thalamic regions (Cash et al., 2018; Sha et al., 2012; Simón-Sánchez et al., 2012; Whitwell et al., 2012; Yokoyama & Rosen, 2012). Meanwhile, *MAPT* gene mutation carriers classically display symmetrical atrophy of the anterior and medial temporal lobes in addition to orbitofrontal cortex thinning (Cash et al., 2018; Rohrer & Warren, 2011; Whitwell et al., 2012; Yokoyama & Rosen, 2012). *GRN* gene mutation carriers, however, tend to display early, predominant frontal lobe atrophy (Simón-Sánchez et al., 2012), which is more pronounced than in other genetic groups and closely resembles atrophy patterns observed in sporadic bvFTD (Sha et al., 2012).

The complex interplay between the clinical syndrome, underlying neuropathology, and genetics in FTD is illustrated in **Figure 4**.

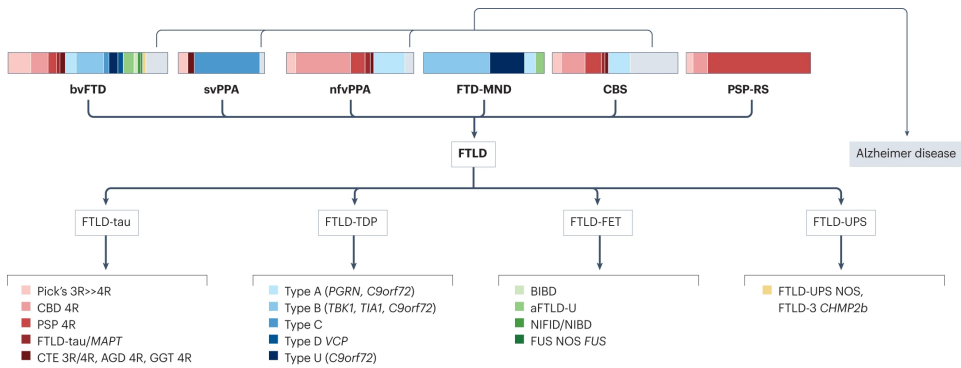

Figure 4. FTD syndromes and associated pathology. Clinical FTD syndromes colour-coded according to the proportion associated with a specific pathology and subtypes of each pathology as well as the associated genetic mutation with each. Genes shown without parentheses represent the only known causes of the associated neuropathological entity (for example, *VCP* in FTLD-TDP, type D), whereas genes shown in parentheses indicate that the pathology is also seen in patients with sporadic disease. 3R, three-repeat; 4R, four-repeat; AGD, argyrophilic grain disease; aFTLD-U, atypical FTLD; BIBD, basophilic inclusion body disease; bvFTD, behavioural variant FTD; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CTE, chronic traumatic encephalopathy; FET, FUS–Ewing sarcoma–TAF15; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; GGT, globular glial tauopathy; MND, motor neuron disease; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; NIBD, neurofilament inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; PSP, progressive supranuclear palsy; PSP-RS, PSP–Richardson syndrome; svPPA, semantic variant primary progressive aphasia; TDP, TAR DNA-binding protein; UPS, ubiquitin proteasome system. Reprinted with permission from Grossman et al 2023, Nat Rev Dis Primers.

2.2.4. Diagnostic criteria for bvFTD

The onset of bvFTD is insidious and determination of its clinical profile is reliant on meticulous history taking from both the patient and a caregiver, typically a close relative. Caregiver histories are vital in the context of FTD as accurate histories may be difficult to elicit from patients themselves due to a loss of insight (a key feature of the disease) (Barber, Snowden, & Craufurd, 1995), or denial/ reluctance to report what may be considered stigmatising symptoms. History taking is routinely conducted through semi-structured interviewing where symptom profiles, onset, sequence, extent, and impact are explored in depth, usually by a physician. This data is synthesised and may be formalised using clinical rating scales, such as the frontal behavioural inventory (Kertesz, Davidson, & Fox, 1997), the neuropsychiatric inventory (Cummings et al., 1994) or the more recently the Cambridge behavioural inventory (Hancock & Larner, 2008) and the Genetic Frontotemporal Dementia Initiative (GENFI) symptom scale (Samra et al., 2023). History taking is further supported by neuropsychological testing which allows more objective quantification of cognitive deficits and monitoring of their evolution over time. Establishing a clinical profile concordant with bvFTD is essential in establishing a diagnosis of bvFTD at any level of certainty. Demonstration of imaging results consistent with bvFTD, evidence of significant functional decline and exclusion of biomarkers strongly indicative of AD or other neurodegenerative process is required to fulfil probable criteria. A definite diagnosis is achieved by providing evidence of FTLD neuropathology, which may be confirmed either histologically or genetically. The international consortium criteria for diagnosing bvFTD (Rascovsky et al., 2011) is republished in **Table 2**. Application of these criteria by an experienced physician, following assessment of clinical features at presentation, yields a sensitivity of 86% for possible bvFTD, and 76% for probable bvFTD, with pathologically confirmed FTLD serving as the gold standard (Rascovsky et al., 2011).

Table 2. International Consensus Criteria for behavioural variant Frontotemporal Dementia

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) 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 symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) 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 symptoms (D.1–D.3) 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 symptoms (E.1–E.3) 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 symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

III. 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 (C.1–C.2) 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

IV. 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

V. 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

* As a general guidance "early" refers to symptom presentation within the first three years. bvFTD: behavioural variant FTD. Reprinted with permission from Raskovsky et al. 2011, Brain.

2.2.5. Risk factors for FTD

Aside from age and family history no risk factors for the development of FTD have been established. The sex distribution in FTD as a whole is equal (Hogan et al., 2016). The distribution differs slightly however between the clinical sub-types, where bvFTD is more common in males and PPA is more common in females (Kertesz, Blair, McMonagle, & Munoz, 2007; D. C. Perry et al., 2017; Spinelli et al., 2017). A similar male predominance is also observed in sporadic bvFTD whilst in genetic bvFTD the sex distribution is considered equal (de Boer et al., 2021; Heuer et al., 2020).

There is wide geographical variability in the distribution of frequencies of genetic subtypes of FTLD (Moore et al., 2020). As a whole the occurrence of genetic FTLD appears to be lower in Asia than Western countries (Fukuhara et al., 2014). Generally, there is a paucity of literature on racial differences in FTD though one autopsy study from the USA reported that FTLD is significantly more common amongst Caucasians than African Americans (Graff-Radford, Besser, Crook, Kukull, & Dickson, 2016). Importantly, reported racial and geographical variations in FTD are susceptible to and likely influenced by differential access to healthcare services and associated socioeconomic, societal, and cultural factors.

2.2.6. Disease modifiers

As discussed above, individuals with FTD are typically diagnosed in the sixth decade, though AAO varies widely in the literature with reports of first symptoms emerging from the third to the tenth decade of life (Antonioni et al., 2023). Despite this, only 13% of individuals develop symptoms before the age of 50 and just 30% after 65 years of age. (Antonioni et al., 2023; Moore et al., 2020; Onyike & Diehl-Schmid, 2013). Genetic FTD typically manifests earlier than sporadic FTD. In the largest international series of genetic FTD to date the mean AAO was 58.2 years for carriers of *C9orf72* expansions, 61.3 for carriers of *GRN* mutations and 49.5 for carriers of *MAPT* mutations (Moore et al., 2020). In all three genetic groups AAO correlated with parental and to a greater extent, mean family AAO (Moore et al., 2020). Family membership accounted for 17, 14, and 66% of the respective variance in AAO in *C9orf72*, *GRN* and *MAPT* mutation carriers (Moore et al., 2020). Aside from family membership, the specific gene mutation accounted for 2% of the variance in AAO for *GRN* mutation carriers and 48% for *MAPT* mutation carriers. The remaining variance remains unexplained though several genetic disease modifiers have been identified in genetic FTD and are reviewed comprehensively by Antonioni et al 2023 (Antonioni et al., 2023). Of these, single nucleotide polymorphisms of the late endosomal and lysosomal transmembrane protein encoded by TMEM106B, are the most well studied. In TDP-43 associated FTD, TMEM106B is a major modifier of disease penetrance in *GRN* and *C9orf72*

mutation carriers. Both risk and protective alleles of TMEM106B have been described, with homozygous carriership of the protective allele rarely found in symptomatic *GRN* mutation carriers (Van Deerlin et al., 2010; Finch et al., 2011; Cruchaga et al., 2011; Antonioni et al., 2023; Fenoglio, Scarpini, Serpente, & Galimberti, 2018; Pottier et al., 2018; Feng, Lacrampe, & Hu, 2021). To the best of our knowledge however, no replicated impact on AAO has been reported.

Several studies have identified an impact of inflammation on *GRN*-associated FTD pathogenesis (Bossù et al., 2011; Martens et al., 2012). Additionally, symptomatic patients with *GRN* mutations have been found to carry an increased risk of co-existing autoimmune disease (Miller et al., 2013). As such, there is speculation that environmental factors related to an altered neuroinflammatory response to, for example traumatic brain injury (Menzel et al., 2017) or systemic inflammation may modify the AAO in *GRN* mutation carriers. These mechanisms, however, are as yet poorly understood and incompletely studied. *MAPT* mutation carriers with FTD and the presence of the *Apolipoprotein* (*APOE*) *ε4* allele have been shown in one unreplicated study to have an earlier AAO than individuals with other *APOE* genotypes (Koriath et al., 2019). With regards to *C9orf72* expansion carriers, there is conflicting evidence surrounding the relevance of *C9orf72* hexanucleotide repeat expansion length (Fournier et al., 2019; Gijselinck et al., 2016; Moore et al., 2020; Nordin et al., 2015; van Blitterswijk et al., 2013). Several studies have identified DNA methylation age acceleration to be associated with a decreased AAO and shorter disease duration in *C9orf72* expansion carriers (Gijselinck et al., 2016; Russ et al., 2015; M. Zhang et al., 2017). More recently, a study of *C9orf72* expansion carriers identified a locus on chromosome 6 containing two overlapping genes (*LOC101929163* and *C6orf10*) where alleles of a polymorphism at rs9357140 have been associated with AAO (M. Zhang et al., 2018). This finding is however unreplicated. Lastly, one study of parental-offspring relationships in *C9orf72* revealed a significant correlation in AAO only in the mother-son relationship (Barbier et al., 2017), which authors suggest may be related to unknown X-linked genetic modifiers.

Meanwhile, whilst environmental disease modifying factors including educational attainment, occupational attainment and engagement in leisure activities have been shown to provide resilience to the neuropathological burden of FTD (as discussed previously in section 2.1.), they have yet to be shown to be associated with AAO in FTD (Borroni et al., 2009; Gazzina et al., 2019; Dodich et al., 2018; Perneczky et al., 2007; Placek et al., 2016; Enrico Premi et al., 2020; Premi et al., 2012).

2.2.7. Mapping disease onset and progression

Neurodegeneration in FTD is considered to begin in foci, referred to as epicentres. Disease epicentres typically display prominent neuroradiological aberrations (discussed above) which have anatomical and functional connections to brain

regions that degenerate at later stages of the disease (Grossman et al., 2023; Zhou et al., 2012). Anatomical epicentres of bvFTD include the anterior cingulate (AC) and frontoinsula cortices. Unique to these regions are populations of morphologically specialised layer 5b, glutaminergic projection neurons; von Economo neurons (VENs) and fork cells (Seeley et al., 2006; E. J. Kim et al., 2012). These neurons are selectively targeted in bvFTD and display vulnerability to FTLD pathology (Seeley et al., 2008; Seeley, Carlin et al. 2006; E. J. Kim et al., 2012; Santillo, Nilsson, & Englund, 2013). Whilst the function of these neurons is unknown, they are present only in humans, great apes, and other intelligent species capable of complex social interaction (Santillo et al., 2013). As such, and with consideration for their size and topographic restriction to the AC and frontoinsula they are assumed to facilitate sophisticated social-emotional-autonomic functions (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Seeley, 2008) whilst increasing the speed of information transmission and enhancing local cortical structural integrity (Stevens, Hurley, & Taber, 2011). The loss of VENs is significantly correlated with cognitive deficits in FTD (Gami-Patel et al., 2022).

With regards to progression, though incompletely defined multiple mechanisms are considered to contribute to FTLD spread. It is theorised that affected neurons may share core intrinsic cellular characteristics or vulnerability factor(s). As such, protein misfolding may begin independently within neurons of a similar type in response to a common genetic or environmental trigger (Grossman et al., 2023). Less selectively, pathological spread may progress to adjacent healthy neurons through intercellular transmission via the uptake of toxic, misfolded disease proteins following their release into the extracellular fluid by dying neurons (Frost, Ollesch, Wille, & Diamond, 2009). This cell-to-cell, connectivity-independent mechanism may describe the local accumulation of pathology that often characterizes early disease. The spatial spread of FTLD pathology is not exclusively however described by cell-cell, contiguous disease propagation (Brown et al., 2019). Moreover, pathological progression in FTD occurs in predictable non-contiguous anatomical patterns (Broe et al., 2003). These patterns are potentially explained by connectivity-dependent, trans-synaptic spread, where the transport of misfolded disease protein conformers is guided by networks via axons, across synapses and into healthy neurons of an affected network (de Calignon et al., 2012; E. J. Kim et al., 2020; Porta et al., 2018; Seeley, Crawford, Zhou, Miller, & Greicius, 2009). According to this network-based hypothesis, disease proteins behave in a prion-like manner, to induce proteins to adopt the disease-specific conformation which subsequently propagates exponentially though the affected network (Frost & Diamond, 2010; Liu et al., 2012; de Calignon et al., 2012; Vogel et al., 2020). Other, not mutually exclusive, contributors to network-based degeneration may include chronic hypometabolism and loss of trophic support related to network-level inhibition–excitation imbalance (Palop, Chin, & Mucke, 2006) or intrinsic vulnerability factors (both histological and genetic) held in common among networked brain regions (Fu, Hardy, & Duff, 2018; Grossman et al., 2023). Related to the network-based

hypothesis, the AC and frontoinsula represent key hubs of the salience network (SN), a large-scale network which processes relevant stimuli by integrating sensory, emotional, and cognitive information, becoming active during tasks requiring attentional selection, task switching, and self-regulation of behaviour (Farb et al., 2013; D. Fedeli, Del Maschio, Caprioglio, Sulpizio, & Abutalebi, 2020; Seeley et al., 2007). The SN is recognized as an important neural substrate in bvFTD (Zhou et al., 2010) with dysfunction confirmed on histopathology (Seeley et al., 2009) and resting-state functional MRI. (Farb et al., 2013; Zhou et al., 2010). Not only is there topographical correlation between hubs of the salience network and early neuropathological insult in bvFTD, but decreased functional connectivity of the SN in bvFTD is correlated with symptom presence, cognitive performance and clinical disease severity (Agosta et al., 2013; Birba et al., 2022; Borroni et al., 2012; Caminiti et al., 2015; Day et al., 2013; Ferreira, Lindberg, Santillo, & Wahlund, 2022; S. H. Kim et al., 2022; Ng et al., 2021; Seeley, 2010; Zhou et al., 2010). In addition, individuals with bvFTD display a reduced tendency to form specialized clusters in the SN (Ng et al., 2021) and possess fewer network hubs leading to decreased efficiency of the overall network (Ferreira et al., 2022). Patterns of connectivity within and between SN structures may reliably distinguish patients with FTD from healthy control subjects (Farb et al., 2013; Moguilner et al., 2021) and individuals with Alzheimer disease (Zhou et al., 2010). Furthermore, it is believed that the rapid early decline in the initial stages of FTD may be explained by a model of neurodegeneration which emphasizes breakdown of SN network connectivity prior to appreciable structural changes detected on standard neuroimaging (Chow et al., 2012; Day et al., 2013). Whilst regard for the SN as a "target network" in bvFTD is supported by multiple lines of evidence and represents a useful and well endorsed heuristic it does not completely describe the pathological spread observed in bvFTD (Seeley et al., 2009; Warren, Rohrer, Schott, et al., 2013). Some studies have indeed identified no association between functional connectivity of the SN and bvFTD (Canu et al., 2017; Hafkemeijer et al., 2017) whilst others report altered functional connectivity between the SN and non-SN regions (Agosta et al., 2013; Caminiti et al., 2015). Moreover, functional connectivity differences in individuals with bvFTD have been described in distinct networks outside of the SN, including but not limited to the default mode network (DMN), a network typically regarded as anticorrelated to the SN (Borroni et al., 2012; Farb et al., 2013; Ng et al., 2021; Premi et al., 2016; Trojsi et al., 2015) (Ferreira et al., 2022).

2.2.8. Disease progression & survival

Survival from symptom onset in FTD is approximately 8-10 years (Coyle-Gilchrist et al., 2016; Garcin et al., 2009; Le Ber et al., 2006). Median survival times vary according to the clinical syndrome. In bvFTD sub-types, survival is shortest in individuals with FTD combined with ALS (2.8 years) and longer in bvFTD without an accompanying motor disorder (9.6 years) (Kansal et al., 2016). Age and sex are

not known to be associated with survival and the effect of education is equivocal (Kansal et al., 2016). In dominantly inherited genetic FTD, survival and disease duration both vary according to genotype. The mean age at death and disease duration has been reported to be 58.5 and 9.3 years respectively in *MAPT* mutation carriers, 65.3 and 6.4 years in *C9orf72* expansion carriers, and 68.8 and 7.1 years in *GRN* mutation carriers (Moore et al., 2020). As observed with AAO, the variability in age at death in the Moore et al 2020 was partially explained by the specific mutation and even more so by family membership. In the *MAPT* group the specific mutation explained 61% of this variance and family membership 74%. In the *GRN* group, 9% of the variability in age of death was explained by the specific mutation, whereas 20% was explained by family membership. In the *C9orf72* group, family membership explained 19% of the variability in age at death. Factors influencing disease progression are discussed in **Chapter 2** in the context of reserve. At the time of writing, there are currently no licensed disease modifying treatments for bvFTD and pharmacological intervention is symptomatic, aimed at alleviating neurobehavioral symptoms. There is however limited evidence for the efficacy of these interventions in bvFTD and as such these medications do not hold licences for use in this disease (Trieu et al., 2020). The primary focus of management is thus that of on non-pharmacological intervention, which largely includes evaluation and optimisation of a patient's living environment.

2.3. Gyrification

Gyrification describes a developmental process where grooves (sulci) and ridges (gyri) form on the brains surface, increasing its surface area in order to accommodate a growing number of neurons. Sulci develop in a hierarchical manner during gestation. The deepest and most stable, primary sulci (such as the central and cingulate sulcus) are formed earliest, between gestational weeks (GW) 11 and 32 (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995), as depicted in **Figure 6**. Primary sulci are genetically determined and their presence, position, orientation, and temporal development are consistent both between individuals and between hemispheres of the same individual (Borrell & Reillo, 2012; Welker; Fernández, Llinares-Benadero, & Borrell, 2016; Lohmann, Von Cramon, & Colchester, 2008; Gabriele Lohmann, D Yves Von Cramon, & Helmuth Steinmetz, 1999; L. E. White et al., 1997). Secondary sulci develop between GW 22-34 and tertiary sulci develop later, after GW 34 (Armstrong et al., 1995). These sulci are less heritable and currently considered more stochastic than primary sulci, determined by a mutual interaction between biomechanical tensions, cellular mechanisms, the intrauterine environment, and genetic determination (Dieni et al., 2004; G. Lohmann, D. Y. von Cramon, & H. Steinmetz, 1999; Céline Amiez, Wilson, & Procyk, 2018; Llinares-Benadero & Borrell, 2019; T. White, Su, Schmidt, Kao, & Sapiro, 2010).

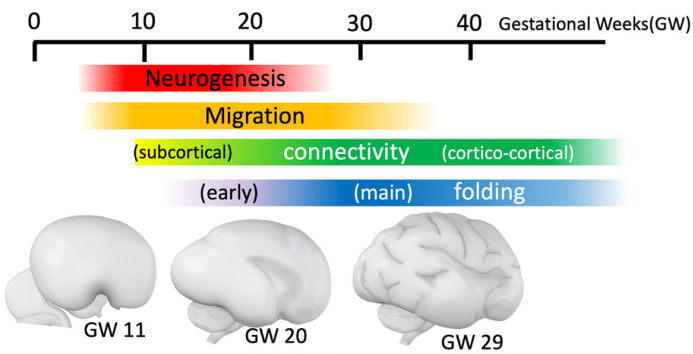

Figure 6. Timing of major events in human cortical development. Reprinted from Van Essen et al 2020, PNSAS, licenced under CC BY-NC-ND, https://creativecommons.org/licenses/by-nc-nd/4.0/.

Whilst a complete summary of the mechanisms thought to be involved in gyrification is extensive and beyond the scope of this thesis, an awareness of certain models and lines of research are relevant to this work. One of the earliest and probably the most extensively documented theory of gyrification in the literature is

the tension-based morphogenesis model, described by Van Essen in 1997 (D. C. Van Essen, 1997). This model emphasizes a critical contribution of mechanical tension in driving gyrification. Cortical structures are interconnected by association fibres which strive to minimise their length whilst preserving connectivity, resulting in reduced aggregate wiring length which enhances processing speed and energy efficiency. The tension-based morphogenesis model states that regional differences in connectivity and resultant mechanical tension drives the formation of gyri and sulci (D. C. Van Essen, 1997). This original model is now however considered incomplete, and was therefore revised and updated in 2020 (D. C. Van Essen, 2020). This revision is constructed on five tenets (outlined below) and provides a more comprehensive account of the mechanical processes thought to contribute to gyrification.

Five tenets of the mechanical mechanisms involved in gyrification

Tenet 1. Radially biased tension promotes tangential cortical expansion and is supplemented by cerebrospinal fluid pressure at early ages.

Tenet 2. Differential tangential expansion along the cortex promotes folding.

2A. Pathway-specific tension promotes gyral folds.

2B. Tethering tension promotes buckling along the cortex/core boundary.

Tenet 3. Tangential tension in the outer cortical layer and trans-sulcal pial adhesion promotes buckling and sulcal invagination.

Tenet 4. Three-dimensional geometry (patters of proliferation and migration) biases the location of folds and the axis of folding.

Tenet 5. Tension reduces wiring length and interstitial space.

The broader literature largely supports a predominant role of differential tangential cortical expansion in the formation of gyri. This process involves disproportionate accelerated expansion of the superficial cortical plate relative to deeper cortical layers gives rise to in-plane pressure which is dissipated by out-of-plane folding (Finlay & Darlington, 1995; Mota & Herculano-Houzel, 2015; Ronan et al., 2014; David C. Van Essen & Dierker, 2007; Akula, Exposito-Alonso, & Walsh, 2023). Relatedly, the specificity of gyrification patterns is closely linked to the region-specific expansion of the developing cortex. This expansion is driven by progenitor cell, (particularly basal Radial Glial Cell (bRGCs)) density and proliferation. (Ronan & Fletcher, 2015). Regions with greater progenitor cell proliferation and resultantly thicker subventricular zones, containing larger bRGC pools exhibit increased surface area with greater local gyrification indices (Ronan & Fletcher, 2015; Borrell & Götz, 2014; Llinares-Benadero & Borrell, 2019). In animal studies,

genetic enhancement of regional progenitor cell proliferation and bRGCs abundancy has been associated with a considerable increase in local gyrification (Nonaka-Kinoshita et al., 2013), whereas reducing proliferation led to the development of smaller gyral folds (Reillo, de Juan Romero, García-Cabezas, & Borrell, 2011). In lissencephalic species (lacking gyri or sulci) where comparatively smaller bRGCs pools are observed than in gyroencephalic species, genetically increasing bRGC abundancy has consistently led to the formation of gyrification (Florio et al., 2015; Stahl et al., 2013). Importantly however, gyrification in animals has been manipulated through other means without observing a concomitant increase in the number of bRGC (Rash, Tomasi, Lim, Suh, & Vaccarino, 2013) suggesting that the cellular mechanisms underlying gyrification are multifaceted (Ronan & Fletcher, 2015).

Cytoarchitecturally, studies of enucleation across animal species demonstrate that early (during the first half of gestation) but not late (during the second half of gestation) induced enucleation leads to a 70% reduction in primary visual cortex gyrification (Rakic, 1995). These results suggest a relationship between thalamo-cortical and cortico-cortical connectivity in gyrification and that axons contribute significantly to the formation of pattern-specific gyrification (Ronan & Fletcher, 2015). Additionally, these results imply that gyrification, (at least in this region), is partially predetermined at a point prior to the second half of gestation.

In addition to factors discussed above regional gyrification is under a variable degree of genetic regulation. Thousands of genes, macromolecules, signalling pathways (including but not limited to the Wnt/ β-catenin and Sonic hedgehog pathways) and regulatory molecules have been identified as key regulators of various aspects of morphogenesis and the cellular mechanisms involved in gyrification (Llinares-Benadero & Borrell, 2019; Piao & Walsh, 2004). Briefly, genetic factors that act to increase the tangential expansion of the cortex (though increasing proliferation or the divergent trajectory of migrating neurons) result in an increased degree of gyrification, while factors that decrease expansion (such as reducing radial migration and proliferation potential) decrease gyrification (Kriegstein, Noctor, & Martínez-Cerdeño, 2006; Lui, Hansen, & Kriegstein, 2011; Reillo et al., 2011; Ronan & Fletcher, 2015; Grasby et al., 2020; Rakic, 1988). Finally, the duration of mitosis and neurogenesis are directly correlated to gyrification (Rakic, 1995). Disruptions to mitosis, by genetic manipulation of β-catenin (which controls the number of cells in cycle) (Chenn & Walsh, 2002), or of caspase (which controls apoptosis) (Haydar, Kuan, Flavell, & Rakic, 1999), have a

predictable effect on the degree of gyrification, and have been used to contrive gyrification in otherwise lissencephalic species.

2.4. The anterior cingulate

2.4.1. Anterior cingulate anatomy

As discussed previously, the anterior cingulate (AC) is a focal point of neurodegeneration in bvFTD and is central to Studies I-IV of this thesis. The AC is a bilateral medial frontal lobe structure which overlies the corpus callosum, dorsally and lies ventral to the superior frontal gyri. Its anatomical boarders consist of the callosal sulcus ventrally and the cingulate sulcus dorsally. The posterior limit of the AC is determined by cortical cytoarchitectural features, originally described by the German neuropsychiatrist Korbinian Brodmann. Specifically, using the nomenclature used by Palomero-Gallagher et al 2008, the precingulate subregion, (Brodmann areas (BA) 24, 25, 32 and 33; formally the anterior cingulate cortex) contains a mainly agranular layer IV, whilst the postcingulate subregion (BA 23 and 31; formally the posterior cingulate cortex ([PoCC]) exhibits a prominent layer IV (Brodmann, 1909; Vogt, Nimchinsky, Vogt, & Hof, 1995). Macroscopically, this boarder may be approximated on a sagittal plane by a vertical line extending through the middle (or tip) of the first gyrus anterior to where the ascending marginal sulcus (ascending ramus) joins the prominent cingulate sulcus (CS) horizontally (McCormick et al., 2006). Since Brodmann's original description of a two-region cingulate cortex several cingulate subdivisions and nomenclatures have been suggested, the most widely acknowledged of which is a four-region neurobiological model, originally proposed by Vogt et al (Vogt, Berger, & Derbyshire, 2003; Vogt, Vogt, & Laureys, 2006). This model dichotomises the ACC based on local structural circuitry, functional imaging observations, and variations in neurotransmitter receptors (N. Palomero-Gallagher, Vogt, Schleicher, Mayberg, & Zilles, 2009; Vogt et al., 2003). The anterior segment of the precingulate region (formally the ACC), retains the ACC nomenclature, and the posterior segment is termed the mid-cingulate cortex (MCC) (N. Palomero-Gallagher et al., 2009; Vogt et al., 2003). Of functional relevance (see below), a subgenual portion of the ACC (sACC), consisting largely of Brodmann's Area 25 is also described in both models (Palomero-Gallagher, Mohlberg, Zilles, & Vogt, 2008). The two- and four-region models are displayed in **Figure 5**.

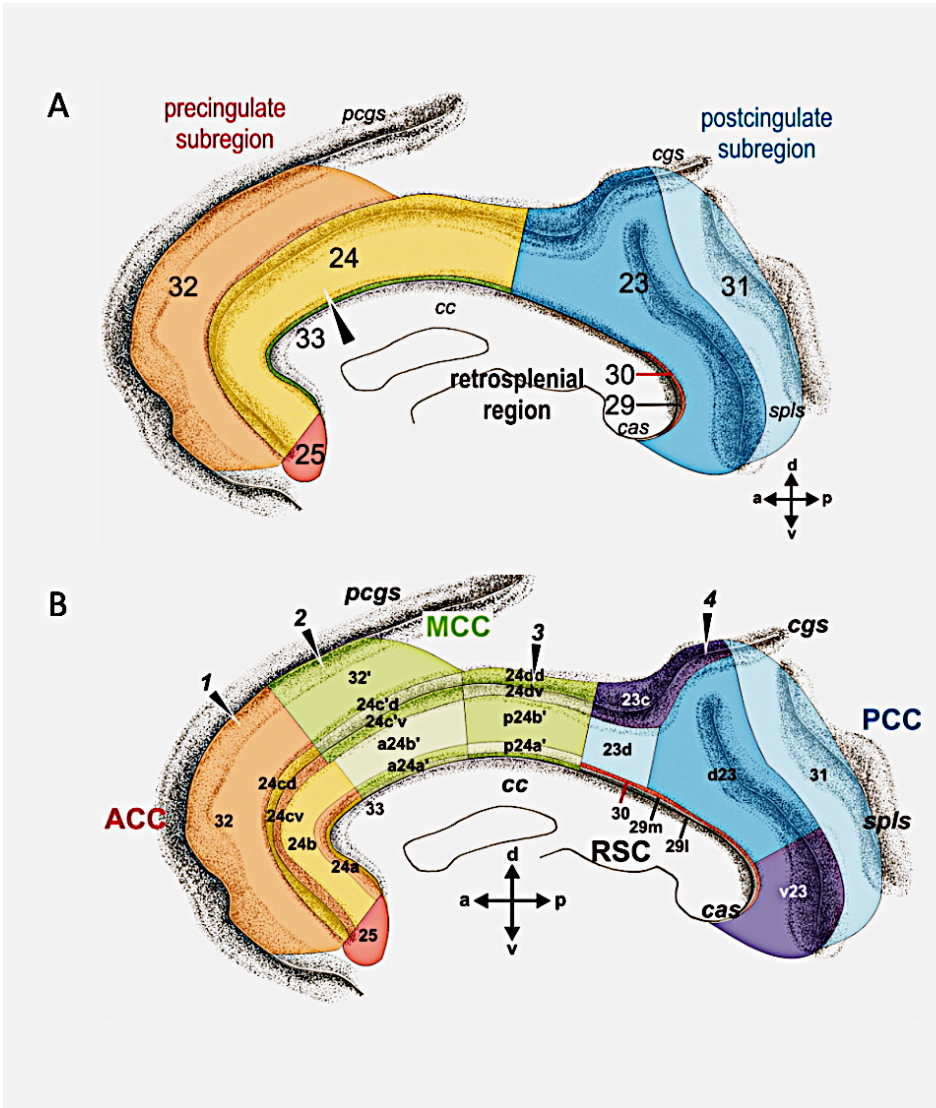

Figure 5. The two and four-region cingulate model. A. The cingulate cortex as defined by Brodmann 1909. Schematic drawing showing the regions, subregions and areas defined by Brodmann within the human cingulate cortex. The precingulate subregion encompasses areas 33, 25, 24, and 32; the postcingulate subregion areas 23 and 31; the retrosplenial region areas 29 and 30. The callosal (cas), cingulate (cgs), paracingulate (pcgs), and splenial (spls) sulci were ‘‘opened’’ to show areas within them. B. The four-region neurobiological model and cytoarchitectural areas [Vogt et al, 2004]. The callosal, cingulate (cgs), paracingulate (pcgs) and splenial sulci were ‘‘opened’’ to show areas within them. The anterior-cingulate cortex (ACC) areas (33, 25, 24a, 24b, 24cv, 24cd, and 32) are coded in orange/red; mid-cingulate cortex (MCC) areas (33, a24a , a24b , a24c v, a24c d, p24a , p24b , 24dv, 24dd) in green; posterior cingulate cortex (PCC) areas (23d, 23c, d23, v23, 31) in blue; and RSC areas (29l, 29m, 30) in blue/purple. Arrowheads mark the four levels at which autoradiographs were obtained in the original article publishing the image. Reprinted with permission from Palomero-Gallagher et al. 2008, Hum. Brain Mapp.

2.4.2. Anterior cingulate connectivity and function

Key to understanding the function of any particular brain region is an appreciation of its connectivity. Structural connectivity to and from the anterior cingulate cortex (ACC) is predominantly provided by the cingulum bundle (CB), a white matter tract which runs beneath the cingulate gyrus, containing fibres of different lengths, the longest of which extend from the orbitofrontal gyrus to the anterior temporal pole (Bubb, Metzler-Baddeley, & Aggleton, 2018; Catani & Thiebaut de Schotten, 2008). In addition to the cingulate bundle, the ACC is connected to adjacent gyri via short corto-coctical association fibres (U-fibres). Post-mortem injection studies in non-human primates have identified extensive bidirectional connections between the ACC and the orbitofrontal, dorsolateral frontal, primary and secondary motor, and insular cortices (Gasquoine, 2013). Specifically, the MCC has connections with cognitive (the dorsal and lateral prefrontal) and motor (the premotor and motor) cortical regions as well as pain and motor thalamic nuclei (Gasquoine, 2013; Stevens et al., 2011). By comparison, the ACC is highly connected to areas known to be important for emotion (e.g., amygdala), autonomic (e.g., lateral hypothalamus, brainstem centres), memory (e.g., hippocampal region), and reward (e.g., orbitofrontal cortex, ventral striatum) related functions. Finally, the sACC has greatest connectivity with limbic (amygdala, ventral striatum and hippocampus) and autonomic (hypothalamus) regions (Shen et al., 2023). These anatomical findings are broadly supported by structural connectivity studies in humans utilising diffusion tensor imaging (Stevens et al., 2011).

Connectivity may also be studied functionally, most commonly utilising functional MRI (fMRI) techniques in which subjects are scanned either at rest or whilst preforming a task. Here, time-series of regional fluctuations in blood flow and oxygenation (blood-oxygen level dependency [BOLD]), reflecting underlying local activity are studied. Regions displaying similar temporal activity profiles are deemed to be functionally connected. Resting-state fMRI (rsfMRI) studies of the ACC identify predominant functional connectivity with areas implicated in affective processing and anti-correlation with regions involved in cognitive or sensorimotor processing (Stevens et al., 2011). In contrast, the MCC is correlated with areas primarily involved in cognition and sensorimotor processing (Stevens et al., 2011). Large-scale resting-state networks, detected using rsfMRI, describe groups of brain regions that show synchronised activity patterns when the brain is at rest. These networks represent the brain's intrinsic connectivity architecture, reflecting how regions interact and communicate to maintain baseline cognitive and physiological functions. ACC subregions are identified as major hubs anchoring multiple large-

scale brain networks, including the salience (MCC), executive control (anterior MCC), default mode (sACC) and sensorimotor (sACC) networks (Shen et al., 2023). A plethora of studies have examined task-based functional connectivity of the ACC, as such associations with numerous cognitive processes have been described, a summary of which is beyond the scope of this thesis. Though task-based studies should be interpreted with caution, there is relatively broad agreement in the literature that the MCC performs a predominantly "cognitive" function involved in conflict-monitoring, response-selection, and execution, whilst the ACC is predominantly "affective", involved in emotion assessment, emotion-related learning, and autonomic regulation (Stevens et al., 2011).

2.5. The Paracingulate sulcus

2.5.1. Paracingulate anatomy

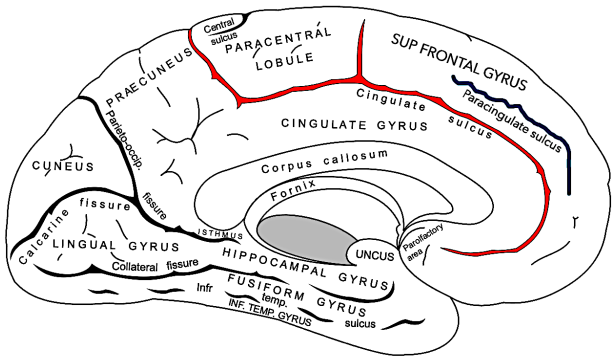

Figure 7. Medial surface of the left cerebral hemisphere. The paracingulate sulcus is traced in blue and the cingulate sulcus in traced in red.

The extensive morphological heterogeneity of the AC may be classified according to the presence or absence of a Paracingulate Sulcus (PCS). The PCS is a tertiary sulcus which, where present, runs predominantly dorsal and parallel to the CS in a rostro-caudal direction on the medial surface of the AC. Crucially, PCS presence is determined prenatally (during the third gestational trimester) and presence remains stable throughout life, largely unaffected by maturation or environmentally induced neuroplastic changes (A. Cachia et al., 2016). Sulcal morphological characteristics, including width and depth do however vary with age and brain maturation. (A. Cachia et al., 2016; Clark et al., 2010).

Though the PCS is consistently reported to be more frequent in left (vs. right) hemispheres of healthy individuals there is broad variation in reported hemispheric frequencies across studies, largely due to inconstancies in PCS classification protocols. PCS patterns are classified with respect to bilateral PCS presence. As such, four potential patterns may be described; absent bilaterally, present bilaterally, leftward dominant (presence of a left but not right PCS) and rightward dominant (presence of a right but not left PCS). At present the ontogenesis of PCS presence remains unknown. One unreplicated, yet large twin study identified an increased frequency of leftward dominant PCS patterns in twins (monozygotic and dizygotic) compared to non-twin siblings, where the proportion of similar hemispheres did not

differ between monozygotic and dizygotic twins but did differ from non-twin siblings (Céline Amiez et al., 2018). Furthermore, statistical estimates of heritability in Amiez et al 2018, did not reveal additive effects on the occurrence of a PCS in the left or right hemisphere (Céline Amiez et al., 2018). Together these findings suggest a strong influence of environmental factors, (the intrauterine environment) and a relatively weaker genetic influence on PCS development. Whilst there is inconsistency in the literature, in the largest study of PCS presence to date (n = 614), gender was not found to be associated with, or a modulator of PCS presence (Céline Amiez et al., 2018). Similarly, handedness and race are not associated with PCS presence (Céline Amiez et al., 2018).

A present PCS denotes the presence of an underlying paracingulate gyrus (PCG) with implications on AC microanatomy. Where a PCS is absent, area BA32' always begins at the deepest point of the CS. However, where a PCS is present the dorsal boundary of BA24c' is shifted to include almost half of the dorsal bank of the CS. (Vogt, Nimchinsky et al. 1995), see **Figure 8**. Importantly, neighbouring banks of the ACC and Paracingulate Cortex (PCC), (BA 24c' and 32') are cytoarchitecturally nearly indistinguishable, more similar to one another than any other cytoarchitectonic area in the medial wall of the cerebrum (N. Palomero-Gallagher et al., 2009; Smith, 1907). As such there is suggestion that the PCC may be regarded as an expansion of the ACC (corresponding to BA24c' and BA32') (Nicola Palomero-Gallagher, Mohlberg, Zilles, & Vogt, 2008; Vogt et al., 1995). The implications of this shift in BA areas are unknown but are thought to have functional consequences. A relevant consideration for FTD is that BA24 subdivisions have different densities of VENs, which, as discussed above, are selectively targeted bvFTD (Nimchinsky, Vogt, Morrison, & Hof, 1995; Santillo et al., 2013).

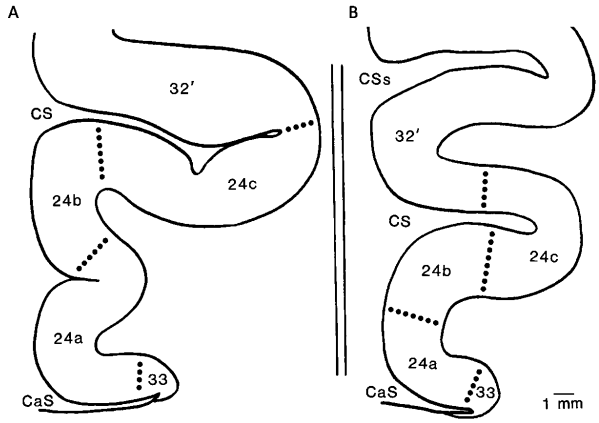

Figure 8. Schematics of two coronal sections through the anterior cingulate cortex. A. Displays a section with a cingulate sulcus (CS) but no paracingulate sulcus. B. Displays a section with both a cingulate and paracingulate sulcus (CSs). The depths of the CS and the size and distribution of the cytoarchitectural areas are different in each case. CaS denotes the callosal sulcus. Brodmann areas are represented by their corresponding numbers. Reprinted with permission from Vogt al. 1995, J Comp Neurol.

2.5.2. Paracingulate connectivity and function

The PCG is primarily connected structurally by U-fibres, short association fibres which extend to the AC proper and together form a localised white matter network (Wysiadecki et al., 2021). Deep of the superficial U-fibres lie longitudinal fibres which course within the PCG when present and are otherwise identified medially and inferiorly to the cingulate sulcus, within the cingulate gyrus where the PCS is absent (Komaitis et al., 2019). This tract is regarded by some as subcomponent Ia of the superior longitudinal fasciculus (SLF-Ia) (Komaitis et al., 2019; Wysiadecki et al., 2021) and by others as either a division of the cingulate bundle (Wu, Sun, Wang, Wang, & Ou, 2016) or even a tract of U-fibres (Maldonado, Mandonnet, & Duffau, 2012).

From the perspective of intrinsically connected networks, the SLF-I is considered a major subcortical connection of the DMN, a resting state network activated when the brain is resting (but alert), and attention is focused on internal tasks such as memory retrieval and self-reflection (Yagmurlu, Middlebrooks, Tanriover, & Rhoton, 2016). The cingulum bundle meanwhile represents a key hub of the SN, discussed above (Seeley et al., 2007). PCS presence has been identified to alter the organisation of resting-state functional connectivity in target voxels overlapping components of both the SN and the DMN (D. Fedeli et al., 2020).

In task-based functional analyses, activation of the left paracingulate has been observed during verbal cognitive tasks (Herholz et al., 1996; Crosson et al., 1999), whilst the right paracingulate is active during tasks testing spatial working memory (Owen, Evans, & Petrides, 1996). Furthermore, PCS presence has been shown to alter the functional organisation of cognitive, (including feedback (C. Amiez et al., 2013), prediction error (Jahn, Nee, Alexander, & Brown, 2016) and word generation (Crosson et al., 1999)) but not pain (C. Amiez et al., 2013) or motor (Loh, Hadj-Bouziane, Petrides, Procyk, & Amiez, 2017) related fMRI activity in the AC. Whilst these studies are unreplicated, they suggest a functional impact of PCS presence which is more cognitive than either sensory or motor. Numerous works have studied various cognitive functions in relation to PCS presence and patterns, a summary of which is presented in **Table 3**. PCS presence has been associated with a number of higher-order functions, in short possession of a left PCS or asymmetric PCS pattern is generally considered cognitively advantageous, whilst bilateral PCS absence is considered disadvantageous.

Table 3. Study summary: The impact of paracingulate sulcal presence on cognitive function

Study Reference	Cognitive function & Task	Population	Main Findings
Amiez et al. 2018 (Céline Amiez et al., 2018)	Alertness: Mini-Mental State Examination (MMSE) Episodic memory: Picture Sequence memory test Executive function/ Cognitive flexibility: Dimensional change card sort Executive function: Flanker task Fluid Intelligence: (Penn Progressive Matrices) Self-regulation/Impulsivity: Delay Discounting test Sustained Attention: Short Penn Continuous Performance Test Emotional functions: Negative Affect (Sadness, Fear, Anger)	641 adults 82 monozygotic twin pairs. 53 dizygotic twin pairs. 67 non-twin sibling pairs. 187 subjects without siblings	Twins with a leftward dominant pattern displayed better fluid intelligence than twins displaying symmetric paracingulate sulus (PCS) patterns and vice-versa in non-twins. Whilst the opposite was found in self-regulation/impulsivity.
Buda et al. 2011 (Buda, Fornito, Bergstrom, & Simons, 2011)	Reality monitoring Computer based reality monitoring memory task	53 adults	Individuals with bilaterally absent PCS displayed reduced reality monitoring and ability to introspect metacognitively about their performance.
Borst et al. 2014 (Borst et al., 2014a)	Cognitive control/ Inhibitory control: Animal Stroop task (at age 5). Colour-word Stroop task (at age 9) Verbal working memory: Weschsler Intelligence Scale for children (WISC-IV); forward and backward digital span	18 children (Longitudinal analysis at age 5 and 9 years old)	Children with asymmetrical PCS patterns had better cognitive control efficiency at age 5 and 9 than children with symmetrical patterns. No differences in verbal working memory were identified between children with symmetrical and asymmetrical PCS patterns
Fornito et al. 2004 (Alexander Fornito et al., 2004)	Verbal Executive cognition: Verbal fluency task Controlled Oral Word Association Task (COWAT) Spatial Executive cognition: Spatial working memory task (SWM), a subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB).	30 right-handed male adults.	Leftward PCS asymmetry was associated with better performance across verbal and spatial executive tasks.
Cachia 2014 (Arnaud Cachia et al., 2014)	Cognitive control/ Inhibitory control: Animal Stroop Task Verbal working memory: Weschsler Intelligence Scale for children (WISC-IV); forward and backward digital span	19, 5-year-old, right-handed children	Higher cognitive control efficiency was identified in children with asymmetrical PCS patterns compared with children with symmetrical patterns Working memory was not affected by PCS pattern symmetry
Cachia 2017(A. Cachia et al., 2017)	Cognitive control/ Inhibitory control Flanker test	31 Right-handed female adults (17 Bilinguals. 14 Monolinguals)	A performance advantage was observed in leftward dominant versus symmetric PCS patterns.

			Leftward dominant versus symmetrical PCS patterns were associated with a performance advantage in monolinguals and a performance detriment to bilinguals and vice versa.
Whittle et al. 2009 (S. Whittle et al., 2009)	Temperament; Effortful Control, Negative Affectivity, Surgency, and Affiliation: revised version of the Early Adolescent Temperament Questionnaire (EATQ-R)	153 early adolescents (Mean age 12.6 years old)	A leftward PCS asymmetry was associated with significantly higher temperamental effortful control and lower negative affectivity than a rightward asymmetry in males but not females. A symmetric PCS patterns was associated with higher temperamental affiliation than a rightward asymmetric pattern.
Tissier et al. 2018 (Tissier et al., 2018)	Cognitive control/ Inhibitory control Colour-word Stroop task	19 Children (Mean age 10.5 years old) 19 Adults	Children and Adults with asymmetrical PCS patterns displayed better inhibitory control efficiency than those with symmetrical PCS patterns
Huster et al. 2009 (Huster et al., 2009)	Cognitive control/ Inhibitory control Colour-word Stroop task	16 right-handed adults	Individuals with a leftward PCS pattern recorded quicker response times but similar accuracy to interference-laden stimuli compared to individuals with bilaterally absent PCS
Fedeli et al. 2022 (Davide Fedeli et al., 2022)	Cognitive control/ Inhibitory control Attention Network Task (ANT) Numerical Stroop Task fMRI	42 Adults	ANT: No significant difference in behavioural or functional activity between individuals with symmetrical and asymmetrical PCS patterns. Numerical Stroop Task: Behavioural advantage of asymmetrical PCS patterns. Greater activation of the bilateral medial frontal lobe wall in individuals with symmetrical patterns.
Del Maschio et al. 2019 (Del Maschio et al., 2019)	Cognitive control/ Inhibitory control Flanker Task	157 Adults (63 Bilinguals. 94 Monolinguals)	Asymmetric PCS patterns were associated with a performance advantage in monolinguals and a performance detriment to bilinguals and vice versa

2.5.3. The paracingulate sulcus and disease

Paracingulate sulcal presence and morphology has relevance to a number of neurological diseases and psychiatric disorders. Multiple studies have reported that the leftward dominance of PCS presence observed in healthy individuals is either lost or significantly reduced in individuals with schizophrenia (Fujiwara et al., 2007; Le Provost et al., 2003; Marquardt et al., 2005; M. Yücel et al., 2002; Murat Yücel et al., 2003). Relatedly, in one unreplicated study, individuals with a high genetic risk for psychosis were found to have a lower frequency of PCS than healthy individuals, yet a slightly higher frequency of PCS than individuals with schizophrenia (Koo et al., 2008). Compared to non-hallucinating individuals with schizophrenia and healthy controls, hallucinating individuals with schizophrenia possess PCS of shorter lengths and less medial prefrontal local gyrification (Jane R Garrison et al., 2015; Rollins et al., 2020; Garrison, Fernyhough, McCarthy-Jones, Simons, & Sommer, 2019). Similarly, in one study of undifferentiated schizophrenia, left PCS length was found to be shorter in individuals with schizophrenia than controls (Alex Fornito et al., 2006). The reduced leftward dominance of PCS presence in schizophrenia is an established finding, indicative of a potential neurodevelopmental aberration (Le Provost et al., 2003).

Outside of schizophrenia and psychosis, a lower frequency of left hemisphere PCS presence has been reported in patients with obsessive-compulsive disorder (Shim et al., 2009) and altered PCG connectivity has been correlated with generalized epilepsy (Kay, Holland, Privitera, & Szaflarski, 2014) and epilepsy drug resistance (Szaflarski, Kay, Gotman, Privitera, & Holland, 2013). At present however these studies remain unreplicated.

Collectively, these studies provide a body of evidence indicating that both the presence and morphology of the PCS is relevant to disorders and diseases presumed to be associated with AC pathology. This is of particular significance to bvFTD, a disease with a known epicentre in this region. To the best of the author's knowledge, prior to the commencement of the work reported in this thesis, PCS presence and morphology had not been studied in relation to bvFTD.

3. Rational and aims

The anterior cingulate is a focal point of neurodegeneration in bvFTD, afflicted early and extensively in the disease process. The impetus for this thesis stems from studies of schizophrenia, where a reduced leftward dominance of paracingulate sulcal presence is an established finding, indicative of a potential neurodevelopmental aberration. At the outset of this thesis, exploration of the impact of paracingulate sulcal presence in bvFTD was unstudied, despite the established findings in schizophrenia and the overlapping symptomology and loci of presumed pathology between these two diseases. This gap underscores the need for this work. As such, this thesis presents a series of neuroimaging studies aiming to explore the role of the paracingulate sulcus in behavioural variant Frontotemporal Dementia and its effects on cerebral structural and functional connectivity.

The primary aims were as follows:

I. To investigate the prevalence of the PCS in sporadic bvFTD and explore its impact on disease expression.

II. To replicate the disease expression analyses performed in Study I in a novel cohort of sporadic bvFTD and explore the impact of the PCS on disease progression and survival.

III. To investigate the impact of PCS presence on cerebral structural and functional connectivity.

IV. To determine the prevalence of the PCS in genetic bvFTD and explore its impact on disease expression and progression.

4. Methods

4.1. Study settings

The studies presented in this thesis included participants from seven independent observational cohorts, representing a broad international collaboration across multiple countries. All cohorts recruited participants from either memory or neurology clinics and employed a multidisciplinary approach to diagnosis. This approach included clinical, cognitive, neuropsychological, biofluid (serum, plasma, and cerebrospinal fluid (CSF), and neuroimaging examination. Healthy, cognitively intact controls (HC) were recruited to all cohorts and subjected to similar conditions as patients. The diagnosis of bvFTD was uniformly made across all cohorts using International bvFTD Consortium Criteria (Rascovsky et al., 2011), ensuring diagnostic consistency. Exclusion criteria typically excluded individuals with significant medical illness preventing participation with study protocol and individuals with significant neurological or psychiatric comorbidity. All studies were ethically approved by relevant institutional or regional committees and written consent was obtained from all participants. A summary of the cohorts contributing to the studies presented in this thesis are summarised in **Table 4.**

Table 4. Study settings summary

Cohort	Site(s)	Background	Participants	Exclusion Criteria	Exposures	Diagnosis of bvFTD
Bio-FINDER 2 (clinical trial no. NCT03174938, http/://www.biofinder.se/two/)	Sweden Memory and Neurology Clinics at Skåne University Hospitals and The Memory clinic in Ängelholm, Sweden.	Study: Prospective longitudinal cohort Aim: initiated in order to improve diagnostic and prognostic methods and develop biomarkers for dementia and Parkinson's related disorders. Launched: 2017 Recruitment: Ongoing	Adults (>18 years old) with SCD, MCI, AD, FTD, nfvPPA, svPPA, PSP, PDD, DLB, MSA, and Healthy Controls	Significant medical disease impeding study participation. Current significant alcohol or substance misuse. Significant neurological or psychiatric comorbidity. Refusal of lumbar puncture, MRI, or PET. Inability to speak and understand Swedish.	Clinical history and examination, Caregiver history, Cognitive & Neuropsychological testing, Bio samples: CSF, serum, +/- DNA, Imaging: Tau PET, Amyloid PET, MRI	According to the International Behavioral Variant FTD Consortium Criteria (Rascovsky et al., 2011) following multidisciplinary assessment
The Genetic Frontotemporal Dementia Initiative (GENFI) (https://www.genfi.org/)	International – 40 sites across the UK, the Netherlands, Belgium, France, Spain, Portugal, Italy, Germany, Switzerland, Sweden, Denmark, Finland, Croatia, Serbia, Turkey, and Canada	Study: Prospective longitudinal cohort Aim: To enhance the understanding of genetic FTD, in order to develop biomarkers for identifying disease onset and allow tracking of disease progression. To develop a trial-ready cohort and develop trial outcome measures. Initiated: 2015, currently in phase II Recruitment: Ongoing	Patients and first-degree adult (>18 years old) relatives of individuals with genetic FTD	Significant medical disease impeding study participation, Contraindication to MRI or LP, Pregnancy	Clinical history and examination, Caregiver history, Cognitive & neuropsychological testing, Bio samples: CSF, serum, plasma, DNA Imaging: MRI	According to the International Behavioral Variant FTD Consortium Criteria (Rascovsky et al., 2011) following multidisciplinary assessment

Penn FTDC University of Pennsylvania Centralized Observational Research Repository on Neurodegenerative disease (UNICORN)	USA The Penn Frontotemporal Dementia Neurology clinic, Philadelphia and greater Philadelphia area at the University of Pennsylvania, Pennsylvania, USA.	Study: Prospective longitudinal cohort Aim: To improve the diagnosis, develop new markers of prognosis and discover therapeutic targets that can enhance and further the development of treatment trials aimed at treating the underlying biology of FTD and related disorders Initiated: 2003 Recruitment: Ongoing	Adults (18 years old) with FTD, AD, DLB, ALS, PSP, CBS, PPA, PCA, other neurodegenerative disease, neurodegenerative disease family history + Healthy Controls	A condition or situation, which could confound the study findings or may interfere significantly with a person's participation, Contraindication to MRI or LP. Pregnancy	Clinical history and examination, Caregiver history, Cognitive & neuropsychological testing, Bio samples: CSF, serum, plasma, DNA Imaging: MRI	According to the International Behavioral Variant FTD Consortium Criteria (Rascovsky et al., 2011) following multidisciplinary assessment
Amsterdam Dementia Cohort (https://www.alzheimercentrum.nl/wetenschap/amsterdam-dementia-cohort/),	The Netherlands Alzheimer Centre Amsterdam, The Netherlands	Study: Longitudinal cohort, mixed retrospective, and prospective Aim: To combine patient care and research in dementia Initiated: 2000 Recruitment: Ongoing	All adults (>18 years old) referred to the Amsterdam Alzheimer's centre, including but not limited to individuals with AD, SCD, MCI, FTD, DLB, VaD, CJD, CBD, PSP + Healthy Controls	Significant medical disease impeding study participation	Clinical history and examination, Caregiver history, Cognitive & neuropsychological testing, Bio samples: CSF, serum, plasma, +/- DNA, EEG Imaging: MRI +/- FDG PET, Amyloid PET	According to the International Behavioral Variant FTD Consortium Criteria (Rascovsky et al., 2011) following multidisciplinary assessment
LUPROFS Lund Prospective Frontotemporal Dementia Study (LUPROFS)	Sweden Memory Clinics at Skåne University Hospital, Malmö/Lund, Sweden	Study: Longitudinal cohort, mixed retrospective and prospective data Aim: Initiated: 2008 Recruitment: Ended 2019	Adults (18 years old) with FTD and associated disorders and Healthy Controls	Significant medical disease impeding study participation, > 3 lacunar strokes or any number of other strokes, Current significant alcohol or substance misuse, Significant neurological or psychiatric comorbidity. CSF	Clinical history and examination, Caregiver history, Cognitive & neuropsychological testing, Bio samples: CSF, serum, plasma, +/- DNA, Imaging: MRI	According to the International Behavioral Variant FTD Consortium Criteria (Rascovsky et al., 2011) following multidisciplinary assessment

				biomarker analysis strongly suggestive of AD. Inability to speak and understand Swedish		
FTD @ UCL/ LIFTD The Longitudinal Investigation of FTD study (Z6364106/2015/12/52)	UK National Hospital for Neurology and Neurosurgery specialist cognitive disorders clinic in London, United Kingdom	Study: Longitudinal cohort, mixed retrospective, and prospective Aim: to develop biomarkers of disease onset and progression, thus allowing the tracking of sporadic FTD over time and forming outcome measures for clinical trials Initiated: 2008 Recruitment: Ongoing	Adults (18 years old) with FTD + Healthy Controls	Significant neurological or psychiatric comorbidity.	Clinical history and examination, Caregiver history, Cognitive & neuropsychological testing, Bio samples: CSF, serum, plasma, DNA Imaging: MRI	According to the International Behavioral Variant FTD Consortium Criteria (Rascovsky et al., 2011) following multidisciplinary assessment
Empathy in FTD	Sweden Memory Clinics at Skåne University Hospital, Malmö/Lund, Norrlands University Hospital, Umeå and Karolinska University Hospital, Huddinge,	Study: Cross sectional Aim: to explore of social cognition in FTD Initiated: 2016 Recruitment: Ended 2022	Adults (18 years old) with FTD + Healthy Controls	Significant medical disease impeding study participation, CDR >1, > 3 lacunar strokes or any number of other strokes, Current significant alcohol or substance misuse, Significant neurological or psychiatric comorbidity. CSF biomarker analysis strongly suggestive of AD. Inability to speak and understand Swedish.	Clinical history and examination, Caregiver history, Cognitive & neuropsychological testing, Bio samples: CSF, serum, plasma, +/- DNA, Imaging: MRI	According to the International Behavioral Variant FTD Consortium Criteria (Rascovsky et al., 2011) following multidisciplinary assessment

Abbreviations: Alzheimer's Disease; ALS, Amyotrophic Lateral Sclerosis; BioFINDER 2, The Swedish BioFINDER-2 Study; bvFTD, Behavioural Variant Frontotemporal Dementia; CBD, Corticobasal Degeneration; CBS, Corticobasal Syndrome; CDR, Clinical Dementia Rating; CJD, Creutzfeldt-Jakob Disease; CSF, Cerebrospinal Fluid; DLB, Dementia with Lewy Bodies; DNA, Deoxyribonucleic Acid; EEG, Electroencephalography; FDG PET, Fludeoxyglucose F18 Positron Emission Tomography; FTDC, Frontotemporal Dementia Clinic; FTD, Frontotemporal Dementia; FTD@UCL/LIFTD, The Longitudinal Investigation of FTD Study; FTLD-CDR, Frontotemporal Lobar Degeneration-modified Clinical Dementia Rating; GENFI, The Genetic Frontotemporal Dementia Initiative; HC, Healthy Controls; LIFTD, Longitudinal Investigation of FTD; LP, Lumbar Puncture; LUPROFS, Lund Prospective Frontotemporal Dementia Study; MCI, Mild Cognitive Impairment; MRI, Magnetic Resonance Imaging; MSA, Multiple System Atrophy; nfvPPA, Non-fluent Variant Primary Progressive Aphasia; PCA, Posterior Cortical Atrophy; PD, Parkinson's Disease; PDD, Parkinson's Disease Dementia; Penn FTDC, The Penn Frontotemporal Dementia Neurology Clinic; PET, Positron Emission Tomography; PPA, Primary Progressive Aphasia; PSP, Progressive Supranuclear Palsy; rs-fMRI, Resting State Functional Magnetic Resonance Imaging; SCD, Subjective Cognitive Decline; svPPA, Semantic Variant Primary Progressive Aphasia; UCL, University College London; UNICORN, University of Pennsylvania Centralized Observational Research Repository on Neurodegenerative Disease; VaD, Vascular Dementia.

4.2. Summary of study methodology

An overview of the methodology employed in Studies I-IV is outlined below in **Table 5.** For a more comprehensive description the reader is referred to the studies and their supplementary material which are published in full in the appendices.

Table 5. Summary of methods

Study	N	Study settings	Study design	Procedures	Outcomes	Statistical Analysis
I	307 (sporadic bvFTD 105, AD 92, HC 110)	LUPROFS (Sweden), Bio-FINDER 2 (Sweden), Empathy in FTD (Sweden), FTD@UCL /LIFTD (UK)	Cross-sectional study	Structural T1-MRI	PCS frequency Interhemispheric PCS asymmetry PCS pattern AAO (in bvFTD)	Chi-squared test, McNamar's chi-squared test, t-test, Linear regression
II	186 sporadic bvFTD	Penn FTDC (USA), Amsterdam Dementia Cohort (Netherlands)	Retrospective analysis	Structural T1-MRI	AAO Disease Progression (FTLD-CDR) Survival Cortical Atrophy Local gyrification Index	t-test, Linear regression, Pearson's correlation, Linear mixed effects models, Kaplan-Meier, Cox proportional-hazard regression
III	129 HC	Bio-FINDER 2 (Sweden)	Cross-sectional study	Structural T1 and Diffusion-weighted MRI rs-fMRI	Structural connectivity (tract segmentation analysis) Functional connectivity (rs-fMRI)	General linear models, Pearson's correlation
IV	583 (genetic bvFTD; 122 *C9orf72*, 100 *GRN*, 88 *MAPT and* 273 HC)	GENFI (Multi-centre, International)	Retrospective analysis	Structural T1-MRI	PCS frequency AAO Disease Progression (FTLD-CDR)	Chi-squared test, t-tests, Binomial tests General linear models, Linear mixed-effects models

Abbreviations: bvFTD, behavioural variant frontotemporal dementia; AD, Alzheimer's disease; HC, healthy controls; *C9orf72*, Chromosome 9 Open Reading Frame 72; *GRN*, Granulin; *MAPT*, Microtubule-Associated Protein Tau; LUPROFS, Lund Prospective Frontotemporal Dementia Study; BioFINDER 2, The Swedish BioFINDER-2 study; FTD@UCL/LIFTD, The Longitudinal Investigation of FTD study; Penn FTDC, The Penn Frontotemporal Dementia Centre; GENFI, The Genetic Frontotemporal Dementia Initiative; MRI, magnetic ressonance imaging; rs-fMRI, resting state functional MRI, PCS, paracingulate sulcus, AAO, age at onset; FTLD-CDR, Frontotemporal Lobar Degeneration-modified Clinical Dementia Rating.

4.3. Paracingulate sulcus identification and classification

The PCS may be identified neuroradiologically, *in vivo* through manual examination of T1-weighted MRI data. As such, high-resolution whole brain volumetric MRI data was obtained from all participants from each of the contributing cohorts. In order to optimise reliability between our studies we developed a standardised protocol for the measurement and classification of the PCS, based on Garrison's established method (Garrison, Fernyhough, McCarthy-Jones, Haggard, & Simons, 2015). Reliability studies were performed using this protocol with test MRI data from healthy controls. In these studies, our protocol achieved an intra-rater agreement of 98.33%, Cohens Kappa 0.96 and an inter-rater agreement of 94.44%, Cohens Kappa 0.85. For a comprehensive protocol description, the reader is referred to the supplementary material of the presented studies in this thesis, published in the appendices. Briefly, participants sagittal T1 imaging data were examined bilaterally, approximately 4mm lateral to the midline for potential hemispheric PCS presence. Where present the PCS was located as the sulcus running predominantly horizontal, dorsal, and parallel to the cingulate sulcus (CS). Measurement was performed from the sulcus' anterior limit, defined as the point at which the sulcus begins to extend posteriorly and parallel to the CS from an imaginary line perpendicular to the anterior commissure (AC) – posterior commissure (PC) line (M. Yücel et al., 2001). The endpoint of the PCS was defined as the point where the sulcus was interrupted by a distinct, predominantly vertical gyri considered non-PCS in nature. The PCS must originate within the first (top left) quadrant on a sagittal plane where $x = 0$, $y = 0$ marks the point of the AC. The PCS may however extend beyond the first quadrant. A minimum sulcal depth was required in order to satisfy criteria, whereby the PCS must be appreciable on at least four consecutive sagittal slices (equivalent to a total depth of $\geq$ 4mm) to be considered present. PCS measurement was performed on the sagittal slice where the anteroposterior PCS length was shortest of the four longest consecutive sagittal slices where the PCS was identifiable. PCS were classified in a binary fashion according to length as "present" ($\geq$20 mm) or "absent" (<20 mm), as is standard amongst established PCS classification protocols (Del Maschio et al., 2019; J. R. Garrison et al., 2015; Le Provost et al., 2003; Ono, Kubik, & Abernathey, 1990; M. Yücel et al., 2002). Sulcation ratings were performed by two blinded raters, LH and AS and rater disagreement was resolved by consensus consistently throughout all studies. For a critical discussion of this methodology please refer to section 6.2.1.

Figure 9. Paracingulate Sulcus Measurement and Classification
62-year-old male with probable behavioral variant frontotemporal dementia displays a Leftward pattern of paracingulate asymmetry. A. Sagittal slice (left) of the left hemisphere 3mm left of the midsagittal line displaying a left paracingulate sulcus (PCS) (red), length ≥20mm and a cingulate sulcus (CS) (green). B. Sagittal slice (left) of the right hemisphere 3mm right of the midsagittal line displaying an CS (green) with absence of a right PCS.

5. Results

The main results of the included studies are described here. For a more comprehensive report including results of additional and sensitivity analyses please see the individual articles and supplementary material, published in the appendices.

5.1. Study I

	Analysis	**N**	**Result**
Primary Analysis	Left PCS frequency in sporadic-bvFTD, AD and HC	307 (sporadic-bvFTD 105, AD 92, HC 110)	Similar left hemisphere paracingulate sulcal frequencies of 0.72, 0.79 and 0.70 were observed in sporadic-bvFTD, AD and HC respectively, (χ^2 = 2.38, p = 0.30).
Secondary Analyses	Right PCS frequency in sporadic-bvFTD, AD and HC	307 (sporadic-bvFTD 105, AD 92, HC 110)	Similar right hemisphere paracingulate sulcal frequencies of 0.57, 0.61 and 0.57 were observed in sporadic-bvFTD, AD and HC respectively, (χ^2 = 0.36, p = 0.84).
	Interhemispheric PCS asymmetry in sporadic-bvFTD, AD and HC	307 (sporadic-bvFTD 105, AD 92, HC 110)	A leftward asymmetry of PCS presence was observed in all groups with the following indices sporadic-bvFTD; 2.0 AD; 2.7 and HC; 1.78, p = 0.67.
	The association between PCS presence and AAO in sporadic-bvFTD	105 sporadic-bvFTD	The mean AAO was 3.39 years later in individuals with a present right PCS (63.77 years) than in individuals with an absent right PCS (60.38 years), (*t* = -2.09, *df* = 88.64, p = 0.039, Cohen's *d* = 0.42). A similar AAO was observed in individuals with a present (62.17 years) and absent (62.72 years) left PCS, (Mean difference 0.55 years, *t* = 0.34, *df* = 62.0, p = 0.74, Cohen's *d* = 0.07).

5.2. Study II

	Analysis	N	Result
Primary Analysis	The association between right PCS presence and AAO in sporadic-bvFTD	186 sporadic -bvFTD	Mean AAO was 2.44 years later (Cohen's d = 0.29, 95% confidence interval (CI) [0.41, ∞], p = 0.02, one-sided) in individuals with a present (mean AAO 60.20 years) versus absent right PCS (57.76). A one-sided univariate linear regression model identified a significant association between right PCS presence and AAO, (β = 2.44, p = 0.03). This result was retained in a one-sided multivariate model, adjusting for sex and education, (β = 2.20, p = 0.04).
Secondary Analyses	The association between right PCS presence and disease progression in sporadic-bvFTD	44 sporadic -bvFTD	Individuals with FTLD-CDR data were followed for a median of 15.83 months. FTLD-CDR sum of boxes and global scores at baseline were similar in individuals with present and absent right PCS after adjusting for age, sex, and education, (β = -1.02, CI [-2.30–0.27], p = 0.12 and β=-0.24, CI [-0.16–1.89], p = 0.1, respectively). In a linear mixed effects model with fixed effects for age, sex and education, there was a non-significant increase in the rate of clinical disease progression in individuals possessing a right PCS, (FTLD-CDR sum of boxes; β = 0.26, CI [-0.79-1.32], p = 0.63 and FTLD-CDR global score; β = 0.09, CI [-0.11-0.29], p = 0.37).
	The association between right PCS presence and survival in sporadic-bvFTD	185 sporadic -bvFTD	Individuals were followed for a median of 7.71 years (Interquartile range 5.00–10.87). Mean age at death was similar in individuals with present (66.94 years, (Standard deviation (SD) 9.66) and absent (67.62, (7.38)) right PCS, p = 0.7. Survival was significantly affected by right PCS presence, (χ^2 = 6.6, p = 0.01). The unadjusted risk of death per year after AAO was 65.1% greater in individuals possessing a right PCS (Hazard ratio (HR) 1.65, CI [1.13-2.42], p = 0.01). Risk of death increased to 83% following correction for baseline FTLD-CDR, AAO, sex, and years of education (n = 130, HR 1.83, CI [1.09 - 3.07], p = 0.02).
	The association between right PCS presence and cortical thickness in sporadic-bvFTD	176 sporadic -bvFTD	Individuals were at a similar clinical disease stage at time of MRI imaging, with no association identified between baseline FTLD-CDR Sum of boxes scores and right PCS presence, corrected for time from MRI imaging to CDR-FTLD scoring (β = -0.71, CI [-1.99-0.57], p = 0.27). Twenty-three regions were initially identified with significant differences in cortical thickness according to right PCS presence. All however failed to survive cluster correction for multiple analysis.

5.3. Study III

	Analysis	N	Result
Primary Analyses	The association between ipsilateral PCS presence and local structural connectivity	125 HC	Using the TractSeg method individuals with a present left PCS displayed reduced structural organisation of the cingulum, evidenced by a lower Fractional Anisotropy (FA) (β = -0.02, CI -0.01 – -0.0008 µm2/ms, p = 0.02) than that observed in individuals with an absent left PCS. Using the Xtract method where the cingulum is sub-divided into three divisions the greatest structural disorganisation was observed in the peri-genual cingulum (CBG). Here presence of a left PCS was associated with decreased FA in the ipsilateral CBG (β = -0.009, CI -0.04 – -0.008 µm2/ms, p = 0.002). Furthermore increased Radial Diffusivity (RD) (β = 2.22 x10-5, CI 7.58e-06 – 3.69e-05 µm2/ms, p = 0.003) and tract volume (β = 0.10, CI 0.02 – 0.18 µm2/ms, p = 0.012) was identified in the CBG in individuals with a present left PCS, indicating increased diffusion perpendicular to the principal diffusion direction and increased U-fibre presence. Reduced tract organisation, indicated by lower FA was also identified in the left dorsal cingulum in the presence of an ipsilateral PCS (β = - 0.009, CI -0.02 – -0.0009 µm2/ms, p = 0.03). RD and tract volumes were however similar in this tract. In the offsite left temporal cingulum, left PCS presence was not associated with altered FA or tract volume. There were however small but significant increases in mean diffusivity (β = 1.6e-05, p = 0.04) and RD (β = 1.6e-05, p = 0.04) in the temporal cingulum in individuals with a present PCS relative to individuals with an absent PCS.
	The association between ipsilateral PCS presence and functional connectivity	129 HC	Group wise intra-network resting state functional connectivity (rsFC) in ipsilateral hemispheric and whole brain analyses of all predefined salience, default mode and visual networks were similar when comparing individuals with a present and absent left and right PCS. A significant component representing a dispersed functional network was identified in individuals with an absent left PCS relative to individuals with a present left PCS at p = 0.01, controlling for family wise error rate. The greatest link density was found converging on the left anterior cingulate gyrus, extending inferiorly towards the frontal medial orbitofrontal gyrus and the right anterior cingulate gyrus. More extended connections were also found to the frontal superior medial gyrus, the left and right posterior cingulate gyrus, as well as scattered connections to subcortical structures including the left amygdala, the right posterior hippocampus, and left thalamus.

5.4. Study IV

	Analysis	N	Result
Primary Analyses	PCS frequency in genetic-bvFTD	583 (genetic-bvFTD: *C9orf72* 122, *GRN* 100, *MAPT* 88. HC 273)	Similar left and right PCS frequencies were observed between non-mutation and mutation carriers in all genetic groups: *C9orf72* *C9orf72* (left: χ^2 = 3.21, p = 0.07, right: χ^2 = 0.72, p = 0.4), *GRN* (left: χ^2 = 3.21, p = 0.07, right: χ^2 = 1.27, p = 0.26) and *MAPT* (left: χ^2 = 3.04, p = 0.08, right: χ^2 = 0.13, p = 0.72). Left and right PCS frequencies were similar between mutation carriers of each genetic group (left: χ^2 = 0.04, p = 0.98, right: χ^2 = 3.59, p = 0.17).
	The association between PCS presence and AAO in genetic-bvFTD	189 (genetic-bvFTD: *C9orf72* 110, *GRN* 45, *MAPT* 34)	The presence of a right PCS was not significantly associated with AAO after controlling for sex, education, and family membership in mutation carriers, when analysed as a single group (β = -0.39, CI [-2.73 – 1.94], p = 0.74). When genetic groups were analysed individually presence of a right PCS was associated with a significantly later AAO in the *GRN* group, (β = 5.25, CI [0.16, ∞], p = 0.045, one-sided). Right PCS presence was not associated with AAO in the *C9orf72* (β = -1.70, CI [-4.68 – 1.28], p = 0.26) or *MAPT* (β = -1.73, [-6.15 – 2.58], p = 0.43) groups.
Secondary Analyses	The association between PCS presence and disease progression in genetic-bvFTD	189 (genetic-bvFTD: *C9orf72* 110, *GRN* 45, *MAPT* 34)	Individuals were followed for a median of 2.16 years after symptom onset. After adjusting for education, sex and baseline age, CDR® plus NACC FTLD sum of boxes at baseline were similar in individuals with present and absent right PCS in mutation carriers when analysed collectively (β = 0.77, CI [-1.31–2.85], p = 0.47) and in individual gene groups (*C9orf72* (β = 0.15, CI [-2.69–2.99], p = 0.92); *GRN* (β = 1.01, CI [-3.38–5.41], p = 0.64); *MAPT* (β = 4.00, CI [-2.19–10.19], p =0.19). After adjusting for the fixed effects of education, sex and baseline age and the random effects of family membership, right PCS presence did not significantly alter the rate of clinical disease progression, according to the CDR® plus NACC FTLD sum of boxes in either the entire carrier cohort (β = -0.05, CI [-0.63–0.53], p = 0.86) or individual genetic groups (*C9orf72* (β = -0.20, CI [-0.94–0.53], p = 0.59); *GRN* (β = -0.75, CI [-3.43–1.85], p = 0.57); *MAPT* (β = -0.46, CI [-0.68-9.66], p = 0.42). Post-hoc analysis following the identification of two latent-classes, identified that *GRN* individuals with lower baseline disease severity who possessed a right PCS progressed quicker than *GRN* individuals in the same class with an absent right PCS (β = 0.82, CI [0.24-1.41], p = 0.008)

6. Discussion

6.1. Results in context and future prospects

The studies presented in this work investigated the impact of a neurodevelopmental property, determined during gestation, namely the hemispheric presence of a paracingulate sulcus on a neurodegenerative disease, bvFTD. In this endeavour the frequency of PCS presence and its effect on disease expression and progression were studied in populations of sporadic (Study I & II) and genetic (Study IV) bvFTD. Additionally, the impact of PCS presence on survival was studied in sporadic bvFTD (Study II). In parallel the impact of PCS presence on structural and functional connectivity was studied in a healthy population (Study III).

6.1.1. PCS frequency in bvFTD

As reported in healthy individuals (Le Provost et al., 2003; T. Paus et al., 1996; M. Yücel et al., 2001; M. Yücel et al., 2002), a leftward dominance of PCS presence was identified consistently across all studied populations of sporadic and genetic bvFTD.

In appropriately powered studies with pre-registered primary aims, individuals with sporadic bvFTD exhibited similar PCS frequencies to those of healthy individuals and AD (Study I). Correspondingly, hemispheric PCS frequencies were similar in gene mutation carriers and non-carriers (Study IV). Furthermore, we did not identify a difference in PCS frequency between *C9orf72*, *GRN* and *MAPT* mutation carriers.

Whilst neurodevelopmental consequences of dominantly inherited genetic mutations causative of FTD have been reported with respect to structural intracranial properties, including brain (Finger et al., 2023; Bertrand et al., 2018) and intraventricular (Tavares et al., 2019) volumes, this does not appear to be the case for PCS development. Moreover, we do not find evidence to contradict the notion that PCS development is under predominantly environmental control, as suggested by Amiez et al 2018 (Céline Amiez et al., 2018), discussed in section 2.5.1. Furthermore, results from Studies I, II and IV are not concordant with findings in schizophrenia where the leftward dominance of PCS presence observed in healthy

individuals is either lost or significantly reduced (Fujiwara et al., 2007; Le Provost et al., 2003; Marquardt et al., 2005; M. Yücel et al., 2002; Murat Yücel et al., 2003).

6.1.2. The impact of PCS presence on sporadic bvFTD

In sporadic FTD, an association between the presence of a right paracingulate sulcus and a later age at onset was demonstrated initially in a pre-registered secondary analysis of Study I. This result was subsequently replicated in Study II in a novel, adequately powered cohort designed with the primary aim of exploring this association. Importantly, we demonstrated this effect to be independent of education and sex, variables which have independently been associated with cognitive reserve in FTD (Beyer et al., 2021; Maiovis et al., 2018; Perneczky et al., 2007; Enrico Premi et al., 2020; Premi et al., 2012) and bvFTD.(Borroni et al., 2009; Illan-Gala et al., 2021). In the context of bvFTD, a disease with an expected survival time from diagnosis of 8-10 years (Garcin et al., 2009), the magnitudes of the reported delay in AAO, (3.40 and 2.44 years in Study I & II, respectively) in individuals with a present right paracingulate sulcus are considered clinically meaningful.

Longitudinal analysis of clinical disease progression did not reach statistical significance in Study II, possibly due to underpowering. However, the direction of the observed result may indicate accelerated disease progression following AAO in individuals with a present right PCS. Relatedly, presence of a right PCS was associated with significantly worse survival in sporadic bvFTD following AAO in Study II. These results are suggestive of a prognostic implication of right PCS presence in sporadic bvFTD but require replication in an appropriately powered cohort.

Collectively results from Study I and II identify that neurodevelopmentally derived gyrification in a region with a predilection to early and extensive pathological insult in bvFTD provides resilience to disease expression and possibly influences disease progression and survival. These findings have important consequences; they develop our understanding of the natural history of sporadic bvFTD, provide evidence for the first proxy of brain reserve in FTD, and elucidate a link between neurodevelopmental variability and the expression of a neurodegenerative disease. Notably, neurodevelopment, at least in this period, is a phenomenon that has not been previously associated with a neurodegenerative disease.

This perspective is important for future research, not only from a standpoint of scientific curiosity but also because accurately determining the age at onset is essential for optimising clinical trial design. These studies provide support for the inclusion of PCS presence in disease models and clinical trials of sporadic bvFTD.

6.1.3. The impact of PCS presence on genetic bvFTD

A statistically significant association between left and right PCS presence and AAO was not identified in the genetic bvFTD group when analysed collectively, or individually in *C9orf72* and *MAPT* carrier groups. In *GRN* gene mutation carriers however, presence of a right PCS was associated with a 4.93 year later AAO than that observed in those with an absent right PCS. The magnitude and direction of this result is similar to that which we report in sporadic bvFTD. There is plausible explanation for why this may be the case in *GRN* but not *C9orf72* or *MAPT* gene carriers with genetic bvFTD. Of important consideration, these genetic subtypes of FTD are associated with differing patterns of early neurodegeneration with variable AC engagement. *GRN* gene mutation carriers display predominant early frontal lobe atrophy (Simón-Sánchez et al., 2012), which is more pronounced than in the other genetic sub-types of bvFTD and closely resembles the pattern of atrophy observed in sporadic bvFTD (Sha et al., 2012). Furthermore, family membership explains a smaller degree of the variation in AAO in *GRN* mutation carriers (14%) compared to *MAPT* (66%) and to a much lesser extent, *C9orf72* (17%) carriers (Moore et al., 2020). It is therefore conceivable that in *GRN* carriers, where genetic factors have a lesser impact on AAO, developmental factors, such as the presence of a right PCS, play a more significant role. Despite the convincing magnitude of the later AAO observed in *GRN* mutation carriers possessing a right PCS and the demonstrated parallels with sporadic bvFTD replication of this analysis in a larger, appropriately powered *GRN* carrier cohort is indicated. Confirmation of these findings could have significant implications for the design of future therapeutic trials for bvFTD caused by *GRN* mutations. Although also underpowered, results from the AAO analyses in the *MAPT* and *C9orf72* gene groups did not indicate a delay in AAO for individuals with a right PCS and conversely a non-significant earlier AAO was observed in these gene groups.

Disease progression in genetic bvFTD was not associated with either left or right PCS presence, either when analysed collectively or by individual gene group. However, further post-hoc analysis identified two latent classes within the entire carrier cohort, differing primarily according to baseline disease severity. Among Class 2 *GRN* mutation carriers (with comparatively low baseline disease severity scores), individuals with a right PCS exhibited a significantly faster rate of disease progression compared to those in the same class with an absent right PCS, despite otherwise similar baseline characteristics. This finding considered alongside the AAO analysis is in keeping with results observed in sporadic bvFTD. Similar findings were not observed in Class 1 *GRN* mutation carries, who at study commencement were at a more advanced stage of their disease. At this phase, widespread neurodegeneration is expected, which we suggest may have diminished the impact of a localized, unilateral brain reserve proxy, namely, presence of a right PCS. Additionally, analyses in later disease phases are highly sensitive to attrition,

potentially biasing results and obscuring the identification of any effect of right PCS presence on disease progression in this class.

An obvious limitation of Study IV is its small sample size. The number of participants recruited fell short of pre-study power calculations, resulting in insufficient statistical power to reliably test hypotheses related to AAO and disease progression. Future work in this field should strive to accomplish a population satisfying this study's preregistered power calculations in order to conclusively test the impact of PCS presence on AAO and disease progression in genetic FTD.

6.1.4. Brain reserve

Brain reserve is a concept lacking a rigid biological definition. Instead, evidence is gathered by studying potential brain reserve proxies. Collectively, the results identified in Studies I, II and IV align with brain reserve theory and provide a body of evidence with which we propose that right PCS presence represents a proxy of brain reserve in sporadic bvFTD and *GRN* mutation carriers. Specifically, presence of a right PCS provides early resilience to bvFTD disease expression, evidenced by a later AAO in sporadic bvFTD (Study I and II) and *GRN* mutation carriers (Study IV). After which, compensatory reserve mechanisms become overwhelmed, and an accelerated rate of clinical decline is observed. This is reflected in the accelerated disease progression reported in sporadic bvFTD (as suggested by the results directionality, despite not establishing statistical significance), (Study II) and Class 2 GRN carriers (Study IV) as well as the poorer survival reported in sporadic bvFTD following AAO (Study II).

Albeit, somewhat contrary to this claim is the result of the atrophy analysis in sporadic bvFTD (Study II). Here similar levels of cortical atrophy were observed in individuals with present and absent right PCS despite similar levels of baseline clinical disease severity. In accordance with reserve theory, greater cortical atrophy was expected in this analysis in individuals possessing a right PCS, reflecting increased tolerance to disease burden. Notably, this this analysis was however subject to several methodological limitations and appropriate powering was not uncertain. Of importance, the model used in this analysis did not directly adjust for disease severity. Furthermore, a disconnect between cortical atrophy and clinical disease expression has been described in bvFTD (Davies et al., 2006; Devenney et al., 2015). As such, cortical thickness may not serve as a reliable proxy of pathological burden and applying this methodology may be ineffective in gathering evidence for brain reserve proxies in bvFTD. The natural expansion here would be to evaluate pathological burden with FDG-PET imaging or, as they become available, PET tracers targeting neuropathology.

6.1.5. The impact of paracingulate sulcation on structural and functional connectivity - the neurobiological substrate of brain reserve

The precise neurobiological substrate of brain reserve remains unknown, though is considered to be underpinned by a combination of contributing factors which may include; greater synaptic density, neurone quantity and brain size, as well as favourable metabolic properties and cerebral blood flow (Beyer et al., 2021; Maiovis et al., 2018; Perneczky et al., 2007; Placek et al., 2016). With evidence suggesting that the presence of a right PCS may serve as a proxy for brain reserve in bvFTD, Study III explored possible neurobiological mechanisms responsible for this function.

Structural connectivity

As discussed in section 2.3, gyrification is considered to reflect the density of structural connectivity in a given region. The degree of cortical folding is partially pathway-specific, dependent on mechanical tensions along axons, dendrites and glial processes connecting brain regions (Hilgetag & Barbas, 2006; Toro & Burnod, 2005; D. C. Van Essen, 1997, 2020; Welker, 1990). The impetus for this thesis stemmed from reports of a reduced leftward dominance of PCS presence in individuals with schizophrenia, which is considered to be a consequence of weaker or dysfunctional local AC connectivity, beginning during gestation (Le Provost et al., 2003). In Study III, we demonstrate that where a left PCS is present the ipsilateral cingulum bundle, specifically its anterior portions (peri-genual > dorsal), display increased orientational dispersion and in the most anterior portion of this bundle (the peri-genual cingulum), greater tract volume. We suggest that these findings are indicative of an increased density of short association or U-fibres, which connect adjacent gyri and display a complex orientation relative to neighbouring major long-white mater tracts, leading to increased gyrification. This suggestion is grounded by three principles: (1.) Inclusion of U-fibres in large tracts, referred to as a transverse inaccuracy contributes to increase the tract volume within a larger white matter tract and effect local diffusivity (Jbabdi & Johansen-Berg, 2011). (2.) U-fibres have lower orientational coherence resulting in lower fractional anisotropy (FA) values. Where U-fibres are incorporated into a major tract the overall orientational coherence becomes lessened resulting in a lower FA. (3.) U-fibres follow the pattern of cortical folding and as such are orientated perpendicularly to the axonal fibres of the cingulum bundle (Movahedian Attar et al., 2020). U-fibre orientation and microstructure may therefore contribute to the observed diffusivity matrices as water molecules diffuse more freely in a radial direction with respect to the cingulum bundle. **Figure 9** illustrates a schematic representation of these findings.

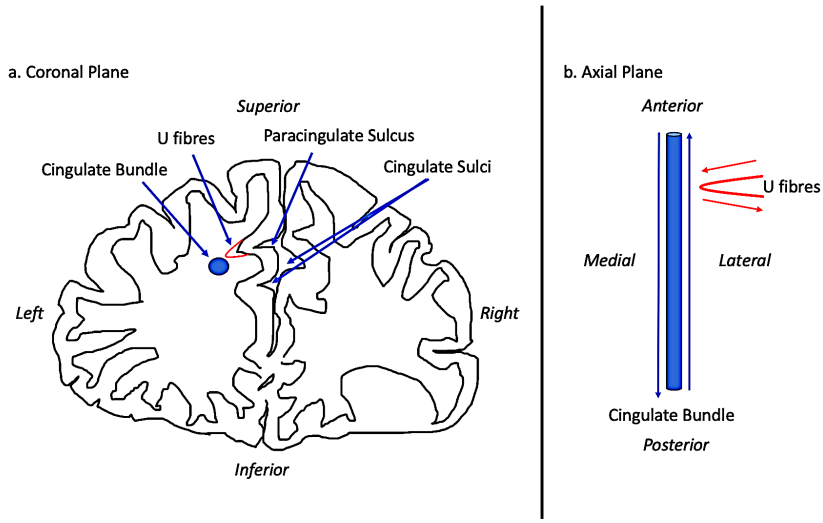

Figure 9. Panel (a) Schematic of a coronal cross-section of the frontal lobe of an individual with a present left and absent right paracingulate sulcus. The blue circle represents a cross-section of the cingulum bundle along its axis. Adjacent perpendicular U-fibres are represented in red and are thought to be partially responsible for gyrification and the formation of a paracingulate sulcus. In panel (b) the schematic is appreciated from an axial plane. The cingulate bundle is represented in blue with blue arrows representing the predominant axial transmission along the length of the bundle. U-fibres are represented in red with transmission along fibres represented by red arrows. Transmission along the cingulate bundle and adjacent U-fibres occur perpendicular to one another. Where there are increased U-fibres, such as in the presence of a paracingulate sulcus we may assume that U-fibres adjacent to the cingulate bundle may be attributed to the bundle increasing its volume and radial diffusivity whilst decreasing it's fractional anisotropy.

In the context of bvFTD and results reported in Studies I, II and IV, we suggest that presence of a right PCS in sporadic bvFTD and *GRN* mutation carriers with bvFTD may provide a greater density of local structural connectivity, underpinned by increased U-fibre density which in turn provides resilience to the effects of bvFTD neuropathology. Resultantly disease expression occurs comparatively later in individuals possessing a right PCS relative to those who do not. Following the accumulation of significant neurodegeneration however, (corresponding with phenoconversion) the protective effect of the PCS and increased U-fibre density becomes overwhelmed and following this point an accelerated rate of clinical disease progression occurs reflecting the more advanced stage of the disease at this point.

To the best of our knowledge this work is the first of its type and though indicative of U-fibre presence, determination may only be achieved through comprehensive assessment requiring ultra-high-resolution acquisitions as well as advanced imaging tractography methods specifically designed to identify and map U-fibres, which is indicated in future study. Perhaps less strenuously, further study may consider a

similar approach to that performed in Study III, however restricting analyses to a tract region of interest (ROI) overlapping the expected region of the PCS. Furthermore, standardised PCS classification criteria include sulci which overlap either the ACC, the MCC or both. Given these regions differ both cytoarchitecturally and functionally (Vogt, 2019; N. Palomero-Gallagher et al., 2009), further study may consider sub-classification of PCS according to their presence overlapping these regions.

Functional connectivity

In Study III an association between PCS presence and resting-state functional connectivity (rsFC) in predefined resting state networks (the SN, the DMN and the offsite visual network) was not identified using our seed-based rsfMRI approach in healthy individuals. We believe these negative findings may reflect our theory driven methodology in which network connectivity was analysed in accordance with parcellations corresponding to predefined networks mapped to Montreal Neurological Institute (MNI) space. Notably, this method was coarse and reliant on consistent network topography between source networks used to derive the predefined networks (which did not account for PCS presence) and networks of individuals in our cohort. Future seed-based study in this field may consider analysing network connectivity in networks derived directly form a voxel-based analysis.

In further analysis, using a voxel-based approach, presence of a left hemisphere PCS was shown to alter the functional architecture of resting-state connectivity in healthy individuals. Individuals with an absent PCS displayed a significant network component with greater rsFC, which was not present in individuals with a present left PCS and represented a more diffuse pattern of functional architecture. This component was comprised of the left and right anterior cingulate and frontal medial orbitofrontal gyrus with more extended connections to the left and right frontal superior medial gyrus and the posterior cingulum, as well as scattered connections to subcortical structures, the left amygdala, the right posterior hippocampus, and left thalamus. In this component distributed network nodes were enlisted creating an alternate specialisation profile with auxiliary processing power drawn from more distal regions outside of the anterior cingulate. We suggest that this dispersed network becomes operational where the PCS is absent and instead a highly localised network is presumed to exist where a PCS is present. As such, cognitive advantages reported in the literature (Borst et al., 2014b; A. Cachia et al., 2017; Alexander Fornito et al., 2004; Sarah Whittle et al., 2009) associated with the presence of a left PCS may be underpinned by an efficient highly localised network dependent on U-fibres. These observations are in line with the tension-based morphogenesis theory of gyrification (D. C. Van Essen, 1997) and support the notion that well interconnected brain regions display strong patterns of functional connectivity

(Segall et al., 2012; van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). Extending this concept to disease, we speculate that a highly connected localised network existing in the presence of a PCS may explain findings discussed above in bvFTD in Studies I, II and IV and inversely, why left PCS absence has been associated with both schizophrenia and obsessive-compulsive disorder (M. Yücel et al., 2002) (Shim et al., 2009).

The impact of sulcal morphology on rsFC has been explored previously. In the neighbouring ventromedial prefrontal cortex, Lopez-Persem et al 2019 report an impact of sulcal variability on rsFC topography (Lopez-Persem, Verhagen, Amiez, Petrides, & Sallet, 2019) and a correlation between ventromedial prefrontal cortex resting state activity and sulcal depth, with greater activity observed in the proximity of sulci, potentially representing a highly connected local network dependent on high U-fibre density. Fedeli et al 2020 explored rsFC with respect to PCS presence, similarly to the results presented in Study III, an association between individuals with absent PCS and enhanced long-distance rsFC was identified (D. Fedeli et al., 2020). Albeit, this connection was formed with the cerebellum, a region not identified as a highly connected region to the medial frontal lobe ROI used in our work and therefore not investigated further for connectivity differences according to PCS presence in the second part of our voxel-based analysis. Fedeli et al 2020 also reported associations between whole brain PCS patterns and distinct profiles of rsFC, indicating a functional effect of gyral variation. These results were however diffuse and lacked clarification. Employing a different methodology, Loh et al 2018 observed no association between paracingulate sulcal presence and rsFC in left hemisphere motor ROIs within the midcingulate (Loh et al., 2017). RsFC analysis in relation to whole brain PCS pattern was not performed in our work due to powering. Further study in this field should investigate this topic in order to identify if findings from Fedeli et al 2020 may be replicated. Furthermore, functional connectivity in relation to PCS presence may be studied further in sub-divisions of the AC, as described in the previous section.

Laterality

Cognitive functions including decision making and conflict monitoring, associated with salience network activity and typically impaired early in bvFTD are predominantly performed in the right hemisphere. (Lütcke & Frahm, 2008; Weiss et al., 2018). More broadly, social functioning is also considered predominantly right-lateralised, with substantial evidence supporting a right-hemispheric functional asymmetry of social processing (Brancucci, Lucci, Mazzatenta, & Tommasi, 2009; Borod et al., 1998; Chick, Rolle, Trivedi, Monuszko, & Etkin, 2020). This lateralisation is highly relevant to the symptomatology of bvFTD and aligns with the laterality of the findings reported in Studies I, II and IV.

In Study III, structural and functional connectivity differences were observed only in relation to left hemisphere PCS presence. In the context of the tension-based morphogenesis theory of gyrification, presence of a PCS would be expected to be associated with increased local ipsilateral U-fibre density in both hemispheres. Notably however, the findings we observe are subtle and importantly indirect indicators of U-fibre presence. Moreover, U-fibres are known to display an asymmetrical distribution, with greater structural integrity in the left hemisphere (Movahedian Attar et al., 2020). Given the subtlety of our findings and our approach to analysing structural connectivity it is understandable that we observe findings in the left but not the right hemisphere.

Lateralising findings were not identified in our seed-based functional connectivity analyses in predefined resting state networks in Study III. The salience network does however display lateralising qualities and is known to be organizationally dominant in the right hemisphere (Seeley et al., 2007; Y. Zhang et al., 2019) with multimodal structural and functional imaging studies (Cauda et al., 2011; Y. Zhang et al., 2019) (Seeley et al., 2007; Y. Zhang et al., 2019) identifying stronger and broader intrinsic functional network couplings in the right compared to left dorsal AC. Given this context, it is reasonable that the subtly altered network architecture observed in our functional connectivity analysis would be identified in the left hemisphere, where the network presumed to be impacted by PCS presence is less developed. Notably, the approaches used to analyse structural and functional connectivity in Study III have not been performed previously with respect to PCS presence and replication of this methodology is required in order to substantiate our findings. Finally, macroscopic sulcal variants are not limited to the PCS, several others have been described, including sulcogyral subtypes of the orbitofrontal (Nakamura, Nestor, & Shenton, 2020) and lateral prefrontal cortex (Laird et al., 2005; Tissier et al., 2018; Willbrand, Voorhies, Yao, Weiner, & Bunge, 2022). These anatomical variants have also been associated with cognitive performance and disease, yet they remain unstudied in FTD and present a possible area of future study.

6.2. Methodological considerations

Several methodological considerations are discussed within the study manuscripts contributing to this work, which may be found in the appendices of this thesis. More general considerations relevant to the overall work are presented below.

6.2.1. Reliability

Reliability refers to the consistency and stability of a measure or variable over time, which is essential for ensuring that observed differences in data are due to actual differences rather than measurement error.

Paracingulate sulcus measurement and classification

As discussed previously, there is variability between PCS identification and measurement protocols in the literature, restricting comparison of results between studies. In order to optimise reliability between the studies in this work a standardised protocol for the measurement and classification of the PCS was developed based on Garrison's established protocol (J. R. Garrison et al., 2015). This protocol was tested in reliability studies, achieving an intra-rater agreement of 98.33%, *Cohens Kappa* 0.96 and an inter-rater agreement of 94.44%, *Cohens Kappa* 0.85. To further enhance reliability, PCS sulci were rated is each study by two raters and inconsistency between rater classifications was discussed and resolved by consensus. Despite these considered efforts, methodological reliability was challenged by sulcal variability and the classification of ambiguous sulcal patterns. Whilst an exhaustive discussion of all ambiguous sulcal patterns is beyond the scope of this thesis, several frequently observed pattens presented classification difficulty are discussed below and depicted in **Figure 10**.

Broken or segmented PCS candidates

A number of potential PCS candidates were observed to be interrupted, "broken" or "segmented" along their length by predominantly vertical gyri, as has been described by Leonard et al 2009 (Leonard, Towler, Welcome, & Chiarello, 2009). Whilst many protocols advocate measuring and summing segments of these sulci (Garrison et al., 2019) our protocol stipulated that discontinuous PCS lacking an individual segment ≥20 mm in length should be classified as "absent". This criterion was included as attempts to classify segmented PCS candidates reduced inter and intra-rater reliability in pre-study training and created concern for false positive inclusion of non-PCS structures. It must however be acknowledged that this practice comes at the cost of reducing the sensitivity of PCS identification.

Short PCS candidates

As is standard amongst PCS classification protocols and included in our protocol, PCS presence is defined by a numeric cut-off. Where the anterior-posterior length is ≥ 20mm, the PCS candidate is classified as present, where it is < 20mm it classified as absent. In spite of this criteria, strong PCS candidates are frequently observed, whose macroscopic appearance and loci resemble that of a PCS but are not classified as such as they do not meet length criteria. This raises questions about what these "short" sulci (and their respective gyri) represent and how their presence effects structure, function, and disease. Defining length in this context is arbitrary, and using a continuous numeric cut-off to determine the existence of an inherently binary anatomical structure is methodologically questionable. Future refinements of PCS classification protocols should take this limitation into account.

Posterior PCS candidates, interruptions, and overlaps

The CS is frequently interrupted by rami projecting dorsally and caudally from the cingulate proper, referred to by Paus et al 1996 as "interruptions", and Leonard et al 2019 as "overlaps" (Tomáš Paus et al., 1996; Leonard et al., 2009). Whilst many PCS candidates originate in this manner, those which arise close to the anterior boarder of the second quadrant, which may be considered "posterior interruptions", or "rostral PCS" are of an intuitively more uncertain neurobiological origin. In our studies, these sulci were classified as PCS as they met protocol criteria.

Intralimbic or intracingulate sulci

An intralimbic or intracingulate sulcus is defined by Paus et al (T. Paus et al., 1996) as a shallow sulcus between the CS and the supracallosal sulcus. These sulci are however not always shallow and when deep and long can pose classification difficulties. In our work, consensus was reached that in cases where these sulci met depth criteria and the dorsal ramus was separated posteriorly from the cingulate gyrus proper (the ventral ramus) for ≥4 consecutive slices, the sulcus was classified as a PCS. Where this was not the case the sulci between the cingulate rami was determined to be intracingulate.

The approach to handling ambiguous sulcal formations in PCS classification protocols is important to future study. Reliable analysis requires that structures identified as a PCS are truly paracingulate in nature. As with the determination of all neuroanatomical features there is no clear gold standard, and it remains debatable whether priority should be given to macroscopic appearance, histology, or connectivity. Ideally, classification protocols would verify PCS candidates' neurobiology through advanced neuroimaging and post-mortem analyses. For individual studies however this approach is too labour-intensive. A more optimal solution would be to establish an international working group to develop a standardised PCS classification protocol, which could be validated

cytoarchitecturally and functionally. In the interim, studies in this field may consider sub-classifying ambiguous sulci and either analysing them as separate entities or excluding them from analyses, as performed by Del Maschio et al 2019 (Del Maschio et al., 2019). Whilst tightening protocol parameters in this manner might improve reliability and enhance both internal and external validity, it could also lead to false negative exclusion of true PCS and reduction of participant numbers, compromising statistical power. Revising our current protocol to account for the classification of all possible sulcal variabilities is again impractical. Instead, assuming the rater has a degree of familiarity with AC anatomy, the current protocol would benefit from introducing a degree of educated subjectivity, with two pragmatic additions; (1.) The PCS candidate should not be better accounted for by another sulcus, non-paracingulate in origin. (2.) The PCS should provide the dorsal border of an identifiable PCG.

In Study II, we attempted to identify PCS using an automated method in which gyrification over an AC ROI was used as a proxy of PCS presence. Although results of this analysis indicated that this method was unsuitable, further exploration of alternative automated methods of PCS identification is recommended. To account for cytoarchitectural and functional differences between the ACC and MCC, further study may consider segmenting and sub-classifying the PCS with respect to its position relative to the ACC and MCC. A vertical line traced at the anterior border of the genu of the corpus callosum has been proposed by Vogt et al 2003, as a practical anatomical landmark for creating sub-divisions which is clearly visible on sagittal MRI slices and could easily be incorporated into an MRI classification protocol. Determination of appropriate length cut-offs in this situation is however more difficult and will require careful consideration prior to application in study.

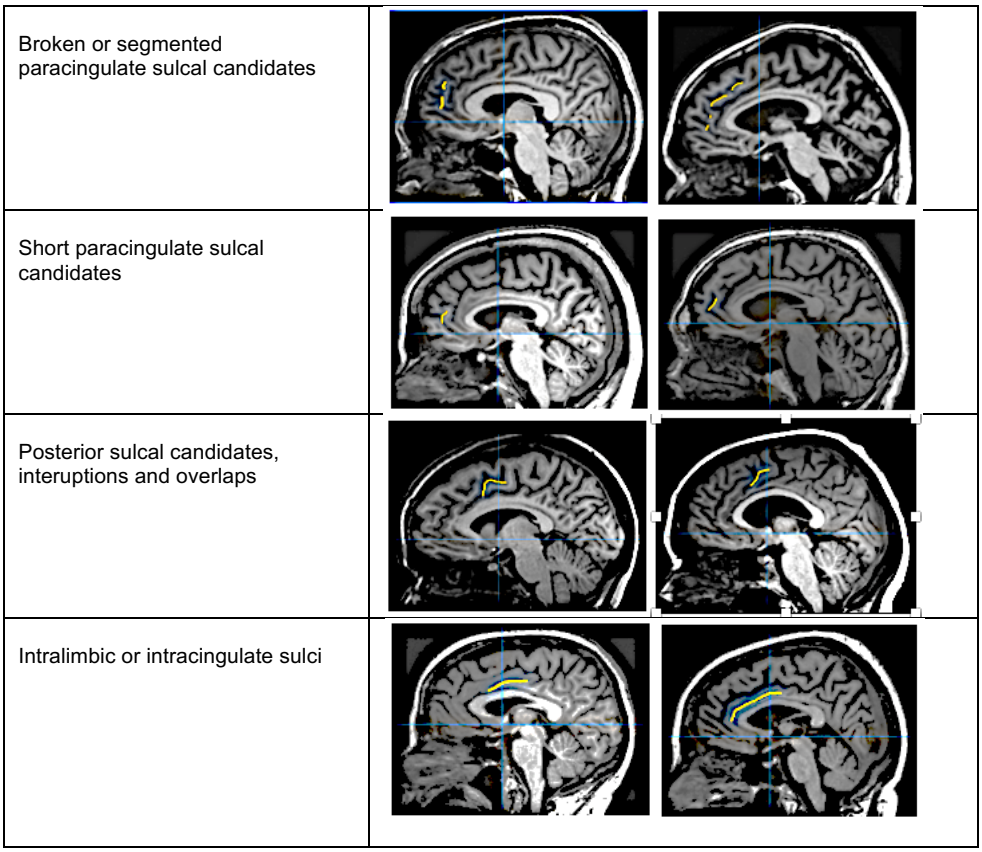

Figure 10. Ambiguous Sulci. Sagittal T1-weighted MRI slices of individuals displaying ambiguous sulci, traced in yellow.

6.2.2. Age at onset and disease progression

In studies I, II, and IV, AAO was determined retrospectively based predominantly on data collected from symptomatic study participants with bvFTD and their informants, typically a close relative. Asking a cognitively impaired individual, who, as a hallmark of their disease, may also lack insight, to report when their symptoms began has obvious limitations. Consequently, this process is highly reliant on informant reports. These reports are however susceptible to recall bias and rely on an informant, often a layperson, accurately identifying clinical symptoms of bvFTD at the earliest point in their development. A feat difficult even for a trained physician. Of further consideration, in Study IV, many individuals were aware that they belonged to a genetic FTD family, some of these individuals were also aware of their own genetic diagnosis. This knowledge may have influenced

interpretations of early symptoms and thereby AAO data. For these reasons, accurately identifying AAO in bvFTD is challenging. To enhance accuracy, strategies may include refinement of patient and informant interviews for symptomatic participants and neuropsychological assessments and digital monitoring of behaviour and motor features for pre-symptomatic carriers. Frequent longitudinal tracking of symptoms in pre-symptomatic carriers, along with increasing public and healthcare provider awareness of the clinical profile of bvFTD and refining consensus criteria also have important roles in increasing the accuracy of determining AAO. Most importantly, the field currently lacks objective disease fluid and imaging biomarkers for tracking onset and progression in FTD. Once established, biomarker cut-offs and quantification will likely capture more meaningful timepoints of disease onset and progression, relevant to both research and clinical intervention, which will surpass the limitations of relying on history taking to determine AAO.

Similar considerations apply to tracking disease progression in FTD as to assessing AAO. In studies II and IV disease progression was measured according to the CDR® plus NACC FTLD (T. Miyagawa et al., 2020), a disease staging tool which encompasses eight domains: memory, orientation, judgement, and problem solving, community affairs, home and hobbies, personal care, overall behaviour, and overall language. Each domain is scored on a scale from 0-3, allowing for both global and sum-of-domain scores to be calculated. Similarly to assessing AAO, this tool is reliant on semi-structured interviews with patients and informants. The information recoded is however cross-sectional, focusing on the patient's current condition rather than retrospective accounts, thus there is reduced risk of recall bias. In Europe and Canada disease progression is typically tracked according to the CDR® plus NACC FTLD. Meanwhile, in the USA the multidomain impairment rating (MIR) scale is beginning to be used more frequently and is favoured by the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study. The MIR combines the CDR® plus NACC FTLD with four additional domains: concentration/multitasking, visuospatial functioning, psychiatric features, and motor features. These additional domains aim to capture a fuller spectrum of the manifestations of FTLD disorders. High inter-rater reliability scores (intraclass correlation coefficient (ICC): > 0.8 for the CDR® plus NACC FTLD and > 0.9 for the MIR) have been achieved using both tools (T. Miyagawa et al., 2020) (Toji Miyagawa et al., 2024). In a recent unpublished head-to-head comparison, global MIR scores were reportedly greater than global CDR® plus NACC FTLD scores in 9% of individuals with FTD, mainly driven by motor dysfunction scores, which according to authors highlights the MIR's greater sensitivity to the full functional impact of FTD (Boeve, 2024). Selecting an accurate tool to evaluate disease stage and track clinical change is critical for FTD trials. At present there is no established gold standard. A harmonised international tool for tracking disease severity and

progression in FTD in desirable and would facilitate cross-study comparison and global collaboration.

6.2.3. Pre-registration

Pre-registration is a process in which a research question and analysis plan are defined and submitted to a registry prior to observing outcomes (B. A. Nosek, Ebersole, DeHaven, & Mellor, 2018; Parsons et al., 2022). Pre-registrations are preserved within the register and made discoverable. This process aims to separate hypothesis-generating or postdictive (exploratory) research from hypothesis testing or predictive (confirmatory) research. In prediction, data are used to confront the possibility that the prediction is wrong. In postdiction, the data are already known and the postdiction is generated to explain observations (B. A. Nosek et al., 2018). In theory predictive research prevents overfitting of data, improves transparency, and increases the credibility of reported results. On the contrary, the concern with postdiction is that data may be explored, independent of a clear aim or hypothesis and results may be overconfidently reported. This approach reduces the diagnosticity of the null hypothesis significance test (and it's statistic, the P value), increases the rate of false positive reporting and reduces reproducibility (Swaen, Teggeler, & van Amelsvoort, 2001; B. A. Nosek et al., 2018). Furthermore, postdiction is liable to confirmation bias, in which evidence is extracted and reported where it provides a consistent explanation, whereas inconsistent evidence is neglected. Meanwhile, pre-registration encourages transparency in publication and is correlated with outcomes that suggest reduced publication and reporting biases (B. A. Nosek et al., 2018). Lastly, in competitive research environments pre-registration may facilitate early study ownership and prevent duplication.

In practice however, the rigor of prediction poses a number of challenges. Predictive research has a narrow focus, potentially limiting the discovery of important findings within data. Here, where there is opportunity to discover possibilities not yet considered or where there is little evidence available to create predictions, postdictive research has a critical role (B. A. Nosek et al., 2018). Furthermore, there are instances in predictive research where changes to procedure during study administration are necessary and times where pre-registered assumptions become violated during analysis. Additionally, pre-registration is somewhat time consuming and may lead to research delays. Finally, pre-registration is not infallible. In research undertaking multiple analyses, multiple pre-registrations may be made. This practice degrades the diagnosticity of the P value, falsely rendering explorative research predictive. It should also be noted that pre-registration does not eliminate the possibility of poor statistical practices nor is it able to control the narrative of the research report.

In line with European Union regulations (Commission, 2014), preregistration is a legal requirement in Sweden for clinical trials, other study types are not however

bound by this legislation. Of the studies presented in this thesis, studies I, II and IV were pre-registered, as documented in the methodology sections of these articles. Study III, by comparison was of a more explorative nature and therefore was not pre-registered, this should be considered in interpreting its results. For Studies I, II and IV, one pre-registration was created per study, the pre-registered analysis plans were followed as stringently as possible, all articles were written with a conscious attempt for their narrative to follow pre-registered primary aims and hypotheses and all studies have (or shall, Study IV) be published.

6.2.4. Replication

A replication analysis involves repeating a study's procedures using novel data and observing whether the prior finding recurs (B. Nosek & Errington, 2020; Schmidt, 2009). Replication serves to strengthen the confidence and credibility of scientific claims by providing evidence of their generalisability. Successful replication of a known result can also inform inferences about the external validity of a study's methodology. Replication is especially valuable where the theoretical explanation for a finding remains unclear. More pertinently, it's important to recognise that single studies never definitively confirm or disconfirm theories. Theories make predictions and replications test those predictions. The outcomes of replication studies then help refine, alter, or extend theory (B. Nosek & Errington, 2020).

In this thesis, a result identified in a secondary analysis in Study I, demonstrating a later AAO in individuals with sporadic bvFTD who possessed a right PCS, was successfully replicated in a novel cohort, as a primary analysis in Study II. This successful replication not only supports the generalisability of this finding but also increases confidence in both the result and the proposed neurobiological theory underlying it.

7. Erratum

In Study I, the bvFTD group consisted of 105 participants (2 Possible, **93** Probable (not 92, as stated) and 10 Definite bvFTD), 70 males, 35 females with a mean Age at scan (AAS) of 66.9 years (*SD* 8.15) and AAO of 62.2 (*SD* 8.23).

In Study II, Table 1. The number of bvFTD individuals meeting Probable bvFTD diagnostic classification criteria should read **141** (not 140, as stated) in the Entire population and 91 (not 90) in the Amsterdam Dementia Cohort.

In Study II, the risk of death was enhanced to 83% following correction for baseline FTLD-CDR, AAO, sex, and years of education (HR 1.83, CI [1.09 - 3.07], **p = 0.02**, (not *P* = 0.02, as stated).

In Study II, Figure 2, figure text. The n values have been confused. Red dots represent individuals with a present right paracingulate sulcus (PCS), n = **106** (not 80, as stated). Blue dots represent individuals with an absent right PCS, n = **80** (not 106).

In Study III. Participants were enrolled between **2017** (not 2014, as stated) and 2021.

8. Concluding remarks

This thesis examined the role of the paracingulate sulcus (PCS) in behavioural variant Frontotemporal Dementia (bvFTD). Specific aims included investigating the prevalence of the PCS in bvFTD, exploring associations between PCS presence and disease expression, progression, and survival, as well as studying the effects of PCS presence on cerebral structural and functional connectivity in a healthy population. To this end we show that hemispheric PCS frequencies in both sporadic and genetic bvFTD are similar to those of healthy individuals. Thus, PCS presence is not a risk factor for bvFTD. Across two independent studies, we demonstrate that presence of a right PCS is associated with a later AAO in sporadic bvFTD. In the second of these studies, we present evidence of an accelerated rate of disease progression and reduced survival following AAO in individuals with a right PCS. Collectively, these findings provide evidence for the first proxy of brain reserve in FTD and establish a novel association between intrauterine neurodevelopment and the expression of a neurodegenerative disease – an insight with potential implications for future clinical trials in FTD. In genetic bvFTD, we report a later AAO in *GRN* mutation carriers possessing a right PCS and demonstrate accelerated early disease progression after AAO in a sub-group of these individuals. Lastly, we present evidence of an association between PCS presence and altered structural and functional connectivity, describing a novel link between structure and function and a plausible explanation of how the cognitive advantages of paracingulate sulcal presence may be mediated by a highly connected local functional network reliant on short association fibres.

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Appendices

Appendix I: Coding notes and Specifiers for Major Neurocognitive Disorders

Coding note: Code based on medical or substance etiology. An additional code indicating the etiological medical condition, if known, must immediately precede the diagnostic code for major NCD in most cases, as noted in the coding table on pp. 682–683. An additional code is not used for medical etiologies that are judged to be "possible" (i.e., major NCD due to possible Alzheimer's disease, due to possible frontotemporal degeneration, due to possible Lewy body disease, possibly due to vascular disease, possibly due to Parkinson's disease).
Specify current severity *(see coding table for details)*:
Mild: Difficulties with instrumental activities of daily living (e.g., housework, managing money).
Moderate: Difficulties with basic activities of daily living (e.g., feeding, dressing).
Severe: Fully dependent.
Specify (see coding table for details):
With agitation: If the cognitive disturbance is accompanied by clinically significant agitation.
With anxiety: If the cognitive disturbance is accompanied by clinically significant anxiety.
With mood symptoms: If the cognitive disturbance is accompanied by clinically significant mood symptoms (e.g., dysphoria, irritability, euphoria).
With psychotic disturbance: If the cognitive disturbance is accompanied by delusions or hallucinations.
With other behavioral or psychological disturbance: If the cognitive disturbance is accompanied by other clinically significant behavioral or psychological disturbance (e.g., apathy, aggression, disinhibition, disruptive behaviors or vocalizations, sleep or appetite/eating disturbance).
Without accompanying behavioral or psychological disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral or psychological disturbance.
Coding and Recording Procedures
The following are examples of coding and recording different types of major NCDs. In cases where there is more than one type of associated behavioral or psychological disturbance, each is coded separately. *(For more information, see coding table on pp. 682–683 and coding notes in the specific diagnostic criteria for each major and mild NCD subtype)*:
Major neurocognitive disorder due to probable Alzheimer's disease, mild, with anxiety: G30.9 Alzheimer's disease, **F02.A4** major neurocognitive disorder due to probable Alzheimer's disease, mild, with anxiety.
Major neurocognitive disorder due to possible Alzheimer's disease, moderate, with mood symptoms: F03.B3 major neurocognitive disorder due to possible Alzheimer's disease, moderate, with mood symptoms.
Major neurocognitive disorder due to traumatic brain injury, moderate, with psychotic disturbance and agitation: S06.2XAS diffuse traumatic brain injury with loss of consciousness of unspecified duration, sequela; **F02.B2** major neurocognitive disorder due to traumatic brain injury, moderate, with psychotic disturbance; **F02.B11** major neurocognitive disorder due to traumatic brain injury, moderate, with agitation.
Major neurocognitive disorder due to unknown etiology, severe, with mood symptoms: F03.C3 major neurocognitive disorder due to unknown etiology, severe, with mood symptoms.

Appendix II: Coding notes and Specifiers for Mild Neurocognitive Disorders

Coding note: Code based on medical or substance etiology. An additional code indicating the etiological medical condition must immediately precede the diagnostic code **F06.7z** for mild NCD due to a medical etiology. An additional code is not used for medical etiologies that are judged to be "possible" (i.e., mild NCD due to possible Alzheimer's disease, due to possible frontotemporal degeneration, due to possible Lewy body disease, possibly due to vascular disease, possibly due to Parkinson's disease). See coding table on pp. 682–683. For substance/medication-induced mild NCD, code based on type of substance; see "Substance/Medication-Induced Major or Mild Neurocognitive Disorder." *Note:* **G31.84** is used for mild NCD due to unknown etiology and for mild NCD due to a possible medical etiology (e.g., possible Alzheimer's disease); no additional code for medical or substance etiology is used.

Specify (see coding table for details):

Without behavioral disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.

With behavioral disturbance *(specify disturbance):* If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., apathy, agitation, anxiety, mood symptoms, psychotic disturbance, or other behavioral symptoms). **Coding note:** Use additional disorder code(s) to indicate clinically significant psychiatric symptoms due to the same medical condition causing the mild NCD (e.g., **F06.2** psychotic disorder due to traumatic brain injury, with delusions; **F06.32** depressive disorder due to HIV disease, with major depressive–like episode). **Note:** Mental disorders due to another medical condition are included with disorders with which they share phenomenology (e.g., for depressive disorders due to another medical condition, see the chapter "Depressive Disorders").

Coding and Recording Procedures

The following are examples of coding and recording different types of mild NCDs. *(For more information, see coding table on pp. 682–683 and coding notes in the specific diagnostic criteria for each major and mild NCD subtype)*:

Mild neurocognitive disorder due to probable Alzheimer's disease, without behavioral disturbance: G30.9 Alzheimer's disease, **F06.70** mild neurocognitive disorder due to probable Alzheimer's disease, without behavioral disturbance.

Mild neurocognitive disorder due to possible Alzheimer's disease, without behavioral disturbance: G31.84 mild neurocognitive disorder due to possible Alzheimer's disease, without behavioral disturbance.

Mild neurocognitive disorder due to traumatic brain injury, with behavioral disturbance: S06.2XAS diffuse traumatic brain injury with loss of consciousness of unspecified duration, sequela; **F06.71** mild neurocognitive disorder due to traumatic brain injury, with behavioral disturbance *[with the disturbance being depression]*; **F06.31** depressive disorder due to traumatic brain injury, with depressive features.

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