CHALLENGES IN PHENOTYPING THE FRONTOTEMPORAL DEMENTIA SUBTYPES

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Colofon

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CHALLENGES IN PHENOTYPING THE FRONTOTEMPORAL DEMENTIA SUBTYPES

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Frontotemporal dementia (FTD) is hard to learn, hard to understand, hard to teach, hard to explain, and therefore hard to phenotype.

My sincere thanks to everyone who is fighting against this devastating dementia type; the type that steals more than memory…

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION, AIMS, RESEARCH QUESTIONS AND OUTLINE

GENERAL INTRODUCTION

Where is my mind?

Although, over the years, several philosophers or ecclesiastics have used different definitions for "mind", its dictionary definition is; "*the part of a person that makes it possible for him or her to think, feel emotions, and understand things*" [1]. Perhaps the reason for several definitions of this mystical term is that this topic has always been popular and it has attracted the interest of not only scientists but also artists, novelists, philosophers, and ecclesiastics.

I wonder, would it impress us that much, if Edward Norton in Fight Club had a kidney disorder instead of psychosis or if Cervantes's Don Quixote was suffering from hepatitis. Furthermore, the entire ancient Greek tragedies cannot exist without this topic which creates all well-known eternal fictional characters. Perhaps the most reasonable answer to this question; "why are mental problems quite prominent in literature" might be that our precious minds make us unique, in other words; they make us "us". Therefore, inevitably, people have tried to understand the causes of the mental disorders and historically, they have found three major explanations, namely, supernatural, biological, and psychological [2]. Although, initially, our ancestors have considered that the only reason for all mental problems is the work of the devil [2], eventually, scientists have explored the mechanism of the mental disorders and currently, modern diagnostic criteria are used for identifying them [3, 4].

World health organization reports that the burden of mental disorders continues to grow with significant impacts on health and major social, human rights and economic consequences in all countries of the world and more than 700 million people are suffering from mental disorders [5]. In the elderly population, the most common mental illness is dementia and the most common dementia type is Alzheimer's disease (AD) including in both young and old onset dementias [5].

What if it is not Alzheimer's

AD is the most common cause of dementia [6], and the majority of dementia research has focused on AD. Therefore, in both society and the scientific world, the concept of dementia has become associated with AD [6]. With the focus on AD, amnesia has become the most accentuated symptom of dementia [7], whilst it is increasingly acknowledged that cognitive disorders including AD are not limited to amnesia. A major achievement is the addition of behaviour as a relevant domain to be involved in dementia [4].

According to epidemiological studies, frontotemporal dementia (FTD) is the second most common dementia type among young-onset dementias [8]. FTD is a neurodegenerative disorder that affects the frontal and temporal lobes of the brain. Presently, FTD encompasses clinical disorders that include changes mainly in behaviour, social cognition, language, and executive control [9], and currently, patients with predominant behavioural problems are classified under the term of behavioural variant frontotemporal dementia (bvFTD) [10], whereas patients who have language problems are diagnosed with primary progressive aphasia (PPA) [11]. The characteristic clinical features of bvFTD are disinhibition, loss of empathy, apathy, altered eating habits, compulsive-like ritualistic behaviours, and the neuropsychological profile is executive/generation deficits with relative sparing of memory and visuospatial functions [10]. In order to meet clinical criteria for a diagnosis of bvFTD, there needs to be a constellation of at least three core criteria fitting into those six categories, the patient needs to exhibit a significant functional decline and neuroimaging results must be consistent with bvFTD (usually bilateral predominant frontal/temporal atrophy on MRI or hypo-perfusion/ hypo-metabolism on PET/SPECT) [10].

PPA, on the other hand, is a group of neurodegenerative syndromes related with language problems and mostly related with the left frontotemporal areas [11]. The most recent clinical

research criteria for PPAs include semantic variant of PPA (svPPA), nonfluent/agramamtic variant of PPA (nfvPPA) and logopenic variant PPA (lvPPA) [11]. The classical symptom presentation of svPPA is single-word comprehension deficits and naming problems. The characteristic atrophy pattern of the syndrome is bilateral anterior temporal atrophy, most pronounced on the left side. Whereas patients with svPPA have comprehension problems but are mostly fluent in daily speech, nfvPPA patients have trouble with articulation and speech fluency. The effortful speech can be caused by agrammatism or apraxia of speech [12]. The radiological hallmark of the syndrome is atrophy of the left inferior frontal gyrus, traditionally Broca'sarea, Broadman's area 44, 45 [13]. Although, back in the 90's, due to stroke studies, there was a common analogy between Broca aphasia and nfvPPA, and Wernicke aphasia and svPPA, neurodegeneration focused studies have shown that the mechanism of the language problem in FTD is quite different [14-16] from stroke. For approximately 2 decades, PPAs were divided into semantic dementia and progressive non-fluent aphasia, although several PPA cases did not fit into this binary categorization [17]. The third type of variant that has been fluent with syntactically simple sentences but frequent word-finding pauses, repetition problems, and phonological paraphasias has been described and called lvPPA [11]. The radiological profile of the syndrome of atrophy at the left temporoparietal junction, including the left posterior superior and middle temporal gyri and inferior parietal lobule has also been identified [11, 17]. Another anatomical variant that does not fit the current classification has also been reported by a number of authors; the right temporal variant of frontotemporal dementia (rtvFTD) [18-25]. Behavioural problems, getting lost, memory deficit, prosopagnosia and hyper religiosity have been described as clinical features of the syndrome [18-25]. However, currently, there are no separate diagnostic criteria for the patients with right temporal atrophy and it has been considered as a rare variant of svPPA because it is a radiological counterpart of svPPA [11].

FTD is not a common disorder. A systematic review of 26 epidemiological studies has found that the prevalence of FTD is estimated to be 0.01 to 4.6 per 1000 persons, however, in persons under the age of 65, point prevalence has been in a narrower range (0.07-0.30 per 1000) [26]. In the same study, men and women have been found to be equally affected, and the diagnosis of bvFTD has been four times more prevalent than the language variant frontotemporal dementias, currently known as PPA diagnosis [26]. Of note, a recent study has shown that in the sporadic bvFTD subgroup, males were predominant in contrast to genetic bvFTD (61.6% versus 52.9% males, p=0.04) whereas in the nfvPPA, svPPA and rtvFTD subgroups, genetic cases were underrepresented and within the sporadic cases the sex distribution was equal[27]. Surveillance of FTD in the population is difficult because there are several hurdles in the diagnosis. Perhaps the most important one is that FTD shares many behavioural symptoms with primary psychiatric disorders (PPD) and due to lack of biological biomarkers, psychiatric misdiagnosis is quite common [28].

While FTD encompasses the clinical presentations, the term frontotemporal lobar degeneration (FTLD) is used for pathological conditions that present as clinical FTD or FTD-related disorders such as FTD-amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS) [29]. With previous discoveries, the FTLDs have been classified into four main groups based on the major protein accumulation in the brain: tau protein (FTLD-tau); TAR DNA-binding protein 43 (FTLD-TDP); ubiquitin-positive, TDP-43 negative, and immune stains positive for the fused in sarcoma protein (FTLD-FUS); and a rest group encompassing the remaining few cases characterized by inclusions that label only for markers of the ubiquitin-proteasome system (FTLD-UPS) [30]. Based on the morphology and cortical distribution of the accumulation, these pathological groups are divided into subgroups such as; Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), argyrophilic grain disease (AGD), globular glial tauopathy (GGT) and FTD caused by

microtubule association protein tau (MAPT) for FTLD-tau [30, 31] and the subtypes A, B, C, D and E for FTLD-TDP [32]. Additionally, over the past years, the genetics of FTD have been broadly explored. An autosomal dominant inheritance pattern has been described in 20-30% of all FTD patients [33], most frequently caused by pathogenic variants in the microtubule associated protein tau gene (*MAPT)* and the progranulin gene (*GRN*) or by a hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 gene (*C9ORF72)*and followed by other more rare genes such as valosin-containing protein (*VCP*), chromatin-modifying protein 2B (*CHMP2B*), fused in sarcoma (*FUS*), TAR DNA binding protein (*TARDBP*), TANK binding kinase 1 (*TBK1),* sequestosome 1 *(SQSTM1),* Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10 *(CHCHD10),* optineurin (*OPTN),* cyclin F *(CCNF)* and T-cell-restricted intracellular antigen-1 *(TIA1*) [34]. The autosomal dominant inheritance pattern has been found higher in bvFTD, whereas semantic variant PPA (svPPA) is typically a non-familial sporadic disease [33-35]. Additionally, while the underlying pathologies are heterogeneous in bvFTD, a strong clinicopathological concordance with the underlying FTLD-TDP type C pathology is present in svPPA [36]. These discoveries have provided important contributions to the FTD field. Moreover, they have become a part of the current diagnostic criteria [10, 11]. In order to meet "the definite FTD", either histopathological evidence of FTLD or a known pathogenic mutation must be present. This discrimination is quite important, for instance, while lvPPA is clinically an FTD syndrome [11], since the underlying pathology is related to Alzheimer's disease [37], it has not been considered as an FTLD syndrome [30].

Challenges in phenotyping the FTD subtypes

Phenotyping mental health disorders have always been a real challenge because it must be done purely based on symptoms that are largely self-reported. Every patient with mental problems presents with a range of physical, behavioural, emotional, cognitive and social symptoms that are collected together to diagnose into a "best fit" strategy that will ultimately determine

treatment. An immense amount of investment goes into descriptive diagnosis manuals such as DSM for PPD [38], McKhann criteria for AD [4], Rascovsky criteria for bvFTD [10] and GornoTempini criteria for PPAs [10]. After the discovery of amyloid biomarkers, the diagnosis of AD became more reliable whereas it is quite hard to get an accurate diagnosis for a considerable number of patients with FTD, due to lack of specific biomarkers.

The idea of trying to fit patients into a list of potential diagnostic criteria brings along several problems such as ignoring accompanying symptoms. For example, since FTD is a neurological entity, if the behavioural disturbance is better accounted for by a psychiatric diagnosis, this is considered an exclusion criterion for bvFTD [10]. However, the question is; what is the borderline between neurology and psychiatry? Is the clinical overlap between FTD and PPD just a coincidence? Unfortunately, challenges in clinical practice are not limited to only the behavioural variant of the syndrome. Since the original description of the clinical syndrome of PPA is progressive aphasia without generalized dementia, the current diagnostic criteria centralize aphasia and give little room for other cognitive, behavioural and motor features. Moreover, although the diagnostic criteria of the behavioural and language variants cover the frontal and the left temporal involvements, there has been little attention for the clinical syndrome of FTD patients with predominant right temporal atrophy.

AIMS

This thesis aimed to give a novel, global, historical, and critical overview about the challenges in phenotyping the FTD subtypes by focusing on the limitations of traditional assumptions and the neglected clinical presentations.

SPECIFIC AIMS

1. To understand the birth of the concept of FTD, learn the challenges in the past, and discuss the current limitations and future directions.

2. To provide a novel approach to understand the relationship between FTD and PPD by investigating the anatomical overlap instead of differences.
3. To determine the accompanying cognitive, behavioural, and motor problems next to aphasia in PPA and provide a roadmap to clinicians to manage those patients.
4. To describe the clinical and radiological characteristics of rtvFTD and provide a diagnostic framework to recognize those patients
5. To explore the underlying pathological accumulations and genetic risk factors in rtvFTD to better understand the temporal variants of FTD.

RESEARCH QUESTIONS AND OUTLINE

The challenges mentioned above shaped the structure of this thesis. In **chapter 2**, to understand the evolution of FTD and the split between neurology and psychiatry, we revisited the history pages and also interviewed the pioneers of the field. We derived the brief history of behavioural neurology based on the published literature and reported the opinions of 4 leading experts; Prof. Marsel Mesulam, Prof. David Neary, Prof. Julie Snowden and Prof. Bruce Miller about the current situation and future of the syndrome. The second research question of this thesis was addressed in **chapter 3**. In this chapter, to reveal whether the overlap between FTD and PPD is more than a clinical coincidence, we focused on the potential shared anatomical pathways. We reviewed all published neuroimaging studies (ROI coordinates available) on bvFTD and 3 major PPDs; schizophrenia, bipolar disorder and autism spectrum disorders, and conducted a meta-analysis by re-analyzing the published voxel-based morphometry and diffusion tensor imaging studies. To show the statistically significant overlapping brain areas, we performed three separate pairwise conjunction analyses between bvFTD and schizophrenia, bvFTD and bipolar disorder, and lastly bvFTD and autism spectrum disorders. Following the behavioural part, in **chapter 4**, we focused on the language variants; primary progressive aphasias. Since

phenotyping PPA patients with additional cognitive, behavioural, and motor problems is challenging for general neurologists even in the tertiary care units, to describe the general symptom distribution in PPA, we conducted a 6-year follow-up study. We retrieved all cases diagnosed with PPA based on the recent biomarker-supported diagnostic criteria [10] and reviewed all clinical symptoms, cognitive test scores and progression patterns of each PPA subtype recorded by the dementia experts in the Alzheimer Center Amsterdam. To display the unique clinical pattern next to aphasia of each subtype, recorded symptoms confirmed by objective tests at the initial and follow-up visits for each subtype were clustered, and most common and differential symptoms were identified. **Chapter 5** challenged the assumption that FTD contains only bvFTD and PPAs. Our question was what if it starts on the right side? In this retrospective case control study, of 619 subjects with a clinical diagnosis of FTD or PPA, we included 70 subjects with a negative amyloid status in whom predominant right temporal lobar atrophy was identified based on blinded visual assessment of their initial brain MRI scans. Clinical symptoms were assessed retrospectively and compared with age- and sex-matched patients with AD, and two established variants of FTD; svPPA and bvFTD. To propose a diagnostic framework to increase the recognizability of the syndrome in clinical settings, the core and supportive features were identified and sensitivity/ specificity values were calculated. Additionally, to test the argument that rtvFTD is a mirror image of svPPA, we compared the initial MRI features of the rtvFTD group with the svPPA group. **Chapter 6** and **chapter 7** built on the results of **chapter 5**. Because, to date, as we mentioned in the introduction, rtvFTD has not been considered as a separate variant, therefore its inheritance pattern, underlying genetic risk factors, and pathological accumulations have not been studied systematically. More importantly, our radiological results in chapter 5 suggested the argument that the biological underpinnings of those two temporal variants of FTD is same, whereas clinically, there was differential involvement of the motor system between the 2 syndromes, indicating potential

different disease mechanisms. This inconsistency created our new research question; might the biological background of two temporal variants of FTD different even if the initial atrophy pattern is the same? In **chapter 6**, to study whether the temporal variants of FTD share the same genetic background, we included patients with genetic confirmation from 2 specialized memory centers; Amsterdam Dementia Cohort and Istanbul University Dementia Cohort, and reported the family histories and genetic mutations of rtvFTD and svPPA patients. Our results showed that rtvFTD is heterogeneous genetically, unlike svPPA. To confirm our hypothesis, in **chapter 7**, we asked the question whether the underlying pathology in rtvFTD might also be heterogeneous. We revisited our rtvFTD cohort and retrieved the patients with pathological confirmation. Additionally, we conducted a systematic review to find the autopsy results of the subjects with rtvFTD. Lastly, in **chapter 8** we provided a summary of key findings and placed our results within the context of existing literature.

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CHAPTER 2

FRONTOTEMPORAL DEMENTIA: PAST, PRESENT, AND FUTURE

FRONTOTEMPORAL DEMENTIA: PAST, PRESENT, AND FUTURE

Hulya Ulugut, M. Marsel Mesulam, Julie Snowden, David Neary, Bruce L Miller and Yolande A.L. Pijnenburg

Ready for submission, 2022

Abstract

The history of frontotemporal dementia (FTD) is both very old and very young. It is old, because, as this study will show, its roots are deep and findings on correlates of frontotemporal impairment, dating back to the 19th century, lie remarkably close to present knowledge. It is new, because the term FTD came to the forefront as a neurological entity just a few decades ago. In this qualitative study and literature review, we outline the historical background, the birth and the evolution of the FTD concept. Moreover, we interview four pioneers of the FTD field and report their thoughts about the future of the concept. The interviews highlight current limitations and challenges. Back in the day there was resistance to the idea of dementia subtypes distinct from Alzheimer's disease and IQ-based cognitive assessment obscured distinct dementia profiles. Additionally, the split between neurology and psychiatry slowed recognition of FTD: neurologists ignored behavioural features whereas psychiatrists moved away from a biological approach. Furthermore, the lack of high quality neuroimaging techniques and pathological proof were important barriers. Currently, continuing limitations are the lack of biological biomarkers and biologically oriented psychiatry education. All experts emphasized the importance of the creation of independent centres that have a multidisciplinary approach , drawing on skills of neurologists and psychiatrists as well as psychologists, basic scientists and social workers. Lastly, the future interests of the FTD field would be developing disease modifying therapies which would create new complexities and new topics for behavioural neurologists and FTD researchers.

Keywords: neuropsychiatry, behavioural sciences, history, dementia, frontotemporal dementia, frontal lobe dementia, dementia of the frontal type, pick's disease and frontotemporal lobar degeneration

Introduction

Frontotemporal dementia (FTD) is a clinical disorder associated with neurodegeneration of the cortex of the frontal and temporal lobes, often in conjunction with the degeneration of subcortical brain areas (1-3). This illness presents with a spectrum of behavioural, language, psychiatric and motor problems. Although the name of the disorder emphasizes the major anatomical involvement, the wide spectrum of clinical presentations complicates recognition. Over time, scientists have tried to elucidate the hallmarks of the disorder and phenotype the characteristic presentations. The first clinical diagnostic criteria classified FTD into 3 prototypic syndromes: FTD (behavioural problems predominant), progressive non fluent aphasia and semantic dementia (1). In 2011, consensus clinical diagnostic criteria were revised and FTD was classified as bvFTD (2), whereas semantic dementia and PNFA were classified under the umbrella of PPA, including the svPPA, the nfvPPA and lvPPA (3). Currently both diagnostic criteria are widely used worldwide. The sporadic and genetic forms of the illness have been characterized, furthermore distinct histopathological substrates have been identified (4, 5).

The term FTD is relatively new and significant work was performed following the publication of research diagnostic criteria for FTD in 1994 (6). Since then, a dramatic increase in research activities and publications has expanded our knowledge in this field. Recently the field is discussing the development of diagnostic biomarkers and disease modifying therapies for FTD with the impressive efforts coming from thousands of FTD experts/researchers. .

Importantly, most narratives regarding the history of FTD start with Picks' case report in 1892 (7) and continue with Mesulam's progressive aphasia (1982) (8), Snowden's and Hodges' semantic dementia (1989, 1992) (9,10) , and Neary and Snowden's diagnostic criteria (1998) (1) and comes to current diagnostic criteria published in 2011 by Rascovsky et al (2) and GornoTempini et al (3). Here, one can see that in the last 40 years, FTD research has been extremely active with impressive results. One of the great mysteries in FTD, is what happened between Pick and the contemporary behavioural neurologists and explaining the reason for the 100 years of silence. Secondly, articles focusing on behavioural neurology education, current challenges in the field, potential solutions, and future directions are missing.

In this article, we aim to place current behavioural neurology research in FTD in the context of its history and future. With this aim, we reviewed the literature of the history of behavioural neurology research in FTD. Moreover, to better understand the current status and

future directions in the field, we interviewed four international leaders in FTD research and interrogated them on their visions on the status quo and future of the FTD concept.

Methods

First, we conducted a review of the literature by using the following keywords "neuropsychiatry", "behavioural sciences", "history", "social psychiatry", "mental tests", "dementia", "frontotemporal dementia", "frontal lobe dementia", "dementia of the frontal type", "pick's disease" and "frontotemporal lobar degeneration". Secondly, we used qualitative research methodologies (11) to discuss challenges, potential solutions and future directions in behavioural neurology education and FTD research. We asked four leading scientists in the field to participate in individual semi-structured interviews, followed by a group meeting in which they all participated.

The online interviews were recorded with the permission of the participants. Subsequently, videos were analysed and converted to a text file. The interviewed scientists; Professor M. Marsel Mesulam, the founder of progressive aphasia (8) and the director of the Mesulam Center for Cognitive Neurology and Alzheimer's disease, Professors David Neary and Julie Snowden, the founders of the Manchester FTD cohort which is the first largest non-Alzheimer's Disease cohort in the world (6) and the first neuroscientists who suggested the term "semantic dementia" (9), and lastly Professor Bruce L. Miller who conducted seminal work that has increased the awareness and understanding of FTD. Currently, he is the founder and director of the leading FTD centre; the UCSF Memory and Aging Center.

Table 1 displays the structure of the individual and group interviews. Of note, before submission, the article was checked by the participants and the answers were confirmed by themselves.

Table 1. Interview questions

Individual interview questions	Group meeting questions
1. What is your story regarding behavioural neurology? How did you decide to work in this field? 2. Specific questions for each participant A. For Marsel Mesulam: Could you tell us the story of the identification of primary progressive aphasia? B. For Julie Snowden and David Neary: Could you tell us the story of the Manchester cohort and the first research criteria for FTD? C. For Bruce Miller: Could you share the story of the UCSF Memory and Aging center? 3. What were the challenges at that time and how did you manage them?	1. What are the limitations in the current behavioural neurology education and research? 2. What is your opinion about the split between neurology and psychiatry? What are the positive and negative effects of this separation on FTD research? 3. What is your opinion and expectations about the future of the FTD syndrome? 4. What can be the potential solution to facilitate and better conceptualize current behavioural neurology research?

Results

1. Literature review

The 19th century is a golden age in the history of neuropsychiatry. At that time, the disciplines were broad and neurologists, psychiatrists, surgeons, anatomists, and pathologists worked together, and often, one person had multidisciplinary expertise. The traditional approach was localization by using autopsy techniques to identify the origins of mental illnesses (12). With the influence of the French Revolution, France became the heart of science and art which influenced science across Europe (13). In France, Étienne-Jean Georget (1795–1828), a disciple of Pinel and Esquirol, emphasized the organic aetiology of mental disorders, and Antoine Laurent Bayle (1799–1858) claimed that dementia and mental disorders were both aspects of the same disease (12) whereas Paul Broca (1861) identified the brain region responsible for the motor structure of language (14). In Germany, in 1845, Wilhelm Griesinger wrote his revolutionary book named “Psychische Krankheiten sind

Erkrankungen des Gehirns", "Mental illnesses are diseases of the brain" (12). Following his work, the German-Austrian psychiatrist, neuropathologist and anatomist, Theodor Meynert classified the behavioural onset disorders under the term of "clinical disorders of the forebrain" (15). Meynert's contribution should be emphasized because, beyond his personal achievement, his legendary pupils changed the direction of behavioural neurology. One of his famous students, Carl Wernicke, established the neuroanatomical localization of receptive aphasia (16), whereas another student, Sigmund Freud, focused on the content of what his patients spoke rather than how they spoke (16). Freud separated himself from his peers and he established the new technique, psychoanalysis, which is a clinical method for treating psychopathology through dialogue between a patient and a psychoanalyst (17). Although Freud's fame spread all over Europe, he was influenced by another famous name; Jean-Martin Charcot. Charcot's hospital in Paris, Salpétrière Hospital was a meeting point that hosted many great scientists including Charles Bouchard, Joseph Babinski, Gilles de la Tourette, Pierre Janet, Joseph Jules Dejerine and Sigmund Freud (18). In this scientific milieu, one group (Freud and his followers) dug into childhood traumas to find the aetiologies of psychiatric disorders, whereas another group was studying the organic aetiologies underlying mental disorders. Beyond the Salpétrière Hospital, these two different approaches had influence across the world and triggered the split between neurology and psychiatry.

Although the Paris-Berlin-Vienna triangle was leading behavioural neurology research, another capital, Prague, was highly influential based upon the contributions of Arnold Pick. After his training in Vienna (under the supervision of Meynert) and Berlin (under the supervision of Westphal), Pick turned back to Prague and headed the Prague neuropathological school with his colleague, Oskar Fischer (the second neuropathological school at the time; the other was in Munich where Alois Alzheimer worked) (19). In this school, Fischer reported neuritic plaques in 12 cases of senile dementia (20), whereas Pick published several articles focusing on apraxia, agnosia, memory, consciousness, and psychosis as well as aphasia (19). In 1891, the term "dementia praecox" which is nowadays known as schizophrenia, was first used by Pick (21), in 1892, he published his famous case report presenting with behavioural and language problems and asymmetric left temporal lobe atrophy that retrospectively would be classified as svPPA based on the current diagnostic criteria (3). After his report, Dejerine and Serieux (1897) (18) described a case of sensory aphasia with bilateral anterior temporal atrophy. Pick went on to report four additional cases with temporal lobe atrophy and language disturbances and in 1906, he described a patient

with disinhibition and mixed apraxia who had severe bilateral frontal and left-sided parietal atrophy, with more moderate atrophy of the left temporal lobe (19). Eventually, he proposed a concept to distinguish two forms of linguistic disorders; frontal and temporal variants (19).

In another important scientific hub, Munich, in 1911, Alois Alzheimer performed the pathological analysis of Pick's cases and he showed silver staining argyrophilic cytoplasmic inclusions within neurons (22). In the 1920s, the research on Alzheimer's and Pick's results were expanded and "Pick's atrophy", "Pick's body" and eventually "Pick's disease" were identified by Pick's pupils; Gans, Onari, Spatz and Schneider (23-25).

Even though Alois Alzheimer defined the histological features of Pick's case, these unique inclusions were attributed to Pick (12), however, another case; Auguste D., would make Alzheimer quite famous, even more than Pick (26). Although the neuropsychiatric features of Alzheimer's disease (AD) were neglected for decades, Auguste D. was admitted to Alzheimer's centre for paranoia, progressive sleep disturbance, aggression, and confusion as well as memory deficit (26). He noted distinctive plaques and neurofibrillary tangles in her brain histology (26). This case excited little interest despite an enthusiastic response from his colleague, Emil Kraepelin, who promptly included "Alzheimer's disease" in the 3rd edition of his text "Psychiatrie" in 1910 (27). Thus, Alzheimer's name would be linked forever with one of the most common and feared diseases, although in the same year, Oskar Fischer published the clinicopathological features of 12 cases of senile dementia in which he provided the first description of the neuritic plaque (20). The role of Emil Kraepelin in Alzheimer's fame might be important because Kraepelin was one of the most influential psychiatrists of the time considered as the founder of modern psychiatry (27). He introduced a new system for classifying mental disorders (including dementia) and hypothesized that the main origin of psychiatric disorders is also neurobiological malfunction (17). Moreover, he popularised the term "dementia praecox" (schizophrenia) and characterized this as a progressive neurodegenerative disease that resulted in irreversible loss of cognitive functions (27). Another important name who visited this centre was Austrian psychiatrist and neurologist Constantin von Economo who characterized the Von Economo cells, originally described by Betz, which are currently assumed as the target of FTD (28).

In the following decades of 1900s, research in behavioural neurology continued and the new generation discipline of Meynert (through their mentor Carl Wernicke) paved the way for current knowledge in neuroanatomy and cognitive neurology. One of the assistants of Wernicke, Hugo Liepmann started a debate on the nature of conceptual knowledge and he

suggested that “meaning” is more than knowing the object, it is also related to the relationship of one object to another, both with respect to time and to space (29) which might be retrospectively interpreted as the basis of semantic domain (30). Furthermore, Rosenfeld presented a case with naming problems, word comprehension deficit, fluent speech, preoccupations and with left temporal pole predominant atrophy (31) which we can conclude that his case was a semantic dementia case based on our current knowledge (30). Another student, Karl Kleist published his famous brain map that displays the function of each brain area (32). Conversly, another pupil, Kurt Goldstein was anti-localizationist and influenced by the Gestalt psychology and he conceived his holistic approach to the brain in which he postulated that function in a damaged area could be compensated through the capacity of other areas (33, 34).

Unfortunately, World War II left its mark on this period and would change the destiny of neuropsychiatry. Many of the scientists mentioned were living in Germany or at least had a connection with Germany. Moreover, some of them and/or their mentors were Jewish (12, 35). The rise of Nazism in central Europe affected the entire field (not only the Jewish community), because several German-based neuroscientific works were considered as representing instances of a “Jewish science” (12). Several researchers were arrested or forced emigration. Others met a tragic fate. One of them was Oskar Fischer who deserved major credit for the description of what is called Alzheimer’s disease today. He was murdered by the Nazis (36)

Apart from these single stories, nearly 30% of all those expulsed doctors of academics who practiced neurology and psychiatry immigrated to North America which influenced the American scientists and clinical brain sciences became the leading topic in the field (12, 17, 35). The high percentage of immigrating neuropsychiatrists (the largest group of medical specialists following that of the internists), is striking in this regard: They represented the classical nerve doctors (Nervenaerzte) in the tradition of Emil Kraepelin (35). Here, the name of one of those scholars must be mentioned; Professor Alfred (Fred) Quadfasel. Like his mentor Goldstein, Quadfasel, was released on the condition that he would agree to leave the country. He was accepted to the Boston Veterans Administration and was appointed head of the neurological department in 1947 (35, 37). Quadfasel’s impact was not limited to his scientific work, he influenced his famous pupil, Norman Geschwind’s work on aphasiology and neuropsychology, and he encouraged Geschwind to study classical texts of neurology from the nineteenth and early-twentieth century that exposed him to traditional localizationist

theory (35, 38). He introduced him to the original paper by Dejerine of the first postmortem case of a patient with alexia without agraphia. Geschwind spoke many languages, he preferred to read the original papers rather than mistranslated or misinterpreted documents and he realized that many crucial findings in behavioural neurology had been reported about decades before, yet forgotten by the medical community (38).

In the meantime, the rest of the field was facing an intellectual polarization due to the post-Freudian effect. Predictably, the immigration of the Freudian ideas occurred as well (17, 35). Several scientists fell under the influence of psychoanalysis, and inevitably, psychiatry's roots within neurobiology were abandoned (39), furthermore, the division between neurology and psychiatry became explicit (12). In 1948, the American Academy of Neurology published the "pure" neurological issues and separate neurology departments were established throughout the United States (12). Afterwards, in 1965, the Residency Review Committee for Psychiatry and Neurology, an accrediting body separate from the American Board of Psychiatry and Neurology, deleted psychiatric training as a mandatory experience for neurologists (39). Although some scholars did not agree with this separation and several attempts were made for a reunion, the situation became an irreversible status (12). Dr. Francis Braceland, former secretary and president of the American Board of Psychiatry and Neurology, summarized the situation with those words: "To get neurologists and psychiatrists of that period in time to sit down together without police present was in itself an accomplishment…"(39). After this separation, neurologists focused on those brain disorders with cognitive and behavioural abnormalities that also presented with somatic signs such as stroke, multiple sclerosis, Parkinson's disease, etc., whereas psychiatrists focused on those disorders of mood and thought associated with no or only minor physical signs found in the neurological examination (12, 39). This oversimplified approach closed the doors of cognitive and behavioural neurology to neurologists. By the '70s, neurologists found a new bridge between cognitive science and neurology, and vascular aetiology was the accepted cause of senility (40). Following this connection, researchers revisited their old topic "dementia", and Alzheimer's neuropathology became more popular and a major shift occurred in the field (41). Despite Alzheimer's research dominance, a few groups continued their early pioneers' work in Boston, which would build the current insights of FTD in the US; the Geschwind école (38). With the seminal contributions of the first and second generation discipline of Geschwind including Frank Benson, Antonio Damasio, M. Marsel Mesulam, Jeffrey Cummings, and Bruce L. Miller, neuro-behavioural syndromes could become a trending topic

in the US. In 1967, Frank Benson reported two clusters of aphasia located anterior and posterior parts of the fissure of Rolando (42). In 1985, his student Jeffrey Cummings identified the aphasia profile in AD (43), and another student Bruce Miller described the clinical, neuropsychological and SPECT characteristics of frontal lobe degeneration in 1991 (44). Around the time, Marsel Mesulam described patients with non-fluent and fluent aphasia without Alzheimer's pathology, and in 1982, suggesting the term primary progressive aphasia (8). These scientific advances led to American neurologists to mention Pick's name again. Furthermore, the phrase "don't pick Pick's disease" which led to the misconception that Pick's disease was both very rare and indistinguishable from AD during life, was questioned (40).

Although the Second World War negatively affected all scientific activities in Europe, a series of European researchers were re-examining the Pick's disease which paved the way of current knowledge in FTD. Sjögren et al., (1952) in Sweden (45), van Mansvelt (1954) (46) and Schenk (1959) (47) in the Netherlands, Escourolle (1958) in France (48) wrote, seminal articles/books/theses emphasizing the positive family history in Pick's disease, the relationship with motor neuron disease (MND) and, clinical and histological differences between AD and Pick disease. Furthermore, Switzerland based scientists Constantinidis, Richard and Tissot proposed a new neuropathological classification of Pick's disease into three types (A, B, and C), depending on the presence or absence of Pick's bodies and ballooned neurons; this system was widely used until it was replaced by the recent classification of FTLD (49). This second wind for FTD in Europe recalled Pick's name once more. In this era, the epochal work of the Lund group, especially the names of Lars Gustafson, David Ingvar, and Arne Brun must be mentioned because they started to collect patients with non-Alzheimer type frontal lobe degeneration and published their 20 year follow-up results. This revolutionary cohort revealed the clinical picture (50), regional cerebral blood flow abnormalities (51, 52), white matter changes (53), and the pathological features of the syndrome (54, 55). In parallel in Manchester, Neary and Snowden were also collecting dementia patients with non-Alzheimer's disease. They described the dementia of frontal type (56), its single photon emission tomography characteristics (57), and its relationship with motor neuron disorder (58). Additionally, they coined the term semantic dementia and they suggested that the temporal regions would be the principal site of pathology in semantic dementia (9).

In addition, all over the world, interest in developing neuropsychiatric tests to assess different cognitive domains assisted recognition of selective cognitive deficits in neurodegenerative disorders. Although, in 1869, Harlow described the "frontal lobe syndrome" after his research on the famous Phineas Gage who suffered a dramatic change in behaviour as a result of an accident in which a large iron rod was driven completely through his left frontal lobe (59), over the years, psychological assessment moved away from focusing on focal brain impairments. Modern cognitive tests originated through the work of James McKeen Cattell who coined the term "mental tests" (60), and followed Francis Galton's development of physical and psychological tests (61). However, Alfred Binet who invented the first practical IQ test influenced the field strongly and cognitive assessment became mostly "intelligence" centred (62). Nevertheless, in 1950s, assessing different cognitive domains became popular again. British psychologist Donald Broadbent (1958) described differences between automatic and controlled processes that comprised a basis for research on attention and executive functioning (63). However, an important foundation for understanding the functions of frontal lobe can be found in the works of Russian psychologist Alexander Luria (1960s) (64-67). Luria gave the first extensive description of the frontal lobe syndromes in soldiers with focal brain lesions during the war and emphasized the role of the frontal lobe in control of behaviour, programming, regulation and verification of activity (64-67). In 1972, Tulving revealed the distinction between semantic and episodic memory (68) In 1975, in London, Elisabeth Warrington identified the selective semantic impairment as a separate cognitive deficit (69).

All those scientific advances contributed recognition of FTD directly or indirectly. However, importantly, the Lund and Manchester groups joined forces and they published the famous Lund and Manchester criteria for FTD in 1994 (6). The first initiative for global collaboration came from Sweden. In 1986, the Lund dementia research group organized an international conference on FTD as a satellite symposium of the 10th International Congress of Neuropathology (70). This conference played a bridge role and its overwhelming impression was the need for further promotion of research interaction between the researchers active in this field (70). The awaited second International Conference on FTD took place in Lund, in 1992 with contributions from research centres in England, United States, France, Japan, Denmark, Sweden, and other countries (70). Benson's progressive frontal dysfunction (71), Miller's progressive right frontotemporal degeneration (72), Knopman's dementia lacking distinctive histology (73), Neary, Snowden and Mann's clinical-pathological correlates of

frontotemporal lobar atrophy (74) and Mitsuyama's presenile dementia with MND (75) were some of the highlights of the conference. These eminent studies showed that FTD is a separate entity and developing new diagnostic criteria for FTD became a necessity. Inevitably, in 1998, the first consensus diagnostic criteria for FTD have been published by this international team (1).

The collaboration in research continued, and the annual frequency of publications dramatically accelerated. The Lund initiative led to the formation of international society for frontotemporal dementias (ISFTD) which aims to unite FTD researchers in the world and organizes the biennial FTD conferences. In the next years, numerous prominent names provided incredible contribution that re-shaped the current status of the syndrome and day by day, we are reading new studies that increase our belief in curative treatments of this devastating disorder.

2. Interviews with the pioneers of the field

The literature review provides a historical overview about the birth of FTD. However, to better understand the challenges in the field and future directions we interviewed four pioneers of the field. The questions listed in table 1 were asked and the answers of M. Marsel Mesulam (MMM), David Neary (DN), Julie Snowden (JS), and Bruce L. Miller (BLM) were reported separately for the individual interviews. The overall summary of the interactive discussion group interview was reported in table 2.

2.1 Individual interviews

2.1.1 What is your story regarding behavioural neurology? How did you decide to work in this field?

MMM: I had been interested in psychophysiology. The question that I had was how our body can be connected to our mind. I read Freud, took courses on psychoanalysis and the biological basis of psychiatry. So, I applied to Massachusetts Institute of Technology (MIT) for psychology and Harvard for medicine. I was accepted to both, and I decided to go to medical school because it was more flexible. Here I can mention 2 things that happened in medical school and might have affected my decision. There was a discussion in the class about HM who lost his memory after bilateral temporal lobectomy. It raised new questions in my mind. If the hippocampus is so important in memory, how does the hippocampus know about what

we are doing unless it has input from parts of the brain that deal with the experience. There was no information about this. However, there was one person at Harvard medical school that was the most knowledgeable; Norman Geschwind. I went to Norman and asked my question; "do you know anything about this?" He said "No! But I just hired a new anatomist who is upstairs. Why don't you go and ask him?" That is how I came to meet Deepak Pandya and later Gary Van Hoesen and started my neuroanatomy career. The second event that was equally important is that, at that time, medical students did rotations in different disciplines such as neurology, obstetrics etc. I did my rotation in neurology at Norman Geschwind's department in Boston City Hospital. And the first patient that I saw as a student was a man who had an infarction in the left posterior cerebral artery, and who had pure alexia without agraphia, quite a rare syndrome. So these events increased my interest in behavioural neurology as well as neuroanatomy. I went to do an internship at the University of Pennsylvania which was 6 months neurology, 6 months psychiatry. Then I chose Norman Geschwind's department for my neurology residency and stayed on for my behavioural neurology fellowship, which was really on neuroanatomy.

DN: I had a long-standing interest in psychology and psychiatry and part of my post graduate education was in psychiatry.I decided, nevertheless, to become a neurologist. In the early 1970s I started my residency in London at the National hospital for neurology and neurosurgery, working,like other neurologists at the time, on the peripheral nervous system. A colleague gave me the collected works of Norman Geschwind, which had a profound influence on me. Happily, a few months later, Norman Geschwind arrived in London and I learned a great deal from his lectures. He introduced me also to Frank Benson when he visited London. Late in 1976, I had the opportunity of spending three months at Geschwind and Benson's neurobehavioral unit in Boston. I saw patients with cognitive impairment andmet influential people working there at the time. I read widely, including Freud's"OnAphasia", which criticizes extreme forms of localization. So, I was exposed to different perspectives. When I returned to Manchester, I knew that I wanted to become a cognitive neurologist even though the sub-specialty did not exist at the time. I also knew that I needed collaboration. Therefore, I visited the psychology department where I met Julie Snowden.

JS: My storybegins with David (Neary). I was a doctoral student in the psychology department when David Neary came seeking collaborators. I was excited at the prospect of studying patients with neurological disorder andjumped at the opportunity of joining his team. I had begun to be influenced by British psychologists such as Elizabeth Warrington and Freda

Newcombe, who were carrying out pivotal studies with neurological patients that identified sub-processes in cognitive functions through the demonstration of double dissociation. So, David's proposal was timely. I found the patients fascinating . We were fortunate in obtaining regional funding for combinedclinical and research work and later established ourselves as a health service funded clinical service.

BLM: I came to science late. In college I identified as a hippie; and a social activist. I didn't initially study science but was fascinated by human behaviour. When I fell in love with science and medicine I thought that I was going to be a family doctor, taking care of people in underserved and rural communities but I increasingly became fascinated by the brain. For me, neurology was obvious because in the US, psychiatry was not really anatomical and biological. I came to the University of California, Los Angeles (UCLA) to work with Frank Benson, because I heard about him. Frank was Norman Geschwind's student. He was one of the superb clinicians that Norman recruited and Frank was really interested in psychiatry. Jeffrey Cummings was also there and he also had a strong influence on my thinking. At the time, Frank and Jeff wrote the premier book on dementia called "Dementia; a clinical approach". They noted that you could differentiate different molecular subtypes of dementia based on their clinical characteristics. Jeff went to London in 1981 and he worked with LW Duchen to describe five pathologically proven cases with Kluver Bucy syndrome and discovered that a number of them had Pick's disease. So, Jeff and Frank were aware of the clinical features of FTD compared to Alzheimer's. I was really excited by this idea that dementia was not just one thing. I was particularly excited about the psychiatry of the prefrontal cortex as Jeff and Frank taught to me. When I was a fellow, Frank wanted me and my neuropsychologist friend Kyle Boone, to find everyone who had a prefrontal leucotomy to see what they looked like clinically. We found a few. And then I met Arne Brun from Sweden who had collected the largest cohort in the world with psychiatrist Lars Gustafson. They were diagnosing them but no one believed them. Some suggested that FTD was a Swedish disease while others suggested that this was just Alzheimer's disease. That was the Alzheimer bias of the 1980s. I began to work with Arne, and he came to do his sabbatical in UCLA. He studied the cases that I was collecting with FTD. He encouraged me to write a paper about it. So in around 1991 I wrote a paper on FTD. If Frank, Jeff and Arne had not been that generous, I might not have done this. As I got interested in this field, I realized that there was a history that was really rich before I ever was born.

2.1.1 Could you tell us the story of the identification of primary progressive aphasia?

MMM: When I finished my residency I became an assistant professor in neurology. Norman Geschwind asked me to establish a new clinic in Boston called the Behavioral Neurology Unit. Nowadays such a clinic is quite common but back in the days, it was quite unique. And we started to see all kinds of patients with cognitive problems. I had patients with stroke, with degenerative disorders such as Alzheimer, with temporal lobe epilepsy, Tourette syndrome. People were coming to our clinic from around the country. Even from other countries because either they did not have a diagnosis or they wanted to have a second opinion. At that time, neurodegenerative diseases that led to dementia were also supposed to cause problems with memory. And conversely, if you had aphasia, it had to be related to a focal lesion such as stroke, gun shots… etc. I had a number of patients that were not following any of these two rules. These patients would come with a slowly progressive aphasia, a problem that looked neurodegenerative but without a memory problem or stroke or tumour. Those patients would have gone to a lot of doctors without getting a diagnosis. Some of them would be referred to the psychiatrist who would say that "ohh these symptoms are really stress related". Or in another scenario, they would go to the neurologists, and the neurologist would say; "ooh you have a stroke but we cannot see it!" Or they were sent to ENT specialists who looked for vocal cord lesions. So I started to see a number of such patients, and I reported them in a paper in Annals called "Slowly Progressive Aphasia Without Dementia". And as soon as it was published, I started to get letters from around the world from neurologists saying they had seen such patients. And then I wrote an editorial changing the name to "primary progressive aphasia". This syndrome is quite useful for two reasons. First, it has told us a lot about the heterogeneity of dementia, and it has told us a lot about the anatomy of language.

1.1.2 Could you tell us the story of the Manchester cohort and the first research criteria for FTD?

JS&DN: David's Boston visit encouraged him to establish a clinical diagnostic unit,the Cerebral Function Unit. We expected to study focal brain lesions, as he had done in Boston. Indeed, initially, we carried out a study of stroke aphasia, giving us experience of traditional focal aphasias. However increasingly, we received referrals of patients with progressive disorders, chieflyfrom psychiatrists, concerned that. they were missing a potentially treatable neurological disorder. We developed an assessmentprotocol, designed to tease out distinct areas of cognitionsystematically. We were influenced by the Boston approach, and also by developments in cognitive neuropsychology in Britain that involved separating out processes underlying cognitive functions.The analytical approach that we adopted differed from

traditional cognitive assessment, with its reliance on IQ test scores. We saw that far from having global impairment of cognition, which was the prevailing view of dementia, patients showed distinct patterns. In particular, some patients had prominent breakdown in social conduct and executive functions,contrasting withthe typical picture in Alzheimer's disease. We were also seeing different profiles in family members: one with behavioral problems and another with language impairment. This suggested to us a relationship between these focal presentations. We also noted that some 'frontal-lobe' patients developed motor neurone disease, establishing a further link. A crucial development was our collaboration with Lars Gustafson and Arne Brun in Lund, Sweden. We were introduced to them through a neurochemist colleague, so were able to be a part of the first Lund meeting in 1986. We shared our experience both of clinical characteristics and the associated pathology. Some cases had tau pathology, with ballooned cells and inclusion bodies consistent with traditional pathological descriptions of Pick's disease, but many others did not. Their pathology was characterised by nerve cell loss and microvacuolation. Our patients with 'frontal lobe' dementia and MND invariably showed this latter type. Our ongoing collaboration led to the publication of the Lund-Manchester clinical and pathological criteria for FTD in 1994.

2.1.3 Could you share the story of UCSF Memory and Aging center?

BLM: Frank died in 1996 and when that happened I decided that I could leave. I was a bit isolated, but I got a job offer from another centre in Southern California to set up a programme. I was going to go but I became friends in 1984 with Stanley Prusiner. I sent him a case of Gerstmann–Sträussler–Scheinker syndrome; a genetic prion disease. This helped him to find the genetic basis of prions. So we became friends. And then in 1998, he offered me an endowed chair at the University of California at San Francisco (UCSF). There was no behavioural neurology at the faculty at the time, and the previous chair at UCSF hated behavioural neurology. Stan said we needed a clinic, so we could push forward the basic biology of dementia. We needed a national Alzheimer Center. So I came to San Francisco and the idea was that I was going to establish an Alzheimer Center at UCSF. In addition, I established a strong relationship with many of the faculty. The residents enjoyed my teaching about the mental status in UCSF. It was a great neurology program but lacked much teaching about the entire cerebral cortex. So the residents started coming and I slowly shaped a program with my colleagues, Joel Kramer, Rosalie Gearhart, and Howie Rosen

2.1.4 What were the challenges at that time and how did you manage them?

MMM: The lack of high resolution neuroimaging and pathological proof were the most important problems. But even in my first PPA paper, I had demonstrated the left sided asymmetric atrophy. One patient had a brain biopsy. We found no plaques, no tangles, just a loss of cells. Then a couple of years later, we were able to have a PET scan which showed the hypometabolism on the left, and autopsies started to come in, and we had a better idea of the heterogeneity. And for a while, there was a tremendous controversy over whether PPA was a separate disease or just AD. At that time, people didn't understand the difference between syndrome and disease. However, this is now understood and there is no additional debate necessary.

DN: The accepted view in the 1980s was that there were just two causes of dementia: AD and vascular dementia, and we encountered resistanceto the idea of a separate disorder. Our main practical problem was that we had no pathological proof nor good qualityimaging. I read a Lancet article about single photon emission computed tomography (SPECT), so we developed this in Manchester. Our early images were grainy with poor resolution, yet they distinguished predominant posterior hypoperfusion in AD and anterior changes in our presumed FTD patients. It was our first independent verification of the clinical distinctions that we were identifying. Another important piece of the jigsaw was pathology. I knew a young pathologist, David Mann, who was working in Manchester Medical School on AD. We began a collaborationand set up the Manchester Brain Bank.Even with pathological proof that we were dealing with a disorder distinct from AD we still encountered scepticism. Our colleagues in Lund had a similar experience. It was suggested to us that 'frontal' type dementia might be a rare disorder seen only in the North of England and Sweden and linked to Viking genes!

JS: We saw our first semantic dementia patient, subsequently pathologically confirmed,in the early 1980s. The patient's problems were framed in terms of memory. The patient complained "I can't remember things", yet close analysis showed the memory disorder to be one of semantic memory: difficulty remembering words and people and what things were for. It highlighted to me the limitations of cognitive assessment that relies solely on overall test scores, since such scores potentiallymaskdifferent reasons for task failure. In my opinion, the emphasis on IQ testing hindered recognition and acceptance of distinct profiles of dementia.There was also the view "Why are you trying to define new types of dementia? You cannot treat it, so what is the point?"

BLM: Frontal lobe was a perfect problem between neurology and psychiatry, because neurology emphasized peripheral nerves, muscles, movement and seizures whereas psychiatry didn't think about the anatomy of behaviour. So the school of behavioural neurology had so much to explain about topics that both fields had ignored. Honestly, I loved what everyone was doing within behavioural neurology but Frank had a huge influence on me. Because he went to London to work with psychiatrists to tell this idea; biologically oriented psychiatry. I don't think that the time was ready. But it was a big step to deal with this problem.

2.2 Group interview

In this part, all highlights reported by the experts were summarized in Table 2.

Table 2. Group interview; expert opinions

What are the limitations in the current behavioural neurology education and research?	**What is your opinion about the split between neurology and psychiatry? What are the positive and negative effects of this separation on FTD research?**
● Current behavioural neurology education/research is based on patients with neurodegenerative diseases. The classic background in anatomical neurocircuitries such as derived from monkey studies that are crucial for understanding the mechanisms is missing. ● Training in cognitive neurology is patchy across the world and not systematic. ● There are limited data on FTD in middle/low-income countries or underrepresented populations in high-income countries. ● Tau-PET has limited value for distinguishing FTD. ● Developing the biological diagnostic biomarkers are the most urgent needs in FTD research	● The split hindered the recognition of FTD because neurologists have paid little attention to cognition and behaviour, whereas psychiatrists have had little training in neurological examination and neuroimaging. ● The distinction between specialties is likely to lead to referral biases. Even if they see the same patient, psychiatrists tend to report depression, mania or hypochondriasis while neurologists emphasize aphasia, executive dysfunction, or semantic problems. ● The positive effects might be related to practical clinical management. Neurologists would not want to take care of psychosis, neurosis, or schizophrenia and probably psychiatrists would not want to take care of neuropathology. Secondly, neurologists take care of the acute treatment of dementia whereas psychiatrists can provide long term support ● The behavioural features of FTD do not fit standard psychiatric

	classifications. Perhaps it is an advantage if neurologists do not force unusual behavioural features into preexisting psychiatric categories.
What is your opinion and expectations about the future of the FTD syndrome?	**What can be the potential solution to facilitate and better conceptualize current behavioural neurology research?**
● The new consciousness that the behavioural neurologist has to learn which was not there during the stroke era is the complexity of neurodegenerative disorders. For example, if you need to give advice to someone who has a TDP 43 related aphasic syndrome it would not be the same with someone who is presenting with a behavioural disorder. Therefore there are two levels that need to be addressed separately; (1) the clinical syndrome, (2) the underlying disease. ● Maybe in the near future, there would be a new potential of genetic profiling even for people without a family history. Following this, the next push might be molecule-based therapies. ● The future of the field will be diagnostic biological biomarkers and disease-modifying treatments. This is a realistic goal that we can achieve ● Of note, everything we discover will get more complex. How do we rehabilitate this, how do we work with the family, with society, and so on? Therefore, behavioral neurologists will have big responsibilities and roles beyond diagnosing patients and providing medication.	● A multidisciplinary approach is crucial to ensure the integration of different aspects of the condition: cognitive, behavioural, physical, social. Unlike the classical department system at medical schools, specialized centers are necessary to bring different sciences together. This physical proximity enables clinicians and basic scientists to work together, to create a real interdisciplinary system concretely not abstractly. ● These specialized centers need freedom. They need to control the space, the money, and the administrative decisions. ● There is some improvement now in that there is greater overlap and communication between disciplines. Cognitive/behavioural neurology became a recognized branch of neurology, whereas neuropsychiatry became a recognized branch of psychiatry. ● The recommendation for young clinicians and researchers would be visiting the specialized centers to have a high quality of education.

Conclusion

This article aimed to conceptualize the past, present and the future of FTD to better understand from whence we came and to where we will go. Over the years, topics, names, techniques, places changed but behavioural neurologists always tried to understand how the brain works (Figure 1).

From the historical point of view, it is interesting to see that quite a seminal work has already been done by the 19th century scientists despite the lack of current technological privileges. They described the canonical terms and their localizations such as aphasia, apraxia, alexia, agraphia as well as the features of behavioural disturbances and they paved the way of neuropsychiatry. However, somehow a big silence happened and this fruitful atmosphere was able to be re-created by the new generation FTD researchers more than 100 years later. Although World War II stopped the entire scientific activities in Europe and Freudian influence separated the paths of neurology and psychiatry, the key factor might be losing the multidisciplinary approach. Because as we reported in the literature review section, back in the days, either researchers had more than one speciality or they were working with people from different backgrounds. The centers led by famous names such as Thedor Meynert, Alois Alzheimer, and Jean Martin Charcot worked as a scientist factory that educated several pioneers that have different approaches and thoughts. This freedom enabled different perspectives to work together; localizationist theory, anti-localizationist ideas, even psychoanalisis. However, modern medical education has been formed by disciplines or departments such as neurology, psychiatry or pathology. Inevitably, clinicians have followed the trajectory that starts with medical school then residency at a department which also worsened the split between neurology and psychiatry. FTD became ignored by both disciplines since neurologists did not know how to assess behaviour and psychiatry was not biologically oriented. However, the pioneers of the field noticed the gap in the field, and re-initiated the tradition of interdisciplinary approach. More importantly, the independent and collaborative work of those centers catalyzed the recognition of FTD and in a very short period of time, our knowledge about neurodegeneration has increased. Furthermore, beyond the reunion of neurologists, neuropsychologists, psychiatrists and basic scientists, they opened new doors for philosophers and social scientists. Because FTD created a new way of thinking about human behaviour; the big question “where is the boundary of abnormality?” Additionally, this new era initiated the new way of cognitive assessment and encouraged psychologists to assess all cognitive domains by novel tests unlike the classic oversimplified IQ based neuropsychological assessments.

One of the messages of this article is that limitations have always been and will always be there. Once our colleagues were dealing with technical limitations such as the lack of access to neuroimaging and pathology, then they fought against the rigid idea of one type of

dementia, and currently we are talking about developing diagnostic biomarkers and disease modifying agents.

Some limitations about our methodology should be addressed. Several articles in Japanese, Russian, Italian, French and especially in German were not available in the searching databases. Since we couldn't retrieve many of the original documents we derived the information mostly from translated articles, other reviews and commentaries. This limitation highlights once more the importance of the international collaboration.

In short, FTD is an area of neurology that has been written about centuries before, yet forgotten by most of the medical community, and has re-born in the past four decades. From a poorly recognised or considered a quirk of Viking origin, it is now accepted worldwide as a major cause of early onset dementia. The lesson that we have learned from the history and the interviews, collaboration/interaction is the key factor to facilitate the FTD research and multidisciplinary independent centers are crucial to educate the new generation and recruit talented scientists that will give new directions to the future of behavioural neurology. As Mesulam, Snowden, Neary and Miller said, how fascinating it is, trying to understand this incredibly interesting jigsaw; human behaviour.

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CHAPTER 3

OVERLAP OF NEURO-ANATOMICAL INVOLVEMENT IN FRONTOTEMPORAL DEMENTIA AND PRIMARY PSYCHIATRIC DISORDERS; A META-ANALYSIS

OVERLAP OF NEURO-ANATOMICAL INVOLVEMENT IN FRONTOTEMPORAL DEMENTIA AND PRIMARY PSYCHIATRIC DISORDERS; A META-ANALYSIS

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ABSTRACT

Despite significant symptomatic overlap between behavioral variant frontotemporal dementia (bvFTD) and primary psychiatric disorders (PPD), a potential overlap in their structural anatomical changes has not been studied systematically. In this MRI based meta-analysis, we included studies on bvFTD, schizophrenia, bipolar disorder, and autism spectrum disorder that (1) used voxel-based morphometry analysis to assess regional gray matter volumes (GMV) and (2) reported the coordinates of the regional GMV. Separate analyses were performed comparing clusters of coordinate-based changes in the GMV (n=24,183) between patients and controls and overlapping brain regions between bvFTD and each PPD were examined. We found that GMV alterations in the prefrontal and anterior cingulate cortex, temporal lobe, amygdala and insula comprise the trans-diagnostic brain alterations in bvFTD and PPD. Our meta-analysis revealed significant anatomical overlap which paves the way for future investigations of shared pathophysiological pathways, and our cross-disorder approach would provide new insights to better understand the relationship between bvFTD and PPD.

Keywords: Dementia; frontotemporal dementia; behavior; autism spectrum disorder; bipolar disorder; schizophrenia

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder that predominantly affects the frontal and/or temporal lobes (1, 2). The most common subtype is the behavioral variant (bvFTD) that presents with behavioral disturbances such as disinhibition, social awkwardness, loss of insight, apathy, loss of empathy, stereotypical behavior, and changes in eating habits (2). One of the earliest and core symptoms of bvFTD is a gradual loss of social cognition (3), which in turn interferes with behavioral and personality aspects.

From a clinical perspective, a number of major primary psychiatric disorders (PPD), such as schizophrenia (SZ), bipolar disorder (BD) and autism spectrum disorder (ASD) strongly resemble bvFTD (4, 5). More specifically, impaired social cognition is one of the core features of PPD(6). Therefore, both bvFTD and major PPD might be considered as "social brain disorders" (7). Additionally, in daily clinical pactice, the elated mood and lack of insight in mania can strongly resemble bvFTD (8). Lastly, both the positive and negative symptoms of SZ (e.g. delusions and hallucinations versus social withdrawal, paucity of spontaneous speech, and concreteness, respectively) are very similar to what is seen in bvFTD (9). Not surprisingly, ~50% of bvFTD patients receive a prior psychiatric diagnosis (4) due to similar and overlapping diagnostic criteria for bvFTD and various PPD (2, 10). The relationship between psychiatric symptoms and neurodegenerative disease becomes particularly evident in carriers of a C9orf72 repeat expansions. It has been shown that family members of C9orf72 mutation carriers have a higher prevalence of SZ and BD, whereas C9orf72 related FTD can present with SZ, BD or ASD symptoms (11-15). Moreover, young cases with a diagnosis of SZ and BD may have underlying FTD neuropathology (Valakoulis, 2009). Based on this empirical overlap, a potential shared neurobiological background between bvFTD and SZ (16-18), BD (19) and ASD (13) has been postulated by independent authors. Their hypotheses, however, remain to be tested.

Based on the clinical overlap and given the significant structural alterations in the frontotemporal brain regions in patients with PPD in large scale studies yielded by the ENIGMA (Enhancing NeuroImagingand Genetics through Meta-Analysis) Consortium (20), in this cross-disorder analysis, we hypothesize that bvFTD and PPD share a biological vulnerability of specific neuroanatomical networks. The identification of shared neuroanatomical vulnerabilities between bvFTD and PPD is important, because such a finding may support a conceptual framework of how these disorders are related and if they have common pathophysiological pathways that could be targeted by treatment. Voxel based

morphometry (VBM) is a commonly used neuroimaging methods that measure gray matter (GM) structure (21). In this cross-disorder comparison, we aimed to identify the overlapping GM differences of bvFTD and PPD including SZ, BD and ASD by using a voxel-wise, coordinate-based meta-analytical approach.

METHODS

2.1 Search Strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (22). Studies included in this meta-analysis were collected by using Medline (Pubmed), Embase, and BrainMap databases, covering the literature until April 2020. We registered our meta-analysis on the Open Science Framework (https://osf.io/9kxrb).

Since different methodologies can affect the volumetric results, we avoided combining various analyses. We, therefore, focused on whole-brain VBM analysis to measure GM volume that is widely used within the neuroimaging scientific community. Therefore, to avoid any misinterpretation we excluded GM alterations when investigated using cortical thickness measurements (with FreeSurfer).

2.1.1 Pubmed & Embase

Relevant structural gray matter neuroimaging studies were retrieved using keywords in the form of medical subject heading (MESH) or Emtree terms and free text terms in the title and abstract (tiab), as follows: “Voxel based Morphometry” OR “VBM” OR “Gray matter” in combination with either (I) “Frontotemporal Dementia” OR “Pick’s disease” OR “Frontotemporal Lobar Degeneration” (II) “Schizophrenia”(III) “Bipolar Disorder” OR “Manic Depression” (IV) “Autism Spectrum Disorder” OR “Asperger Syndrome”. For overview of the full electronic search strategy see Supplementary materials.

2.1.2 BrainMap

A search for BrainMapwas conducted by using Sleuth 3.0.3 software to retrieve structural neuroimaging studies (23). Studies were selected from the BrainMap’s Voxel-Based Morphometry database. Inclusion criteria for selecting structural gray matter (GM) neuroimaging studies were set, as follows: “Experiment + Contrast + Gray Matter” and “Experiments + Imaging Modality +MRI” in combination with (1) “Subjects + Diagnosis + Frontotemporal Dementia” or “Subjects + Diagnosis + Frontotemporal Lobar Degeneration”

(2) “Subjects + Diagnosis + Schizophrenia”(3) “Subjects + Diagnosis + Bipolar Disorder” (4) “Subjects + Diagnosis + Autism Spectrum Disorders” or “Subjects + Diagnosis + Asperger’s Syndrome”.

2.2 Study Selection

To be included in our meta-analysis, studies had to fulfill the following inclusion criteria: (1) conducted structural neuroimaging analysis comparing patients with healthy controls (2) used the Rascovsky (2), Neary (1) and McKhann (24) diagnostic criteria for bvFTD , Autism Diagnostic Interview-Revised (ADI-R) for ASD or Diagnostic and Statistical Manual of Mental Disorders (DSM) III, IV, 5 (10) or international statistical classification of diseases and related health problems: tenth revision (ICD-10) for SZ, BD and ASD (3) conducted a VBM analysis for GM volume (4) reported coordinates in Montreal Neurological Institute (MNI) or Talairach stereotactic standard space (5) only included patients over 16 years old (6) reported GM alterations, which reported peak coordinates of statistical significance at the whole brain level (7) were written in English. Studies were excluded when (1) no original data was reported e.g., letters to the editor, meta-analyses, or review studies (2) study sample overlapped with those of another publication. In case of sample duplication, the studies from the same institution/cohort at the same period of time were identified and the study with the largest sample size was selected.

Endnote database (Version 9) was used to register all citations in our search. Duplicated studies were removed based on overlapping authorship, study description, year of publication and journal. The titles and abstracts of the citations were then screened by two independent authors (CT and HU) to determine their relevance for inclusion. Disagreements between authors were resolved by consensus or by the decision of a third author (YP). Full-text articles of the relevant citations were then assessed to determine whether the study met the predefined inclusion criteria (Supplementary material PRISMA flow charts, Figure 1-8).

2.2.1 Patient Selection

In the selection of patients from the included studies we used several diagnostic criteria. For bvFTD we only selected subjects who had been diagnosed with bvFTD, subjects with other FTD subtypes such as semantic, logopenic or non-fluent variant primary progressive aphasia were excluded. Studies including subjects with schizophrenia, psychosis or schizophreniform disorder were included in the SZ diagnostic group. This included both patients with chronic and first-onset psychosis. Subjects diagnosed with BD type I or II or first-episode mania were

included in the BD diagnostic group. For the ASD diagnostic group, subjects were included when diagnosed with ASD, Asperger syndrome or Pervasive Developmental Disorder (-Not Otherwise Specified) (PDD(-NOS)). Lastly, some studies included multiple diagnostic groups. For this case, we included separate patient groups in comparison with healthy controls.

2.3 Data recorded in the database

The following data of study characteristics were extracted from full-text articles: sample size and percentage of females in the group, age of the subjects at the time of MRI (mean age and standard deviation), diagnostic criteria used, global IQ or Full scale IQ (autism studies), mood state at time of MRI (bipolar disorder studies),field strength of the MRI scanner, slice thickness (in mm), smoothing applied (full width at half maximum in mm), threshold p-value, software used for analysis, nuisance covariates (Supplementary Table 1-8).

2.4 Data Extraction and Analysis of VBM studies

Separate analyses were performed comparing clusters of voxels with alterations in regional GM volume between patient groups and healthy controls. The analyses were performed at a cluster forming threshold (CFT; reported with each p value and Activation Likelihood Estimation (ALE) thresholds in the results, clusters with greater ALE values than this threshold were considered statistically significant) computed using a $p < 0.05$, false discovery rate (FDR) corrected (with no assumptions to correlations within the dataset) and a conservative minimum cluster volume of 200 mm3 using BrainMap's GingerALE (version 3.0.2). Peak coordinates for GM volume were extracted from eligible studies and were converted to MNI 152 template using the Lancaster transformation before analysis (25). The data in MNI coordinates were entered in BrainMap's GingerALE 3.0.2. The details of the procedure can be found on the website (http://brainmap.org/ale/index.html). Briefly, meta-analysis calculations were performed using the latest ALE algorithm in GingerALE. The likelihood of anatomical differences between groups was estimated on the basis of the coordinates reported by the included studies in this meta-analysis (26). A modeled map was constructed by combining foci at each voxel. The statistical maps were thresholded using a cluster-level, family-wise error (FWE) corrected $p < 0.05$. The coordinate of the weighed center was generated for each cluster. Within the cluster, the maximum ALE value and its coordinates were identified, which was then assigned to the MNI location of the cluster in the MNI 152 atlas. Based on the collected coordinates, single datasets were created by Ginger

ALE for each diagnostic group. Separated single dataset analyses were conducted to investigate GM alterations within each disorder group. After analyzing the single-dataset for each diagnostic group, we performed three pairwise conjunction analyses to study the overlap between: (1) bvFTD and SZ; (2) bvFTD and BD; (3) bvFTD and ASD. For the conjunction analyses we used a voxel threshold of $p < 0.05$ and a cluster-forming threshold of $p < 0.001$ (27).

2.5 Quality assessment

The study quality of all included articles was assessed using, the Joanna Briggs Institute (JBI) quality assessment tool (28). The nine-point checklist assesses the rigor of inclusion criteria, subject selection, measurement of exposure, measurement of condition, identification of confounders, strategies for confounders, measurement of outcome, and statistical analysis (Supplementary material Table 5-8). Due to the methodology of our included studies, "measurement of exposure" has not been taken into account in the final quality assessment. The JBI quality assessment tool is a recommended methodological quality (risk of bias) assessment tool and is widely used in VBM studies (29-31).

RESULTS

3.1 Search Results

A total of 13,205 studies were retrieved following our systematic search strategy for VBM studies contrasting GM volume alterations, of which 2,225 for bvFTD, 7,135 for SZ, 2,079 for BD, 1,766 for ASD. Ultimately, 258 studies met the final inclusion criteria and were included in our review. Of these, 24 studies concerned bvFTD (patients n=496, controls n=602), 150 SZ (patients n=7,094, controls n=7,332), 64 BD (patients n=3127, controls n=4248), and 20 ASD (patients n= 643, controls n= 641; Table 1, Supplementary Figure 1-4).

Overall, our search yielded a sample size of 11,360 patients and 12,823 controls in VBM studies. The details of the collected demographical data are displayed in Table 1, and demographics for each separate study can be found in Supplementary Table 1-4. Of note, some studies lacked information on sex distribution or age. In these cases, estimates of missing values for sex distribution and age were imputed with weighted means.

Additionally, PRISMA flowcharts (Supplementary Figure 1-4), characteristics of the included studies (Supplementary Table 1-4), images (axial MRI slides) for each analysis (Supplementary Figure 5-11), peak coordinates (Supplementary Table 9-15), reported ROI

coordinates for lower and higher values, and related brain regions are displayed in Supplementary material and GingerALE results in NIFTI file format are added as Supplementary files.

Table 1: Demographic data of the diagnostic groups

Gray matter	**Diagnosis**	**bvFTD**	**SZ**	**BD**	**ASD**
	Number of patients (female)	496 (~160)	7094 (~2617)	3127 (~1820)	643 (101)
	Number of healthy controls (female)	602 (~250)	7332 (~2986)	4248 (~2380)	641 (~100)
	Number of studies	24	150	64	20
	Mean age (patient)	62.0	~32.8	39.5	28.9
	Mean age (healthy control)	~64.2	~32.5	~37.9	29.1
Total	Number of subjects	1098	14426	7375	1284

bvFTD: behavioural variant frontotemporal dementia, **ASD:** autism spectrum disorders, **BD:** bipolar disorder, **SZ:** schizophrenia. (~: The number of the female population or the mean age has not been provided in some of the studies. Therefore, we calculated the estimated value)

3.1.1 Quality assessment

The overall scores of the quality assessment for each diagnostic group were displayed in Table 2. Between 93-97% of the included studies for each diagnostic group, fulfilled the quality criteria of the JBI quality assessment tool, indicating that the included studies were of high quality. A detailed overview of the quality assessment for each item per study can be found in the Supplementary materials (Supplementary Table 5-8).

Table 2: Quality assessment of voxel-based morphometry studies of gray matter included in the meta-analysis

Study	Inclusion criteria	Study subjects	Exposure	Measurement of condition	Confounding factors	Strategies for confounding factors	Outcome measurement	Statistical analysis	Final score٩
bvFTD	100%	83%	#	100%	100%	92%	100%	100%	96%
SZ	97%	77%	#	100%	100%	75%	100%	100%	93%
BD	100%	85%	#	100%	100%	97%	100%	100%	97%
ASD	100%	85%	#	100%	100%	90%	100%	100%	96%

ASD: autism spectrum disorder, **BD**: bipolar disorder, **bvFTD**: behavioral variant frontotemporal dementia, **SZ**: Schizophrenia,
= Not applicable
٩ Due to the methodology of our included studies, "exposure" has not been taken into account in the final score

3.2 Single-Dataset Analysis

3.2.1 Behavioral variant FTD

The number of the studies and sample demographics are displayed in Table 1. Whole brain coordinate-based meta-analysis of VBM studies demonstrated lower GM volume in bvFTD patients compared with controls in brain areas involving the bilateral frontal areas (superior, medial, inferior), bilateral cingulate (especially anterior part), bilateral caudate, putamen, globus pallidus, bilateral insula, temporal cortex (superior, medial, fusiform), amygdala, hippocampus, parahippocampus and the right uncus (Figure 1, Supplementary Table 9 & Supplementary Figure 5). No larger GM volume in the patient group was detected.

3.2.2 Schizophrenia

The number of the studies and sample demographics are displayed in Table 1. Regions of smaller GM volume relative to healthy controls were observed in the bilateral cingulate (especially anterior cingulate), the bilateral frontal and temporal lobes (superior, medial, inferior) insular, parietal areas (left predominant), bilateral caudate, bilateral thalamus, bilateral amygdala, left hippocampus and the left uncus. Only one statistically significant cluster was detected as larger GM volume in SZ pointing out the right precentral gyrus (Supplementary Table 10 & Supplementary Figure 6). When all volumetric alterations in SZ were combined, GM volumes in the anterior cingulate, frontal, temporal and insular lobes, thalamus, caudate, amygdala and hippocampus were significantly different compared to healthy controls (Figure 1, Supplementary Table 10 & Supplementary Figure 6).

3.2.3 Bipolar Disorder

The number of the studies and sample demographics are displayed in Table 1. Significantly smaller GM volume was found in the bilateral frontal lobes (superior, medial, inferior), bilateral cingulate (especially anterior cingulate), bilateral insula, bilateral temporal lobes (superior and medial), amygdala, and hippocampus. Although the larger volumes in putamen was highly reported in studies on BD, none of those clusters were significant in our analysis. The combination of smaller and larger GM volumes in BD revealed that volumetric brain alterations in BD were related with the bilateral prefrontal areas, anterior cingulate, insula, amygdala, hippocampus and temporal lobes (Figure 1, Supplementary Table 11 & Supplementary Figure 7).

3.2.4 Autism Spectrum Disorder

The number of the studies and sample demographics are displayed in Table 1. Patients with ASD showed significantly smaller GM volume, predominantly in the temporal areas. Lower GM volume was observed both in cortical areas including temporal (especially fusiform gyrus) and insular areas, as well as in subcortical areas, including amygdala, putamen and hippocampus. Although, some studies reported larger GM volumes especially in the frontal areas, no significant cluster was detected in the separate analysis of larger GM volumes in ASD. The combined analysis pointed out the putamen, and temporal areas including cortical temporal, fusiform, amygdala and parahippocampal areas. (Figure 1, Supplementary Table 12 & Supplementary Figure 8).

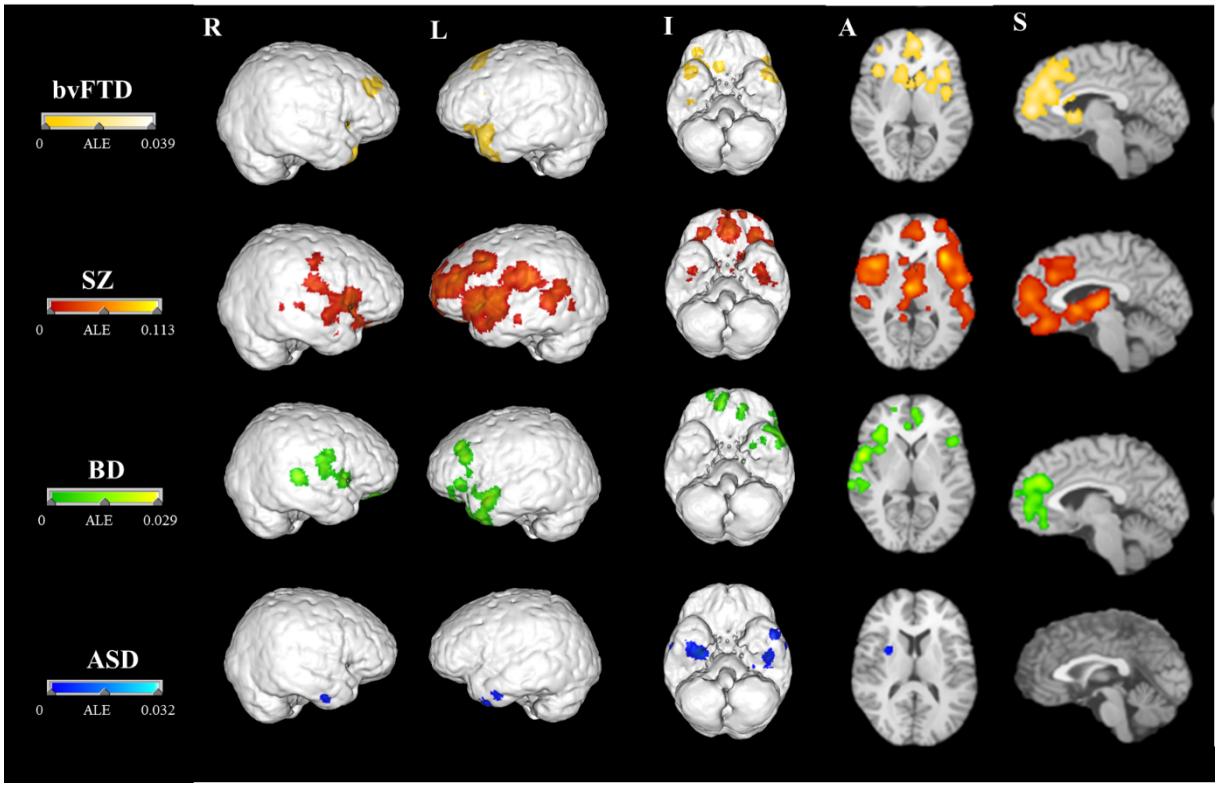

Figure 1: Meta-analytic results of regional gray matter alterations in the diagnostic groups. All results were thresholded at cluster-wise threshold $p < 0.05$ (FWE-corrected). The ALE-scores are demonstrated. For the coordinates, brain regions and detailed presentation of each axial slide for each disorder see supplementary material. R: right, L: left, I: inferior, A: axial, S: sagittal, bvFTD: behavioral variant frontotemporal dementia, SZ: schizophrenia, BD: bipolar disorder, ASD: autism spectrum disorders

3.3 Conjunction Analysis

Across all studies, the clear majority of peak voxels represented GM volumetric changes in patients (bvFTD, SZ, BD and ASD) compared with control individuals. Consistent GM alterations across all diagnostic groups highlighted included the amygdala, insula, cingulate cortex and the medial prefrontal cortex. (Figure 2, Supplementary Table 13-15 & Supplementary Figure 9-11). Although we did not conduct a direct volumetric analysis, basal ganglia involvement including caudate, putamen, and globus pallidus was more eminent in bvFTD. While GM alterations in caudate were recorded also in SZ and putamen in ASD, GM alterations in globus pallidus were not one of the statistically significant clusters in SZ, BD and ASD compared to their respective healthy controls. Of note, GM changes in thalamic area were more prominent in SZ whereas statistically significant clusters in this area were not observed in other diagnostic groups.

3.3.1 Overlapping structural brain abnormalities between behavioral variant FTD and schizophrenia

GM differences were indicated by conjunction analysis in the bilateral prefrontal areas (medial and inferior), anterior cingulate, insula, amygdala, hippocampus, caudate and the superior temporal lobe in both bvFTD and SZ compared with controls (Figure 2, Supplementary Table 13 & Supplementary Figure 9).

3.3.2 Overlapping structural brain abnormalities between behavioral variant FTD and bipolar disorder

Overlapping gray matter alterations between bvFTD and BD was observed in the medial and inferior prefrontal areas as well as insula, anterior cingulate, and the left superior temporal lobe (Figure 3, Supplementary Table 14 & Supplementary Figure 10).

3.3.3 Overlapping structural brain abnormalities between behavioral variant FTD and autism spectrum disorder

Conjunction analysis revealed overlapping areas with gray matter alterations between bvFTD and ASD in the temporal medial and inferior area, amygdala, uncus, putamen and insula (Figure 3, Supplementary Table 15 & Supplementary Figure 11).

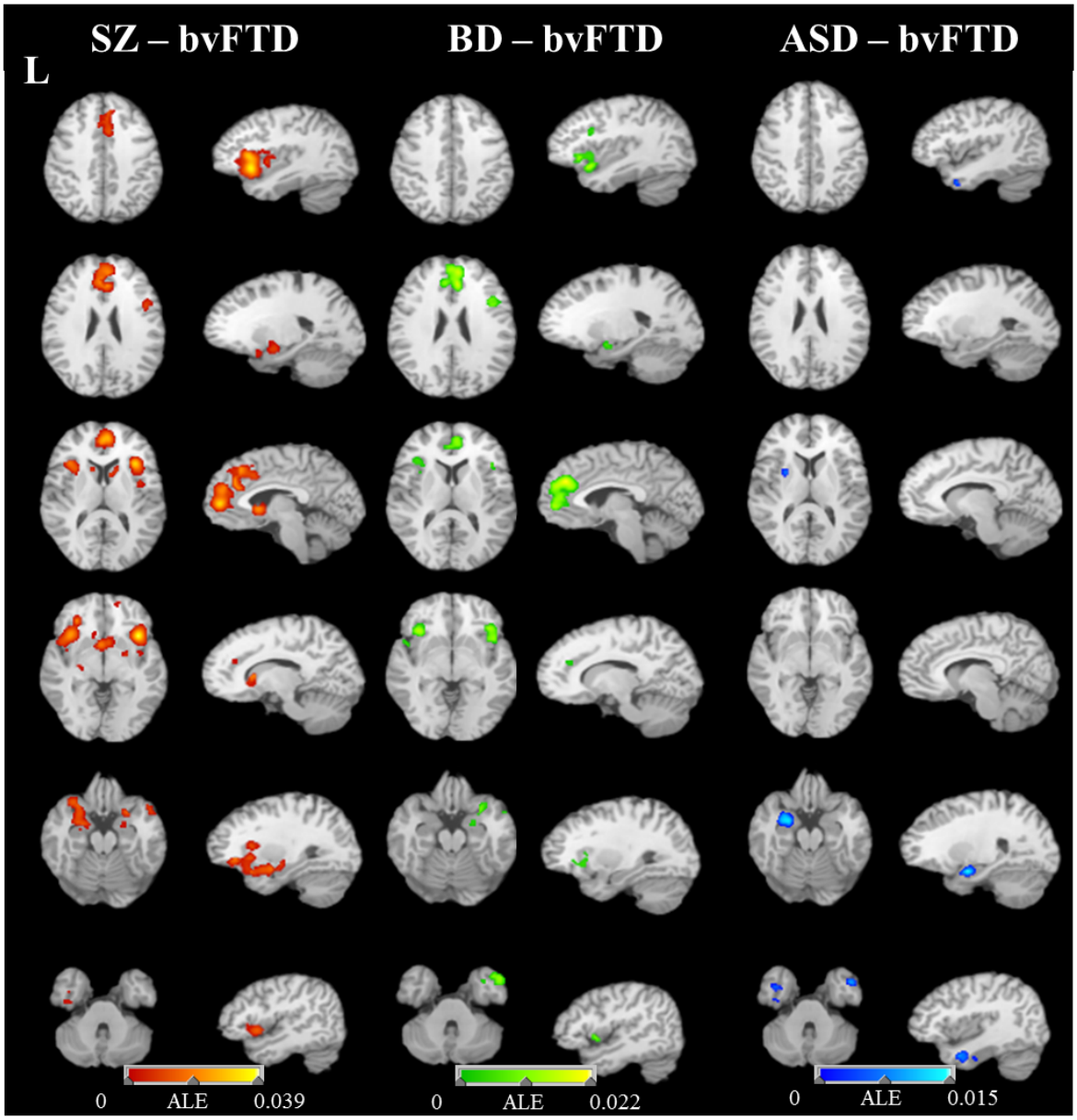

Figure 2: Meta-analytic results of overlapping gray matter alterations among the diagnostic groups. Brain regions involved in the conjunction analysis of behavioral variant frontotemporal dementia and each psychiatric diagnostic group. All results were thresholded at cluster-wise threshold $p < 0.05$ (FWE-corrected). The ALE-scores are demonstrated. For the coordinates, brain regions and detailed presentation of each axial slide for each disease group see supplementary material. L: left, bvFTD: behavioral variant frontotemporal dementia, SZ: schizophrenia, BD: bipolar disorder, ASD: autism spectrum disorders

DISCUSSION

In this cross-disorder analysis, we aimed to identify the overlapping anatomical correlates of bvFTD and PPD. We conducted a meta-analysis of structural neuroimaging studies in bvFTD, SZ, BD and ASD by using an unbiased technique, anatomical likelihood estimation. Brain GM volumetric alterations in the prefrontal, temporal, insular and limbic areas were observed

in bvFTD, SZ and BD, whereas GM volume changes prominently in temporal regions were detected in ASD. Our results identified the prefrontal cortex, temporal lobe, amygdala, insula, anterior cingulate cortex as overlapping brain areas with structural alterations in bvFTD and PPD, especially in SZ and BD. This shared morphometric signature might explain the overlapping clinical phenotypes of those disorders, and open the doors for the study of common pathophysiological pathways in both types of disorders.

Brain structural abnormalities have been widely reported in SZ (32), BD (33) and ASD (34), but there is no published meta-analysis reporting the overlapping structural brain abnormalities between bvFTD and those found in PPD, despite their significant clinical overlap. In line with the literature, beyond frontotemporal cortical areas, the anterior cingulate, insular and subcortical areas including caudate, putamen, globus pallidum and amygdala, were affected in bvFTD (35-37). Remarkably, regional volume differences were observed in the same areas in SZ and BD as well. Conjunction analysis confirmed that prefrontal, cingulate, insular lobes and amygdala were the shared regions with GM alterations, showing structural alterations in bvFTD and SZ and BD. Not surprisingly, these results have already been published as the overlapping brain areas between SZ and BD (38), but it has not been associated with bvFTD before. Interestingly, over the years, the same anatomical areas have been reported by different authors using different terms such as the neuroanatomical localizations of psychiatric disorders (39, 40), brain morphometric changes in SZ (32, 41), BD (42, 43) and ASD (34, 44). Additionally, similar areas have been reported as the atrophy pattern of bvFTD (35, 36), anatomical model of apathy (45-47), disinhibition (48, 49), loss of empathy (50, 51), emotion regulation system (45, 47, 51), social cognition (6, 52), and limbic-thalamo-prefrontal cortical circuitry (53, 54). Another important point is that bvFTD (55, 56) and the psychiatric disorders studied here are heritable disorders with variable genetic architectures (57-62). Whereas monogenetic causes underlie bvFTD in 20-30% of cases (63), SZ and BD are highly polygenic (58, 61). SZ and BD share polygenic overlap, whereas ASD is characterized by both polygenicity and a low percentage (< 5%) of rare mutations (58, 60-62, 64). It is conceivable that through various mechanisms of action, these social brain disorders affect the same neuro-anatomical networks (57, 62). Our radiological approach is pertinent because neuroimaging studies may offer clues about the effects of the potential shared genetic etiology. Recent ENIGMA-GWAS collaborations have hypothesized that if some brain regions show volumetric case-control differences and others not, these areas may be more vulnerable to the genetic and environmental risk factors, and they have termed it

"selective brain region vulnerability" (65). Indeed, it was found that selective brain region vulnerability overlapped between SZ and BD and was positively associated with their respective genetic background (65). Consistent with these results, a large body of literature has reported substantial genetic etiologic overlap between SZ and BD (66-69). The results of the present study raise the question whether an etiological overlap between SZ, BD and bvFTD might exist.

Apart from the overlapping areas, our separate group analyses were in line with previous meta-analyses focusing on the GM morphometric changes in bvFTD (35), SZ (32, 41, 70), BD (42, 43, 71). However, there was a discrepancy between our results and a large ENIGMA study suggesting larger frontal lobe volumes in ASD (34). The potential explanations of this inconsistency might be the use of different volumetric analysis techniques. In this mentioned study (34), FreeSurfer cortical thickness analysis has been used whereas we only included VBM studies in our meta-analysis to avoid the effect of the different neuroimaging data processing techniques on the results. Secondly, the effect might be explained by the fact that their sample size was younger than the study populations we included in our meta-analysis. Since our approach is bvFTD centered which is an adult-onset disorder, we excluded the pediatric population in our study. Consistent with our interpretation, a large longitudinal neuroimaging study on ASD has shown abnormally high volumes (especially in frontal areas) in early childhood, typical values between 10 and 15 years of age, and then abnormal further decline into adulthood (44). Although a numerous explanation such as age and medication effect has been proposed, the mechanism of increased/larger volumes in PPD remains unclear (20). However, this discussion is beyond the scope of this study. Nevertheless, abnormal cortical brain volumes (smaller or larger) in frontotemporal areas occur in ASD which supports our argument that ASD is also a frontotemporal lobe disorder.

This is the first study focusing on the overlapping neuroanatomical signatures in bvFTD and PPD. Although our study contains the largest sample size in the literature there are some limitations that should be addressed. First of all, we included the studies that reported significant clusters and displayed the ROI coordinates. Therefore, other large sample size neuroimaging studies that did not display the ROI coordinates were excluded. Secondly, we included only VBM studies for the GM structural brain changes analysis. Even though it excluded a large number of studies, we restricted ourselves to those methodologies, because variability in the neuroimaging data acquisition, processing, and analysis protocols can affect the sensitivity and apparent variability of other brain imaging measures, making it challenging

to compare different studies. Since negative results might likely have not been published, another strong concern in all meta-analyses is publication bias. On the other hand, our results were in line with large sample size studies like ENIGMA that collects and assesses extracted data and other meta-analyses, suggesting that a potential publication bias or our exclusion criteria did not create a major bias. Additionally, since the prevalence of bvFTD is lower than PPD and due to our strict inclusion criteria, the bvFTD sample size was smaller than those of SZ and BD. Moreover, since we could not use individual data, we were unable to conduct direct volume comparisons between diagnostic groups. Our methodology provided the statistically significant clusters only between patient groups and their respective age and sex matched/ corrected control groups. Therefore the design of the current study does not provide any data to directly compare atrophy severity between bvFTD and PPD. However, we observed GM differences between bvFTD and PPD especially in basal ganglia areas which need to be tested by future better designed methodologies. Moreover, although we cannot generalize our results to all genetic or sporadic subtypes of FTD, this novel approach could initiate future more detailed studies focusing on the relationship between bvFTD and PPD.

To conclude, we found considerable overlap in neuroanatomical involvement between 2 diagnostic groups classified as neurodegenerative (bvFTD) versus non-neurodegenerative (PPD) pointing to shared genetic or environmental selective brain region vulnerability that can explain their clinical overlap. We believe that such a cross-disorder point of view might allow identification of shared disease mechanisms and development of analogous disease modifying treatments.

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SUPPLEMENTARY MATERIALS

Contents

Supplementary Method: Full electronic search strategy for the study selection of voxel-based morphometry studies of gray matter

Search 1: bvFTD
"Frontotemporal Dementia"[Mesh] OR frontotemporal dementi* [tiab] OR fronto-temporal dementi* [tiab] OR pick disease* [tiab] OR pick's disease* [tiab] OR "Frontotemporal Lobar Degeneration"[Mesh] OR frontotemporal lobar degeneration* [tiab] OR frontotemporal lobe degeneration* [tiab] OR fronto-temporal lobar degeneration* [tiab] OR fronto-temporal lobe degeneration* [tiab] OR FTD [tiab]

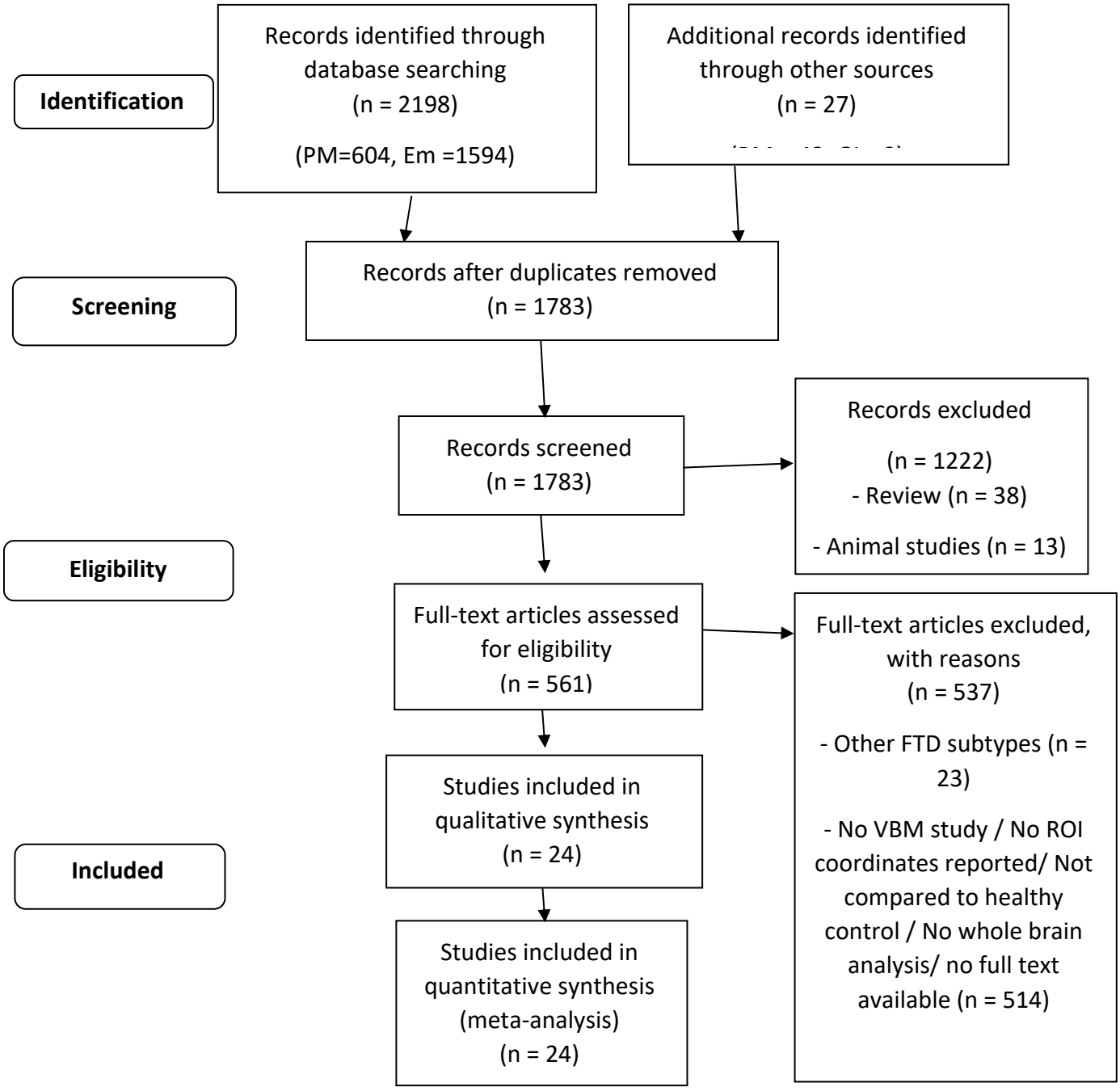
Search 2: Schizophrenia
"Schizophrenia"[Mesh] OR schizophrenia* [tiab] OR schizophrenic disorder* [tiab] OR schizophrenic* [tiab] OR dementia praecox [tiab]

Search 3: Bipolar disorder
"Bipolar Disorder"[Mesh] OR bipolar disorder* [tiab] OR manic depressive psychos* [tiab] OR bipolar affective disorder* [tiab] OR bipolar affective psychos* [tiab] OR bipolar depression [tiab] OR manic disorder* [tiab] OR manic depression [tiab] OR bipolar illness [tiab] OR bipolar illness [tiab]

Search 4: Autism spectrum disorder
"Autism Spectrum Disorder"[Mesh] OR autism [tiab] OR autistic* [tiab] OR kanner syndrome [tiab] OR kanners syndrome [tiab] OR kanner's syndrome [tiab] OR asperger* [tiab] OR rett syndrome [tiab] OR pervasive developmental disorder* [tiab] OR PDD* [tiab]

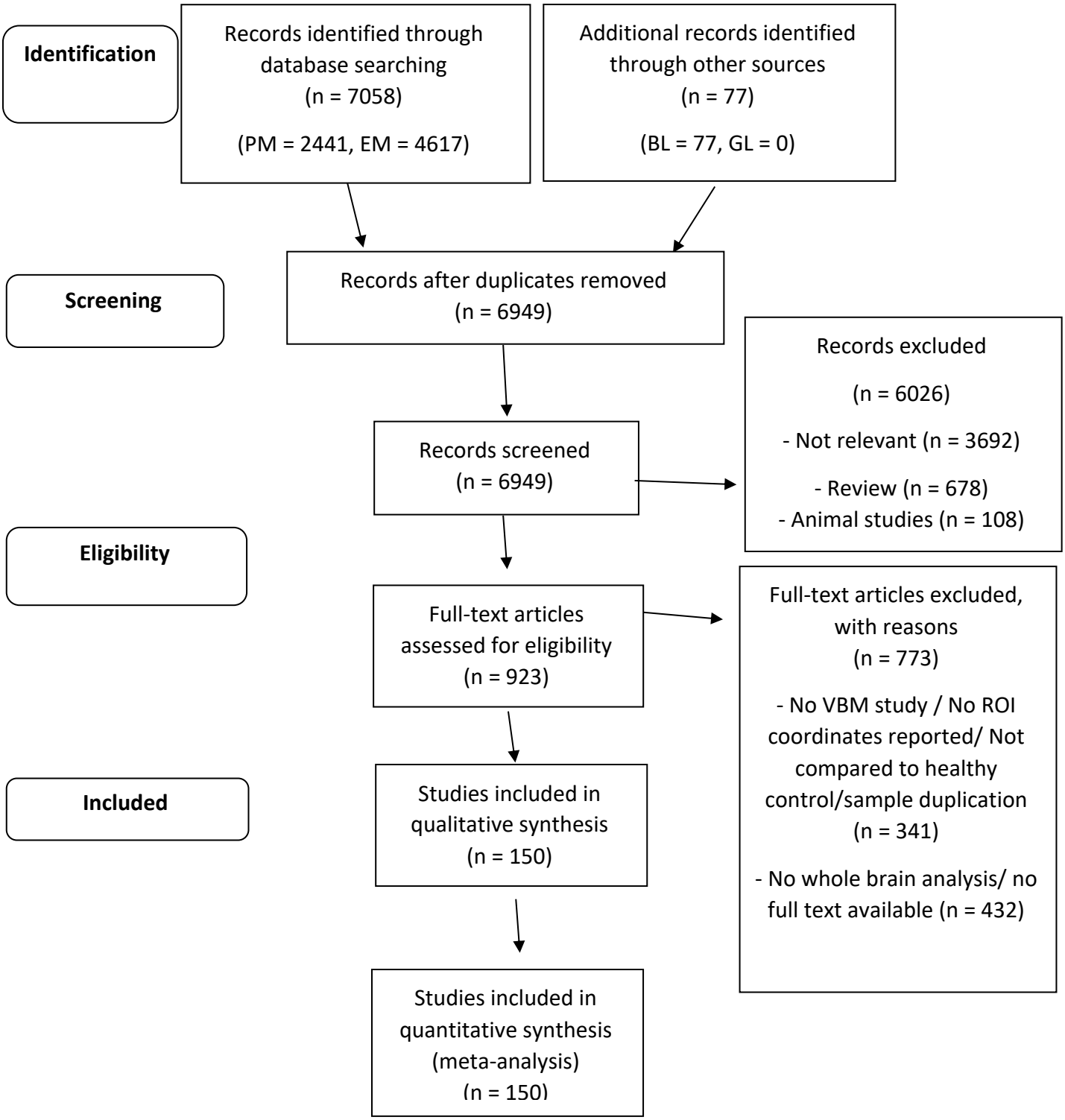
Search 5: Voxel-based morphometry & Gray matter
Voxel based morphometr* [tiab] OR VBM [tiab] OR voxel based [tiab] OR voxel wise [tiab] OR morphometr* [tiab] OR "Gray Matter"[Mesh] OR gray matter* [tiab] OR grey matter* [tiab]

Supplementary Figure 1: PRISMA flowchart for the study selection of structural neuroimaging studies of gray matter in bvFTD



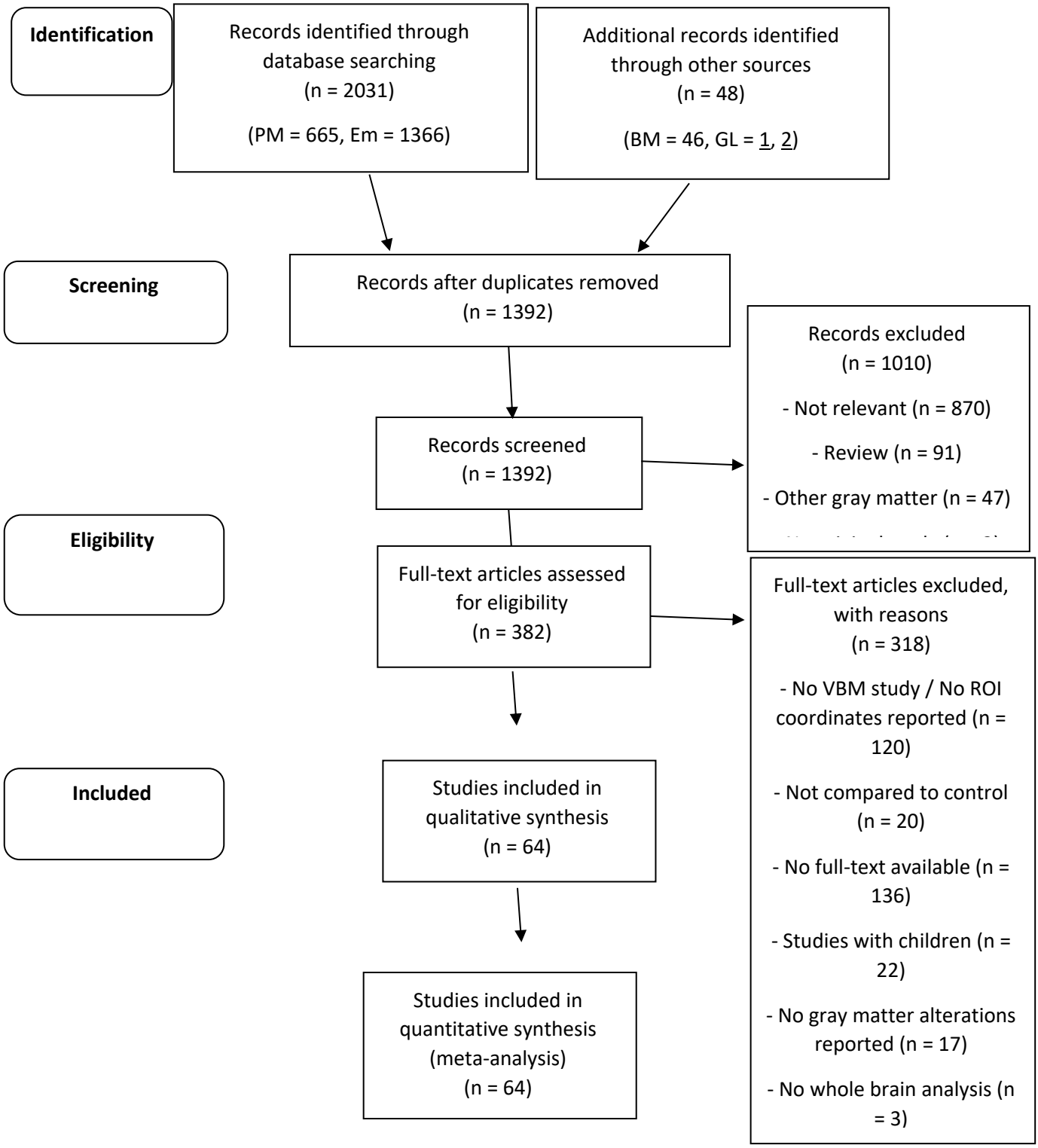
BM = Brainmap. **EM** = Embase. **GL** = Gray literature. **PM** = Pubmed.

Supplementary Figure 2: PRISMA flowchart for the study selection of structural neuroimaging studies of gray matter in SZ



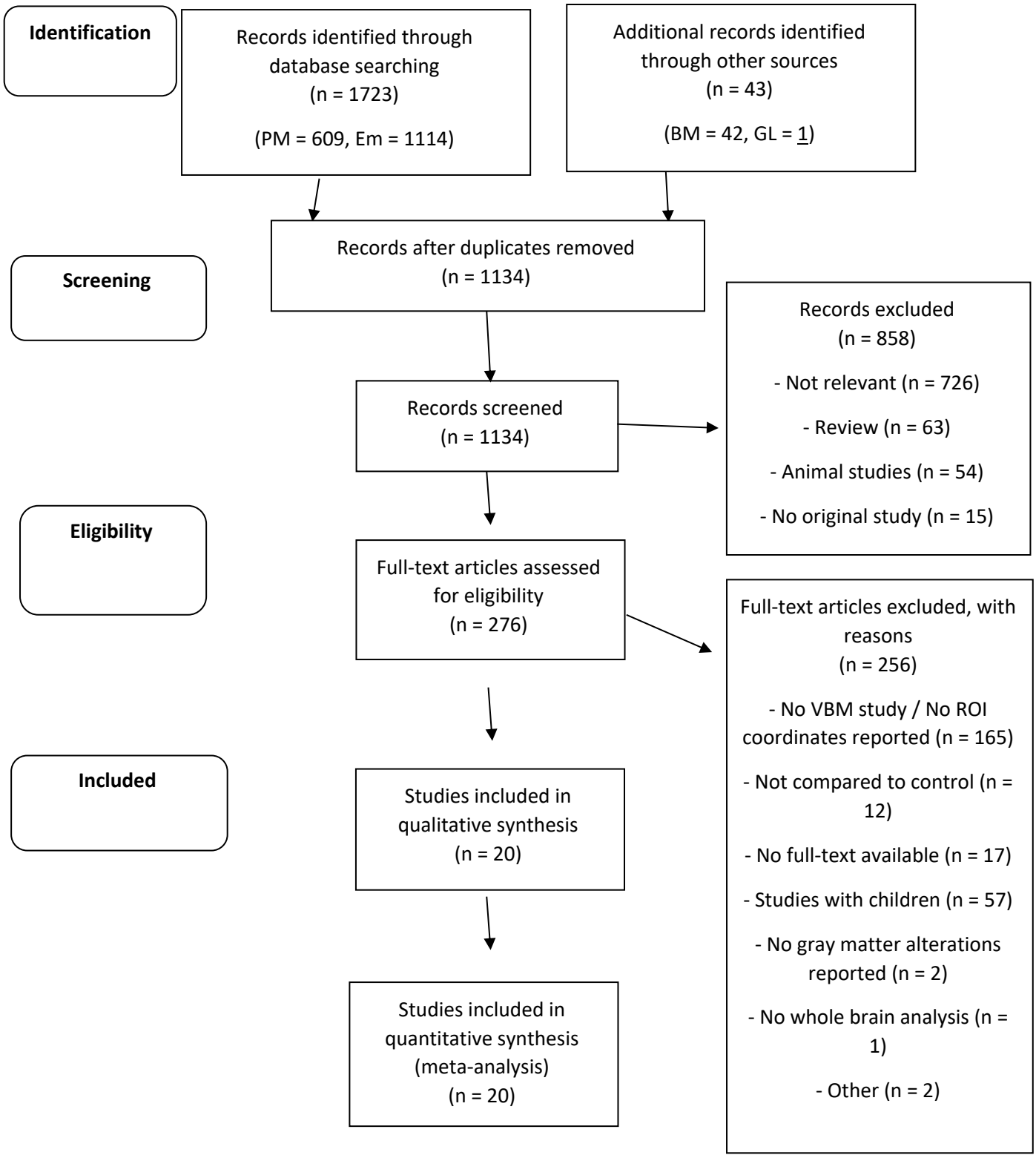
BM = Brainmap. **EM** = Embase. **GL** = Gray literature. **PM** = Pubmed.

Supplementary Figure 3: PRISMA flowchart for the study selection of structural neuroimaging studies of gray matter in BD



BM = Brainmap. **EM** = Embase. **GL** = Gray literature. **PM** = Pubmed.

Supplementary Figure 4: PRISMA flowchart for the study selection of structural neuroimaging studies of gray matter in ASD



BM = Brainmap. **EM** = Embase. **GL** = Gray literature. **PM** = Pubmed.

Supplementary Table 1: Characteristics of voxel-based morphometry studies of gray matter in bvFTD included in the meta-analysis

Author	Sample (female)	Age mean/median (SD or min-max)	Diagnostic criteria	Scanner	Thickness	FWHM	Threshold P-value	Software	Covariances
Agosta et al. 2009	bvFTD 31 (10) HC 56 (32)	58.4 (10.9) 66.5 (9.4)	Neary et al, 1998	1.5T	3.0mm	12mm	Corrected P<0.05	SPM5	Age sex disease severity corrected
Agosta et al. 2012	bvFTD 13 (4) HC 25 (10)	61.0 (7.5) 64.2 (5.8)	Neary et al, 1998	3.0T	5.0mm	8mm	Uncorrected P<0.001	SPM8	Age sex matched
Ash et al. 2009	bvFTD 12 (5) HC 10 (2)	64.8 (13.2) 69.5 (5.1)	Neary et al, 1998	1.5T/3.0 T	2.0mm	8mm	Uncorrected P<0.001 and corrected P<0.05	SPM5	Age education matched
Baez et al. 2019	bvFTD 16 (9) HC 22 (15)	65.8 (7) 62.5 (7.1)	Rascovsky et al. 2011	1.5 T	1.6mm	12mm	P<0.05	SPM8	ICV
Boccardi et al. 2005	FTD 9 (2) HC 26 (15)	62.0 (5.0) 69.0 (8.0)	Neary et al, 1998	1.5T	1.3mm	8mm	Corrected P<0.05	SPM99	Age corrected
Buhour et al. 2017	bvFTD 15 (5) HC 15 (9)	67.0 (8.2) 66.5 (8.3)	Rascovsky et al. 2011	1.5T	1.5mm	12mm	Corrected P<0.05	SPM5	Age sex education matched
Delvecchio et al. 2019	bvFTD 21 (10) HC 20 (15)	72.1(6.4) 49.8 (16.5)	Rascovsky et al. 2011	3T	1mm	6mm	Corrected p<0.05	SPM12	Age Sex
Filippi et al. 2013	bvFTD 12 (4) HC 30 (14)	59.0 (8.0) 59.0 (5.0)	Rascovsky et al. 2011	3.0T	1.0mm	8mm	Corrected P<0.05	SPM8	Aged matched
García-Cordero et al. 2015	bvFTD 11 (6) HC 14 (4)	64.8 (5.0) 57.2 (12.3)	Neary et al, 1998; Rascovsky et al. 2011	1.5T	1.0mm	8mm	Corrected P<0.05	SPM8	Age sex education matched
Grossman et al. 2004	bvFTD 14 (?) HC 12 (?)	63.1 (12.2) 68.5 (9.4)	Neary et al, 1998	1.5T	1.3mm	12mm	Uncorrected P<0.001	SPM99	
Kanda et al. 2008	FTD 13 (0) HC 20 (0)	64.9 65.2	Neary et al, 1998	1.5T	1.5mm	12mm	Uncorrected P<0.001 and corrected P<0.01	SPM2	Age and sex matched
Kim et al. 2007	FTLD-T 6 (1) FTLD-U 8 (2) HC 61 (35)	67.7 (6.3) 60.0 (10.0) 68.0 (8.0)	McKhann et al. 2001	n.a.	n.a.	n.a.	Corrected P<0.05	SPM2	Age sex corrected
Lagarde et al. 2013	bvFTD 16 (7) HC 18 (11)	69.3 (10.0) 67.8 (5.2)	Neary et al, 1998; Rascovsky et al. 2007	3T	1.0mm	8mm	Uncorrected P<0.001 and corrected P<0.05	SPM8	Age and sex corrected
Lee et al. 2014	bvFTD 14 (4) HC 14 (4)	60.8 (6.9) 62.2 (4.7)	Neary et al, 1998; Rascovsky et al. 2011	3.0T/4.0 T	3.0mm/3.5mm	8mm	Corrected P<0.05	SPM8	Age and sex matched
Libon et al. 2009	bvFTD 51 (?)	61.3 (10.6) 68.7 (8.1)	Mckhann et al.	1.5T/3T	1.3mm/1.0mm	4mm	Corrected P<0.05	SPM5	Age and education

	HC 42 (?)		2001; The Lund and Manchester Groups 1994						matched controls
Pardini et al. 2009	FTD 22 (10) HC 14 (?)	60.3 (8.3) n.a.	n.a.	1.5T	1.5mm		Uncorrected P<0.0001	SPM5	Age and education matched
Pereira et al. 2009	FTD-U 9 (4) FTD-T 6 (1) bvFTD 4 (1) FTD-A 3 (1) HC 25 (11)	64.0 (5.7) 61.8 (9.7) 59.8 (7.5) 65.3 (13.2) 63.8 (7.2)	Neary et al, 1998	1.5T	1.5mm	n.a.	Corrected P<0.05	SPM5	Age and sex matched
Rabinovici et al. 2008	FTLD 18 (3) HC 40 (23)	62.5 (8.7) 63.5 (5.8)	McKhann et al. 2001	1.5T	n.a.	12mm	Corrected P<0.05	SPM2	Age sex corrected
Rosen et al. 2002	bvFTD 8 (2) HC 20 (4)	61.8 (45-73) 65.4 (38-82)	Neary et al, 1998	1.5T	1.5mm	12mm	Corrected P<0.05	SPM99	Age and sex matched
Seeley et al. 2008	bvFTD CDR(0,5) 15 (6) bvFTD CDR(1) 15 (5) bvFTD CDR(2-3) 15 (8) HC 45 (22)	65.9 (8.3) 64.3 (8.9) 62.3 (10.3) 68.3 (7.9)	Neary et al, 1998	1.5T	1.5mm	12mm	Corrected P<0.05	SPM2	Age and sex corrected
Whitwell et al. 2005	FTD-U 9 (2) PiD 7 (3) Tau Exon 10+16 5 (2) HC 20 (9)	60.8 (2.8) 51.6 (4.4) 54.9 (2.2) 55.7 (2.8)	McKhann et al. 2001	1.5T	1.5mm	8mm	Uncorrected P<0.0001 and corrected P<0.05	SPM99	Age sex MMSE score corrected
Whitwell et al. 2009	IVS10+16 4 (1) IVS 10+3 3 (0) N279K 3 (3) S305N 2 (2) P301L 4 (2) V337M 3 (2) HC 19 (8)	56 (51-62) 46 (36-49) 49 (43-51) 33.5 (34-37) 52 (45-65) 56 (49-60) 53 (27-65)	Neary et al, 1998	1.5T/3T	n.a.	8mm	Corrected P<0.05	SMP5	Age sex and field strength corrected
Whitwell et al. 2004	Tau positive FTD 9 (?) Tau negative FTD 8 (?) HC 20 (?)	52.0 (8.7) 62.0 (6.8) n.a.	Neary et al, 1998	1.5T	1.5mm	8mm	Corrected P<0.05	SPM99	

Zamboni et al. 2008	FTD 62 (33) HC 14 (7)	61.2 (1.0) 60.6 (1.7)	Neary et al, 1998	1.5T	1.5mm	12mm	Corrected P<0.05	SPM5	Age and education corrected

Supplementary Table 2: Characteristics of voxel-based morphometry studies of gray matter in SZ included in the meta-analysis

Author	Sample (female)	Age (SD)	Diagnostic criteria	Scanner	Thickness	FWHM	Threshold p-value	Software	Covariances
Amann et al., 2016	SZ: 45 (19) HC: 45 (19)	SZ: 43.2 (9.1) HC: 43.3 (9.9)	DSM IV	1.5T	1 mm	9.4 mm	P=0.01	FSL-VBM	Age-sex matched
Ananth et al., 2002	SZ: 20 (10) HC: 20 (10)	SZ: 37.8 (9.5) HC: 38.6 (9.7)	ICD 10 R	2 T	1.5 mm	12 mm	P<0.05	SPM 99	Age-sex-social class- ethnicity matched
Antonova et al., 2005	SZ: 40 (15) HC: 40 (15)	SZ: 40.49 (11.67) HC: 33.72 (12.37)	DSM IV	1.5 T	1.5 mm	12 mm		SPM 99	No difference age, sex, ethnicity, social class
Anderson et al. 2015	Ultratretment resistant SZ: 15 (2) Treatment resistant SZ: 19 (5) HC: 20 (3)	UTR-SZ: 34.3 (7.1) TR-SZ: 33.3 (8.0) HC: 33.3 (8.4)		3 T		7 mm		FSL-VBM	
Asami et al., 2012	First episode SZ: 21 (3) HC: 23 (4)	FESZ: 22.5 (6.7) HC: 22.9 (3.8)	DSM III-IV	1.5 T	1.5 mm	8 mm	P<0.05	SPM 5	matched for age, gender, parental socioeconomicstatus
Beneditti et al., 2009	SZ: 24 (10) HC: 20 (13)	SZ: 37.2 (10.23) HC: 24.8 (6.2)	DSM IV	3 T	5 mm	10 mm	P<0.001 uncorrected	SPM 5	
Bassitt et al., 2007	SZ: 50 (12) HC: 30 (9)	SZ: 31.7 (7.1) HC: 31.2 (7.6)	DSM IV	1.5 T	1.2 mm	12 mm	P< 0.001	SPM 2	No difference age gender
Berge et al., 2011	First psychotic episode: 21 (9) HC: 20 (12)	FPE: 24.81 (4.3) HC: 25.3 (3.7)	DSM IV		1.4 mm	8 mm	P< 0.001 uncorrected	SPM 5	matching age, sex, and handedness,
Bonilha et al., 2008	SZ: 14 (3) HC:13 (2)	SZ: 40 (7) HC: 35 (8)	DSM IV	3 T	1 mm	10 mm		SPM 5	
Bose et al., 2009	SZ: 34 (0) HC: 33 (0)	SZ: 40 (12) HC: 40 (10)	DSM IV	1 T	1.6 mm	12 mm	P< 0.05	SPM 99	Age gender matched
Brown et al., 2011	SZ: 17 (9) HC: 21 (11)	SZ: 44.8 (6.8) HC: 45 (10.2)	DSM IV	1.5 T	1 mm	8 mm	P<0.001	SPM 5	
Bodnar et al., 2014	Persistant negative symptoms SZ: 16 (3) Non PNS SZ: 46 (14) HC: 60 (20)	PNS-SZ: 24.2 (4.3) NPNS-SZ: 23.7 (3.4) HC: 24.8 (3.3)	DSM IV	1.5 T	1 mm	20 mm	P< 0.05	VBM8	
Borgwardt et al., 2009	SZ (Monozygotic twins concordant	MZ con psychotic: 37.7 (9.1)	DSM IV	1.5 T	1.5 mm	8 mm	P< 0.05	SPM 2	Monozigotic twins and no difference with controls in terms

	psychotic): 28 (6) SZ (MZ twins discordant psychotic): 9 (3) MZ controls 34 (10)	MZ disc psychotic: 33.8 (13.1) MZ control: 39.3 (9.5)							of age, sex education, sociodemocraphi factors
Cascella et al., 2010	Non deficit SZ: 31 (10) Deficit SZ: 19 (3) HC: 90 (47)	NDSZ: 44.3 (10.3) DSZ: 35.1 (11.9) HC: 46.3 (12.7)	DSM IV	1.5 T	1.5 mm	8 mm	P< 0.05	SPM 5	
Chow et al., 2011	SZ: 29 (18) HC: 34 (17)	SZ: 30.7 (8.5) HC: 27.8 (10.1)	DSM III-R, DSM IV	1.5 T	1.5 mm	12 mm	P< 0.05	SPM5	
Chua et al., 2006	FEP patients: 26 (17) HC: 38 (22)	FEP patients: 32 (10) HC: 33 (8.1)	DSM IV	1.5 T	3 mm	4.4 mm	P< 0.05	BAMM	Difference between Age, sex and IQ not significant
Cooke et al., 2008	SZ: 52 (12) HC: 30 (6)	SZ: 38.35 (9.89) HC: 32.13 (12.38)	DSM IV	1.5 T	5 mm	8 mm	P< 0.001 uncorrected	SPM 2	Difference between Age, sex not significant
Cui et al., 2011	Paranoid SZ: 23 (7) HC: 36 (15)	Paranoid SZ: 24.78 (5.09) Controls: 26.56 (6.7)	DSM IV	3 T	1 mm	6 mm	P< 0.001	SPM 5	Difference between Age, sex not significant
Chen et al., 2014	SZ: 86 (39) HC: 86 (40)	SZ: 24.52 (0.91) HC: 25.03 (1.00)	DSM IV	3 T	1 mm	8 mm	P<0.05 corrected	SPM 2	Age and sex matched
Corradi-Del'Ácqua et al., 2012	SZ: 68 (25) HC: 77 (37)	SZ: 40.15 (12.06) HC: 39.63 (10.73)	DSM IV	1.5 T	5mm	12 mm	P< 0.05 corrected	SPM 5	
Deng et al., 2009	SZ re-scan within 3 weeks: 10 (6) SZ re-scan beyond 3 weeks: 10 (5) HC: 11 (6)	SZ re-scan within 3 weeks: 29.9 (13.5) SZ re-scan beyond 3 weeks: 26 (10.0) HC: 28.0 (11.7)	DSM IV	1.5 T	3 mm	8 mm	P< 0.001	SPM 2	
Dazzan et al., 2012	Ultra-high risk developed SZ: 19 (7) HC: 74 (37)	UHR-SZ: 18.5 (3.4) HC: 20.7 (3.5)	DSM III R-IV	1.5 T	1.5 mm	12 mm	P< 0.001 uncorrected	SPM 5	
Dean et al., 2020	SZ with catatonia: 43 (11) SZ without catatonia: 43 (9) HC: 86 (22)	SZ with catatonia: 27.4 (8.15) SZ without catatonia: 27.9 (6.63) HC: 29.9 (9.24)	DSM IV	3 T	1 mm	6 mm	P< 0.05 uncorrected	CAT12	Age and sex matched

Delvecchio et al., 2017	SZ: 61 (25) HC: 59 (24)	SZ: 40.8 (11.2) HC: 40.2 (11.3)	DSM IV	1.5 T	1.25 mm	6 mm	P< 0.001 uncorrected	SPM 12	Age and sex matched
Ebdrup et al., 2010	SZ: 38 (12) HC: 43 (13)	SZ: 26.2 (5.7) HC: 26.9 (5.7)	DSM IV	3 T	1 mm	8mm	P< 0.05 corrected	SPM 5	Age sex socio-economic status matched
Euler et al., 2009	SZ: 20 (2) HC: 23 (7)	SZ: 43.26 (10.5) HC: 43.30 (11.9)	DSM IV	1.5 T	1.5 mm	12 mm	P<0.05	SPM 5	
Egashira et al., 2014	Late onset SZ: 22 (18) Early onset SZ: 24 (16) HC: 41 (33)	LOSZ: 58.3 (10.6) EOSZ: 58.2 (8.4) HC: 58.8 (8.8)	DSM IV	1.5 T	1 mm	8 mm	P< 0.001 uncorrected	SPM 8	No statistical difference between age, sex, education
Foong et al., 2001	SZ: 25 (6) HC: 30 (8)	SZ: 37.3 (6.7) HC: 35.1 (7.2)	DSM IV	1.5 T	5 mm	10 mm	P< 0.05 corrected	SPM 99	
Frascarelli et al., 2015	SZ >10 years: 15 (6) SZ ≤ 10 years: 18 (10) HC: 24 (15)	SZ >10 years: 42.7 (7.4) SZ ≤ 10 years: 29.2 (8.6) HC: 30.3 (10.2)	DSM IV	3 T	1 mm	8 mm	P< 0.001 uncorrected	SPM 8	
Fukuta et al., 2013	SZ: 40 (40) HC: 50 (50)	SZ: 44.4 (8.0) HC: 46.8 (8.2)	DSM IV	1.5 T	1.5 mm	12 mm	P< 0.05 corrected	SPM 5	Only female population, age matched controls
Garcia-Marti et al., 2008	SZ: 17 (0) HC: 19 (0)	SZ: 35.71 (6.11) HC: 33.11 (7.61)	DSM IV	1.5 T	1.25 mm	8 mm	P< 0.05 corrected	SPM 2	Only male population, age matched controls
Giuliani et al., 2005	SZ: 41 (12) HC: 34 (17)	SZ: 39.0 (5.6) HC: 34.7 (7.2)	DSM-III-R DSM-IV	1.5 T	1.5 mm	12 mm	P< 0.05 corrected	SPM 2	
Garcia-Marti et al., 2012	SZ: 22 (0) HC: 28 (0)	SZ: 29.78 (11.68) HC: 31.89 (11.01)	DSM IV	1.5 T	1.25 mm	8 mm	P< 0.05 corrected	SPM 5	Only male population, age matched controls
Gong Q et al., 2015	SZ Japanese: 28 (9) HC Japanese: 28 (9) SZ African-Caribbean: 18 (13) HC African-Caribbean: 18 (13) SZ White Caucasian: 29 (14) HC White Caucasian: 29 (14) SZ Chinese: 50 (25) HC Chinese: 50 (25)	SZ Japanese: 25.1 (1.07) HC Japanese: 25 (0.71) SZ African-Caribbean: 26.3 (1.45) HC African-Caribbean: 26.6 (1.62) SZ White Caucasian: 26.5 (0.96) HC White Caucasian	DSM V	3 T	Japanese: 1mm African-Caribbean: 1.2mm White Caucasian: 1.2 mm Chinese: 1mm	8 mm	P< 0.05 corrected	SPM 8	Sex and age matched controls

		: 26.2 (0.97) SZ Chinese: 24.3 (0.87) HC Chinese: 24.3 (0.87)							
Gong X et al., 2014	DISC I gene SZ: 46 (19) HC: 24 (10)	DISC I gene SZ: 24.2 (5.7) HC: 28.3 (5.9)	DSM IV	1.5 T	1.8 mm	8 mm	P< 0.05 corrected	SPM 5	Age sex ethnicity matched
Guo F et al., 2019	SZ: 33 (17) HC: 33 (17)	SZ: 24.3 (8.8) HC: 23.8 (8.4)	DSM V	3 T	1 mm	3 mm	P< 0.05 corrected	FMRIB	Age and sex matched controls
Guo JY et al., 2015	SZ: 33 (14) HC: 71 (28)	SZ: 34.12 (0.63) HC: 34.97 (0.67)	DSM III-R	1.5 T			P< 0.05 corrected	FMRIB	
Guo W et al., 2014	SZ: 20 (4) HC: 43 (18)	SZ: 23.40 (4.35) HC: 23.67 (2.80)	DSM IV	3 T	1.1 mm	8 mm	P<0.001 uncorrected	SPM 8	
Guo X et al., 2014	SZ: 51 (18) HC: 41 (17)	SZ: 22.5 (4.1) HC: 22.8 (3.9)	DSM IV	3 T	1.1 mm	8 mm	P< 0.05 corrected	SPM 8	
Guo X et al., 2013	Short term SZ: 27 (11) Long term SZ: 30 (14) HC: 30 (14)	Short term SZ: 25.1 (6.3) Long term SZ: 25.7 (6.7) HC: 25.6 (6.7)	DSM IV	1.5 T	1.8 mm	8 mm	P< 0.05 corrected	SPM 8	
Ha TH, 2004	SZ: 35 (14) HC: 35 (14)	SZ: 27.8 (6.2) HC: 27.3 (6.7)	DSM IV	1.5 T	1.5 mm	8 and 12 mm (2 times smootin g)	P<0.05 corrected	SPM99	Sex and age matched
Herold R, 2009	SZ: 18 (7) HC: 21 (10)	SZ: 28.7 (10.3) HC: 27.4 (6.5)	DSM IV	1 T	2 mm	8 mm	P< 0.05 corrected	SPM 2	
Hirao K et al., 2008	SZ: 20 (10) HC: 20 (10)	SZ: 36.7 (7.6) HC: 35.0 (7.1)	DSM IV	3 T	1 mm	10 mm	P< 0.05 corrected	SPM 2	Age and sex matched
Honea RA et al., 2008	SZ: 169 (37) HC: 212 (109)	SZ: 36.39 (9.46) HC: 33.31 (9.86)						SPM 2	
Horn H et al., 2010	SZ: 20 (7) HC: 20	SZ: 30.1 (10)	DSM IV ICD 10	1.5 T	1 mm	10 mm			Age and sex matched
Hushoff Pol HE et al., 2004	SZ (MZ discordant) : 11 (5) HC (MZ healthy): 11 (5) SZ (DZ discordant) : 11 (6) HC (DZ healthy): 11 (6)	MZ discordant: 39.00 (11.67) MZ healthy: 37.36 (12.56) DZ discordant: 34.55 (8.95)	DSM IV	1.5 T					

		DZ healthy: 32.55 (9.08)							
Hushoff Pol HE et al., 2001	SZ: 159 (47) HC: 158 (52)	SZ: 35.6 (12.4) HC: 37.7 (14.0)	DSM IV	1.5 T	1 mm	8 mm	P< 0.05 corrected	SPM 99	
Hooker CI et al., 2011	SZ: 21 (4) HC: 17 (4)	SZ: 44.33 (10.18) HC: 43.75 (11.75)	DSM IV	4 T	1.5 mm	8 mm	P< 0.05 corrected	SPM 8	
Hu M et al., 2013	FES: 51 (17) HC: 45 (16)	FES: 22.29 (3.95) HC: 23.20 (2.58)	DSM IV	3 T	1.1 mm	8 mm	P< 0.05 corrected	SPM 8	Age sex education matched
Huang X et al., 2017	SZ: 24 (10) HC: 26 (9)	SZ: 24.25 (6.64) HC: 23.15 (5.36)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 8	Age and sex matched
Ivleva EI et al., 2012	SZ: 19 (9) HC: 10 (6)	SZ: 39.89 (10.66) HC: 43.9 (9.86)	DSM IV	3 T	1.2 mm	12 mm	P< 0.05 corrected	SPM 8	
Jayakumar et al., 2005	SZ: 18 (9) HC: 18 (9)	SZ: 24.9 (6.3) HC: 25.7 (7.5)	DSM IV	1.5 T	1 mm	8 mm	P< 0.05 corrected	SPM 2	Age and sex matched
Job DE et al., 2001	SZ: 36 (19) HC: 34 (11)	SZ: 21.17 (2/37) HC: 21.35 (3.66)	APA 94	1 T	1.88 mm	12 mm	P< 0.05 corrected	SPM 99	Age and sex matched
Kasparek T et al., 2007	SZ: 22 (0) HC: 18 (0)	SZ: 23.7 (4.8) HC: 24.1 (1.6)	ICD 10	1.5 T		12 mm	P< 0.001 uncorrected	SPM 2	Age and sex matched
Kasparek T et al., 2010	SZ: 49 (0) HC: 127 (0)	SZ: 23.6 (4.6) HC: 24.8 (3.0)	ICD 10	1.5 T		12 mm	P< 0.05 corrected	SPM 5	Age matched, all cases are male
Kasparek T et al., 2009	SZ: 58 (0) HC: 18 (0)	SZ: 23.8 (4.7) HC: 24.1 (1.6)	ICD 10	1.5 T		12 mm	P< 0.001 uncorrected	SPM 2	Age matched, all cases are male
Kawada R et al., 2009	SZ: 26 (15) HC: 26 (15)	SZ: 36.7 (8.6) HC: 36.3 (8.8)	DSM IV	3 T	1 mm	12 mm	P< 0.05 corrected	SPM 5	Age and sex matched
Kawasaki Y et al., 2007	SZ: 30 (0) HC: 30 (0)	SZ: 24.7 (4.4) HC: 25.4 (4.4)	DSM IV	1.5 T	1 mm	12 mm	P< 0.05 corrected	SPM 99	Age and sex matched
Kawasaki Y et al., 2004	SZ: 25 (11) HC: 50 (22)	SZ: 25.8 (4.5) HC: 25.0 (5.3)	DSM IV	1.5 T	1 mm	12 mm	P< 0.05 corrected	SPM 99	Age and sex matched
Kawasaki Y et al., 2008	SZ: 50 (25) HC: 50 (25)	SZ male: 25.9 (4.8) SZ female: 26.6 (4.6) HC male: 25.1 (5.1) HC female: 24.4 (6.6)	ICD 10	1.5 T	1 mm	12 mm	P< 0.05 corrected	SPM 2	Age and sex matched
Koutsouleris N et al., 2007	SZ: 175 (54) HC: 177 (45)	SZ: 31.5 (9.2) HC: 31.7 (10.2)	DSM IV	1.5 T	1.5 mm	12 mm	P< 0.05 corrected	SPM 2	Age and sex matched

Kubicki M et al., 2002	SZ: 16 (2) Affective psychosis: 16 (3) HC: 18 (2)	SZ: 26 (7.5) Affective psychosis: 23.7 (4) HC: 24.0 (4.5)	DSM IIIR	1.5 T	1.5 mm	12 mm	P< 0.05 corrected	SPM 99	Age and sex matched
Keymer- Gaussal et al., 2018	FES-SZ: 23 (11) FES-nonSZ: 18 (8) HC: 41 (16)	FES-SZ: 26.7 (6.16) FES-nonSZ: 25.33 (4.56) HC: 27.29 (5.04)	DSM IV	3 T	1 mm	5 mm	P< 0.05 corrected		
Kim GW., 2017	SZ: 22 (10) HC: 22 (10)	SZ: 31.7 (10.1) HC: 31.6 (9.5)	DSM IV	3 T	1.5 mm	6 mm	P< 0.05 corrected	SPM 8	
Koelkebeck K., 2019	SZ Japan: 83 (41) HC Japan: 120 (52) SZ Germany: 80 (33) HC Germany: 83 (29)	SZ Japan: 37.36 (9.2) HC Japan: 32.19 (11.1) SZ Germany: 29.25 (7.6) HC Germany: 30.58 (8.6)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 12	Age gender education matched
Kong L., 2012	SZ: 20 (13) HC: 20 (10)	SZ: 25.6 (7.2) HC: 24.1 (3.5)	DSM IV	1.5 T		8 mm	P< 0.05 corrected	SPM 8	
Lui S., 2009	SZ: 68 (38) HC: 68 (37)	SZ: 24.2 (8.6) HC: 24.7 (8.8)		3 T	1 mm	8 mm	P< 0.05 corrected	SPM 2	Age and sex matched
Lui S., 2009	SZ (Proband familial): 10 (5) SZ (Proband sporadic): 10 (5) HC: 10 (5)	Proband familial: 22.0 (8.2) Proband sporadic: 21.2 (7.5) HC: 23.0 (7.9)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 2	Age and sex matched
Lee DK., 2020	SZ: 65 (37) HC: 65 (29)	SZ: 36.98 (7.88) HC: 34.52 (8.93)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 8	Corrected based on age and sex
Lee JS., 2011	SZ: 46 (18) HC: 56 (25)	SZ: 29.5 (5.8) HC: 28.6 (3.7)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 5	No statistical significance
Lei W., 2015	SZ-D: 44 (26) SZ-ND: 44 (26) HC: 44 (26)	SZ-D: 22.91 (6.89) SZ-ND: 23.16 (6.99) HC1: 22.55 (6.25)	DSM IV	3 T	1 mm	6 mm	P < 0.05	SPM 8	Age and sex matched
Lei W., 2019	SZ-ND: 20 (8)	SZ-ND: 22.20 (6.65)	DSM IV	3 T	1 mm	6 mm	P < 0.05	SPM 8	Age gender corrected

	SZ-D: 14 (4) HC: 32 (9)	SZ-D: 21.79 (5.35)							
Liao J., 2015	SZ: 93 (36) HC: 99 (46)	SZ: 27.0 (6.6) HC: 25.8 (5.4)	DSM IV	3 T	1 mm	8 mm	P < 0.05	SPM 8	Age gender corrected
Madre M., 2020	SZ: 128 (54) HC: 127 (54)	SZ: 41 (10) HC: 39 (10)	DSM IV	1.5 T	1 mm	20 mm	P < 0.05	VBM 6	Age and sex matched
Mane A., 2009	SZ: 15 (3) HC: 11 (3)	SZ: 25.56 (5.77) HC: 31.31 (4.36)	DSM IV	1.5 T	1 mm	8 mm	P < 0.05	SPM 5	HC older than SZ, sex difference not significant
Marcelis M., 2003	SZ: 31 (16) HC: 27 (15)	SZ: 30.7 (7.5) HC: 35.5 (9.8)	ICD	1.5 T	3 mm	4.5 mm	P <0.05		Age sex adjusted
Marti Bonmati L., 2007	SZ: 21 (0) HC: 10 (0)	SZ: 39 (10) HC: 35 (7)	DSM IV	1.5 T	1.25 mm	12 mm	P < 0.05 corrected	SPM 2	Age adjusted
McIntosh AM., 2004	SZ: 26 (13) HC: 49 (26)	SZ: 36.85 (13.7) HC: 35.27 (11.1)	DSM IV	1.5 T	1.7 mm	12 mm	P< 0.01	SPM 99	Age and sex matched
Meda AS., 2008	SZ: 200 (78) HC: 200 (99)	SZ: 39.7 (12.0) HC: 40 (14.8)	DSM IIIR- IV	1.5 T	1.5 mm	8 mm	P< 0.05 corrected	SPM 2	Age and sex matched
Meisenzahl EM., 2008	FES: 93 (26) Recurrent SZ: 72 (16) HC: 177 (54)	FES: 28.2 (7.6) Recurrent SZ: 35.6 (10.3) HC: 31.5 (9.2)	DSM IV	1.5 T	1.5 mm	12 mm	P< 0.05 corrected	SPM 2	Age and sex adjusted
Molina V., 2011a	SZ: 38 (12) HC: 24 (8)	SZ: 34.4 (10.5) HC: 38.3 (8.3)	DSM IV	1.5 T	1.1 mm	8 mm	P<0.001 uncorrected	SPM 8	Age and sex ajdusted
Molina V., 2010	Kraepelinian SZ: 26 (9) Non Kraepelinian SZ: 19 (8) HC: 41 (18)	Kraepelinian SZ: 36.3 (11.6) Non Kraepelinian SZ: 36.9 (12.0) HC: 29.4 (9.0)	DSM IV	1.5 T	1 mm 1.5 mm	6 mm	P< 0.001 corrected	SPM 8	Age and sex adjusted
Molina V., 2011b	SZ: 30 (14) HC: 31 (13)	SZ: 34.1 (10.6) HC: 36.8 (12.19)	DSM IV	1.5 T	1 mm		P< 0.001 uncorrected	SPM 8	None of the cases had been included in any previous MRI report made by their group.
Moorhead TWJ., 2005	SZ: 39 (18) HC: 34 (15)	SZ: 48.6 HC: 48.6	DSM IIIR	1 T	1.5 mm		P< 0.001 uncorrected	SPM 99	Age and sex matched
Maggioni E., 2017	SZ dataset 1: 243 (91) SZ dataset 2: 109 (42) HC dataset 1: 383 (188) HC dataset 2: 107 (55)	SZ dataset 1: 33.24 (9.41) SZ dataset 2: 39.1 (8.78)	DSM IV	3 T	1 mm	6 mm	P < 0.05 corrected	SPM 12	Age and sex adjusted

		HC: dataset 1: 30.4 (9.2) HC dataset 2: 39.02 (10.26)							
McDonald C., 2005	SZ: 25 (7) HC: 52 (28)	SZ: 37.3 (10.2) HC: 39.3 (11.8)	DSM IV	1.5 T	1.5 mm	4 mm	P< 0.001 uncorrected	SPM 99	No statistical significance among age and sex
Minagatowa T.M., 2009	FES: 88 (36) HC: 86 (40)	FES: 28.9 (8.6) HC: 28 (8.4)	DSM IV	1.5 T	1.5 mm	12 mm	P < 0.05 corrected	SPM 2	Age sex matched
Nagashima T., 2012	Polydipsic SZ: 8 (0) Non polydipsic SZ: 8 (0) HC: 8 (0)	P- SZ: 43.75 (6.58) Non-P SZ: 43.63 (7.67) HC: 44.75 (3.77)	DSM IV	1.5 T	1.25 mm	8 mm	P< 0.001 uncorrected	SPM 5	Age matched
Nakamura K., 2013	SZ: 34 (14) HC: 51 (21)	SZ: 24.7 (5.5) HC: 23.9 (1.8)	ICD 10	1.5 T	1 mm	10 mm	P < 0.05 corrected	SPM 8	
Neckelmann G., 2009	SZ: 12 HC: 12	SZ: min 19-max 50 HC: min 19- max 50	DSM IV	1.5 T	1.4 mm	12 mm	P < 0.01 corrected	SPM 99	Matched
Nenadic I., 2015	FES: 24 (12) HC: 49 (23)	FES: 24.9 (3.1) HC: 23.8 (3.0)	DSM IV	3 T	1 mm	12 mm	P< 0.001 uncorrected	SPM 8	Age and sex matched
Nenadic I., 2015b	ZNF804A genotype SZ: 62 (18) HC: 54 (29)	SZ: 31.6 (11.5) HC: 29.5 (9.9)	DSM IV	1.5 T	1 mm	12 mm	P< 0.001 uncorrected	SPM 8	No statistical difference among age, sex
Nenadic I., 2015c	SZ: 34 (13) HC: 34 (16)	SZ: 32.97 (8.91) HC: 34.33 (10.62)	DSM IV	3 T	1 mm	12 mm	P < 0.05 corrected	SPM 8	
O'Daly O.G., 2007	SZ: 28 (3) HC: 32 (4)	SZ: 33 (10) HC: 34 (8)	DSM IV	1.5 T	3 mm		P < 0.01 corrected		Age and sex matched
Ohnishi T., 2006	SZ Val gene: 19 (8) HC: 38 (22)	SZ Val gene: 45.98 (15.29) HC: 41.47 (13.42)	DSM IV	1.5 T	1.23 mm		P< 0.05 corrected	SPM 2	
Ortiz-Gil J., 2011	Cognitively preserved SZ: 23 (6) Cognitively impared SZ: 26 (6) HC: 39 (9)	Cognitively preserved SZ: 40.10 (10.22) Cognitively impared SZ: 42.38 (8.23) HC: 40.10 (11.58)	DSM IV	1.5 T		4 mm	P< 0.05 corrected	SPM 5	Age and sex matched
Oertel-Knochel V., 2012	SZ: 31 (15) HC: 37 (20)	SZ: 38.00 (11.24) HC: 39.36 (9.97)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 8	Age and sex matched
Onay A., 2017	SZ: 20 (10) HC: 16 (9)	SZ: 36.5 (10.5)	DSM IV	1.5 T	1 mm	8 mm	P < 0.01 corrected	SPM 8	Age and sex matched

		HC: 34.4 (9.1)							
Ota M., 2017	SZ: 37 (20) HC: 62 (45)	SZ: 36.2 (9.5) HC: 40.6 (13.3)	DSM V	1.5 T	1.23 mm	6 mm	P<0.001 uncorrected	SPM 8	No statistical difference among age and sex
Paillere M.L., 2001	SZ: 20 (0) HC: 20 (0)	SZ: 29 (7.2) HC: 26 (6)	DSM IV	1.5 T	1.5 mm	10 mm	P< 0.01 corrected	SPM 96	Age matched
Pomarol-Clotet E., 2010	SZ: 32 (11) HC: 32 (11)	SZ: 41.56 (8.79) HC: 41.03 (11.04)	DSM IV	1.5 T	1 mm	5 mm	P<0.05 corrected	FSL-VBM	Age and sex matched
Prasad K.M.R., 2007	SZ: 30 (7) HC: 44 (21)	SZ: 24.66 (7.71) HC: 24.9 (6.84)	DSM IV	1.5 T	1.5 mm	12 mm	P<0.05 corrected	SPM 2	
Picado M., 2015	SZ: 20 (9) HC: 20 (8)	SZ: 32.55 (6.9) HC: 33.20 (6.6)	DSM IV	1.5 T	2 mm	12 mm	P< 0.05	SPM 5	Age and sex matched
Premkumar P., 2008	SZ: 64 (16) HC: 25 (10)	SZ: 38.6 (9.6) HC: 36.4 (11.1)	DSM IV	1.5 T	1.5 mm	8 mm	P< 0.001 uncorrected	SPM 2	
Price G., 2010	SZ: 48 (15) HC: 47 (20)	SZ: 26.2 (16-50) HC: 24.8 (16-37)	DSM IV	1.5 T	1.2 mm	12 mm	P< 0.05 corrected	SPM 2	Age and sex corrected
Qiu L., 2011	SZ: 33 (14) HC: 29 (12)	SZ: 23.45 (4.05) HC: 23.17 (3.05)	ICD 10	3 T	1 mm	12 mm	P< 0.05 corrected	SPM 5	Age and sex matched
Quide Y., 2019	SZ: 60 (24) HC: 61 (27)	SZ: 41.16 (11.05) HC: 35.98 (10.92)	ICD 10	3 T	0.9 mm	15 mm	P< 0.05 corrected	SPM 12	Age corrected
Rosa P.G.P., 2014	FES: 32 (6) HC: 34 (15)	FES: 28.2 (8.5) HC: 30.8 (8.3)	DSM IV	1.5 T			P< 0.05 corrected	SPM 2	Age sex corrected
Salgado-Pineda P., 2003	SZ: 13 (0) HC: 13 (0)	SZ: 23.76 (5.65) HC: 23.36 (4.58)	DSM IV	1.5 T	1 mm	8 mm	P< 0.001 uncorrected	SPM 99	Age matched
Salgado-Pineda P., 2014	SZ: 14 (5) HC: 14 (5)	SZ: 37.3 (8.9) HC: 34.6 (6)	DSM IV	3 T	3 mm	6 mm	P < 0.05 corrected	SPM 5	Age sex matched
Salgado-Pineda P., 2004	SZ: 14 (7) HC: 14 (7)	SZ: 25.05 (4.05) HC: 25.14 (3.32)	DSM IV	1.5 T	5 mm	8 mm	P< 0.05 corrected	SPM 2	Age sex matched
Schiffer B., 2013	SZ+ conduct disorder: 27 (0) SZ no conduct disorder: 23 (0) HC: 25 (0)	SZ+ conduct disorder: 36.2 (7.7) SZ no conduct disorder: 35.7 (8.7) HC: 33.0 (10)	DSM IV	1.5 T	1 mm	8 mm	P< 0.001 uncorrected	SPM 99	Age matched, all cases are male
Schuster C., 2012	SZ: 27 (13) HC: 40 (22)	SZ: 59.9 (9.1) HC: 62.2 (7.8)	DSM IV	1.5 T	1 mm	8 mm	P< 0.05 corrected	SPM 2	
Shaplaske J., 2002	SZ: 72 (0) HC: 32 (0)	SZ: 34.1 (8.5) HC: 33.3 (8.7)	DSM IV	1.5 T	3 mm	4.2 mm	P< 0.05	SPM 99	Age sex matched

Sigmundsson T., 2001	SZ: 27 (1) HC: 27 (2)	SZ: 34.9 (7.6) HC: 32.2 (6.7)	DSM IV	1.5 T	3 mm				Age sex matched
Suzuki M., 2002	SZ: 45 (22) HC: 11 (7)	SZ: 26.4 (5.2) HC: 21.5 (5)	ICD 10	1.5 T	1 mm	12 mm	P< 0.05 corrected	SPM 96	
Suzuki M., 2005	SZ: 22 (11) HC: 20 (10)	SZ: 36.9 (5.1) HC: 36.7 (6.1)	ICD 10	1.5 T	1 mm	12 mm	P< 0.05 corrected	SPM 99	Age and sex matched
Sapara A., 2016	Insight negative SZ: 20 (4) HC: 20 (5)	Insight negative SZ: 37.80 (7.85) HC: 35.25 (10.93)	DSM IV	1.5 T	1.5 mm		P< 0.05 corrected	SPM 8	Age corrected
Schaufelberger M.S., 2007	Psychosis: 122 (56) HC: 94 (41)	Psychosis: 28.5 (8.4) HC: 30.2 (8.4)	DSM IV	1.5 T	1.5 mm	8 mm	P< 0.05 corrected	SPM 2	No difference in age, gender
Schiffer B., 2010	SZ: 12 (0) HC: 14 (0)	SZ: 37.8 (9.0) HC: 36.7 (11.4)	DSM IV	1.5 T	1 mm	14 mm	P< 0.05 corrected	SPM 5	Age matched
Song J., 2015	SZ: 71 (42) HC: 35 (24)	SZ: 35.6 (14.7) HC: 33.9 (14.5)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 8	Age and sex matched
Spalthoff R., 2018	SZ: 51 (17) HC: 102 (33)	SZ: 35.18 (10.88) HC: 33.15 (9.6)	DSM IV DSM V	3 T	1 mm	15 mm	P< 0.05 corrected	SPM 12	Results are corrected for age and sex
Stegmayer K., 2014	SZ: 43 (27) HC: 34 (12)	SZ: 34.1 (10.9) HC: 37.1 (12.3)	DSM IV	3 T	1 mm	8 mm	P< 0.001 uncorrected	SPM 8	Corrected for age and sex
Tian L., 2011	SZ: 33 (13) HC: 30 (12)	SZ: 22.63 (3.76) HC: 22.77 (3.34)	ICD 10	3 T	1 mm	6 mm	P< 0.05 corrected	SPM 5	Age and sex matched
Tomelleri L., 2009	SZ: 70 (25) HC: 79 (38)	SZ: 39.73 (10.94) HC: 40.29 (11.91)	DSM IV	1.5 T	5 mm	12 mm	P<0.05 corrected	SPM 5	No difference in age and sex
Tragellas J.R., 2007	SZ: 32 (11) HC: 32 (18)	SZ: 39.6 (8.8) HC: 35.8 (9.3)	DSM IV	1.5 T	1.5 mm	12 mm	P<0.05 corrected	SPM 2	
Torres U.S., 2016	SZ: 161 (50) HC: 151 (64)	SZ: 30.4 (8.3) HC: 30.6 (9.0)	DSM IV	1- 1.5 T		8 mm	P< 0.05 corrected	SPM 8	Age sex scanner type corrected
Van Harren., 2007	SZ: 96 (26) HC: 113 (37)	SZ: 32.22 (11.10) HC: 35.28 (12.25)	DSM IV	1.5 T					Age sex corrected
Venkatasubramanian G., 2008	SZ: 30 (9) HC: 27 (8)	SZ: 30.1 (8.3) HC: 27.4 (7.8)	DSM IV	1.5 T	1 mm	12 mm	P<0.05 corrected	SPM 2	
Van Tol M.J., 2014	SZ: 51 (7) HC: 51 (14)	SZ: 34.04 (11.40) HC: 36.14 (10.93)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 8	Age sex corrected
Vicens V., 2016	SZ: 22 (12) HC: 44 (24)	SZ: 45.1 (11.3) HC: 45.2 (12.2)	DSM IV	1.5 T	1 mm	8 mm	P< 0.05 corrected	FSL	Age and sex matched

Volz H.P., 2000	SZ: 75 (23) HC: 75 (22)	SZ: 34.71 (10.45) HC: 31.2 (9.0)	DSM IIIR	1.5 T	1 mm	8 mm	P< 0.001 uncorrected	SPM 99	Age sex matched
Watson D.R., 2012	SZ: 25 (6) HC: 25 (6)	SZ: 28.8 (9.0) HC: 28.2 (8.5)	ICD 10	1.5 T	1.5 mm	4 mm	P< 0.05 corrected	SPM 5	Age and sex matched
Whitford T.J., 2006	FES: 41 (16) HC: 47 (14)	FES: 19.8 (3.3) HC: 19.3 (3.8)	DSM IV	1.5 T	1 mm	8 mm	P< 0.05 corrected	SPM 2	Age and sex matched
Wilke M., 2001	SZ: 48 (21) HC: 48 (21)	SZ: 33 (9.07) HC: 32.97 (9.84)	DSM IV	1.5 T	0.9- 1.4 mm	12 mm	P< 0.001 uncorrected	SPM 99	Age and sex matched
Wolf R.C., 2008	SZ: 28 (8) HC: 14 (5)	SZ: 33.1 (7.0) HC: 30.9 (9.5)	DSM IV	1.5 T	1 mm	8 mm	P< 0.05 corrected	SPM 5	Age sex corrected
Wang J., 2019	ECT-SZ: 21 (11) Drug-SZ: 21 (12) HC: 23 (12)	ECT-SZ: 29.2 (7.1) Drug SZ: 30.7 (6.9) HC: 31.2 (5.9)	DSM IV	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 8	Age sex corrected
Wang J., 2017	SZ-cognitive deficit: 16 (5) SZ-non cognitive deficit: 18 (11) HC: 21 (11)	SZ-cognitive deficit: 22.63 (6.71) SZ-non cognitive deficit: 24.5 (6.70) HC: 22.38 (3.94)	DSM IV	3 T	1 mm	8 mm	P<0.05 corrected	SPM 8	Age sex corrected
Witthaus H., 2009	FES: 23 (7) HC: 29 (12)	FES: 26.4 (6.1) HC: 25.7 (5.2)	DSM IV	1.5 T	1 mm	12 mm	P< 0.05 corrected	SPM 2	Age sex corrected
Wolf R.C., 2020	Paranoid SZ: 14 (10) HC: 25 (11)	Paranoid SZ: 56.6 (14.4) HC: 53.1 (8.1)	DSM IV	1 T	0.9 mm	18 mm	P< 0.05 corrected	SPM 12	Age sex corrected
Wu F., 2018	FES: 43 (15) Chronic SZ: 39 (15) HC: 56 (23)	FES: 26.42 (8.02) Chronic SZ: 29.97 (6.97) HC: 25.07 (5.85)	DSM IV	3 T	1 mm	8 mm	P < 0.05 corrected	SPM 8	Age sex corrected
Xu L., 2009	SZ: 120 (51) HC: 120 (65)	SZ: 42.1 (12.9) HC: 42.8 (16.57)	DSM IIIR- IV	1.5 T	1.5 mm	12 mm	P< 0.05	SPM 5	Age and sex corrected
Yamada M., 2007	SZ: 20 (10) HC: 20 (10)	SZ: 38.8 (7.2) HC: 39.1 (7.1)	DSM IV	3 T	1 mm	12 mm	P< 0.05	SPM 2	Age and sex matched
Yang C., 2014	SZ: 30 (15) HC: 30 (15)	SZ: 21.45 (4.68) HC: 24.32 (4.52)	DSM IV	1.5 T	1.8 mm		P< 0.05 corrected	HAMMER	Age and sex matched
Yang Z., 2019	SZ: 37 (16) HC: 28 (12)	SZ: 42.03 (8.44) HC: 40.54 (10.87)	DSM IV	3 T	1 mm	8 mm	P< 0.001 corrected	SPM 12	Age and sex matched

Yonatema E., 2003	SZ: 14 (9) HC: 28 (18)	SZ: 24.5 (4.9) HC: 23.4 (5.8)	ICD 10	1.5 T	1 mm	12 mm	P< 0.001 uncorrected	SPM 99	Age and sex matched
Yue Y., 2016	SZ: 20 (10) HC: 24 (11)	SZ: 24.45 (5.51) HC: 24.79 (6.11)	ICD 10	3 T	1 mm		P< 0.05 corrected	SPM 8	Age and sex matched
Yuksel C., 2012	SZ: 43 (15) HC: 58 (20)	SZ: 38.7 (10.6) HC: 36.4 (10.5)	DSM IV	3 T	1.33 mm	12 mm	P<0.05 corrected	FSL	Age sex corrected
Zhang Y., 2013	SZ: 33 (14) HC: 29 (12)	SZ: 23.5 (4.0) HC: 23.2 (3.0)	DSM IV	3 T	1 mm	12 mm	P< 0.05 corrected	SPM 5	Age sex matched
Zierhut K.C., 2013	SZ: 34 (12) HC: 36 (15)	SZ: 34.6 (8.84) HC: 31.0 (7.06)	ICD 10	3 T	1 mm	8 mm	P< 0.05 corrected	SPM 5	Age sex corrected

Supplementary Table 3: Characteristics of voxel-based morphometry studies of gray matter in BD included in the meta-analysis

Author	**Sample (female)**	**Age (SD)**	**Mood state (EU/MA/DE/MIX)**	**Medication (%)**	**Diagnostic criteria**	**Scanner**	**Thickness**	**FWHM**	**Threshold p-value**	**Software**	**Covariances**
Adler et al. 2005	BD 32 (13) HC 27 (15)	31.2 (9.4) 30.5 (9.7)	0/5/2/0 NA	23 (72) NA	DSM-IV	3T	1 mm	12 mm	p < 0.001	SPM99	Age Gender
Almeida et al. 2009	BD 27 (17) HC 28 (15)	31.9 (7.3) 30.8 (10.6)	17/0/10/0 NA	24 (89) NA	DSM-IV	3T	1 mm	12 mm	Uncorrected p < 0.001	SPM5	Age Total GMV
Alonso-Lana et al. 2016	BD-CP 33 (15) BD-CI 28 (11) HC 28 (16)	44.13 (6.6) 46.17 (7.4) 44.01 (6.0)	33/0/0/0 28/0/0/0 NA	33 (100) 28 (100) NA	DSM-IV	1.5T	1 mm	9.4 mm	p < 0.05	FSL-VBM	
Altamura et al. 2017	BD-NS 17 (13) BD-WS 10 (1) HC 27 (11)	38.7 (8.2) 35.7 (13.2) 34 (10)	? ? NA	17 (100) 10 (100) NA	DSM-IV	3T	1 mm	6 mm	Corrected p < 0.05	SPM12	Age Gender ICV
Altamura et al. 2018	BD-NP 46 (23) BD-P 62 (35) HC 56 (27)	33.7 (11.8) 27.27 (8.7) 25.3 (7.37)	38/2/6/0 55/3/4/0	31 (68) 50 (81) NA	DSM-IV	3T	?	6 mm	p < 0.001	SPM12	Age Gender
Amann et al. 2016	BD 45 (19) HC 45 (19)	42.9 (9.2) 43.3 (9.9)	15/15/15/0 NA		DSM-IV RDC	1.5T	1 mm	4 mm	Corrected P < 0.01	FSL-VBM	
Ambrosi et al. 2013	BD-II 20 (15) HC 21 (15)	41.95 (13.1) 34.61 (10.8)		19 (95) NA	DSM-IV	1.5T	1 mm	8 mm	p < 0.05	SPM8	

Baez et al. 2019	BD 13 (10) HC 22 (15)	61.9 (9.1) 62.5 (7.1)	13/0/0/0 NA		DSM-IV	1.5T	1 mm	12 mm	p < 0.05	SPM8	ICV
Brown et al. 2011	BD 15 (8) HC 21 (11)	46.2 (10.6) 45.0 (10.2)			DSM-IV	1.5T	1 mm	8 mm	Corrected p < 0.05	SPM5	ICV
Cai et al. 2015	BD 23 (7) HC 23 (10)	25.7 (6.6) 28.2 (3.8)			DSM-IV	3T		8 mm	Uncorrected p < 0.001	SPM8	
Chen et al. 2007	BD 24 (18) HC 25 (18)	38.2 (11.0) ?	? NA	20 (83)	DSM-IV	1.5T	1.6 mm	12 mm	p < 0.05	SPM2	Age Gender ICV
Chen et al. 2012	BD 18 (0) HC 27 (0)	32.0 (7.6) 31.3 (6.8)	0/18/0/0 NA	18 (100) NA	DSM-IV	3T	1 mm	8 mm / 6 mm	Uncorrected p < 0.001	SPM5	Age Gender ICV
Chen et al. 2018	BD 43 (26) HC 47 (25)	27.9 (9.1) 29.7 (9.2)	0/0/43/0 NA	0 (0)	DSM-IV	3T	1 mm	6 mm	Uncorrected p < 0.001	SPM12	Age Gender Years of education ICV
Cui et al. 2011	BD 24 (9) HC 36 (15)	28.42 (6.6) 26.56 (6.7)	0/0/24/0 NA	24 (100)*	DSM-IV	3T	1 mm	6 mm	p < 0.001	SPM5	Age Gender Whole brain GMV
de Azevedo-Marques Périco et al. 2011	BD 26 (16) HC 94 (41)	27.1 (8.5) 30.2 (8.4)	?/?/?/? NA	19 (73)	DSM-IV	1.5T	1.5 mm	8 mm	p < 0.001	SPM2	Gender Whole brain GMV
Delaloye et al. 2009	BD 17 (?) HC 17 (?)	69.00 (5.9) 69.24 (6.0)	17/0/0/0	14 (82)	DSM-IV	3T	0.9 mm	8 mm	Uncorrected p < 0.001	SPM5	
Delvecchio et al. 2019	BD 12 (7) HC 20 (15)	58.8 (7.6) 49.8 (16.5)	12/0/0/0	12 (100)	DSM-IV	3T	1 mm	6 mm	Corrected p < 0.05	SPM12	Age Gender
Doris et al. 2004	BD 11 (5) HC 16 (9)	40.5 (11.6) 39.1 (10.5)	11/0/0/0	11 (100)	DSM-IV	2T	1 mm	8 mm	Corrected p < 0.05	SPM99	
Eker et al. 2014	BD 28 (12) HC 28 (17)	36.4 (7.8) 34.9 (9.4)		27 (96)	DSM-IV	3T	5 mm	8 mm	Uncorrected p < 0.001	SPM8	Age Gender ICV
Ekman et al. 2017	BD-NP 82 (48) BD-P 85 (55) HC 102 (56)	40 (13) 37 (13) 39 (15)	82/0/0/0 85/0/0/0 NA		DSM-IV ADE	1.5T	1.8 mm	8 mm	p < 0.05	SPM12	Age Gender Scanner filter
Ha et al. 2009	BD-I 23 (15) BD-II 23 (15) HC 23 (15)	35.6 (11.1) 35.2 (10.0)	? ? NA	17 (74) 12 (52)	DSM-IV	1.5T	1 mm	8 mm	p < 0.001	SPM2	

		36.0 (9.4)									
Hajek et al. 2013	BD 12 (6) HC 11 (8)	45.6 (8.9) 46.0 (8.6)	? NA	? NA	DSM-IV	1.5T	1.5 mm	8 mm	Corrected p < 0.001	SPM8	Age
Hajek et al. 2014	BD-DG 33 (17) HC-EG 11 (7)	51.6 (12.3) 43.1 (10.4)	? NA	? NA	DSM-IV	1.5T	1.5 mm	3 mm	Corrected p < 0.05	FSL-VBM	Age Gender BMI Medication
Haldane et al. 2008	BD 44 (24) HC 44 (24)	42.7 (11) 43.1 (11.2)	? NA	? NA	DSM-IV	1.5T	1.5 mm	5 mm	Corrected p < 0.01	SPM99	?
Haller et al. 2011	BD 19 (14) HC 47 (22)	68.53 (5.9) 69.77 (6.6)	19/0/0/0	17 (89)	DSM-IV	3T		2 mm	Corrected p < 0.001	FSL 4.1	Age Gender Medication
Hozer et al. 2020	BD-I Li+ 120 (62) BD-I Li- 149 (93) HC 316 (173)	39.2 (11.1) 40.8 (11.6) 36.9 (11.1)	99/?/?/? 118/?/?/?	120 (100) 130 (87)	DSM-IV	1.5 T & 3T	1 - 1.25 mm	3 mm	p < 0.05	FSL	Age Gender History of alcohol misuse Scanning site
Ivleva et al. 2013	BD 115 (79) HC 200 (108)	35.4 (12.5) 39.8 (12.1)		108 (94) NA	DSM-IV	3T		12 mm	p < 0.05	SPM8	Age Gender Handedness Scanning site
Kempton et al. 2009	BD-I 30 (15) HC 52 (25)	39.4 (9.8) 35.2 (13.0)	39.4 (9.8) 35.2 (13.0)	29 (97) NA	DSM-IV	1.5T	1.5 mm	12 mm	Uncorrected p < 0.001	SPM5	ICV
Kim et al. 2013	BD 49 (30) HC 50 (29)	33.8 (11.3) 33.5 (10.5)	?	25 (83) NA	DSM-IV	1.5T	1.5 mm	6 mm	p < 0.05	SPM5	Age Gender ICV
Kozicky et al. 2016	BD-I 41 (21) HC 25 (14)	22.9 (4.0) 22.0 (4.0)	20/4/10/7 NA	? NA	DSM-IV	3T	1 mm	8 mm	Corrected p < 0.05	SPM8	Age Gender
Lee et al. 2017	BD 21 (14) HC 21 (14)	37.0 (11.7) 37.0 (10.4)		21 (100) NA	DSM-IV	3T		8 mm	Uncorrected p < 0.001	SPM12	Age Gender ICV
Lee et al. 2020	BD 65 (36) HC 65 (37)	35.06 (9.2) 34.52 (8.9)	? NA	50 (76.9)	DSM-IV	3T	1 mm	8 mm	Corrected p < 0.017	SPM8	Age Gender Educatoin ICV
Li et al. 2011	BD 24 (9) HC 36 (15)	28.42 (6.6) 26.56 (6.7)	0/17/7/0	24 (100) NA	DSM-IV	3T	1 mm	8 mm / 6mm	Corrected p < 0.05	SPM5	Age Gender Whole brain GMV
Lochhead et al. 2004	BD 11 (5) HC 31 (15)	38.2 (10.8)	? NA	1 (9.1) NA	DSM-IV	1.5T	1.5 mm	12 mm / 8 mm	Corrected p < 0.05	SPM99	Age Gender

		36 (14.0)									
Lyoo et al. 2004	BD 39 (23) HC 43 (19)	38.3 (11.6) 35.7 (10.1)	0/17/22/0 NA	28 (72) NA	DSM-IV	1.5T	3 mm	8 mm	Corrected p < 0.05	SPM99	Age Gender
Maggioni et al. 2017	BD 176 (107) HC 383 (188)	44.7 (12.1) 30.4 (9.2)	23/28/120/1 NA	57 (32.4) NA	DSM	3T	?	6 mm	Corrected p < 0.05	SPM12	Age Gender
Matsubara et al. 2016	BD 10 (7) HC 27 (17)	46.9 (12.3) 48.3 (13.0)	? NA	10 (100) NA	DSM-IV	1.5T	1 mm	8 mm	Corrected p < 0.05	SPM8	Age Gender Premorbid IQ score
Matsuo et al. 2019	BD-JPN 156 (79) BD-USA 36 (26) HC-JPN 777 (499) HC-USA 132 (86)	44.0 (14.6) 40.3 (11.0) 45.0 (15.5) 36.0 (12.6)	? NA	151 (96.8) 20 (55.6) NA	DSM-IV	1.5T / 3T	1 mm / 0.8 mm / 3 mm / 1.2 mm	8 mm	Corrected p < 0.05	SPM8	Age Gender ICV
McIntosh et al. 2004	BD-MFH 19 (12) HC 49 (26)	39.74 (9.2) 35.27 (11.1)	? NA	? NA	DSM-IV	1.5T	1.7 mm	8 mm	p < 0.01	SPM99	Age Gender Height Handedness NGM
Minuzzi et al. 2017	BD 32 (32) HC 36 (36)	29.0 (8.07) 32.8 (8.32)	32/0/0/0 NA		DSM-IV	3T	1 mm	8 mm	p < 0.05	SPM12	Age
Molina et al. 2011	BD 19 (7) HC 24 (8)	38.3 (8.3) 34.6 (8.6)	19/0/0/0 NA	16 (84.2) NA	DSM-IV	1.5T	1.1 mm	8 mm	Uncorrected p < 0.001	SPM8	Age Gender ICV
Mwangi et al. 2016	BD 128 (92) HC 128 (84)	37.6 (11.6) 36.3 (12.3)	34/13/64/17 NA	120 (94) NA	DSM-IV	1.5T	1 mm	?	?	SPM8	
Narita et al. 2011	BD-II-RC 14 (6) BD-II-NRC 17 (8) HC 84 (36)	40.2 (10.9) 41.4 (11.9) 41.1 (11.4)	2/2/10/0 6/2/9/0 NA	13 (92.9) 15 (88.2) NA	DSM-IV	1.5T	1 mm	12 mm	Corrected p < 0.05	SPM5	Age Gender GMV
Nenadic et al. 2015c	BD-I-P 17 (8) HC 34 (16)	37.69 (11.13)	17/0/0/0 NA	17 (100) NA	DSM IV	3 T	1 mm	12 mm	Corrected p < 0.05	SPM 8	?

		34.33 (10.62)									
Nery et al. 2015	BD 25 (17) HC 27 (16)	35.7 (8.9) 31.2 (9.5)	25/0/0/0 NA	25 (100)	DSM-IV	3T		8 mm	p < 0.05	SPM8	Age Gender
Neves et al. 2015	BD 21 (11) HC 21 (11)	39.0 (13.5) 37.9 (78.2)	21/0/0/0 NA	21 (100)	DSM-IV	1.5T		8 mm	Corrected p < 0.05	SPM8	?
Nugent et al. 2006	BD-MD 20 (15) BD-UMD 16 (11) HC 65 (46)	41 (8.3) 37 (7.5) 38 (11.8)	? NA	20 (100) 16 (100) N	DSM-IV	3T	1.2 mm	8 mm / 12 mm	Uncorrected p < 0.001	SPM2	Age Gender Scanner
Oertel-Knöchel et al. 2014	BD 21 (9) HC 20 (8)	35.7 (10.7) 36.9 (11.1)	21/0/0/0 NA	21 (100)	DSM-IV	3T	3 mm	8 mm	Corrected p < 0.001	SPM8	BDI-II BRMAS
Poletti et al. 2016	BD 206 (134) HC 136 (68)	46.2 (13.0) 33.3 (13.0)	0/0/206/0 NA	?	DSM	3T	0.8 mm	8 mm	p < 0.05	SPM8	Age Gender Lithium treatment ICV
Poletti et al. 2017	BD 36 (24) HC 17 (10)	46.2 (14.0) 26.8 (7.9)	?	?	?	3T	0.8 mm	8 mm	Corrected p < 0.05	SPM8	Age Gender Lithium treatment
Redlich et al. 2014	BD 58 (37) HC 58 (37)	37.5 (11.0) 37.7 (9.7)	0/0/58/0	54 (93) NA	DSM-IV	3T	1 mm	8 mm	Corrected p < 0.05	SPM8	Age Gender Site
Rocha-Rego et al. 2014 Cohort 1	BD 26 (14) HC 26 (14)	41.5 (11.3) 41.3 (11.7)	?	19 (73) NA	DSM-IV	1.5T	1.5 mm	8 mm	p < 0.001	SPM5	
Rocha-Rego et al. 2014 Cohort 2	BD 14 (8) HC 14 (8)	37.6 (12.0) 37.4 (11.0)	?	14 (100) NA	DSM-IV	1.5T	1.5 mm	8 mm	p < 0.001	SPM5	
Rossi et al. 2013	BD 14 (5) HC 40 (21)	43 (8) 40 (11)	14/0/0/0 NA	14 (100) NA	DSM-IV	1.5T	?	8 mm	Uncorrected p < 0.001	SPM5	ICV Education Abuse of alcohol and substance
Sani et al. 2016	BD 78 (40) HC 78 (40)	44.6 (13.3) 44.4 (13.3)	29/5/41/3 NA	78 (100) NA	DSM-IV	3T		8 mm	Uncorrected p < 0.05	SPM8	Age
Sariçiçek et al. 2015	BD 28 (20) HC 29 (16)	36.3 (9.5) 33.6 (9.3)	28/0/0/0 NA	28 (100) NA	DSM-IV	1.5T	1 mm	8 mm	p < 0.05	SPM8	ICV Years of education

Shepherd et al. 2015	BD 30 (18) HC 34 (18)	39.1 (12.8) 32.6 (10.6)	? NA	26 (87) NA	ICD-10	3T	0.9 mm	8 mm	Corrected p < 0.05	SPM8	Age Gender
Song et al. 2015	BD 44 (25) HC 35 (24)	34.8 (14.1) 33.9 (14.5)	? NA	44 (100) NA	DSM-IV	3T	1 mm	8 mm	p < 0.05	SPM8	Age Gender Duration of medication intake
Stanfield et al. 2009	BD 66 (36) HC 66 (35)	36.4 (11.1) 39.0 (10.9)	? NA	? NA	DSM-IV	1.5T	1.7 mm	12 mm	Corrected p < 0.05	SPM99	ICV
Tang et al. 2014	BD 27 (17) HC 27 (16)	32.0 (11.2) 32.6 (11.8)	0/0/27/0 NA	? NA	DSM-IV	3T	1.3 mm	8 mm	p < 0.05	SPM8	Age Gender GMV WMV
Tost et al. 2010	BD 42 (23) HC 42 (23)	42.4 (13.1) 42.2 (13.6)	42/0/0/0 NA	37 (88) NA	DSM-IV	1.5T	1 mm	12 mm	Corrected p < 0.05	SPM2	Age
Tu et al. 2017	BD 59 (31) HC 56 (34)	35.5 (8.6) 33.9 (7.6)	? NA	? NA	DSM-IV	3T	?	8 mm	Corrected p < 0.05	SPM12	Age Education ICV
Vai et al. 2020	BD 74 (55) HC 74 (39)	47.3 (9.4) 36.4 (12.5)	0/0/74/0 NA	? NA	DSM-IV	3T	0.8 mm	8 mm	Corrected p < 0.05	SPM12	Age Gender Medication load Number of previous depression episodes
Watson et al. 2012	BD 24 (16) HC 24 (16)	36.0 (10.0) 35.6 (9.7)	? NA	? NA	ICD-10	1.5T	1.5 mm	4 mm	Corrected p < 0.05	SPM5	Age
Yatham et al. 2007	BD 15 (9) HC 15 (9)	36 (13) 36 (13)	0/15/0/0 NA	7 (47) NA	DSM-IV	1.5T	1.5 mm	8 mm	Corrected p < 0.05	SPM99	Age Gender

ADE = Affective Disorder Evaluation. **BD(-I/II)** = Bipolar disorder (Type 1/Type 2). **BDI-II** = Beck Depression Inventory-Second Edition. **BFH** = with Bipolar family history. **BMI** = Body Mass Index. **BRMAS** = Bech-Rafaelsen Mania Rating Scale. **CI** = Cognitively impaired. **CP** = Cognitively preserved. **DE** = Depressed mood state. **DG** = Dysglycemic. **DSM** = Diagnostic and Statistical Manual of Mental Disorders. **EG** = Euglycemic. **EU** = Euthymic mood state. **FSL(-VBM)** = FMRIB Software Library (-Voxel Based Morphometry). **FWHM** = Full width at half maximum. **GMV** = Gray matter volume. **HC** = Healthy control. **ICD** = International Statistical Classification of Diseases and Related Health Problems. **ICV** = Total intracranial volume. **JPN** = Japan. **Li** = Lithium **MA** = Manic mood state. **MD** = Medicated. **MFH** = with Mixed family history. **MIX** = Mixed mood state. **NA** = Not applicable. **NGM** = Number of gray matter voxels from each image in native space. **NP** = Non-psychotic. **NRC** = without Rapid cycling. **NS** = Without substance abuse. **P** = Psychotic. **RC** = with Rapid cycling. **RDC** = Research Diagnostic Criteria. **SADS-L** = Schedule for Affective Disorders and Schizophrenia, Lifetime version. **SD** = Standard deviation. **SPM** = Statistical parametric mapping. **T** = Tesla. **UMD** = Unmedicated. **USA** = United States of America. **WMV** = White matter volume. **WS** = With substance abuse.

* Not received any medications 2–7 months preceding admission

Supplementary Table 4: Characteristics of voxel-based morphometry studies of gray matter in ASD included in the meta-analysis

Author	Sample (female)	Age (SD)	Global IQ / FSIQ (SD)	Diagnostic criteria	Scanner	Thickness	FWHM	Threshold p-value	Software	Covariances
Abell et al. 1999	ASD 15 (3) HC 15 (?)	28.8 (6.6) 25.3 (3.1)	91.4 (15.5) 97.4 (8.6)	DSM-IV	2T		12 mm	Uncorrected p < 0.001	SPM96	Age, gender matched
Craig et al. 2007	ASD 14 (14) HC 19 (19)	37.9 (11.4) 35.0 (14.0)	103.4 (17.0) 111.2 (14.5)	ICD-10	1.5T	1.5 mm	5 mm	p < 0.004	SPM2	Age Gender
David et al. 2014	ASD 15 (8) HC 14 (7)	33.2 (7.4) 32.9 (7.6)		ICD-10 / DSM-IV	3T	1 mm	12 mm	Uncorrected p < 0.001	SPM8	Age Gender
Ecker et al. 2010	ASD 22 (0) HC 22 (0)	27 (7) 28 (7)	104 (15) 111 (10.0)	ICD-10	3T	1.1 mm		p < 0.05	SPM5	
Ecker et al. 2012	ASD 89 (0) HC 89 (0)	26 (7) 28 (6)	110 (15) 113 (12)	ICD-10	3T		4 mm	p = 0.004	FSL4	Age, gender matched
Eilam-Stock et al. 2016	ASD 66 (6) HC 66 (6)	27 (8) 27 (7)	110 (14) 114 (12)	DSM-IV			8 mm	Uncorrected p < 0.005	SPM8	Age matched
Grecucci et al. 2016	ASD 32 (0) HC 50 (0)	24.8 (5.4) 25.2 (5.9)	106.7 (13.8) 115.2 (12.1)	DSM IV	3T		8 mm	Corrected p < 0.05	SPM8	Age Gender
Katz et al. 2016	ASD 23 (0) HC 32 (0)	26.65 (6.51) 29.84 (9.21)	? ?	DSM-IV	3T	?	7 mm	p < 0.005	FSL-VBM	Age, Gender
Kojima et al. 2019	ASD 39 (0) HC 39 (0)	29.9 (6.8) 31.5 (4.5)	107.5 (11.5) 109.8 (8.1)	DSM-IV & ADI-R	3T	2.5 mm	8 mm	Uncorrected p < 0.025	SPM8	Age ICV Handedness
Kosaka et al. 2010	PDD 32 (0) HC 40 (0)	23.8 (4.2) 22.5 (4.3)	101.6 (15.6) 109.7 (7.9)	DSM-IV & DISCO	3T	1.6 mm		Corrected p < 0.05	SPM5	Age ICV
Lai et al. 2013	ASD 60 (30) HC 60 (30)	27.5 (7.4) 27.9 (6.0)	115.2 (13.8) 118.9 (9.5)	ICD-10 / DSM-IV	3T	?	4 mm	p < 0.001	SPM8	Age Scanning site
McAlonan et al. 2002	Asperger 21 (2)^ HC 24 (2)	32 (10) 33 (7)	96 (15) 114 (14)	ICD-10	1.5T	1.5 mm	UN	p < 0.001	SMaRT	Age IQ
Mueller et al. 2013	ASD 12 (3) HC 12 (4)	35.5 (11.4) 33.3 (9.0)	111.3 (13.4) 110.8 (14.4)	ICD-10	3T	4.0 mm	4 mm	Uncorrected p < 0.001	FSL 4.16	Total GMV
Riedel et al. 2014	ASD 30 (11) HC 30 (11)	35.4 (9.1) 35.5 (8.3)	124.5 (12.3) 123.6 (13.8)	DSM-IV & ICD-10	3T		8 mm	Corrected p < 0.05	SPM8	ICV BDI
Sato et al. 2017	Asperger 21 (7)	27.5 (9.3) 26.2 (6.3)	110.2 (12.0) 110.7 (15.3)	DSM-IV	3T		8 mm	p < 0.05	SPM8	Age Gender

	PDD-NOS 15 (4) HC 36 (11)	24.9 (5.5)	24.9 (5.5)							
Schmitz et al. 2006	ASD 10 (0) HC 12 (0)	38 (9) 39 (6)	105 (14) 106 (13)	ICD-10	1.5T	9 mm	10 mm	Uncorrected p < 0.001	SPM99	Age
Toal et al. 2009	ASD without psychosis 16 (0) ASD with psychosis 14 (0) HC 16 (0)	31 (9) 30 (11) 36 (10)	92 (14) 90 (14) 99 (9)	ICD-10 & ADI-R	1.5T			p < 0.05	SPM5	
Toal et al. 2010	ASD 65 (8) HC 33 (3)	31 (10) 32 (9)	98 (21) 105 (12)	ICD-10 & ADI-R & ADOS	1.5T	1.5 mm	8 mm	p < 0.05	SPM2	Total GMV Total WMV
Watanabe et al. 2019	ASD 22 (3) HC 22 (4)	33 (2.0) 30.8 (1.6)	119.7 (2.6) 112.8 (3.0)	DSM-IV / ICD-10 & ADOS	3T		8 mm	p < 0.05	SPM12	Age Full IQ
Wilson et al. 2009	ASD 10 (2) HC 10 (3)	30.10 (9.18) 29.40 (7.91)	91.50 (19.67) 127.20 (9.00)	DSM-IV & ADI & ADOS	1.5T	1.7 mm	12 mm	p < 0.05	SPM2	Total GMV

ADI(-R) = Autism Diagnostic Interview (-Revised). **ADOS (-G)** = Autism Diagnostic Observation Schedule (-Generic). **ASD** = Autism Spectrum Disorder. **BDI** = Beck's Depression Inventory. **DSM** = Diagnostic and Statistical Manual of Mental Disorders. **FSIQ** = Full Scale Intelligence Quotient. **FSL(-VBM)** = FMRIB Software Library (-Voxel Based Morphometry). **FWHM** = Full width at half maximum. **GMV** = Gray matter volume. **HC** = Healthy control. **ICD** = International Statistical Classification of Diseases and Related Health Problems. **ICV** = Total intracranial volume. **NA** = Not applicable. **PDD-NOS** = Pervasive Developmental Disorder Not Otherwise Specified. **SD** = Standard deviation. **SPM** = Statistical parametric mapping. **T** = Tesla. **WMV** = White matter volume.

^ only 17 had VBM analyses

Supplementary Table 5: Quality assessment of voxel-based morphometry studies of gray matter in bvFTD included in the meta-analysis

Study	Inclusion criteria	Study subjects	Exposure	Measurement of condition	Confounding factors	Strategies for confounding factors	Outcome measurement	Statistical analysis	Final score
Agosta et al. 2009	+	+	#	+	+	+	+	+	100%
Agosta et al. 2012	+	+*	#	+	+	+	+	+	100%
Ash et al. 2009	+	+*	#	+	+	+	+	+	100%
Baez et al. 2019	+	-	#	+	+	+	+	+	86%
Boccardi et al. 2005	+	+*	#	+	+	+	+	+	100%
Buhour et al. 2017	+	-	#	+	+	+	+	+	86%
Delvecchio et al. 2019	+	+*	#	+	+	+	+	+	100%

Filippi et al. 2013	+	+*	#	+	+	+	+	+	100%
García-Cordero et al. 2015	+	+	#	+	+	+	+	+	100%
Grossman et al. 2004	+	-	#	+	+	-	+	+	71%
Kanda et al. 2008	+	+*	#	+	+	+	+	+	100%
Kim et al. 2007	+	+	#	+	+	+	+	+	100%
Lagarde et al. 2013	+	+*	#	+	+	+	+	+	100%
Lee et al. 2014	+	+	#	+	+	+	+	+	100%
Libon et al. 2009	+	+*	#	+	+	+	+	+	100%
Pardini et al. 2009	+	-	#	+	+	+	+	+	86%
Pereira et al. 2009	+	+*	#	+	+	+	+	+	100%
Rabinovici et al. 2008	+	+	#	+	+	+	+	+	100%
Rosen et al. 2002	+	+*	#	+	+	+	+	+	100%
Seeley et al. 2008	+	+	#	+	+	+	+	+	100%
Whitwell et al. 2005	+	+	#	+	+	+	+	+	100%
Whitwell et al. 2009	+	+	#	+	+	+	+	+	100%
Whitwell et al. 2004	+	+	#	+	+	-	+	+	86%
Zamboni et al. 2008	+	+*	#	+	+	+	+	+	100%
Total	100%	83%	0%	100%	100%	92%	100%	100%	

+ = Yes
- = No
? = Unclear
= Not applicable
* Clear description of the population from which the study participants were selected was provided, except for the time period
ٔ Due to the methodology of our included studies, "exposure" has not been taken into account in the final score

Supplementary Table 6: Quality assessment of voxel-based morphometry studies of gray matter in SZ included in the meta-analysis

Study	Inclusion criteria	Study subjects	Exposure	Measurement of condition	Confounding factors	Strategies for confounding factors	Outcome measurement	Statistical analysis	Final scoreٔ
Amann et al. 2016	+	+*	#	+	+	+	+	+	100 %
Ananth et al. 2002	-	-	#	+	+	+	+	+	71%
Antonova et al. 2005	+	-	#	+	+	+	+	+	86%
Anderson et al. 2015	+	-	#	+	+	+	+	+	86%
Asami et al. 2012	+	+*	#	+	+	-	+	+	86%

Beneditti et al. 2009	+	+	#	+	+	+	+	+	100 %
Bassitt et al. 2007	-	+*	#	+	+	+	+	+	86%
Berge et al. 2011	-	-	#	+	+	-	+	+	57%
Bonilha et al. 2008	+	?	#	+	+	+	+	+	86%
Bose et al. 2009	+	+*	#	+	+	+	+	+	100 %
Brown et al. 2011	+	+*	#	+	+	-	+	+	86%
Bodnar et al. 2014	+	+	#	+	+	+	+	+	100 %
Borgwardt et al. 2009	+	+	#	+	+	-	+	+	86%
Cascella et al. 2010	+	+*	#	+	+	-	+	+	86%
Chow et al. 2011	+	-	#	+	+	-	+	+	71%
Chua et al. 2006	+	-	#	+	+	+	+	+	86%
Cooke et al. 2008	+	+	#	+	+	+	+	+	100 %
Cui et al. 2011	+	-	#	+	+	+	+	+	86%
Chen et al. 2014	+	+*	#	+	+	+	+	+	100 %
Corradi-Del'Ácqua et al. 2012	+	+	#	+	+	-	+	+	86%
Deng et al. 2009	+	+	#	+	+	-	+	+	86%
Dazzan et al. 2012	+	+	#	+	+	-	+	+	86%
Dean et al. 2020	+	-	#	+	+	+	+	+	86%
Delvecchio et al. 2017	+	+	#	+	+	+	+	+	100 %
Ebdrup et al. 2010	+	+*	#	+	+	+	+	+	100 %
Euler et al. 2009	+	-	#	+	+	-	+	+	71%
Egashira et al. 2014	+	+*	#	+	+	+	+	+	100 %
Foong et al. 2001	-	-	#	+	+	-	+	+	57%
Frascarelli et al. 2015	+	-	#	+	+	-	+	+	71%
Fukuta et al. 2013	+	+*	#	+	+	+	+	+	100 %
Garcia-Marti et al. 2008	+	-	#	+	+	+	+	+	86%
Giuliani et al. 2005	+	-	#	+	+	-	+	+	71%
Garcia-Marti et al. 2012	+	-	#	+	+	+	+	+	86%
Gong Q et al. 2015	+	+	#	+	+	+	+	+	100 %
Gong X et al. 2014	+	+*	#	+	+	-	+	+	86%
Guo F et al. 2019	+	-	#	+	+	+	+	+	86%
Guo JY et al. 2015	+	+	#	+	+	-	+	+	86%
Guo W et al. 2014	+	+*	#	+	+	-	+	+	86%
Guo X et al. 2014	+	+*	#	+	+	+	+	+	100 %
Guo X et al. 2013	+	+*	#	+	+	-	+	+	86%
Ha TH, 2004	+	+	#	+	+	+	+	+	100 %
Herold R, 2009	+	+*	#	+	+	-	+	+	86%
Hirao K et al. 2008	+	+*	#	+	+	+	+	+	100 %
Honea RA et al. 2008	+	+	#	+	+	-	+	+	86%
Horn H et al. 2010	+	+*	#	+	+	+	+	+	100 %
Hushoff Pol HE et al. 2004	+	+	#	+	+	-	+	+	86%
Hushoff Pol HE et al. 2001	+	+	#	+	+	-	+	+	86%
Hooker CI et al. 2011	+	-	#	+	+	-	+	+	71%
Hu M et al. 2013	+	+*	#	+	+	+	+	+	100 %

Huang X et al. 2017	+	+	#	+	+	+	+	+	100 %
Ivleva EI et al. 2012	+	+*	#	+	+	-	+	+	86%
Jayakumar et la. 2005	-	-	#	+	+	+	+	+	71%
Job DE et al. 2001	+	+	#	+	+	+	+	+	100 %
Kasparek T et al. 2007	+	+	#	+	+	+	+	+	100 %
Kasparek T et al. 2010	+	+*	#	+	+	+	+	+	100 %
Kasparek T et al. 2009	+	+	#	+	+	+	+	+	100 %
Kawada R et al. 2009	+	+*	#	+	+	+	+	+	100 %
Kawasaki Y et al. 2007	+	+	#	+	+	+	+	+	100 %
Kawasaki Y et al. 2004	+	+	#	+	+	+	+	+	100 %
Kawasaki Y et al. 2008	+	+	#	+	+	+	+	+	100 %
Koutsouleris N et al. 2007	+	-	#	+	+	+	+	+	86%
Kubicki M et al. 2002	+	+	#	+	+	+	+	+	100 %
Keymer- Gaussal et al. 2018	+	+*	#	+	+	-	+	+	86%
Kim GW. 2017	+	+*	#	+	+	-	+	+	86%
Koelkebeck K. 2019	+	+	#	+	+	+	+	+	100 %
Kong L. 2012	+	-	#	+	+	-	+	+	71%
Lui S. 2009	+	+*	#	+	+	+	+	+	100 %
Lui S. 2009	+	+	#	+	+	+	+	+	100 %
Lee DK. 2020	+	+*	#	+	+	+	+	+	100 %
Lee JS. 2011	+	+*	#	+	+	+	+	+	100 %
Lei W. 2015	+	+	#	+	+	+	+	+	100 %
Lei W. 2019	+	+	#	+	+	+	+	+	100 %
Liao J. 2015	+	+	#	+	+	+	+	+	100 %
Madre M. 2020	+	+*	#	+	+	+	+	+	100 %
Mane A. 2009	+	+*	#	+	+	-	+	+	86%
Marcelis M. 2003	+	+	#	+	+	+	+	+	100 %
Marti Bonmati L. 2007	+	-	#	+	+	+	+	+	86%
McIntosh AM. 2004	+	+*	#	+	+	+	+	+	100 %
Meda AS. 2008	+	+*	#	+	+	+	+	+	100 %
Meisenzahl EM. 2008	+	+*	#	+	+	+	+	+	100 %
Molina V. 2011a	+	+	#	+	+	+	+	+	100 %
Molina V. 2010	+	+	#	+	+	+	+	+	100 %
Molina V. 2011b	+	+	#	+	+	-	+	+	86%
Moorhead TWJ. 2005	+	+	#	+	+	+	+	+	100 %
Maggioni E. 2017	+	-	#	+	+	+	+	+	86%
McDonald C. 2005	+	-	#	+	+	+	+	+	86%
Minagatowa T.M. 2009	+	+	#	+	+	+	+	+	100 %

Nagashima T. 2012	+	-	#	+	+	+	+	+	86%
Nakamura K. 2013	+	+	#	+	+	-	+	+	86%
Neckelmann G. 2009	+	+*	#	+	+	+	+	+	100 %
Nenadic I. 2015	+	+	#	+	+	+	+	+	100 %
Nenadic I. 2015b	+	+	#	+	+	+	+	+	100 %
Nenadic I. 2015c	+	+	#	+	+	-	+	+	86%
O'Daly O.G. 2007	+	+*	#	+	+	+	+	+	100 %
Ohnishi T. 2006	+	-	#	+	+	-	+	+	71%
Ortiz-Gil J. 2011	+	-	#	+	+	+	+	+	86%
Oertel-Knochel V. 2012	+	+*	#	+	+	+	+	+	100 %
Onay A. 2017	+	+*	#	+	+	+	+	+	100 %
Ota M. 2017	+	-	#	+	+	+	+	+	86%
Paillere M.L. 2001	+	-	#	+	+	+	+	+	86%
Pomarol-Clotet E. 2010	+	+*	#	+	+	+	+	+	100 %
Prasad K.M.R. 2007	+	+*	#	+	+	-	+	+	86%
Picado M. 2015	+	+*	#	+	+	+	+	+	100 %
Premkumar P. 2008	+	+	#	+	+	-	+	+	86%
Price G. 2010	+	+	#	+	+	+	+	+	100 %
Qiu L. 2011	+	+*	#	+	+	+	+	+	100 %
Quide Y. 2019	+	+	#	+	+	+	+	+	100 %
Rosa P.G.P. 2014	+	+	#	+	+	+	+	+	100 %
Salgado-Pineda P. 2003	+	+	#	+	+	+	+	+	100 %
Salgado-Pineda P. 2014	+	+	#	+	+	+	+	+	100 %
Salgado-Pineda P. 2004	+	+	#	+	+	+	+	+	100 %
Schiffer B. 2013	+	+*	#	+	+	+	+	+	100 %
Schuster C. 2012	+	+	#	+	+	-	+	+	86%
Shaplaske J. 2002	+	+*	#	+	+	+	+	+	100 %
Sigmundsson T. 2001	+	+*	#	+	+	+	+	+	100 %
Suzuki M. 2002	+	+	#	+	+	-	+	+	86%
Suzuki M. 2005	+	+	#	+	+	+	+	+	100 %
Sapara A. 2016	+	-	#	+	+	+	+	+	86%
Schaufelberger M.S. 2007	+	+	#	+	+	+	+	+	100 %
Schiffer B. 2010	+	+	#	+	+	+	+	+	100 %
Song J. 2015	+	+	#	+	+	+	+	+	100 %
Spalthoff R. 2018	+	+	#	+	+	+	+	+	100 %
Stegmayer K. 2014	+	+*	#	+	+	+	+	+	100 %
Tian L. 2011	+	+	#	+	+	+	+	+	100 %
Tomelleri L. 2009	+	+	#	+	+	+	+	+	100 %
Tragellas J.R. 2007	+	-	#	+	+	-	+	+	71%
Torres U.S. 2016	+	+	#	+	+	+	+	+	100 %

Van Harren. 2007	+	+	#	+	+	+	+	+	100 %
Venkatasubramanian G. 2008	+	+*	#	+	+	-	+	+	86%
Van Tol M.J. 2014	+	+	#	+	+	+	+	+	100 %
Vicens V. 2016	+	-	#	+	+	+	+	+	86%
Volz H.P. 2000	+	-	#	+	+	+	+	+	86%
Watson D.R. 2012	+	+	#	+	+	+	+	+	100 %
Whitford T.J. 2006	+	+	#	+	+	+	+	+	100 %
Wilke M. 2001	+	+	#	+	+	+	+	+	100 %
Wolf R.C. 2008	+	+*	#	+	+	+	+	+	100 %
Wang J. 2019	+	+	#	+	+	+	+	+	100 %
Wang J. 2017	+	+	#	+	+	+	+	+	100 %
Witthaus H. 2009	+	+*	#	+	+	+	+	+	100 %
Wolf R.C. 2020	+	+	#	+	+	+	+	+	100 %
Wu F. 2018	+	+*	#	+	+	+	+	+	100 %
Xu L. 2009	+	+*	#	+	+	+	+	+	100 %
Yamada M. 2007	+	+*	#	+	+	+	+	+	100 %
Yang C. 2014	+	+	#	+	+	+	+	+	100 %
Yang Z. 2019	+	+*	#	+	+	+	+	+	100 %
Yoneyama E. 2003	+	+*	#	+	+	+	+	+	100 %
Yue Y. 2016	+	-	#	+	+	+	+	+	86%
Yuksel C. 2012	+	+*	#	+	+	+	+	+	100 %
Zhang Y. 2013	+	-	#	+	+	+	+	+	86%
Zierhut K.C. 2013	+	-	#	+	+	+	+	+	86%
Total	97%	77%	0%	100%	100%	75%	100%	100%	

+ = Yes
- = No
? = Unclear
= Not applicable
* Clear description of the population from which the study participants were selected was provided, except for the time period
¶ Due to the methodology of our included studies, "exposure" has not been taken into account in the final score

Supplementary Table 7: Quality assessment of voxel-based morphometry studies of gray matter in BD included in the meta-analysis

Study	Inclusion criteria	Study subjects	Exposure	Measurement of condition	Confounding factors	Strategies for confounding factors	Outcome measurement	Statistical analysis	Final score ¶
Adler et al. 2005	+	-	#	+	+	+	+	+	86%
Almeida et al. 2009	+	+*	#	+	+	+	+	+	100%
Alonso-Lana et al. 2016	+	+*	#	+	+	-	+	+	86%
Altamura et al. 2017	+	+*	#	+	+	+	+	+	100%

Altamura et al. 2018	+	+*	#	+	+	+	+	+	100%
Amann et al. 2016	+	+*	#	+	+	+	+	+	100%
Ambrosi et al. 2013	+	+*	#	+	+	+	+	+	100%
Baez et al. 2019	+	-	#	+	+	+	+	+	86%
Brown et al. 2011	+	+*	#	+	+	+	+	+	100%
Cai et al. 2015	+	+	#	+	+	+	+	+	100%
Chen et al. 2007	+	+*	#	+	+	+	+	+	100%
Chen et al. 2012	+	+	#	+	+	+	+	+	100%
Chen et al. 2018	+	+	#	+	+	+	+	+	100%
Cui et al. 2011	+	+*	#	+	+	+	+	+	100%
de Azevedo-Marques Périco et al. 2011	+	+	#	+	+	+	+	+	100%
Delaloye et al. 2009	+	+*	#	+	+	+	+	+	100%
Delvecchio et al. 2019	+	+*	#	+	+	+	+	+	100%
Doris et al. 2004	+	-	#	+	+	+	+	+	86%
Eker et al. 2014	+	+*	#	+	+	+	+	+	100%
Ekman et al. 2017	+	+*	#	+	+	+	+	+	100%
Ha et al. 2009	+	-	#	+	+	+	+	+	86%
Hajek et al. 2013	+	+*	#	+	+	+	+	+	100%
Hajek et al. 2014	+	+	#	+	+	+	+	+	100%
Haldane et al. 2008	+	+	#	+	+	+	+	+	100%
Haller et al. 2011	+	+*	#	+	+	+	+	+	100%
Hozer et al. 2020	+	+	#	+	+	+	+	+	100%
Ivleva et al. 2013	+	+	#	+	+	+	+	+	100%
Kempton et al. 2009	+	-	#	+	+	+	+	+	86%
Kim et al. 2013	+	+*	#	+	+	+	+	+	100%
Kozicky et al. 2016	+	+	#	+	+	+	+	+	100%
Lee et al. 2017	+	+*	#	+	+	+	+	+	100%
Lee et al. 2020	+	+*	#	+	+	+	+	+	100%
Li et al. 2011	+	+	#	+	+	+	+	+	100%
Lochhead et al. 2004	+	+*	#	+	+	+	+	+	100%

Lyoo et al. 2004	+	+*	#	+	+	+	+	100%
Maggioni et al. 2017	+	+*	#	+	+	+	+	100%
Matsubara et al. 2016	+	+*	#	+	+	+	+	100%
Matsuo et al. 2019	+	+	#	+	+	+	+	100%
McIntosh et al. 2004	+	+*	#	+	+	+	+	100%
Minuzzi et al. 2017	+	+*	#	+	+	+	+	100%
Molina et al. 2011	+	-	#	+	+	+	+	86%
Mwangi et al. 2016	+	-	#	+	+	+	+	86%
Narita et al. 2011	+	+*	#	+	+	+	+	100%
Nenadic et al. 2015c	+	+*	#	+	+	+	+	100%
Nery et al. 2015	+	+*	#	+	+	+	+	100%
Neves et al. 2015	+	+*	#	+	+	+	+	100%
Nugent et al. 2006	+	-	#	+	+	+	+	86%
Oertel-Knöchel et al. 2014	+	+*	#	+	+	+	+	100%
Poletti et al. 2016	+	-	#	+	+	+	+	86%
Poletti et al. 2017	+	+*	#	+	+	+	+	100%
Redlich et al. 2014	+	+	#	+	+	-	+	86%
Rocha-Rego et al. 2014 Cohort 1	+	+	#	+	+	+	+	100%
Rocha-Rego et al. 2014 Cohort 2	+	+	#	+	+	+	+	100%
Rossi et al. 2013	+	+	#	+	+	+	+	100%
Sani et al. 2016	+	+	#	+	+	+	+	100%
Sariçiçek et al. 2015	+	+*	#	+	+	+	+	100%
Shepherd et al. 2015	+	+	#	+	+	+	+	100%
Song et al. 2015	+	+	#	+	+	+	+	100%
Stanfield et al. 2009	+	+*	#	+	+	+	+	100%
Tang et al. 2014	+	+*	#	+	+	+	+	100%
Tost et al. 2010	+	+	#	+	+	+	+	100%
Tu et al. 2017	+	+*	#	+	+	+	+	100%

Vai et al. 2020	+	-	#	+	+	+	+	+	86%
Watson et al. 2012	+	+	#	+	+	+	+	+	100%
Yatham et al. 2007	+	+*	#	+	+	+	+	+	100%
Total	100%	85%	0%	100%	100%	97%	100%	100%	

+ = Yes
- = No
? = Unclear
= Not applicable
* Clear description of the population from which the study participants were selected was provided, except for the time period
ٔ Due to the methodology of our included studies, "exposure" has not been taken into account in the final score

Supplementary Table 8: Quality assessment of voxel-based morphometry studies of gray matter in ASD included in the meta-analysis

Study	Inclusion criteria	Study subjects	Exposure	Measurement of condition	Confounding factors	Strategies for confounding factors	Outcome measurement	Statistical analysis	Final score ٔ
Abell et al. 1999	+	-	#	+	+	+	+	+	86%
Craig et al. 2007	+	+	#	+	+	+	+	+	100%
David et al. 2014	+	+*	#	+	+	+	+	+	100%
Ecker et al. 2010	+	+	#	+	+	-	+	+	86%
Ecker et al. 2012	+	+	#	+	+	+	+	+	100%
Eilam-Stock et al. 2016	+	+	#	+	+	+	+	+	100%
Grecucci et al. 2016	+	+	#	+	+	+	+	+	100%
Katz et al. 2016	+	+*	#	+	+	+	+	+	100%
Kojima et al. 2019	+	+	#	+	+	+	+	+	100%
Kosaka et al. 2010	+	+*	#	+	+	+	+	+	100%
Lai et al. 2013	+	+*	#	+	+	+	+	+	100%
McAlonan et al. 2002	+	+*	#	+	+	+	+	+	100%
Mueller et al. 2013	+	+*	#	+	+	+	+	+	100%
Riedel et al. 2014	+	+	#	+	+	+	+	+	100%
Sato et al. 2017	+	-	#	+	+	+	+	+	86%
Schmitz et al. 2006	+	+*	#	+	+	+	+	+	100%
Toal et al. 2009	+	+	#	+	+	-	+	+	86%
Toal et al. 2010	+	+	#	+	+	+	+	+	100%
Watanabe et al. 2019	+	+	#	+	+	+	+	+	100%
Wilson et al. 2009	+	-	#	+	+	+	+	+	86%
Total	100%	85%	0%	100%	100%	90%	100%	100%	

+ = Yes
- = No
? = Unclear
= Not applicable
* Clear description of the population from which the study participants were selected was provided, except for the time period
٭ Due to the methodology of our included studies, "exposure" has not been taken into account in the final score

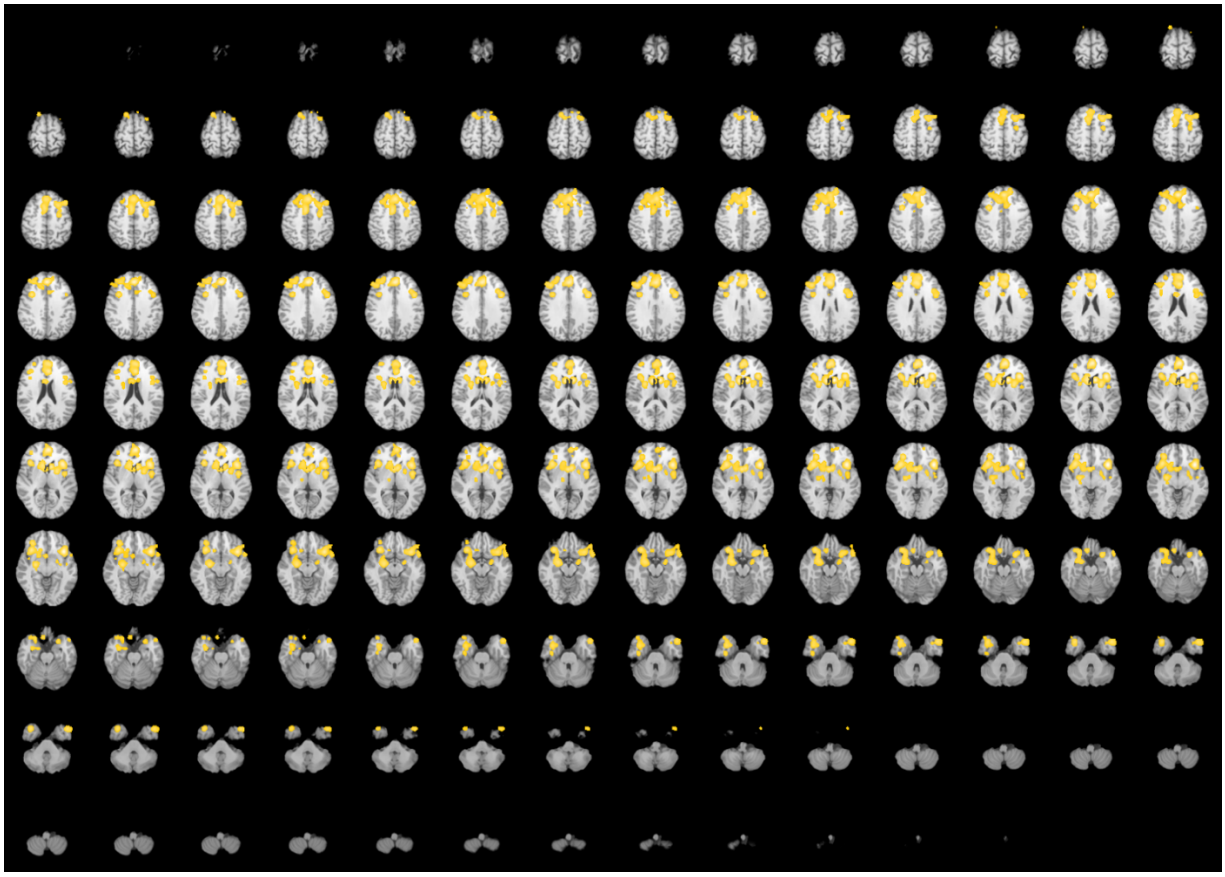
Supplementary Table 9: Gray matter regions involved in the meta-analysis of bvFTD. Illustrated are the clusters, x,y,z peak-coordinates, ALE-value, p-value, Z-score and (MNI 152) anatomical label

Cluster	x	y	z	ALE	P	Z	Label (Nearest Gray Matter within 5mm)
1	-36	16	-6	0.039404165	1,51E-04	6.645.521	Left Cerebrum.Sub-lobar.Insula.White Matter.*
	-8	12	10	0.037847698	5,16E-05	6.462.396	Left Cerebrum.Sub-lobar.Caudate.Gray Matter.Caudate Body
	0	36	32	0.03334342	1,68E-02	5.913.217	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.*.*
	-4	48	6	0.033129226	1,97E-02	58.870.173	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	-34	18	8	0.03217435	4,05E-03	57.664.213	Left Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
	8	10	12	0.03118357	8,47E-03	5.640.761	Right Cerebrum.Sub-lobar.Lateral Ventricle.Cerebro-Spinal Fluid.*
	0	28	44	0.025034625	7,07E-01	48.229.175	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 8
	-2	32	20	0.024564479	9,80E-02	47.576.203	Left Cerebrum.Limbic Lobe.Anterior Cingulate.*.*
	2	6	-2	0.024287447	1,18E+01	47.198.825	Inter-Hemispheric.*.*.*.*
	36	16	-4	0.023921534	1,52E+01	4.667.922	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
	34	20	-8	0.023465166	2,07E-01	4.604.388	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
	-4	8	0	0.02324983	2,40E+01	45.731.087	Left Cerebrum.Sub-lobar.Caudate.Gray Matter.Caudate Head
	34	8	36	0.022731423	3,42E+01	4.498.637	Right Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
	-22	2	8	0.022651047	3,61E+00	4.487.105	Left Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Putamen
	6	2	44	0.021961275	5,75E+00	4.386.956	Right Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 24
	-4	46	20	0.02150522	7,77E+00	43.208.823	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
	-42	6	28	0.021449119	8,09E+00	4.312.024	Left Cerebrum.Frontal Lobe.Precentral Gyrus.Gray Matter.Brodmann area 6
	26	-12	-10	0.02128317	9,06E-01	42.868.676	Right Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Lateral Globus Pallidus
	32	34	-6	0.020844657	1,21E+02	4.221.355	Right Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
	26	2	12	0.01973091	2,52E+02	4.053.864	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	40	28	26	0.019710554	2,55E+02	4.050.791	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
	-46	10	-32	0.019132404	3,71E+02	3.962.119	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	-38	-4	2	0.018883023	4,36E+01	39.236.398	Left Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	-24	14	48	0.018539235	5,42E+02	38.710.725	Left Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
	10	22	40	0.017594665	9,86E+01	3.722.662	Right Cerebrum.Limbic Lobe.Cingulate Gyrus.White Matter.*
	36	8	-34	0.017490275	1,05E+03	37.068.634	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	32	14	12	0.017328683	1,16E+03	3.681.533	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	-24	10	-20	0.016324379	2,16E+03	3.519.407	Left Cerebrum.Frontal Lobe.Subcallosal Gyrus.White Matter.*

38	0	-28	0.01619813	2,33E+02	34.998.186	Right Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
-34	16	28	0.015997685	2,63E+03	34.669.158	Left Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
-40	18	48	0.015675647	3,20E+02	34.140.892	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
-12	42	38	0.0155325215	3,51E+03	33.890.731	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
-40	6	16	0.0155273145	3,51E+03	33.890.731	Left Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
48	32	28	0.015205853	4,26E+02	3.335.238	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
18	22	58	0.014826243	5,37E+03	32.703.598	Right Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
30	36	32	0.014628289	6,06E+02	32.358.208	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
28	4	-16	0.0145475175	6,36E+03	32.219.994	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
-24	-6	46	0.013649919	0.0010918718	30.640.335	Left Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
10	18	-20	0.013623416	0.0011115887	30.586.755	Right Cerebrum.Frontal Lobe.Subcallosal Gyrus.White Matter.*
26	44	28	0.013361762	0.0012977627	30.119.765	Right Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
16	6	-4	0.013346097	0.0013053989	30.101.953	Right Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Lateral Globus Pallidus
-6	14	38	0.012958481	0.0016383181	29.405.184	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 32
-52	10	-14	0.012566523	0.002049338	28.704.658	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
28	20	42	0.011723758	0.0033069393	27.156.851	Right Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
18	34	40	0.011674788	0.0033993984	2.706.542	Right Cerebrum.Frontal Lobe.Sub-Gyral.Gray Matter.Brodmann area 8
32	46	16	0.011528804	0.0036710477	26.809.158	Right Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
36	44	8	0.011518797	0.0036911678	26.790.864	Right Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
40	-16	-30	0.010755114	0.005569598	25.383.015	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
40	18	-26	0.01000079	0.00833993	23.936.896	Right Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 47
-20	-8	-14	0.009978636	0.008429499	23.897.684	Left Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
-48	28	-14	0.009939902	0.008608523	23.820.395	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
14	-18	0	0.009903075	0.0087908255	23.743.126	Right Cerebrum.Sub-lobar.Thalamus.Gray Matter.Mammillary Body
-14	52	-2	0.009417065	0.011311865	22.797.296	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
12	52	24	0.009082261	0.013519635	22.109.504	Right Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
-20	0	-4	0.008743611	0.01613717	21.409.962	Left Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Lateral Globus Pallidus
-22	-4	-4	0.0087071	0.016392566	21.347.048	Left Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Lateral Globus Pallidus
-8	36	2	0.008540665	0.017926501	20.985.906	Left Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.Corpus Callosum
-32	6	-32	0.008513461	0.018211873	20.921.652	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
2	4	12	0.008472155	0.01860103	20.835.397	Inter-Hemispheric.*.*.*.*
-52	8	18	0.008328126	0.02004562	20.528.076	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
-14	26	44	0.008252138	0.020918852	2.035.131	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
-28	-14	-6	0.008039632	0.023440482	19.873.741	Left Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Putamen
20	12	44	0.008002494	0.02393287	19.785.584	Right Cerebrum.Limbic Lobe.Cingulate Gyrus.White Matter.*
-20	26	56	0.007821592	0.026323361	19.378.074	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 6

24	-24	-6	0.007701255	0.028031748	19.105.418	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
-6	28	58	0.0075866953	0.029742327	18.845.942	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
-42	-12	-6	0.007543724	0.030583862	18.722.811	Left Cerebrum.Sub-lobar.Insula.White Matter.*
40	0	-8	0.0072761164	0.035216678	18.091.136	Right Cerebrum.Sub-lobar.Insula.White Matter.*

Supplementary Figure 5: Gray matter regions involved in the meta-analysis of bvFTD. Axial lay-out.



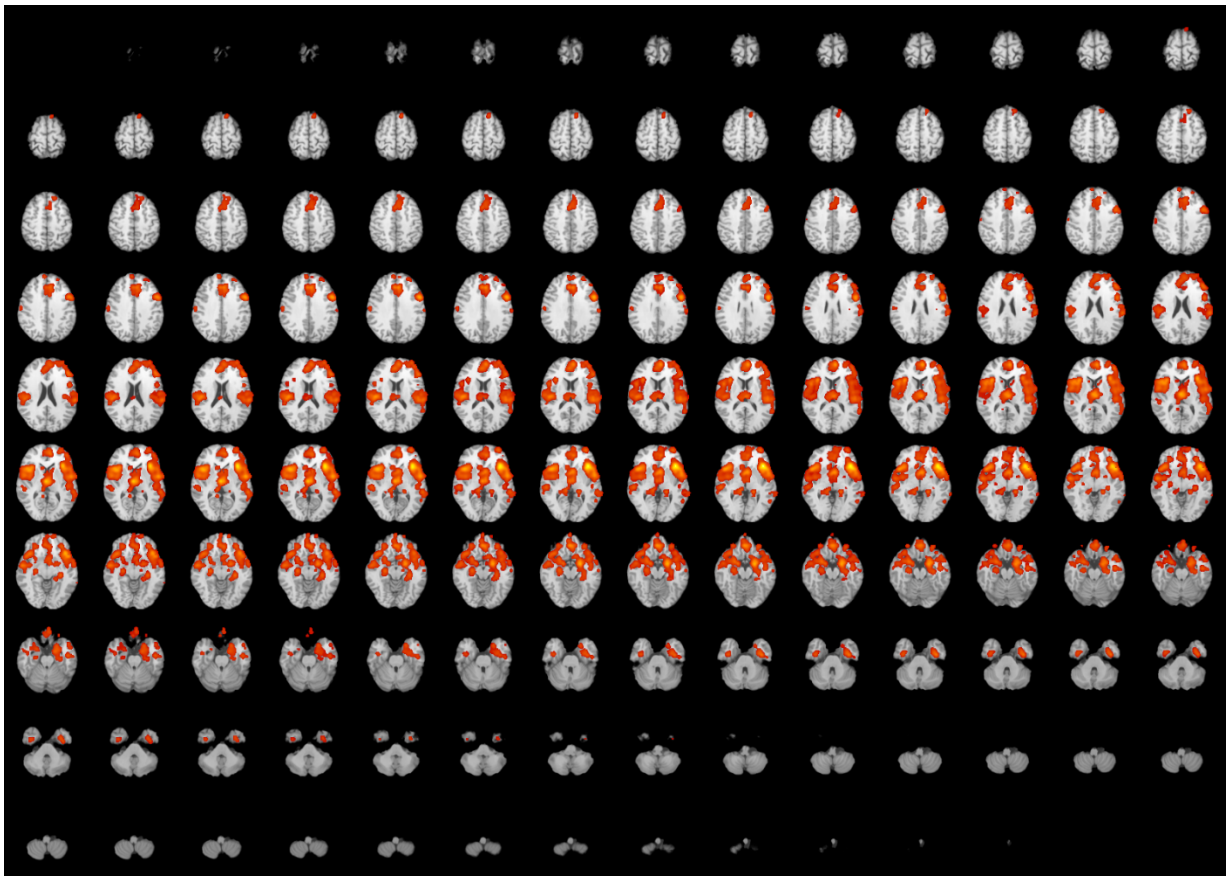
Supplementary Table 10: Gray matter regions involved in the meta-analysis of SZ. Illustrated are the clusters, x,y,z peak-coordinates, ALE-value, p-value, Z-score and (MNI 152) anatomical label

Cluster	x	y	z	ALE	P	Z	Label (Nearest Gray Matter within 5mm)
1	-38	20	-2	0.112593964	4,50E-15	9.588.839	Left Cerebrum.Sub-lobar.Insula.White Matter.*
	2	-14	4	0.0881134	1,35E-08	79.045.687	Inter-Hemispheric.*.*.*.*
	-20	-4	-16	0.0781768	3,51E-06	71.794.243	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Amygdala
	-50	8	28	0.07680539	7,38E-07	7.077.029	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 9
	-52	-4	4	0.07344567	4,46E-06	682.325	Left Cerebrum.Frontal Lobe.Precentral Gyrus.White Matter.*
	-6	50	10	0.06640631	1,71E-03	62.781.363	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
	-4	6	-2	0.06553147	2,67E-03	62.086.167	Left Cerebrum.Sub-lobar.Lateral Ventricle.Cerebro-Spinal Fluid.*

2	36	-14	0.06412528	5,40E-04	60.973.325	Right Cerebrum.Limbic Lobe.Anterior Cingulate.*.*
-4	28	30	0.06033035	3,50E-02	57.908.616	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.White Matter.*
-48	-26	14	0.055240244	3,95E-02	53.692.865	Left Cerebrum.Temporal Lobe.Transverse Temporal Gyrus.White Matter.*
4	28	30	0.054210514	6,38E-02	528.234	Right Cerebrum.Limbic Lobe.Cingulate Gyrus.*.*
-34	-12	-32	0.052461922	1,43E+00	5.133.116	Left Cerebrum.Limbic Lobe.Sub-Gyral.White Matter.*
-60	-28	20	0.051301293	2,41E+00	5.033.227	Left Cerebrum.Parietal Lobe.Postcentral Gyrus.Gray Matter.Brodmann area 40
-46	32	20	0.050383963	3,65E+00	4.953.458	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
-6	42	0	0.048525553	8,29E-01	47.912.455	Left Cerebrum.Limbic Lobe.Anterior Cingulate.White Matter.*
4	42	16	0.04709291	1,55E+01	4.663.469	Right Cerebrum.Limbic Lobe.Anterior Cingulate.*.*
-32	54	0	0.046173614	2,31E+00	4.581.066	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
-28	-30	-10	0.0460277	2,46E+01	45.684.648	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
-58	-38	4	0.04456623	4,58E+00	44.362.645	Left Cerebrum.Temporal Lobe.Middle Temporal Gyrus.Gray Matter.Brodmann area 22
-18	-38	-2	0.044115473	5,53E+00	4.395.186	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
-42	42	8	0.044060692	5,68E+01	43.896.966	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 46
10	-34	0	0.04234558	1,16E+01	4.232.086	*.*.*.*.*
-2	36	-4	0.04194382	1,37E+02	41.939.273	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 24
-30	34	-8	0.040856276	2,13E+01	4.092.738	Left Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
4	38	-8	0.040447056	2,52E+02	4.054.065	Right Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 24
-44	-14	-20	0.039992385	3,03E+02	40.105.157	Left Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
-54	-16	16	0.03806147	6,52E+01	38.255.837	Left Cerebrum.Parietal Lobe.Postcentral Gyrus.Gray Matter.Brodmann area 43
-34	54	16	0.037926424	6,86E+02	38.129.847	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
-28	-22	-18	0.036468543	1,21E+03	36.705.277	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
-40	46	14	0.036307607	1,29E+03	36.547.809	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
2	14	42	0.035994846	1,45E+03	36.232.066	Inter-Hemispheric.*.*.*.*
-10	12	-12	0.03537648	1,84E+03	3.562.716	Left Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
-4	16	44	0.034992896	2,13E+03	35.238.225	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
6	52	32	0.03474178	2,34E+03	34.988.077	Right Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 6
6	46	-14	0.03466645	2,40E+02	3.491.797	Right Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
-46	12	-20	0.03292027	4,59E+03	33.145.335	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 38
-10	22	58	0.03285694	4,69E+02	33.083.944	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
-44	-6	-14	0.032799534	4,80E+03	33.022.532	Left Cerebrum.Temporal Lobe.Sub-Gyral.Gray Matter.Brodmann area 21
-4	56	0	0.03268384	5,01E+03	32.899.604	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 10
-26	48	14	0.031938113	6,55E+03	32.136.993	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
-36	-20	20	0.03177862	6,94E+02	31.971.111	Left Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
-26	48	8	0.030714476	0.0010165506	30.853.539	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
10	16	0	0.030327888	0.0011622893	30.452.876	Right Cerebrum.Sub-lobar.Caudate.Gray Matter.Caudate Head

	-58	-52	14	0.030275926	0.0011828576	30.400.083	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 22
	-26	48	26	0.030219456	0.0012080705	30.336.504	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
	2	60	-12	0.02961822	0.0014893067	29.699.364	Inter-Hemispheric.*.*.*.*
	-16	32	48	0.029317578	0.001652376	29.378.703	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
	10	-48	4	0.029315656	0.001652376	29.378.703	Inter-Hemispheric.*.*.*.*
	-4	12	34	0.028969467	0.0018640163	2.900.302	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 24
	-50	4	-18	0.028624872	0.0021011578	28.625.615	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	-22	54	20	0.028200759	0.002423577	28.170.197	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
	2	16	32	0.027476372	0.0030876275	27.383.275	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.*.*
	-22	-38	-12	0.027113505	0.003492359	2.697.572	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
	-54	-16	-22	0.024755053	0.007481344	2.433.281	Left Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
	-54	-60	-4	0.024466993	0.008198371	23.999.627	Left Cerebrum.Occipital Lobe.Middle Occipital Gyrus.Gray Matter.Brodmann area 19
	24	-38	-2	0.024421228	0.008328217	2.394.205	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
	-60	-20	-14	0.024420537	0.008328217	2.394.205	Left Cerebrum.Temporal Lobe.Middle Temporal Gyrus.White Matter.*
	-18	-46	-2	0.02353507	0.010949964	2.292.099	Left Cerebrum.Occipital Lobe.Lingual Gyrus.White Matter.*
	-14	-18	-12	0.02249803	0.015025459	21.694.186	Left Brainstem.Midbrain.*.*.*
	-14	14	8	0.020494927	0.027077839	19.255.893	Left Cerebrum.Sub-lobar.Caudate.Gray Matter.Caudate Body
2	42	12	2	0.0785002	2,95E-06	72.032.537	Right Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
	46	-20	16	0.06598299	2,13E-03	62.442.217	Right Cerebrum.Sub-lobar.Insula.White Matter.*
	34	16	8	0.063781396	6,42E-04	60.693.645	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	54	-8	-8	0.05421762	6,35E-01	5.283.186	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	50	-2	4	0.05230871	1,53E-01	5.120.253	Right Cerebrum.Sub-lobar.Insula.*.*
	24	0	-18	0.04949107	5,42E-01	4.875.686	Right Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Brodmann area 34
	40	-4	2	0.045517705	3,06E+01	45.224.566	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
	18	-4	-16	0.045175117	3,53E+01	449.169	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	26	-20	-12	0.044266995	5,20E+01	44.088.874	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	54	-28	-2	0.04284118	9,45E+00	42.774.577	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	38	-12	-30	0.038006388	6,65E+01	3.820.738	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
	26	34	-10	0.034750707	2,33E+03	34.998.088	Right Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
	54	-34	18	0.029013164	0.0018385844	2.904.605	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 41
	58	-18	30	0.028278656	0.0023587656	28.257.143	Right Cerebrum.Parietal Lobe.Postcentral Gyrus.White Matter.*
	62	-38	-2	0.022044003	0.01723907	2.114.435	Right Cerebrum.Temporal Lobe.Middle Temporal Gyrus.White Matter.*

Supplementary Figure 6: Gray matter regions involved in the meta-analysis of SZ. Axial lay-out.



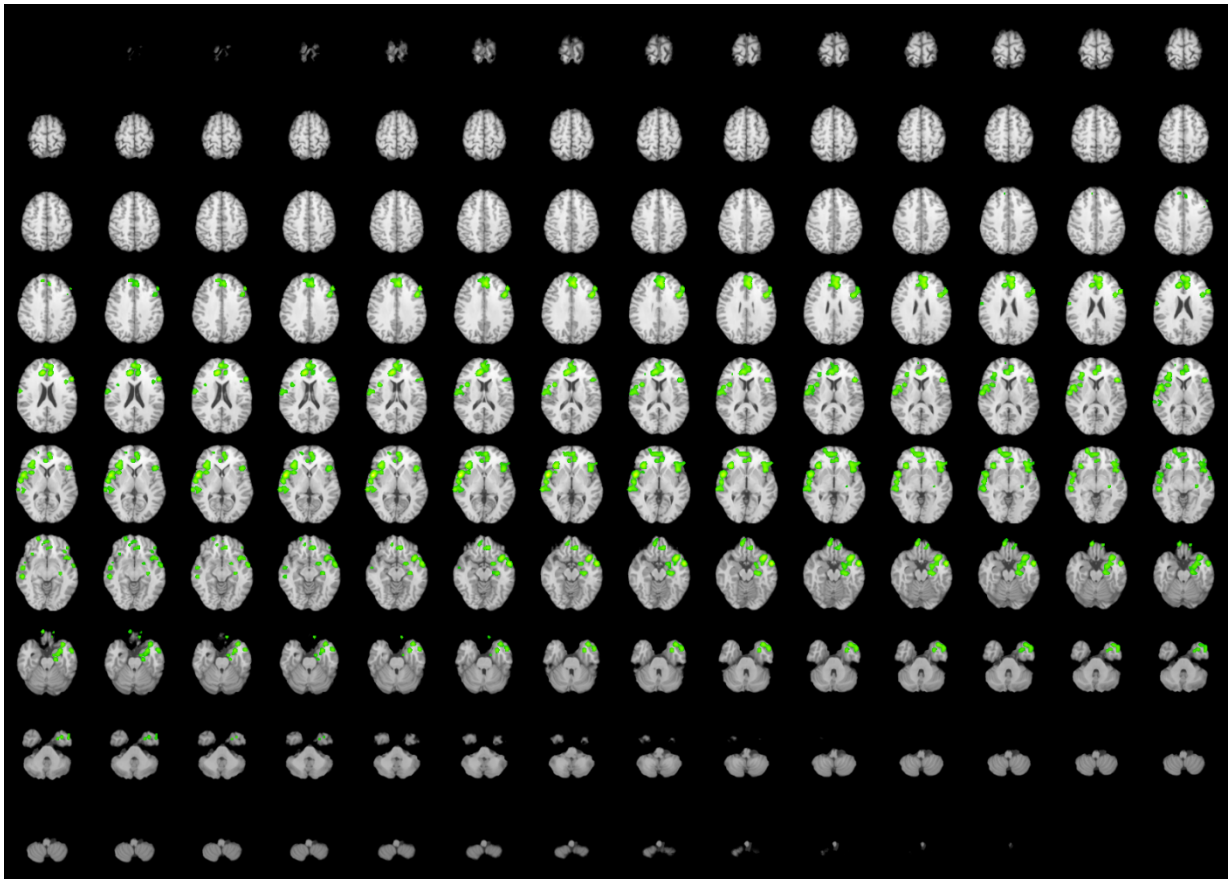
Supplementary Table 11: Gray matter regions involved in the meta-analysis of BD. Illustrated are the clusters, x,y,z peak-coordinates, ALE-value, p-value, Z-score and (MNI 152) anatomical label

Cluster	x	y	z	ALE	P	Z	Label (Nearest Gray Matter within 5mm)
1	-54	0	-16	0.025437681	3,86E+01	44.730.296	Left Cerebrum.Temporal Lobe.Middle Temporal Gyrus.White Matter.*
	-38	12	-16	0.022891147	1,72E+01	41.421.075	Left Cerebrum.Sub-lobar.Extra-Nuclear.Gray Matter.Brodmann area 13
	-52	20	20	0.02041968	6,98E+01	38.088.548	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
	-44	18	10	0.02027842	7,54E+01	37.895.992	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
	-44	14	28	0.01980437	9,84E+02	3.723.213	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
	-50	28	30	0.017211385	4,02E+02	33.513.088	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
	-38	26	-4	0.016070882	7,39E+02	31.790.314	Left Cerebrum.Sub-lobar.Insula.Gray Matter.*
	-40	14	0	0.015634576	9,31E+02	31.113.534	Left Cerebrum.Sub-lobar.Insula.White Matter.*
	-36	14	-30	0.015603795	9,46E+03	3.106.709	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 38
	-26	-22	-16	0.014426765	0.0017328166	29.231.017	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
	-48	6	-30	0.0140162185	0.002131656	2.857.992	Left Cerebrum.Temporal Lobe.Middle Temporal Gyrus.Gray Matter.Brodmann area 21
	-28	2	-24	0.013936577	0.002218905	28.452.392	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Brodmann area 34
	-18	-20	-18	0.01310402	0.0033648289	2.709.934	Left Cerebrum.Limbic Lobe.*.*.*

	-22	-6	-20	0.012717224	0.0040444657	2.648.335	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Amygdala
	-34	-2	-18	0.011077258	0.008778406	23.748.348	Left Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
	-20	0	-12	0.010656523	0.010676784	2.301.674	Left Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	-32	4	-36	0.010422938	0.011945714	22.588.706	Left Cerebrum.Limbic Lobe.Uncus.White Matter.*
	-44	34	-8	0.0098174075	0.015866175	21.477.659	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
	-54	28	-2	0.009780483	0.016178867	21.399.634	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
	-12	-10	-24	0.009691427	0.016869944	21.231.666	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.*.*
	-22	0	-36	0.009156354	0.0216459	20.208.838	Left Cerebrum.Limbic Lobe.Uncus.Gray Matter.Brodmann area 28
2	12	34	18	0.02461411	6,30E+01	43.668.804	Right Cerebrum.Limbic Lobe.Anterior Cingulate.White Matter.*
	-2	38	28	0.022493012	2,17E+02	4.088.946	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
	-6	34	24	0.02110399	4,77E+02	39.018.328	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.White Matter.*
	-6	46	24	0.019710843	1,03E+03	37.107.058	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
	4	50	18	0.019320566	1,28E+03	36.560.898	Inter-Hemispheric.*.*.*.*
	10	44	-18	0.015512318	9,92E+02	30.927.544	Right Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 10
	6	46	-4	0.014717219	0.0014947135	2.968.823	Right Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	-2	48	2	0.014701626	0.0015101023	2.965.674	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	20	56	-6	0.014051987	0.0020997166	2.862.779	Right Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
	-8	34	-14	0.0139855705	0.0021640272	28.532.062	Left Cerebrum.Limbic Lobe.Anterior Cingulate.White Matter.*
	-4	46	8	0.013189895	0.0032204622	2.724.447	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	-4	34	-2	0.013108155	0.0033484832	27.115.488	Left Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.Corpus Callosum
	-4	42	12	0.012996377	0.0035323766	26.937.764	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	-8	40	4	0.012081852	0.0054924767	25.431.771	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	14	46	-2	0.011911028	0.005953714	2.514.876	Right Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	10	44	32	0.01177265	0.006362588	24.913.692	Right Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
	6	32	0	0.010546159	0.011240619	22.821.372	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.Corpus Callosum
	-14	40	-20	0.009868814	0.015491547	21.572.897	Left Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
	-10	30	-24	0.009248117	0.0207362	2.038.776	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
	-2	58	16	0.00906881	0.022611702	20.025.706	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.*.*
	20	50	4	0.008308081	0.032213263	18.492.167	Right Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
3	54	2	2	0.02906225	4,33E-01	4.919.849	Right Cerebrum.Frontal Lobe.Precentral Gyrus.Gray Matter.Brodmann area 44
	36	22	0	0.02124369	4,41E+02	39.208.307	Right Cerebrum.Sub-lobar.Insula.White Matter.*
	60	-10	6	0.017157113	4,13E+03	33.438.916	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 22
	66	-30	2	0.01638197	6,26E+02	3.226.631	Right Cerebrum.Temporal Lobe.Middle Temporal Gyrus.Gray Matter.Brodmann area 22
	38	8	14	0.016297044	6,54E+02	32.143.984	Right Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
	56	-30	-6	0.014573203	0.0016137379	29.451.983	Right Cerebrum.Temporal Lobe.Middle Temporal Gyrus.White Matter.*
	34	6	4	0.013570194	0.0026691353	27.858.796	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*

	54	-8	14	0.012760265	0.0039672167	26.548.471	Right Cerebrum.Parietal Lobe.Sub-Gyral.White Matter.*
	50	-30	2	0.010436345	0.011833498	22.624.924	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	54	-36	4	0.009251951	0.0207362	2.038.776	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*

Supplementary Figure 7: Gray matter regions involved in the meta-analysis of BD. Axial lay-out.

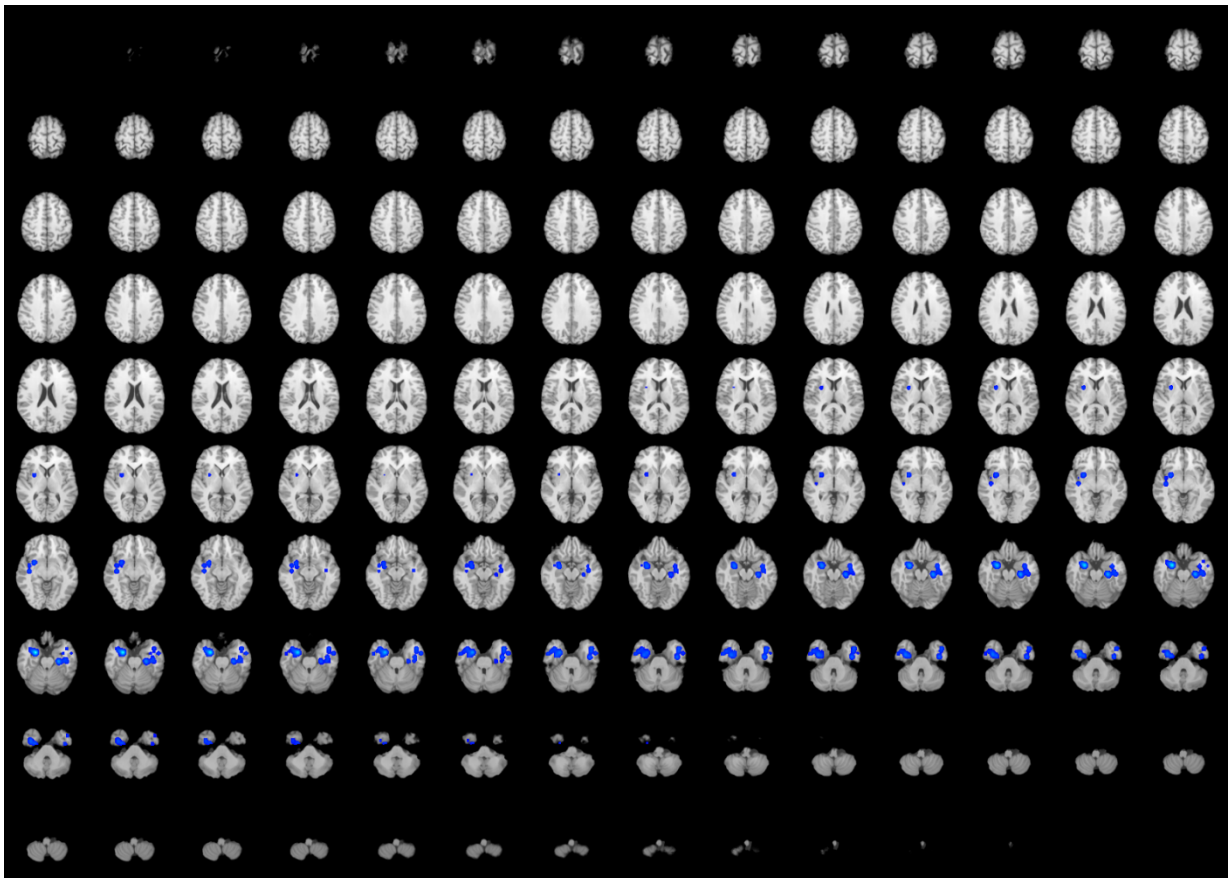


Supplementary Table 12: Gray matter regions involved in the meta-analysis of ASD. Illustrated are the clusters, x,y,z peak-coordinates, ALE-value, p-value, Z-score and (MNI 152) anatomical label

Cluster	x	y	z	ALE	P	Z	Label (Nearest Gray Matter within 5mm)
1	26	-4	-22	0.03249893	2,56E-04	62.154.922	Right Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Amygdala
	36	-8	-34	0.014877337	1,02E+03	37.129.037	Right Cerebrum.Limbic Lobe.Uncus.White Matter.*
	30	-12	-34	0.011772604	6,72E+02	32.065.992	Right Cerebrum.Limbic Lobe.Uncus.Gray Matter.Brodmann area 28
	28	2	-6	0.011409324	8,21E+02	31.483.958	Right Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Putamen
	38	4	-26	0.010769417	0.0011724941	30.426.579	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 38
	40	-18	-8	0.010459999	0.0014098056	2.986.749	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
	46	-2	-30	0.009627587	0.0023742768	2.823.614	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
	52	-8	-30	0.0086873	0.0048106154	2.589.153	Right Cerebrum.Temporal Lobe.Fusiform Gyrus.White Matter.*
	28	2	8	0.007920734	0.007960442	24.107.242	Right Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Putamen

	40	-6	-10	0.0074935853	0.0109751	22.912.285	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
2	-24	-24	-20	0.021817863	8,43E+00	47.878.566	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Brodmann area 35
	-38	-14	-30	0.013710767	2,16E+03	35.194.335	Left Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
	-42	4	-28	0.01213801	5,46E+03	3.265.463	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	-42	-2	-28	0.011091235	9,82E+02	30.955.184	Left Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
	-34	-6	-18	0.010656627	0.0012479431	30.238.397	Left Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
	-52	-6	-26	0.010416082	0.0014596626	29.761.074	Left Cerebrum.Temporal Lobe.Middle Temporal Gyrus.Gray Matter.Brodmann area 21
	-40	-20	-22	0.009637194	0.0023613202	28.253.675	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
	-42	-24	-20	0.009135563	0.0032959778	27.167.842	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
	-36	-22	-22	0.009121978	0.0033394783	27.124.414	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
	-36	-16	-16	0.008247319	0.0062898346	24.954.522	Left Cerebrum.Sub-lobar.Lateral Ventricle.Cerebro-Spinal Fluid.*

Supplementary Figure 8: Gray matter regions involved in the meta-analysis of ASD. Axial lay-out.



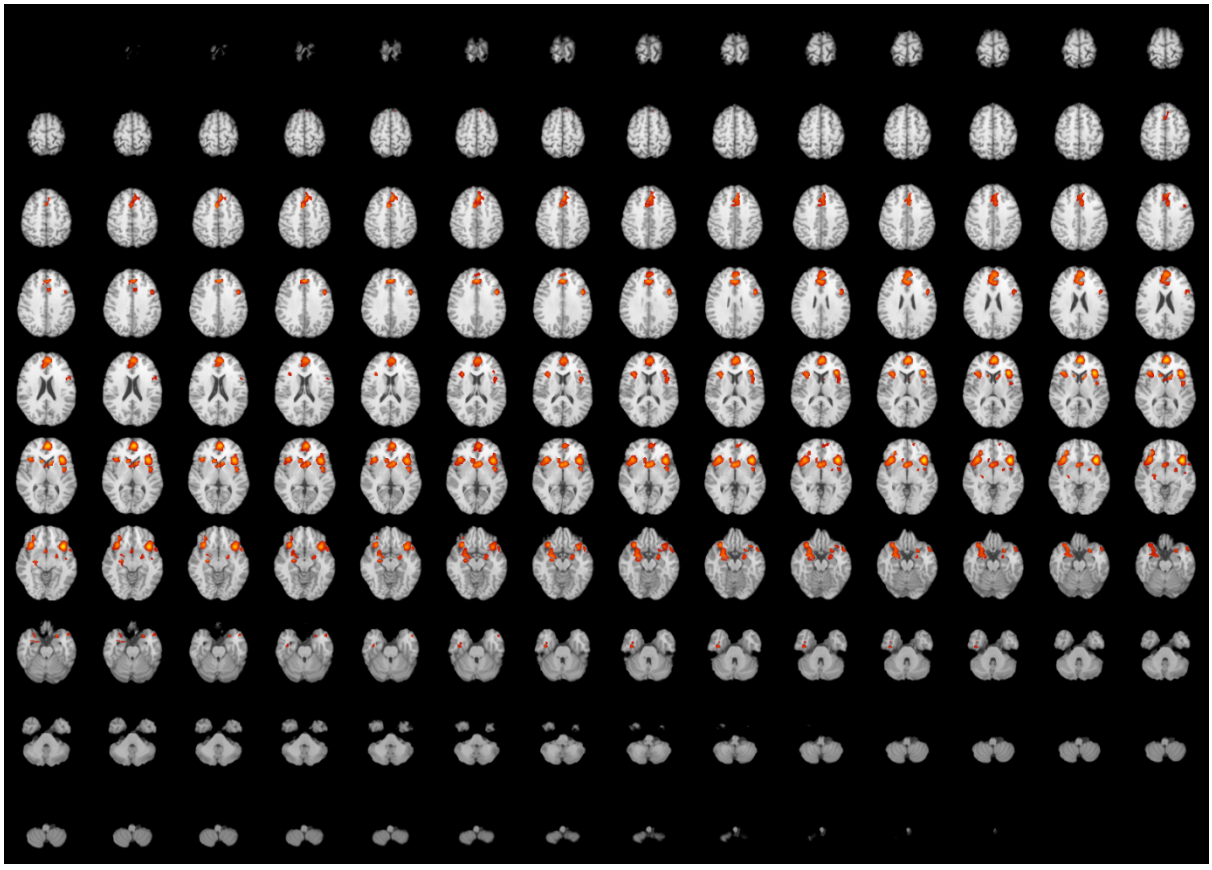
Supplementary Table 13: Gray matter regions involved in the conjunction analysis of bvFTD and SZ. Illustrated are the clusters, x,y,z peak-coordinates, ALE-value, p-value, Z-score and (MNI 152) anatomical label

Cluster	x	y	z	ALE	Label (Nearest Gray Matter within 5mm)
1	-4	48	6	0.033129226	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32

	2	34	30	0.02727013	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.*.*
	-2	34	30	0.024228198	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 32
	-2	26	44	0.02338598	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 8
	-4	46	20	0.02150522	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
	6	6	44	0.020203093	Right Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 24
	-6	14	38	0.012958481	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 32
	6	20	38	0.010227373	Right Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 32
	6	38	2	0.008488507	Right Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 24
	-14	54	-2	0.0082814535	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
	-14	26	44	0.008252138	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
2	36	16	-4	0.023921534	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
	34	20	-8	0.023465166	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
	30	34	-4	0.020341748	Right Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
	26	-14	-10	0.019185204	Right Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Lateral Globus Pallidus
	26	-6	-14	0.01883952	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	32	14	12	0.017328683	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	28	4	-16	0.0145475175	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	24	-24	-8	0.0074184923	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
3	-36	16	-6	0.039404165	Left Cerebrum.Sub-lobar.Insula.White Matter.*
	-34	18	8	0.03217435	Left Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
	-38	-4	2	0.018883023	Left Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
	-40	6	14	0.014039626	Left Cerebrum.Sub-lobar.Insula.White Matter.*
4	2	6	-2	0.024287447	Inter-Hemispheric.*.*.*.*
	-4	8	0	0.02324983	Left Cerebrum.Sub-lobar.Caudate.Gray Matter.Caudate Head
	-8	10	6	0.021492597	Left Cerebrum.Sub-lobar.Caudate.Gray Matter.Caudate Body
	10	14	6	0.020690465	Right Cerebrum.Sub-lobar.Caudate.Gray Matter.Caudate Body
5	-42	6	28	0.021449119	Left Cerebrum.Frontal Lobe.Precentral Gyrus.Gray Matter.Brodmann area 6
	-50	8	18	0.007941167	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
6	-50	10	-16	0.011949021	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	-46	10	-26	0.011099436	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	-54	6	-10	0.008491157	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	-20	-8	-14	0.009978636	Left Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*
7	-22	-4	-6	0.008440233	Left Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Lateral Globus Pallidus
8	-24	8	-20	0.015826315	Left Cerebrum.Frontal Lobe.Subcallosal Gyrus.White Matter.*
9	40	-16	-30	0.010755114	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
10	-42	-12	-8	0.007497516	Left Cerebrum.Sub-lobar.Insula.White Matter.*
11	-8	26	58	0.0073720636	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.White Matter.*
12	38	-4	-32	0.0066072983	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
13	36	-4	-30	0.009837231	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
14	36	-8	-28	0.0070786965	Right Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
15	38	-6	-28	0.0076729725	Right Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*
16	-52	4	-14	0.0069540115	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
17	40	0	-6	0.0067006466	Right Cerebrum.Sub-lobar.Insula.White Matter.*

18	-6	36	0	0.006967484	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 24
19	8	26	34	0.0070543764	Right Cerebrum.Frontal Lobe.Cingulate Gyrus.White Matter.*

Supplementary Figure 9: Gray matter regions involved in the conjunction analysis of bvFTD and SZ. Axial lay-out.

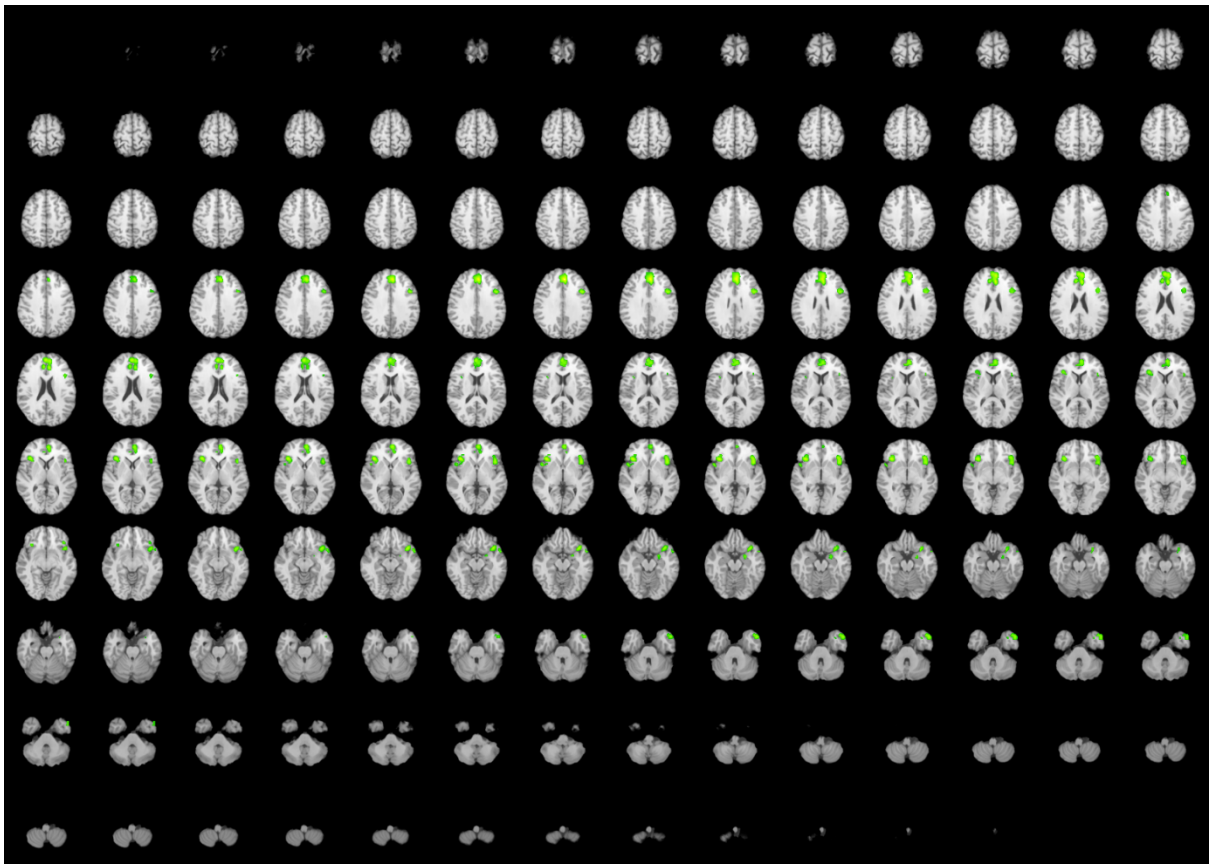


Supplementary Table 14: Gray matter regions involved in the conjunction analysis of bvFTD and BD. Illustrated are the clusters, x,y,z peak-coordinates, ALE-value, p-value, Z-score and (MNI 152) anatomical label

Cluster	x	y	z	ALE	Label (Nearest Gray Matter within 5mm)
1	-2	38	28	0.022493012	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 9
	-4	46	24	0.018407727	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.White Matter.*
	2	50	20	0.01827757	Inter-Hemispheric.*.*.*.*
	-2	48	2	0.014701626	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	8	34	22	0.01434914	Right Cerebrum.Limbic Lobe.Cingulate Gyrus.White Matter.*
	-4	46	8	0.013189895	Left Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 32
	4	40	12	0.01130454	Right Cerebrum.Limbic Lobe.Anterior Cingulate.*.*
	-8	36	2	0.008540665	Left Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.Corpus Callosum
2	-36	12	-12	0.016874313	Left Cerebrum.Sub-lobar.Insula.White Matter.*
	-40	14	0	0.015634576	Left Cerebrum.Sub-lobar.Insula.White Matter.*
	-38	24	-4	0.015412565	Left Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
	-40	18	8	0.01015339	Left Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
3	36	20	-2	0.01888671	Right Cerebrum.Sub-lobar.Insula.White Matter.*
	38	22	2	0.018848862	Right Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13

	32	30	0	0.0088992305	Right Cerebrum.Frontal Lobe.Sub-Gyral.White Matter.*
	36	12	2	0.0077541545	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
4	-42	10	28	0.017264292	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.White Matter.*
5	-48	8	-32	0.013540193	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 38
	-42	12	-32	0.01158044	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
6	46	8	0	0.0110414345	Right Cerebrum.Sub-lobar.Insula.White Matter.*
7	-52	6	-14	0.009129736	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
	-50	10	-12	0.009045211	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 22
8	-22	-6	-16	0.009099911	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Amygdala
9	6	36	6	0.0080051385	Right Cerebrum.Limbic Lobe.Anterior Cingulate.Gray Matter.Brodmann area 24
10	-32	6	-34	0.007680879	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
11	34	10	14	0.008177022	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
12	36	10	0	0.0076925773	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.*
13	36	12	14	0.008015143	Right Cerebrum.Sub-lobar.Insula.White Matter.*
14	-30	6	-32	0.007383193	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
15	-26	4	-20	0.0070591257	Left Cerebrum.Limbic Lobe.Subcallosal Gyrus.Gray Matter.Brodmann area 34
16	40	8	0	0.007336806	Right Cerebrum.Sub-lobar.Extra-Nuclear.White Matter.*

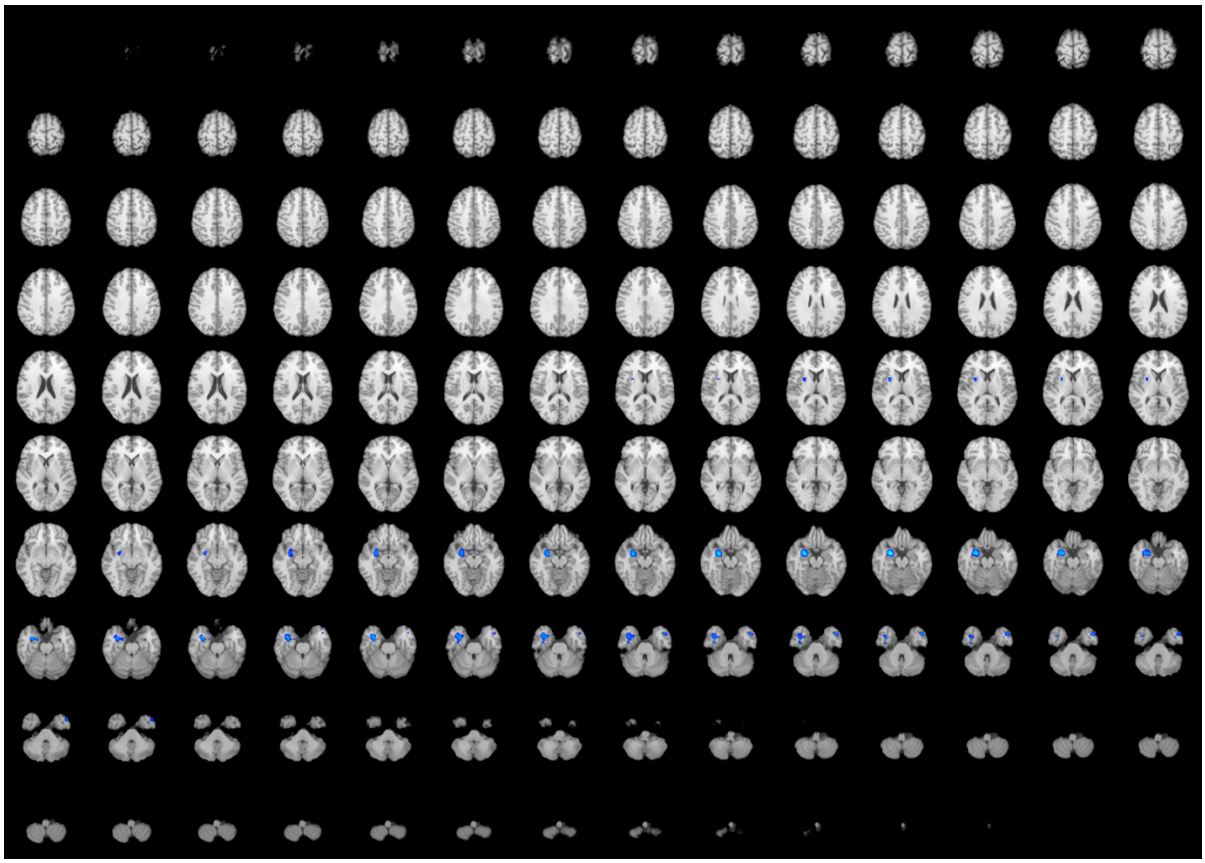
Supplementary Figure 10: Gray matter regions involved in the conjunction analysis of bvFTD and BD. Axial lay-out.



Supplementary Table 15: Gray matter regions involved in the conjunction analysis of bvFTD and ASD. Illustrated are the clusters, x,y,z peak-coordinates, ALE-value, p-value, Z-score and (MNI 152) anatomical label

Cluster	x	y	z	ALE	Label (Nearest Gray Matter within 5mm)
1	24	-6	-18	0.015233796	Right Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Amygdala
	34	-2	-26	0.012000168	Right Cerebrum.Limbic Lobe.Uncus.White Matter.*
	28	0	-28	0.008719846	Right Cerebrum.Limbic Lobe.Uncus.White Matter.*
2	-44	6	-30	0.010400165	Left Cerebrum.Temporal Lobe.Superior Temporal Gyrus.White Matter.*
3	28	2	8	0.007920734	Right Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Putamen
4	38	-12	-30	0.0069467314	Right Cerebrum.Temporal Lobe.Sub-Gyral.White Matter.*
5	36	-16	-32	0.004415852	Right Cerebrum.Limbic Lobe.Parahippocampal Gyrus.White Matter.*

Supplementary Figure 11: Gray matter regions involved in the conjunction analysis of bvFTD and ASD. Axial lay-out.



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CHAPTER 4

THE NATURAL HISTORY OF PRIMARY PROGRESSIVE APHASIA: BEYOND APHASIA

THE NATURAL HISTORY OF PRIMARY PROGRESSIVE APHASIA: BEYOND APHASIA

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ABSTRACT

Primary progressive aphasia (PPA) is divided into three prototypical subtypes that are all characterized by their single core symptom of aphasia. Although later in their course other cognitive, behavioural and motor domains may become involved, little is known about the progression profile and survival of each subtype relative to the other subtypes. In this longitudinal retrospective cohort study, based on the recent biomarker-supported diagnostic criteria, 24 subjects diagnosed with semantic variant (svPPA), 22 with non-fluent variant (nfvPPA) and 18 with logopenic variant (lvPPA) were collected and followed-up for one to six years. Symptom distribution, cognitive test and neuropsychiatric inventory scores, progression into another syndrome, and survival were assessed. Over time, lvPPA progressed with broader language problems (PPA-extended) and nfvPPA progressed to mutism whereas semantic impairment remained the major problem in svPPA. Apart from linguistic problems, svPPA developed pronounced behavioural disturbances whereas lvPPA exhibited a greater cognitive decline. By contrast, in nfvPPA motor deficits were more common and the mortality rate was higher than in the other subtypes (2.8 years, IQR=2.3, p=0.009). Furthermore, within five years (IQR=2.5) after clinical onset, 65.6% of the patients additionally fulfilled the clinical criteria for another neurodegenerative syndrome (PPA-plus). Fourteen out of 24 (58%) svPPA patients additionally met the diagnostic criteria of behavioural variant frontotemporal dementia (5.1 year, IQR=1.1) whereas the clinical features of 15/18 (83%) lvPPA patients were consistent with Alzheimer disease dementia (4.5 years IQR=3.4). Furthermore, 12/22 (54%) of the subjects with the nfvPPA progressed to meet the diagnostic criteria of corticobasal syndrome, progressive supranuclear palsy or motor neuron disease (5.1 years IQR=3.4). Despite aphasia being the initial and unique hallmark of the syndrome, our longitudinal results showed that PPA is not a language limited disorder and progression differs widely for each subtype, both with respect to the nature of symptoms and disease duration.

Key words: dementia; frontotemporal lobar degeneration; frontotemporal dementia; aphasia; primary progressive aphasia; mortality; survival analysis; natural history

INTRODUCTION

Since the original description of the clinical syndrome of primary progressive aphasia (PPA) in six patients by Marsel Mesulam in 1982 [1], studies have focused on defining its clinical phenotypes, underlying molecular pathologies, and genetic background. Currently, the syndrome is divided into three variants; the semantic variant (svPPA), non-fluent/ agrammatic variant (nfvPPA) and logopenic variant (lvPPA) [2]. SvPPA typically presents with loss of word and/or object meaning, decreased confrontation naming and surface dyslexia associated with anterior temporal atrophy on neuroimaging. nfvPPA is characterized by effortful speech, reduced speech production, and agrammatism in the presence of impairment of the left posterior frontal and insular regions. The third syndromic variant is lvPPA presents with word-finding difficulties and repetition problems while its radiological hallmark is temporo-parietal atrophy on the left side [2].Although the previous literature has suggested that nfvPPA is the most heritable PPA variant (30–40% with a family history) [3], a study with a more detailed methodology showed that a clear autosomal dominant history is quite rare in all PPA subtypes [4].. On the other hand, while svPPA and nfvPPA are related with frontotemporal lobar degeneration (FTLD) pathologies, lvPPA links to Alzheimer's disease pathology [5, 6].

It is known that the current diagnostic criteria do not cover all PPA patients and one third to one half of PPA syndromes is unclassifiable [7, 8]. Therefore, Mesulam and colleagues (2014) have used the term "PPA mixed" to designate the patients who have both comprehension deficits and grammatical errors, which is usually based on underlying Alzheimer's disease pathology [9]. On the other hand, several other studies have shown that the unclassified group might present more complex language problems [7, 8, 10]. Another challenging issue for clinicians is that over the disease course, patients who initially perfectly fulfilled the diagnostic criteria for one of the PPA subtypes develop additional symptoms within and outside the language domain. Louwersheimer et al., (2015) have used the term "PPA extended" to cover those cases who fulfill the core criteria of one PPA subtype initially and subsequently progress with characteristic language symptoms of another PPA subtype [10], whereas Rogalski and Mesulam (2009) have proposed the term "PPA+(plus)" to specify the progression into other neurodegenerative syndromes accompanying the PPA diagnosis [11]. Nevertheless, to our knowledge, the patterns of the PPA-extended and PPA-plus forms of the three PPA subtypes has never been studied systematically in a well categorized PPA cohort.

To date, the available longitudinal studies in PPA were either published before the publication of the current diagnostic criteria in 2011 or have focused on one subtype or one cognitive domain [12-16]. To our knowledge, two former longitudinal cohort studies have used the current classification and focused on the entire disease course of the syndrome [17, 18]. Unfortunately, the lack of information about the amyloid status of the subjects, survival of each subtype as well as missing detailed descriptions of symptomatology make these studies difficult to interpret. Additionally, an overall view on the progression profiles, and the patterns of PPA-extended and PPA-plus forms of the PPA subtypes are missing. This is crucial to provide adequate and satisfying information to patients about the prognosis of their disease as well as a roadmap to clinicians to better predict potential problems at the follow-up visits. Therefore, we set out to evaluate detailed symptom distribution, cognitive test performance, neuropsychiatric status, progression into PPA-extended and PPA-plus, and survival per PPA subtype in a large memory clinic cohort.

METHODS

1. Patient selection

One hundred twenty six subjects who fulfilled the current diagnostic criteria of PPA[2] were included retrospectively from the Amsterdam Dementia Cohort[19] between January 2011 and March 2019. Since the aim of the study is to show the progression pattern of each subtype, the unclassified patients were excluded (n=14). We also excluded the cases that at a closer look had the clinical profile and neuroimaging features of right temporal variant frontotemporal dementia (n=5) [20]. This is important because, it has been shown that right temporal variant frontotemporal dementia is not a primary language disorder and it exhibits a different progression pattern compared to svPPA [20-22]. Of note, all excluded rtvFTD cases were right handed. Additionally, the cases that were not a Dutch native speaker (n=3), had no records of amyloid status (n=1), or had less than one year of clinical follow up (n=39) were also excluded. All remaining subjects had either CSF amyloid beta-42 levels (n=54) or amyloid PET results (n=32) available (Supplementary material 1). Their initial neuroimaging (MRI n=62, CT n=2, FDG PET n=14) met the radiological diagnostic criteria of PPA[2] (Supplementary figure 1). The eventual selection yielded a sample of 64 subjects with PPA and based on the current diagnostic criteria[2], 24 subjects were diagnosed with svPPA, 22 with nfvPPA and 18 with lvPPA (Supplementary figure 2).

2. Clinical assessment, longitudinal follow-up and data collection

All subjects had undergone a detailed neurological and neuropsychological assessment at the initial visit, and all of them had been followed throughout their disease course by an experienced behavioural neurologist (Y.P or P.S). Family history of dementia was considered positive when the Modified Goldman score was 1 [4]. Education level was scored by using the Verhage system[23].

The characteristic symptoms of dementia spectrum disorders were routinely recorded during the neurological interviews at our center. From the case notes, symptoms were clustered in the following groups; language/ speech, cognitive, behavioral/mood and motor dysfunction (Supplementary material 2). Listed symptoms were recorded as present or absent for each subject for each visit and sub-classified as "initial symptoms" (at the initial visit) and "follow-up symptoms" (only rated when reported follow-up). After the initial visit, the subsequent visit in between 10-14 months was considered as "first year follow-up", 22-26 months; "second year follow-up", 34-38 months; "third year follow-up", 46-50 months; "fourth year follow-up", 58-62 months; "fifth year follow-up" and 70-74 months; "sixth year follow-up".

The following clinical data that are systematically recorded in our cohort were abstracted from all case notes: measures of functional severity [Clinical Dementia Rating Scale (CDR)], activities of daily living [Amsterdam instrumental activities of daily living (IADL) questionnaire], the patients' behavioral and psychological status [neuropsychiatric inventory (NPI)]. Cognitive functions were assessed with a standardized neuropsychological test battery, including global cognition [Mini Mental State Examination (MMSE)], episodic memory [visual association test (VAT) A and the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT)], executive functions [Frontal assessment Battery (FAB) and digit span backward], semantic memory [category fluency animals], confrontation naming [VAT naming and Boston naming test] and visuospatial functions [Visual Objective and Space Perception (VOSP)- fragmented letters] [19].

The appearance of the progression into another PPA subtype was referred to as "PPA-extended [10] and the progression into another neurodegenerative syndrome was referred to as "PPA-plus"[11]. The time from aphasia onset to PPA plus was based on the time up till meeting the diagnostic criteria for the second syndrome such as behavioral variant frontotemporal dementia (bvFTD), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), motor neuron disease (MND) and Alzheimer's disease [24-28].

3. Statistical analysis

Analyses were conducted using SPSS Statistics, version 24.0 (IBM) and R Studio (R Core Team, 2018).

Differences in frequencies of categorical variables between groups (svPPA, nfPPA and lvPPA) were assessed with chi-square and continuous variables were compared between groups with one-way ANOVA or Kruskal-Wallis analysis depending on the distribution of the variables based on Shapiro-Wilk normality test. Post hoc comparisons were corrected for multiple comparisons using the Bonferroni correction. Change over time in cognitive functioning was assessed using linear mixed models (LMM) with a random intercept and slope for each subject. Separate models were run for each cognitive test (dependent) with time (measured on a continuous level) as independent variable, separately for each diagnostic group. Nonparametric survival analyses were conducted using Kaplan Meier estimates [inter-quartile range (IQR)] with post hoc Mantel Cox log rank tests to calculate mortality rate and progression into PPA-plus. The results were thresholded at a corrected p-value of < 0.05.

4. Standard protocol approvals, registrations, and patient consents

The local Medical Ethics Committee approved a general protocol for using the clinical data for research purposes (Protocol No: 2016.061).

Data availability

Anonymized data can be made available by request to the corresponding author.

RESULTS

Table 1 displays the clinical and demographic features per diagnostic group. The gender distribution was almost equal in the lvPPA group. However, the majority of svPPA subjects were male, whereas the nfvPPA group was female predominant (p=0.02). Mean age, mean symptom or follow-up duration, the CDR and IADL scores did not differ between diagnostic groups. All svPPA patients were amyloid negative whereas one (4%) nfvPPA and 15 (83%) lvPPA patients had a positive amyloid status (supplementary material 1). A few subjects were left-handed in all groups, but no statistical difference in the distribution of handedness was found (p=0.86). Of note, to establish receptive language dominance in left-handed subjects, we checked whether clinical symptoms showed concordance with the anatomic distribution of cortical atrophy and clinical presentation. All left-handed patients demonstrated the same

pattern of lateralized atrophy as the right-handers, suggesting that they were left-hemisphere dominant for language.

Table 1 Clinical and demographic features

	svPPA	nfvPPA	lvPPA	p
N	24	22	18	-
Gender/ Female (%)	8 (33.3)	16 (72.7)	10 (55.6)	**0.02**
Age mean ± SD, years	63.6 ± 6.7	66.1 ± 6.6	66.5 ± 6.2	0.29
Education level *	5.29 (0.75)	4.68 (0.95)	5.50 (1.10)	**0.01**
Handedness/ Right	22 (91.7)	21 (95.5)	17 (94.4)	0.86
Symptom duration mean ± SD, years	3.6 ± 1.4	2.5 ± 1.6	3.3 ± 1.5	0.06
Follow-up period mean ± SD, years	2.74 (1.49)	2.49 (1.34)	3.05 (1.23)	0.44
CDR mean ± SD	0.66 (0.28)	0.61 (0.52)	0.69 (0.25)	0.82
Reduction in ADL (%)	13 (54.2)	12 (54.5)	10 (55.6)	0.99
Genetic mutation (gene)	-	C9orf72 (n=1) GRN (n=1)	-	-

*: Verhage score

svPPA; semantic variant primary progressive aphasia, nfvPPA; non-fluent variant primary progressive aphasia, lvPPA; logopenic variant primary progressive aphasia, CDR: clinical dementia rating, ADL: Activities of daily living, GRN: progranulin, C9orf72: chromosome 9 open reading frame, SD: standard deviation

A positive family history for FTD was present in one nfvPPA patient who had a hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (C9orf72) gene, and for AD in 2 lvPPA patients, whereas none of the svPPA patients had a clear autosomal dominant inheritance of any type of dementia. In none of the subjects pathological confirmation had been achieved. Besides the patient with C9orf72 repeat expansion, another

nfvPPA patient carried a pathogenic variant in the progranulin gene [c.415T>C, p.(Cys139Arg), missense variant [29]] whose modified Goldman score was 2. Figure 1 displays the yearly clinical evaluation of each subtype with a minimum of one year, extending up to six years of follow-up. In order to ascertain the distinct clinical profile and the progression pattern of each subtype, the most pronounced symptoms are displayed in figure 2 and detailed longitudinal symptom distribution is displayed in supplementary material 3. Figure 3 gives an overview of the different neuropsychological test scores. Baseline scores and annual change are displayed in supplementary material 4. Additionally, initial NPI scores are displayed in supplementary figure 3.

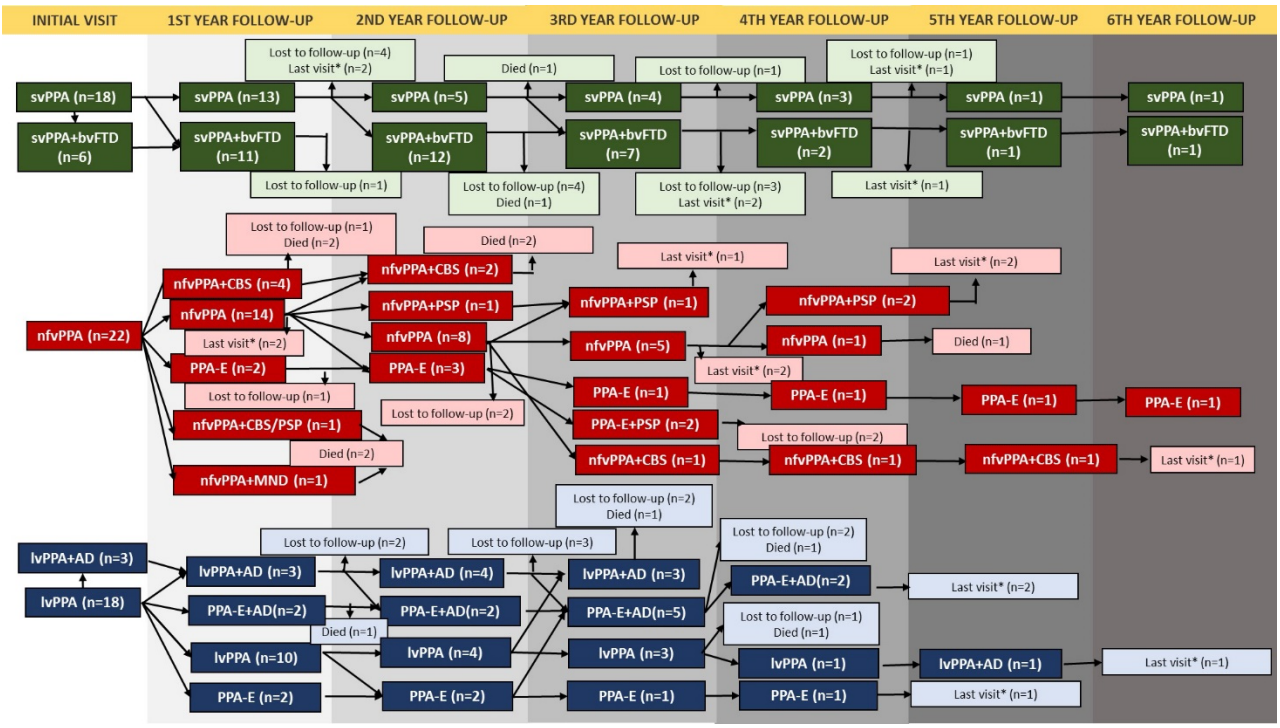

Figure 1: Clinical evaluation of PPA subtypes over time. svPPA: Semantic variant primary progressive aphasia, bvFTD: Behavioral variant frontotemporal dementia, nfvPPA: non-fluent variant primary progressive aphasia, PPA-E: Primary progressive aphasia-extended, CBS: Corticobasal syndrome, PSP: progressive supranuclear palsy, MND: Motor neuron disease, lvPPA: logopenic variant primary progressive aphasia, AD: Alzheimer's disease. *: last visit. Those subjects have been diagnosed recently and they are still under follow-up. The indicated visit is the last visit of the subject

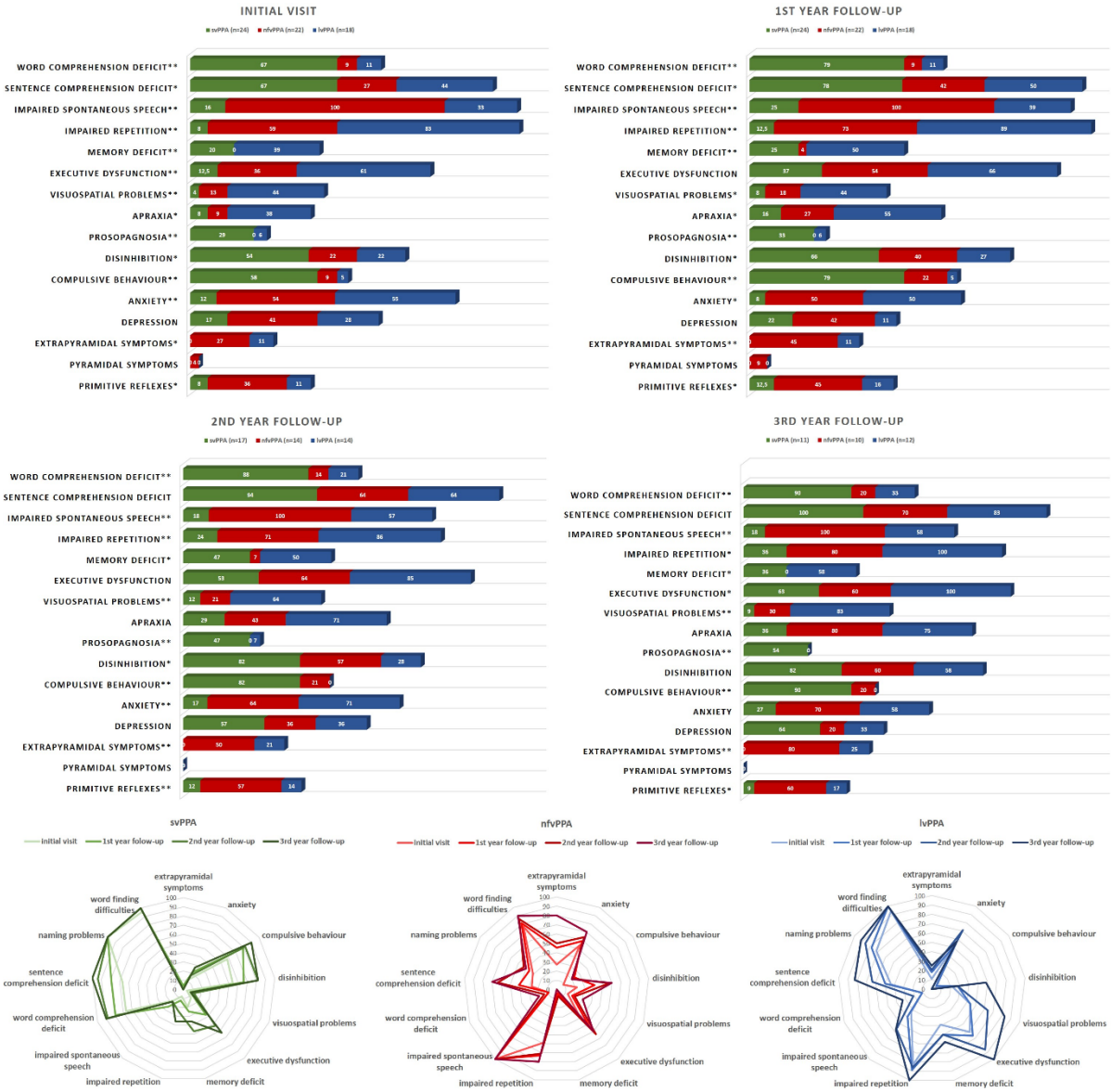

Figure 2: Symptom distribution of PPA subtypes over time. svPPA Semantic variant primary progressive aphasia, nfvPPA Nonfluent variant primary progressive aphasia, lvPPA Logopenic variant primary progressive aphasia. *$p < 0.05$, **$p < 0.01$

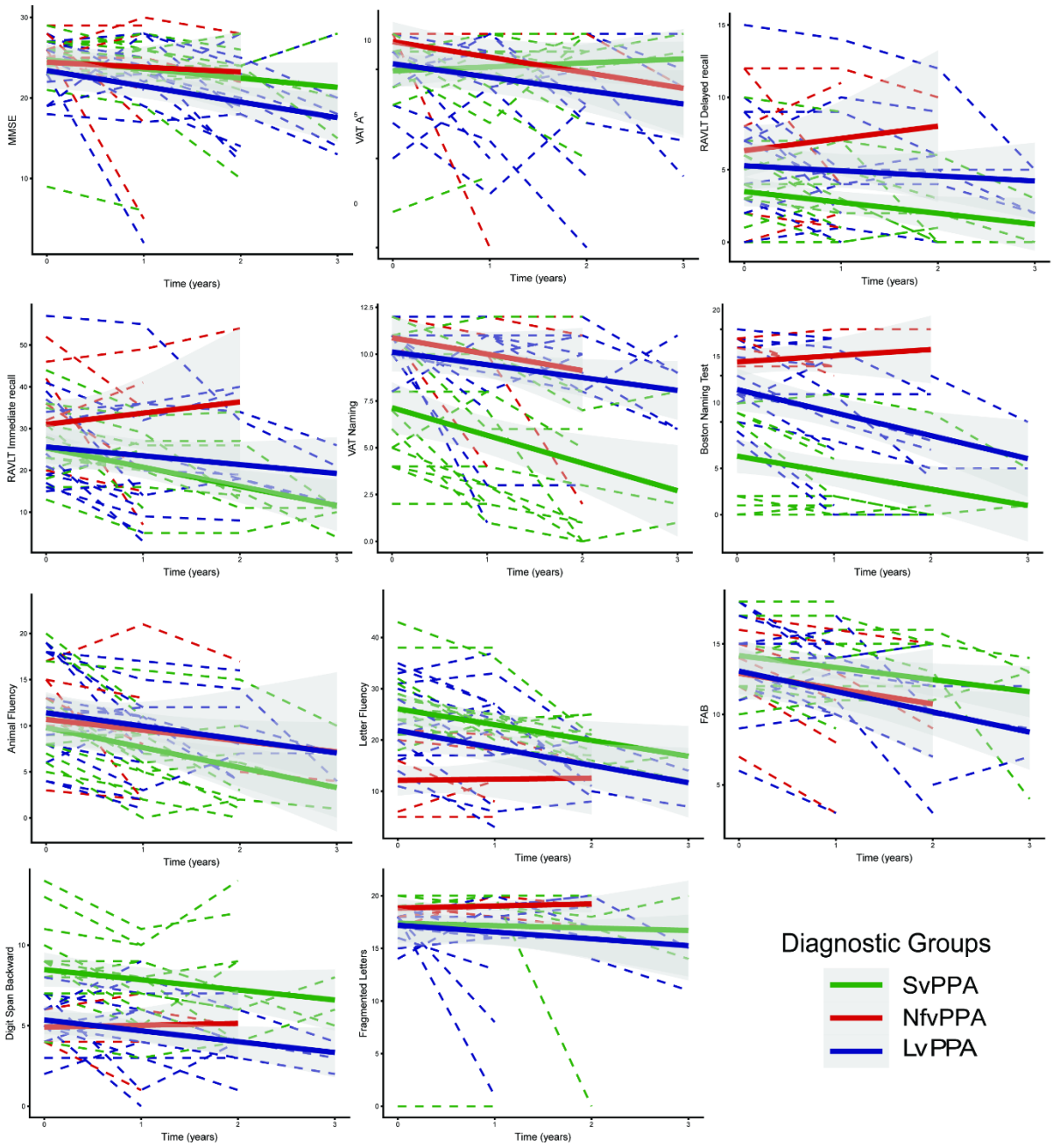

Figure 3: Cognitive test performance of the subtypes over time. svPPA Semantic variant primary progressive aphasia, nfvPPA Nonfluent variant primary progressive aphasia, lvPPA Logopenic variant primary progressive aphasia. MMSE mini-mental state examination, VAT visual association test, RAVLT Dutch version of the Rey Auditory Verbal Learning Test, FAB frontal assessment battery

1. Initial clinical profiles of the 3 PPA variants

As expected, language difficulties were the main problem in all diagnostic groups and since our inclusion criteria were based on the current classification system, the type of deficits where in line with the respective diagnostic criteria.

Although baseline MMSE score did not differ significantly across the subtypes, lvPPA subjects reported more widespread cognitive problems such as memory deficits ($p<0.01$), executive dysfunction ($p<0.01$), apraxia ($p=0.01$) and visuospatial problems ($p<0.01$). Moreover, they exhibited worse performance on the FAB and the VOSP fragmented letters test, indicating executive and visuospatial dysfunction, although the difference was not statistically significant. Of note, although memory deficits were reported more commonly in lvPPA, svPPA subjects performed worse on the verbal memory tests initially (Figure 2,3).

Behavioral problems were much more prominent in svPPA than in the other groups, especially disinhibition and compulsiveness ($p=0.03$, $p<0.001$ respectively). Loss of empathy and dietary changes were also more common in svPPA, however the difference was not significant. Furthermore, loss of insight was often present in the svPPA group whereas nvfPPA and lvPPA subjects were more aware of their symptoms ($p=0.001$). Additionally, NPI results showed that neuropsychiatric symptoms were more prevalent in svPPA, as indicated by the scores for changing eating habits, irritability, euphoria and disinhibition. On the other hand, nfvPPA subjects were more depressive, whereas lvPPA subjects were more anxious. However, it should be noted that regarding NPI scores, except disinhibition, the differences were not significant. Another common behavioral problem was apathy which occurred in all subtypes. (Supplementary figure 3).

Motor symptoms were observed almost uniquely in nfvPPA. Extrapyramidal deficits were recorded in 27% of nfvPPA subjects at the initial visit, which was more common than in other groups ($p=0.02$). One nfvPPA subject demonstrated pyramidal symptoms whereas it was not recorded in svPPA and lvPPA.

2. Progression to PPA extended

Although linguistic problems maintained predominant in all subtypes during the disease course, patients developed various cognitive and behavioral problems as well as motor deficits. Regarding language problems, during the disease course the nfvPPA and lvPPA patients developed several additional language problems that formally met the diagnostic criteria of another PPA syndrome, which we refer to as “PPA extended”. On the other hand, in svPPA, loss of semantic knowledge remained the main problem with a significant decline on the naming and semantic memory tests. Although the other language problems of svPPA subjects such as repetition problems and reduced spontaneous speech were not sufficient to apply PPA-extended, they showed a significant decline on the letter fluency test over time. Of

note, none of the svPPA subjects progressed to mutism and dysarthria was never recorded in svPPA. Mutism was recorded in 8 subjects during follow-up of which 7 had nfvPPA. nfvPPA subjects declined on repetition as well as single word and sentence comprehension. Morever 4 of the nfvPPA patients also met the diagnostic criteria of svPPA (PPA-extended) over time. However, during the entire disease course, PPA extended was the most common in lvPPA group. Over time, half of the lvPPA subjects also fulfilled the svPPA and/or nfvPPA diagnostic criteria (lvPPA+svPPA=5, lvPPA+nfvPPA= 3, lvPPA+svPPA+nfvPPA=1), and except one subject, all of the lvPPA-extended subjects also fulfilled the amnestic variant of the Alzheimer's disease diagnostic criteria with underlying amyloid positivity. Additionally, nfvPPA and lvPPA patients declined significantly on the semantic memory test, however, not more than svPPA subjects.

3. Progression to PPA plus

Apart from linguistic dysfunction, global cognitive decline was observed in all groups over time, especially in svPPA and lvPPA. While svPPA and lvPPA exhibited a decline on the MMSE ($p=0.001$), it did not decline significantly in the nfvPPA group. lvPPA subjects reported pronounced memory deficits, executive dysfunction and visuospatial problems at the follow-up visits with a greater decline on the visual and verbal memory tests ($p<0.05$), FAB ($p<0.001$), digit span backward ($p=0.01$) and VOSP fragmented letters ($p=0.14$). However, it should be noted that svPPA subjects also showed a significant decline on the verbal memory tests and approximately half of the svPPA subjects reported episodic memory deficits (problems with remembering recent events) in the second year of the disease course. Of note, our retrospective design was not sufficient to distinguish the contribution of the semantic impairment to the episodic memory deficits. On the other hand, nfvPPA showed a relatively benign progression pattern on the cognitive tests in comparison to other subtypes, however, they developed apraxia over the disease course. Additionally, executive dysfunction became a prominent symptom for both svPPA and nfvPPA as well as lvPPA and all subtypes exhibited a significant decline on the FAB.

Even at the initial visit, behavioral changes were quite common in svPPA. Moreover, although aphasia is the most prominent symptom, 6 svPPA cases had additional behavioral problems that formally met the diagnostic criteria for possible bvFTD. During the follow-up, svPPA subjects developed even more behavioral problems. Eventually, 14out of 24 (58%) svPPA subjects formally met the diagnostic criteria of bvFTD in their follow-up. Although

both nfvPPA and lvPPA groups developed disinhibition over the disease course, compulsive behavior was observed almost uniquely in svPPA ($p<0.001$ in all visits).

Over the disease course, motor symptoms remained more prevalent in the nfvPPA group than in the other groups. Remarkably, 80% of nfvPPA subjects had extrapyramidal signs at the third year of follow-up. However, over time, only 3 lvPPA subjects developed extrapyramidal symptoms whereas it was never observed in svPPA.

From baseline to the last visit, in total 42 patients (65.6%) additionally formally met the diagnostic criteria of another neurodegenerative syndrome, which we refer to as "PPA plus". Median time from clinical onset to PPA-plus was 5 years (IQR=2.5) that did not differ significantly among the subtypes (Figure 4). Fourteen svPPA patients met the diagnostic criteria of bvFTD (5.1 year IQR=1.1). By contrast, nfvPPA exhibited a heterogeneous progression pattern (5.1 years IQR=3.4). Twelve nfvPPA patients developed an atypical form of parkinsonism, of which five were categorized as progressive supranuclear palsy (PSP), six as corticobasal syndrome (CBS) and one patient with features of both PSP and CBS. In addition, two out of five subjects with PSP-PPA plus also developed several comprehension deficits, which was referred as PPA-extended. During the entire follow-up, only one nfvPPA subject had pyramidal signs and was reclassified as MND-PPA plus. This case, carrying a C9orf72 mutation, fulfilled the diagnostic criteria of MND after one year of follow-up and died 3 months later. Fifteen out of 18 lvPPA patients acquired global cognitive impairment, in line with the diagnostic criteria of dementia due to Alzheimer's disease and all of them were amyloid positive as well (4.5 years IQR=3.4), and 8 of them were PPA-extended. In the remaining 3 amyloid negative lvPPA patients, language problems were more predominant and one of them developed severe comprehension deficits; also fulfilled the diagnostic criteria of svPPA after two years of follow-up.

4. Mortality

During the follow-up period, 12 out of 64 subjects deceased. Seven of them had nfvPPA, 3 lvPPA and 2 svPPA.

DISCUSSION

In this retrospective longitudinal cohort study to compare the natural history between PPA subtypes, we investigated overlapping and distinguishing clinical features, and progression

pattern of the three PPA subtypes. Even though aphasia is by definition the earliest and common feature of the syndrome, our results highlighted that PPA constitutes a heterogeneous clinical syndrome and additional cognitive, behavioral and motor deficits emerge with time. After diagnosis, each subtype exhibited a typical progression pattern (PPA-extended and PPA-plus). Whereas a strong relationship existed between svPPA and the clinical features of bvFTD, subjects with nfvPPA developed motor impairment and progressed into various forms of neurodegenerative syndromes such as CBS, PSP and MND. Patients with lvPPA progressed with multiple cognitive domain deficits into Alzheimer's disease dementia at follow-up, and PPA-extended forms were more common in lvPPA; especially in the amyloid positive group.

Regarding linguistic problems, over time, nfvPPA and lvPPA patients developed symptoms that exceeded the core criteria whereas svPPA patients did not. At a closer look, in accordance with previous longitudinal studies, lvPPA declined on repetition[30-32], naming[30-32], comprehension[32] and speech production[14, 31] while nfvPPA declined on comprehension and repetition [13]. On the other hand, the most important change over time in svPPA was the development of sentence comprehension problems, which has been reported previously [30, 33]. Although svPPA patients declined on the letter fluency test just like was reported in a recent longitudinal study[14], they were more fluent compare to the other subtypes and neither mutism/dysarthria nor PPA-extended was observed in svPPA.

Although not mentioned in the diagnostic criteria of svPPA [2], it is common knowledge that behavioural changes similar to those occurring in bvFTD are often evident at presentation in these patients [11, 34-36]. Consistent with this observation, particularly, disinhibition and compulsive behavior were common in svPPA, next to irritability, euphoria and a change in eating habits. Supporting the association between compulsive behavior and temporal lobes [20, 21, 37], compulsiveness was observed uniquely in svPPA both initial and follow-up visits. Additionally, in line with earlier studies [34, 38], apathy was common in all subtypes and lvPPA and nfPPA subjects were more aware of their symptoms, which might be related to feeling more anxiety, in contrast to svPPA[35, 38, 39].

Remarkably, in comparison with the other PPA subtypes, lvPPA displayed a broad range of initial cognitive problems such as memory deficits, apraxia, executive and visuospatial dysfunction and a more rapid and generalized cognitive decline over the disease course which was also confirmed in the smaller subgroup that received the longitudinal cognitive tests, consistent with previous work[40-43]. However, executive dysfunction became one of the

prominent symptoms in svPPA and nfvPPA as well as lvPPA over the disease course. In addition, svPPA demonstrated verbal memory impairment whereas nfvPPA developed apraxia over time.

One of the important results of our study is that despite the relatively benign early presentation, a high proportion of nfvPPA cases developed motor disturbances such as MND, PSP and CBS and it is conceivable that these syndromes increase mortality risk. Although, only 12 patients deceased in the follow-up and a larger sample size longitudinal study has reported a longer survival in nfvPPA [44], a large body of literature has showed a significant shorter survival in FTD patients with motor disturbances [45, 46] . The relationship between pyramidal, extrapyramidal symptoms and nfvPPA have been reported previously[11, 47-50] and some authors have suggested that apraxia of speech is the clinical marker of progression to PSP and CBS [48]. Although apraxia of speech was not evaluated in individual patients in this retrospective study, in line with the literature [51], mutism was recorded much more often in nfvPPA than in other subtypes.

Compared with other cohort studies, our sample was older than an American population-based cohort [52], however younger than other European population-based patient groups[14, 17, 18]. Our svPPA sample was male predominant whereas the nfvPPA sample was female predominant. Although the general assumption is that PPA occurs with approximately equal prevalence across sexes [9], sex distribution has shown a variety in previous studies and there is no solid consistency [17, 18, 52].

This is the first biomarker-based, systematic longitudinal cohort study from a well-structured dementia clinic that provides detailed symptomatology, progression pattern and survival of each PPA subtype. However, there are some limitations that should be addressed. First of all, the study was performed retrospectively and since we adhere to the most recent diagnostic criteria of 2011, our sample size is relatively small. Secondly, longitudinal NPI data were not available and because of drop-outs and progression, the eligible longitudinal cognitive test data were limited. A larger sample size would be helpful to evaluate the underlying risk factors and clinical predictors of progression to PPA-plus and mortality. Another limitation might be the lack of genetic or pathological confirmation. However, we provided the amyloid status of each patient that is informative about underlying Alzheimer's disease pathology. Moreover, showing the progression pattern of FTD related genetic and/or pathological subtypes is beyond the scope of this study. The main aim of the study is giving an overview to clinicians about the progression pattern of the well identified PPA subtypes based on the

current clinical diagnostic criteria. For this purpose, we used the terms PPA-extended and PPA-plus to emphasize that those patients had a primary PPA diagnosis initially and developed additional symptoms. Emphasizing the evolution of new symptoms that lead to a secondary, parallel diagnosis might facilitate the recognition of the various PPA subtypes. Additionally, our results support the recent argument suggesting that FTLD syndromes are not discrete in the clinical features of their respective clinical criteria, but instead exist as a multidimensional spectrum [53]. Note that this is not an argument for creating new labelling systems or new subtypes, however, it might be a useful answer of one important question; what should we expect next?

In conclusion, although, by definition, aphasia is the only and predominant symptom in PPA [1, 2], it does not take long before other symptoms occur. More importantly, its progression pattern is subtype specific. Although svPPA seems to be more homogeneous with respect to its language profile, healthcare providers and caregivers should be aware of behavioral disturbances that might arise, whereas global cognitive decline and broad language problems due to underlying Alzheimer's disease pathology should be expected for lvPPA. nfvPPA patients may be least affected on the behavioral and cognitive domains initially, but show a progression to other neurodegenerative syndromes, particularly those associated with motor impairment with a high mortality risk.

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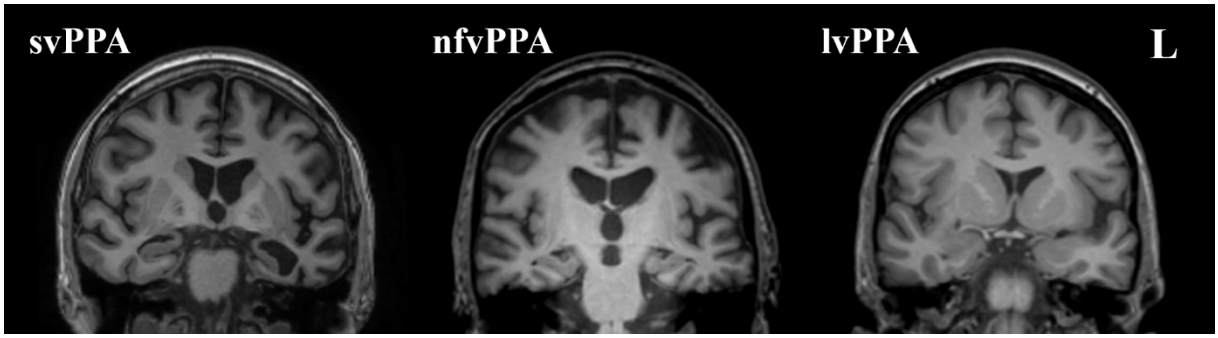
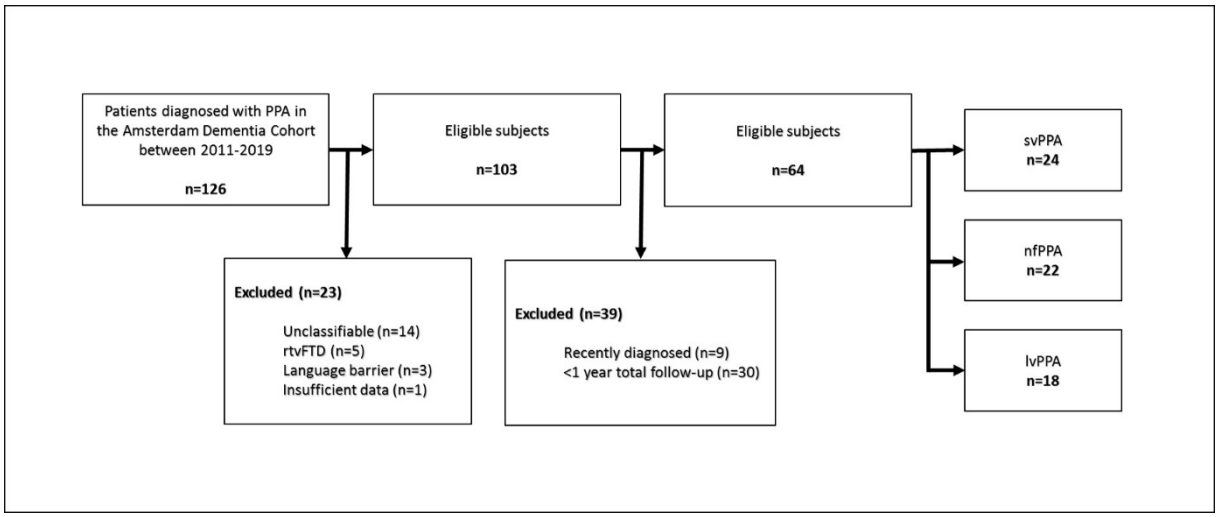
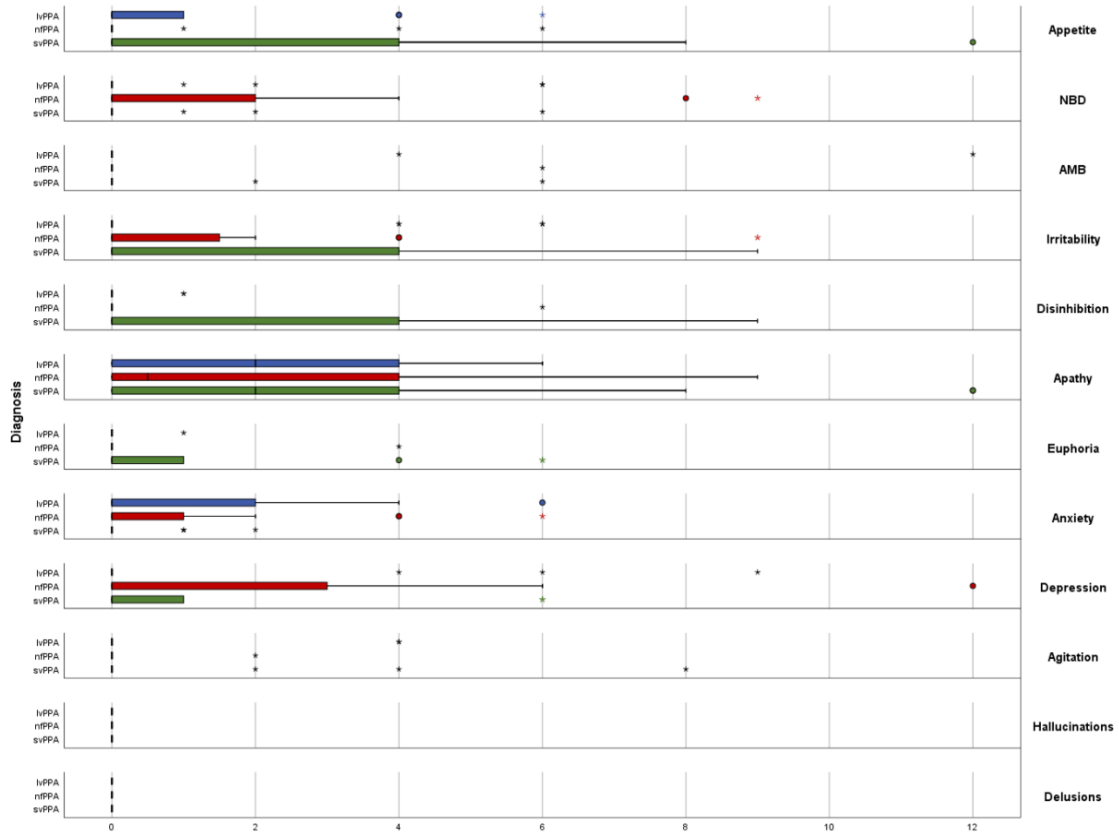
SUPPLEMENTARY MATERIAL



Supplementary Figure 1: Atrophy pattern of the subtypes. svPPA: Semantic variant primary progressive aphasia. Predominant left anterior temporal atrophy. nfvPPA: Nonfluent variant primary progressive aphasia. Predominant left posterior frontoinsular atrophy. lvPPA: Logopenic variant primary progressive aphasia. Predominant left posterior perisylvian atrophy, L: Left



Supplementary Figure 2: Patient selection scheme. PPA: Primary progressive aphasia, rtvFTD: Right temporal variant frontotemporal dementia, svPPA: Semantic variant primary progressive aphasia. nfvPPA: Nonfluent variant primary progressive aphasia. lvPPA: Logopenic variant primary progressive aphasia



Supplementary Figure 3: Neuropsychiatric inventory scores of the subtypes. svPPA: Semantic variant primary progressive aphasia. nfvPPA: Nonfluent variant primary progressive aphasia. lvPPA: Logopenic variant primary progressive aphasia, NBD: Night time behavioral disturbances, AMB: Aberrant motor behavior.

Supplementary Table 1: Amyloid status of the subjects

Diagnosis	**CSF_AB42** (pg/mL)	**CSF_Tau** (pg/mL)	**CSF_p-Tau** (pg/mL)	**PET scan**	**PET Amyloid**	**Amyloid status**
svPPA	632 (H)	107 (L)	n.a.	n.a.	n.a.	Non-indicative of AD
svPPA	895 (H)	331 (L)	39 (L)	n.a.	n.a.	Non-indicative of AD
svPPA	1047 (H)	247 (L)	40 (L)	n.a.	n.a.	Non-indicative of AD
svPPA	1098 (H)	358 (L)	44 (L)	n.a.	n.a.	Non-indicative of AD
svPPA	n.a.	n.a.	n.a.	Flutemetamol	Negative	Non-indicative of AD
svPPA	1098 (H)	413 (H)	45 (L)	n.a.	n.a.	Non-indicative of AD
svPPA	n.a.	n.a.	n.a.	Flutemetamol	Negative	Non-indicative of AD
svPPA	n.a.	n.a.	n.a.	Flutemetamol	Negative	Non-indicative of AD
svPPA	561 (H)	621 (H)	65 (H)	n.a.	n.a.	Non-indicative of AD
svPPA	523 (L)	272 (L)	51 (L)	PIB	Negative	Non-indicative of AD
svPPA	929 (H)	154 (L)	24 (L)	n.a.	n.a.	Non-indicative of AD
svPPA	1351 (H)	600 (H)	66 (H)	n.a.	n.a.	Non-indicative of AD

svPPA	341 (L)	188 (L)	181 (H)	Flutemetamol	Negative	Non-indicative of AD
svPPA	1239 (H)	409 (H)	47 (L)	n.a.	n.a.	Non-indicative of AD
svPPA	1012 (H)	289 (L)	39 (L)	Florbetaben	Negative	Non-indicative of AD
svPPA	535 (L)	593 (H)	60 (H)	Florbetaben	Negative	Non-indicative of AD
svPPA	759 (H)	630 (H)	39 (L)	Florbetaben	Negative	Non-indicative of AD
svPPA	816 (H)	557 (H)	54 (H)	n.a.	n.a.	Non-indicative of AD
svPPA	1538 (H)	466 (H)	50 (L)	n.a.	n.a.	Non-indicative of AD
svPPA	n.a.	n.a.	n.a.	PIB	Negative	Non-indicative of AD
svPPA	1235 (H)	403 (H)	58 (H)	n.a.	n.a.	Non-indicative of AD
svPPA	n.a.	n.a.	n.a.	PIB	Negative	Non-indicative of AD
svPPA	n.a.	n.a.	n.a.	Florbetaben	Negative	Non-indicative of AD
svPPA	1210 (H)	254 (L)	42 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1075 (H)	301 (L)	43 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	n.a.	n.a.	n.a.	PIB	Negative	Non-indicative of AD
nfvPPA	n.a.	n.a.	n.a.	PIB	Negative	Non-indicative of AD
nfvPPA	1614 (H)	476 (H)	41 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	843 (H)	317 (L)	35 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1653 (H)	844 (H)	50 (H)	n.a.	n.a.	Non-indicative of AD
nfvPPA	487 (L)	559 (H)	56 (H)	Flutemetamol	Positive	Indicative of AD
nfvPPA	534 (L)	356 (L)	44 (L)	PIB	Negative	Non-indicative of AD
nfvPPA	497 (L)	140 (L)	27 (L)	PIB	Negative	Non-indicative of AD
nfvPPA	n.a.	n.a.	n.a.	PIB	Negative	Non-indicative of AD
nfvPPA	1013 (H)	278 (L)	34 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	699 (H)	459 (H)	50 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1160 (H)	621 (H)	69 (H)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1057 (H)	247 (L)	34 (L)	Flutemetamol	Negative	Non-indicative of AD
nfvPPA	850 (H)	225 (L)	40 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	872 (H)	267 (L)	34 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1272 (H)	237 (L)	40 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1358 (H)	526 (H)	73 (H)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1078 (H)	306 (L)	41 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	764 (H)	261 (L)	24 (L)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1144 (H)	333 (L)	54 (H)	n.a.	n.a.	Non-indicative of AD
nfvPPA	1700 (H)	288 (L)	43 (L)	n.a.	n.a.	Non-indicative of AD
lvPPA	397 (L)	275 (L)	53 (H)	PIB	Positive	Indicative of AD

lvPPA	445 (L)	877 (H)	81 (H)	PIB	Positive	Indicative of AD
lvPPA	566 (H)	496 (H)	62 (H)	PIB	Positive	Indicative of AD
lvPPA	428 (L)	921 (H)	99 (H)	Flutemetamol	Positive	Indicative of AD
lvPPA	553 (H)	627 (H)	78 (H)	PIB	Positive	Indicative of AD
lvPPA	305 (L)	962 (H)	117 (H)	Flutemetamol	Positive	Indicative of AD
lvPPA	555 (H)	402 (H)	52 (H)	PIB	Positive	Indicative of AD
lvPPA	538 (L)	356 (L)	46 (L)	Flutemetamol	Positive	Indicative of AD
lvPPA	561 (H)	479 (H)	65 (H)	Flutemetamol	Positive	Indicative of AD
lvPPA	621 (H)	369 (L)	53 (H)	Flutemetamol	Positive	Indicative of AD
lvPPA	647 (H)	1510 (H)	133 (H)	n.a.	n.a.	Non-indicative of AD
lvPPA	n.a.	n.a.	n.a.	PIB	Positive	Indicative of AD
lvPPA	926 (H)	407 (H)	78 (H)	n.a.	n.a.	Non-indicative of AD
lvPPA	528 (L)	720 (H)	106 (H)	n.a.	n.a.	Indicative of AD
lvPPA	514 (L)	1154 (H)	90 (H)	Flutemetamol	Positive	Indicative of AD
lvPPA	445 (L)	592 (H)	82 (H)	Florbetaben	Positive	Indicative of AD
lvPPA	620 (H)	590 (H)	83 (H)	n.a.	n.a.	Non-indicative of AD
lvPPA	619 (H)	827 (H)	105 (H)	Flutemetamol	Positive	Indicative of AD

svPPA: semantic variant primary progressive aphasia, nfvPPA: non-fluent variant primary progressive aphasia, lvPPA: logopenic variant primary progressive aphasia, AD: Alzheimer's disease, CSF: cerebrospinal fluid, PET: Positron emission tomography, PIB: Pittsburgh compound B, H: High, L: Low, n.a.: not available

Supplementary Table 2: Categorization of symptoms

Language/speech	Cognitive	Behaviour/ mood	Motor
Word finding difficulties	Memory deficit	Disinhibition	Pyramidal signs
Sentence comprehension deficit	Prosopagnosia	Loss of insight	Extrapyramidal signs
Single word comprehension deficit	Executive dysfunction	Compulsive behaviour	Primitive reflexes
Dyslexia/dysgraphia	Apraxia	Apathy/ inertia	Swallowing problems
Spontaneous speech impairment	Visuospatial problems	Hyper-orality and changing eating habits	Falling
Naming problems		Loss of empathy	Eye movement impairment
Impaired repetition		Depression	
Impaired object knowledge		Anxiety	
Dysarthria			
Mutism			

Supplementary Table 3: Clinical features of the diagnostic groups

Symptoms	Initial visit (%)			1st year follow-up (%)			2nd year follow-up (%)			3rd year follow-up (%)		
Language/ Speech	svPPA (n=24)	nfPPA (n=22)	lvPPA (n=18)	svPPA (n=24)	nfPPA (n=22)	lvPPA (n=18)	svPPA (n=17)	nfPPA (n=14)	lvPPA (n=14)	svPPA (n=11)	nfPPA (n=10)	lvPPA (n=12)
Word finding difficulties	96	77	94	100	81	100	100	86	100	100	90	100
Sentence comprehension deficit	67	27	44	79	41	50	94	64	64	100	70	83

Single word comprehension deficit	67	9	11	79	9	11	88	14	21	90	20	33
Dyslexia/dysgraphia	37	50	50	46	63	72	65	86	93	63	90	100
Spontaneous speech impairment	16	100	33	25	100	39	18	100	57	18	100	58
Naming problems	100	31	72	100	36	78	100	43	86	100	40	92
Impaired repetition	8	59	83	12	73	89	24	71	86	36	80	100
Impaired object knowledge	67	0	6	75	0	6	71	0	7	54	0	8
Dysarthria	0	41	6	0	46	6	0	36	7	0	40	8
Mutism	0	0	0	0	4	0	0	0	0	0	40	0
Cognitive												
Memory deficit	20	0	39	25	4	50	47	7	50	36	0	58
Prosopagnosia	29	0	6	33	0	6	47	0	7	54	0	0
Executive dysfunction	12	36	61	37	54	66	53	64	86	63	60	100
Apraxia	8	9	38	17	27	56	29	43	71	36	80	75
Visuospatial problems	4	13	44	8	18	44	12	21	64	9	30	83
Behavioural/ mood												
Disinhibition	54	22	22	66	41	28	82	57	28	82	60	58
Loss of insight	46	0	17	58	9	28	65	14	36	64	20	42
Compulsive behaviour	58	9	5	79	23	6	82	21	0	90	20	0
Apathy/ inertia	58	50	50	66	63	55	65	71	50	63	80	41
Hyper-orality and changing eating habits	37	13	28	37	18	28	41	21	21	45	20	17
Loss of empathy	25	9	6	33	14	6	47	21	7	45	20	8
Depression	17	41	28	21	45	28	47	36	36	64	20	33
Anxiety	12	54	55	21	59	55	17	64	71	27	70	58
Motor												
Pyramidal signs	0	4	0	0	4	0	0	0	0	0	0	0

Extrapyramidal signs	0	27	11	4	45	18	0	50	21	0	80	25
Primitive reflexes	8	36	11	12	45	16	12	57	14	9	60	17
Swallowing problems	0	18	0	0	23	0	0	7	0	0	0	0
Falling	0	4	0	0	14	0	0	29	0	0	20	8
Eye movement impairment	0	9	0	0	23	0	0	29	0	0	40	0

svPPA: semantic variant primary progressive aphasia, nfvPPA: non-fluent variant primary progressive aphasia, lvPPA: logopenic variant primary progressive aphasia

Supplementary Material 4

Table 1: Baseline cognitive test scores of the diagnostic groups

			svPPA		**nfvPPA**		**lvPPA**		**One-way ANOVA**	
			N	**Mean± SD**	**N**	**Mean±SD**	**N**	**Mean±SD**	**P**	**Group differences**
	Global cognition	MMSE	24	24.83±4.29	22	24.68±4.21	18	23.44±3.43	0.503	NS
Episodic memory	**Visual memory**	VAT A	22	10.14±2.57	20	11.50±1.57	18	10.22±2.16	0.089	NS
	Verbal memory	RAVLT-Immediate recall	21	24.67±9.36	19	31.95±11.51	18	26.22±12.74	0.111	NS
		RAVLT-Delayed recall	21	3.24±2.47	19	6.42±3.70	18	5.44±4.09	**0.015**	nfvPPA, lvPPA>svPPA
Language	**Naming**	VAT naming	23	7.26±3.48	20	10.80±2.12	18	10.50±1.38	**<0.001**	nfvPPA, lvPPA>svPPA
		Boston naming	24	6.46±2.47	18	16.50±2.56	18	13.38±2.38	**<0.001**	nfvPPA, lvPPA>svPPA
	Semantic memory	Animal fluency	23	10.04±4.87	19	10.63±6.44	18	11.67±5.35	0.649	NS
	Fluency	Letter fluency	23	25.70±9.83	17	12.06±6.19	18	20.39±9.38	**<0.001**	svPPA, lvPPA>nfvPPA
Executive function	**Global executive function**	FAB	23	14.13±2.46	20	12.95±4.30	16	12.81±3.60	0.412	NS
	Working memory	Digit span backward	23	8.52±2.97	18	4.83±2.01	17	5.35±1.77	**<0.001**	svPPA > lvPPA, nfvPPA
Visuospatial function	**Visuospatial function**	VOSP-Fragmented letters	19	17.59±1.49	18	18.78±0.81	16	17.44±1.71	0.563	NS

svPPA; semantic variant primary progressive aphasa, nfvPPA; non fluent variant primary progressive aphasia, lvPPA; logopenic variant primary progressive aphasia, MMSE; mini mental state examination, VAT; visual association test, RAVLT; Dutch version of the Rey Auditory Verbal Learning Test, FAB; frontal assessment battery, VOSP; Visual objective and space perception

Table 2: Annual change over time (Linear Mixed Model)

			svPPA			**nfvPPA**			**lvPPA**		
			N	**Estimates (95% CI)**	**P**	**N**	**Estimates (95% CI)**	**P**	**N**	**Estimates (95% CI)**	**P**
	Global cognition	MMSE	24	-1.46 (-2.23 – -0.68)	**0.001**	22	-0.84 (-3.60 – 1.92)	0.556	18	-2.25 (-3.48 – -1.01)	**0.001**

Episodic memory	**Visual memory**	VATA	22	-0.04 (-0.56 – 0.48)	0.883	20	-0.92 (-1.90 – 0.05)	0.073	18	-0.93 (-1.55 – -0.30)	**0.006**
	Verbal memory	RAVLT-Immediate recall	21	-4.24 (-6.09 – -2.39)	**<0.001**	19	-0.76 (-9.35 – 7.82)	0.864	18	-4.04 (-6.42 – -1.65)	**0.002**
		RAVLT-Delayed recall	21	-0.90 (-1.46 – -0.35)	**0.003**	19	-0.46 (-2.46 – 1.53)	0.657	18	-1.08 (-1.75 – -0.41)	**0.004**
Language	**Naming**	VAT naming	23	-1.59 (-2.18 – -1.01)	**<0.001**	20	-1.06 (-2.30 – 0.17)	0.106	18	-0.85 (-1.47 – -0.24)	**0.010**
		Boston naming	24	-1.73 (-2.61 – -0.85)	**0.001**	18	-0.63 (-1.69 – 0.44)	0.292	18	-2.68 (-3.66 – -1.71)	**<0.001**
	Semantic memory	Animal fluency	23	-2.47 (-3.21 – -1.74)	**<0.001**	19	-2.86 (-5.08 – -0.63)	**0.030**	18	-2.03 (-3.07 – -0.99)	**0.001**
	Fluency	Letter fluency	23	-3.76 (-5.25 – -2.27)	**<0.001**	17	-2.19 (-4.70 – 0.31)	0.125	18	-4.19 (-5.94 – -2.44)	**<0.001**
Executive function	**Global executive function**	FAB	23	-0.89 (-1.58 – -0.20)	**0.015**	20	-2.31 (-3.12 – -1.51)	**<0.001**	16	-1.85 (-2.62 – -1.09)	**<0.001**
	Working memory	Digit span backward	23	-0.61 (-1.14 – -0.09)	**0.029**	18	-0.51 (-1.36 – 0.34)	0.263	17	-0.68 (-1.19 – -0.17)	**0.013**
Visuospatial function	**Visuospatial function**	VOSP-Fragmented letters	19	-0.97 (-2.39 – 0.44)	0.191	18	0.14 (-0.30 – 0.57)	0.543	16	-0.88 (-2.03 – 0.27)	0.143

svPPA; semantic variant primary progressive aphasa, nfvPPA; non fluent variant primary progressive aphasia, lvPPA; logopenic variant primary progressive aphasia, MMSE; mini mental state examination, VAT; visual association test, RAVLT; Dutch version of the Rey Auditory Verbal Learning Test, FAB; frontal assessment battery, VOSP; Visual objective and space perception

CHAPTER 5

A CLINICAL-RADIOLOGICAL FRAMEWORK OF THE RIGHT TEMPORAL VARIANT OF FRONTOTEMPORAL DEMENTIA

A CLINICAL-RADIOLOGICAL FRAMEWORK OF THE RIGHT TEMPORAL VARIANT OF FRONTOTEMPORAL DEMENTIA

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Abstract

The concept of the right temporal variant of frontotemporal dementia is still equivocal. The syndrome accompanying predominant right anterior temporal atrophy has previously been described as memory loss, prosopagnosia, getting lost and behavioural changes. Accurate detection is challenging, as the clinical syndrome might be confused with the behavioural variant of frontotemporal dementia, or Alzheimer's disease. Furthermore, based on neuroimaging features, the syndrome has been considered a right-sided variant of the semantic variant of primary progressive aphasia. Therefore, we aimed to demarcate the clinical and neuropsychological characteristics of the right temporal variant frontotemporal dementia vs the semantic variant of primary progressive aphasia, the behavioural variant of frontotemporal dementia and Alzheimer's disease. Moreover, we aimed to compare its neuroimaging profile against the semantic variant of primary progressive aphasia, which is associated with predominant left anterior temporal atrophy. Out of 619 subjects with a clinical diagnosis of frontotemporal dementia or primary progressive aphasia, we included seventy subjects with a negative amyloid status for whom predominant right temporal lobar atrophy was identified based on blinded visual assessment of their initial brain MRI scans. Clinical symptoms were assessed retrospectively and compared with age- and sex-matched individuals with the semantic variant of primary progressive aphasia (n=70), behavioural variant of frontotemporal dementia (n=70) and Alzheimer's disease (n=70). In right temporal variant frontotemporal dementia, prosopagnosia, episodic memory impairment and behavioural changes such as disinhibition, apathy, compulsiveness and loss of empathy were the most common initial symptoms, whereas during the disease course, patients developed language problems such as word-finding difficulties and anomia. Distinctive symptoms of right temporal variant frontotemporal dementia compared to the other groups included depression, somatic complaints, and motor/mental slowness. Aside from right temporal atrophy, the imaging pattern showed volume loss of the right ventral frontal area and the left temporal lobe, which represented a close mirror image of the semantic variant of primary progressive aphasia. Atrophy of the bilateral temporal poles and the fusiform gyrus were associated with prosopagnosia in right temporal variant frontotemporal dementia. Our results highlight that right temporal variant frontotemporal dementia has a unique clinical presentation. Since current diagnostic criteria do not cover specific symptoms of the right temporal variant of frontotemporal dementia, we propose a diagnostic tree to be used when defining diagnostic criteria, and call for an international validation.

Keywords: dementia; frontotemporal dementia; frontotemporal lobar degeneration; prosopagnosia; right temporal lobe atrophy.

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder that predominantly affects the frontal and/or temporal lobes. Three different prototypic FTD syndromes have been described, being semantic dementia (SD), progressive non-fluent aphasia (PNFA) and behavioural variant frontotemporal dementia (bvFTD) (1). In 2011, consensus clinical diagnostic criteria were revised and FTD was classified as behavioural variant (2) whereas SD and PNFA were classified under the umbrella of primary progressive aphasia (PPA), including the semantic variant (svPPA), the nonfluent/agrammatic variant and the logopenic variant of PPA (3). The typical neuroimaging pattern of bvFTD consists of frontal and/or temporal atrophy (2), whereas bilateral anterior temporal atrophy is suggestive of svPPA with usually a greater amount of atrophy on the left side, and predominant left posterior frontal and insular atrophy is the neuroimaging pattern of nfvPPA (3). On the other hand, a number of authors have mentioned a separate syndromic variant that predominantly affects the right temporal lobe (4, 5). The main clinical characteristics that have been associated with the right temporal variant of frontotemporal dementia (rtvFTD) are prosopagnosia, memory deficits, getting lost and profound behavioural changes such as disinhibition and obsessive personality (5-11). Additional symptoms particularly linked to rtvFTD include hyper-religiosity, visual hallucinations and cross-modal sensory experiences (5).

Since the revision of consensus criteria for bvFTD (1) and SD being considered a variant of PPA (3), the syndrome of rtvFTD has been relatively neglected in the literature. In the most recent diagnostic criteria (2), bilateral anterior temporal atrophy has been the "imaging supported diagnostic" criterion for svPPA, and therefore rtvFTD has been classified as svPPA. On the other hand, an early amnestic presentation and behavioural changes may fulfil clinical diagnostic criteria for either bvFTD or Alzheimer's disease (AD) (2,6). Reflective of all this, there is not even agreement on its name. Over the years, the syndrome has been termed as 'right temporal lobe atrophy', 'right variant FTD', 'temporal variant FTD' and 'right temporal variant of FTD' (5,8,12-15), whereas those authors who consider rtvFTD as part of SD use terms like 'right variant of SD', 'right predominant SD' or 'right-lateralized SD' (4,10,11,16-18). However, in most available clinical and radiological studies, the number of patients has been rather limited (n= 6-20 patients) and none of them excluded subjects with underlying Alzheimer's disease pathology based on CSF biomarker profile or amyloid PET (5,6,15-17), except a single post- mortem study (7).

In order to better delineate the potentially unique clinical syndrome of rtvFTD we set out to examine the clinical and neuropsychological profile of rtvFTD and compare it to svPPA, bvFTD, and AD. Additionally, we aimed to identify the neuroimaging pattern of rtvFTD in comparison with svPPA to establish whether these distinct clinical presentations also involve distinct anatomical underpinnings.

METHODS

Patient selection

Six hundred nineteen patients with a clinical diagnosis of FTD and/or PPA whose amyloid status data were available, diagnosed between January 1998 and June 2018 were collected from the Amsterdam Dementia Cohort (19). All patients were diagnosed by a multidisciplinary team according to clinical diagnostic criteria (1,2,6). Thirty-two patients who had a positive AD CSF profile (20) and/or a positive amyloid-PET scan were excluded. Our inclusion criterion was having a predominant temporal lobar atrophy on the right side on the initial brain MRI (Supplemental Figure 1). Therefore, three patients were excluded due to lack of brain MRI scans. All MRI scans had been visually assessed by experienced neuro-radiologists (FB, MW) who were blinded to clinical and para-clinical details. Based on visual assessment (21), subjects were included in the study if temporal cortical atrophy and/or mesial temporal atrophy (MTA) scores (22) were at least more than one grade higher on the right side than on the left side. This yielded a sample of 70 subjects with right predominant temporal lobe atrophy. Hereby, 11.3% of our FTD cohort were identified as rtvFTD. The remaining five hundred fourteen patients showed predominant frontal or equal bilateral temporal or predominant left temporal atrophy and were therefore not included. To elucidate the potential rtvFTD subjects in the excluded groups (patients with positive Alzheimer's disease CSF profile and/or PET scan and patients without MRI), all initial neuroimaging of excluded subjects was also assessed. However, none of the subjects had predominant right temporal lobe atrophy.

Four out of 70 rtvFTD subjects had a postmortem pathological diagnosis showing frontotemporal lobar degeneration with tau pathology (FTLD-tau, n=1, with a mutation in the tau gene), FTLD with TAR DNA binding protein 43 (n=2) and FTLD with fused in sarcoma protein (n=1). Additionally, one subject without a post-mortem examination was carrier of a pathogenic variant in the progranulin gene. To compare the clinical characteristics of the diseases, age and gender-matched, biomarker-based svPPA (n=70), bvFTD (n=70) and AD

patients (n=70) diagnosed between January 1998 and June 2018 were selected from the Amsterdam Dementia Cohort (19), as control groups with an unbiased method (logistic regression model) (23). Additionally, 70 age and sex matched (age: 62.9±8.3, 34% female) healthy volunteers and subjective cognitive decline patients from the Amsterdam Dementia Cohort database were added as a reference for cognitive tests. For the radiological part of the study, we also selected 121 amyloid-β negative cognitively normal subjects (age:57.4±8.9, 41% male, MMSE:29.0±0.8) from the Amsterdam Dementia Cohort. This group served as a reference in voxel-wise contrasts. Supplemental Figure 2 displays the patient selection.

Clinical data collection and assessment

For clinical data analysis, in this retrospective study both qualitative and quantitative methods were used. The case notes written by senior neurologists YP and PS were scrutinized and all described symptoms were extracted. Symptoms were sub-classified as "initial symptoms" (at the initial visit) and "later symptoms" (at any stage of the disease, only rated when reported at follow-up). Similar symptoms were combined into one umbrella term by RH and YP, based on similar meaning and/or cognitive/behavioural domains. Subsequently, 21 single symptoms were categorized in the following four groups; cognitive, language, behavioural, and other symptoms. All 21 symptoms were recorded as present or absent for each patient. As part of their functional assessment, the clinical dementia rating (CDR) was performed (24) in all patients. General cognitive functioning was measured using the mini-mental state examination (MMSE) (25), whereas executive functioning was screened with the Frontal assessment battery (FAB) (26). The patients' behavioural and psychological status was assessed by the neuropsychiatric inventory (NPI) (27).

Neuropsychological assessment

Neuropsychological examination had been performed for diagnostic purposes at first presentation to the Alzheimer Centre Amsterdam. A standard test battery was administered to assess multiple cognitive domains such as episodic memory [visual association test (VAT)A (28) and the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) , executive functions [trail making test (TMT) B (29) and digit span backward (30), semantic memory [category fluency animals] (31), confrontation naming [VAT naming (28), attention [digit span forward] (30) and TMT A (29) and visuospatial functions [Visual Objective and Space Perception (VOSP)] – fragmented letters and VOSP- Dot counting (32) . Details of the

clinical assessment and tests have been published previously (19,33). All data for cognitive, psychological and functional assessment were collected retrospectively.

MRI acquisition and processing

MRI of the brain was acquired on a 1 Tesla, 1.5 Tesla or 3 Tesla whole body MR system (Siemens Magnetom Impact, Avanto and Sonata, GE Healthcare Signa HDXT, Discovery MR750, GE Medical Systems, Milwaukee, WI, USA; Ingenuity TF PET/MR, Philips Medical Systems, Best, The Netherlands; Titan, Toshiba Medical Systems, Japan), using previously described protocols (34,35). Eleven of 70 rtvFTD and 18 of 70 svPPA subjects did not have a suitable MRI available for voxel-based morphometry (VBM) analysis. MRI scans of the remaining 59 rtvFTD, 52 svPPA and 121 control subjects were collected and the structural 3D T1-weighted MR images were segmented into grey matter, white matter and CSF volumes, which were summed to provide the total intracranial volume. Next, diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) was used to generate a study-specific template by aligning grey matter images nonlinearly to a common space in SPM12 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology at University College London). Native space grey matter images were then spatially normalized to the DARTEL template using individual flow fields. Modulation was applied to preserve the total amount of signal, and images were smoothed using an 8mm full-width-at-half-maximum isotropic Gaussian kernel. Visual inspection was performed after each processing step and 8 rtvFTD patients and 6 svPPA patients' images were excluded based on these inspections. All images of the control group were suitable for analysis. Thus, the final selection included 51 rtvFTD patients, 46 svPPA patients and 121 cognitively normal participants and the normalized, smoothed and modulated images of these subjects were used in the VBM analyses. Additionally, the automated anatomical labelling (AAL) atlas was used to extract regional grey matter volumes across 62 regions, which were used in the region-of-interest analyses.

Statistical Analysis

Analyses were conducted using SPSS Statistics, version 24.0 (IBM) and SPM12. Differences in categorical variables between groups (rtvFTD, svPPA, bvFTD, and AD) were assessed with chi-square and continuous variables between groups were assessed with one-way ANOVA or Kruskal-Wallis variance analysis depending on the distribution of the variables based on normality test. Post hoc comparisons were corrected for multiple comparisons using the Bonferroni correction. The results were thresholded at a corrected p-value of < 0.05. The

combination of clinical features that were considered characteristic of rtvFTD based on chart review was reported in a diagnostic tree of rtvFTD including the negative amyloid status and its radiological features. Sensitivity, specificity, positive and negative predictive values of the clinical syndrome were calculated with cross tables with 95% confidence intervals. To identify patterns of neurodegeneration in each syndrome with respect to healthy controls we performed voxel-wise contrasts of grey matter volumes between groups (rtvFTD, svPPA) and controls using general linear models adjusted for age, sex, intracranial volume, and scanner field strength. In addition, to compare the atrophy pattern of rtvFTD and svPPA, an asymmetry index was calculated within regions-of-interest with the formula [AI (%) = 200 * (R - L)/ (R + L) (36). Thus, negative outcomes indicate more atrophy in the right hemisphere, while positive values reflect left lateralized asymmetry. Additionally, in order to identify the anatomical correlate of prosopagnosia, which was observed to be the most distinguishing symptom of rtvFTD, we compared the initial MRI scans of rtvFTD subjects with prosopagnosia (n=37) and without prosopagnosia (n=33) at the initial visit while adjusting for age, sex, intracranial volume, scanner field strength and whole-brain grey matter to intracranial volume ratios.

Ethical Approval

The local Medical Ethics Committee approved a general protocol for using the clinical data for research purposes (Protocol No: 2016.061).

Data availability

Data are available on request from the authors.

RESULTS

Demographic data

Table 1 displays demographic data, symptom duration, follow-up duration and handedness per patient group. The rtvFTD group comprised 49 male and 21 female patients with a mean age of 64.7 years (standard deviation (SD) 8.4) and a mean symptom duration of 2.6 years (SD 1.6). Mean symptom duration and median follow-up duration did not differ significantly between diagnostic groups (p=0.102, p=0.666). Handedness varied among patients, but no statistical differences in the distribution of handedness per group were found (p=0.074). To establish receptive language dominance in left handed, ambidexter and handedness unknown subjects, we checked whether clinical symptoms showed concordance with the anatomic

distribution of cortical atrophy and clinical presentation. All patients demonstrated the same pattern of hemispheric lateralization as the right-handers (Table 1).

Table 1 Demographic data, symptom and follow-up duration, and handedness per group

	rtvFTD	svPPA	bvFTD	AD	p
N	70	70	70	70	-
Gender/ Female	21 (30%)	24 (34%)	25 (35%)	22 (31%)	0.885*
Age mean ± SD, years	64.7± 8.4	64.0 ± 7.6	63.6 ± 6.7	65.1 ± 7.6	0.470#
Handedness left/right/ambidexter/unknown	6/57/1/6	1/55/0/14	7/51/3/9	8/52/0/10	0.074&
Symptom duration mean ± SD, years	2.6 ± 1.6	3.8 ± 1.4	4.4 ± 1.4	3.6 ± 4.6	0.102#
Follow-up period median (min-max), years	2 (0-11)	1 (1-8)	2 (0-11)	2 (1-7)	0.666$

*: Chi-square; #: One-way ANOVA; &: Fisher's exact test; $: Kruskal-Wallis non parametric tests

rtvFTD: right temporal variant frontotemporal dementia, svPPA; semantic variant primary progressive aphasia, bvFTD; behavioural variant frontotemporal dementia, AD; Alzheimer's disease, N: Amount of the patients, min: minimum, max: maximum, SD: standard deviation

Core symptoms of rtvFTD

Detailed initial and later symptoms per disease group are displayed in Table 2. It should be noted that multiple symptoms could be present simultaneously in one patient, hence the total number of symptoms exceeds the number of patients.

Table 2 Clinical features of the diagnostic groups

	Initial (Percent affected)				Later (Percent affected)			
Symptoms*	**rtvFTD**	**svPPA**	**bvFTD**	**AD**	**rtvFTD**	**svPPA**	**bvFTD**	**AD**
Cognitive								
Memory problems	60	25	49	99	90	67	76	100
Prosopagnosia	54	21	4	0	70	29	13	0
Executive dysfunction	21	18	52	83	58	41	80	87
Orientation problems	6	17	27	66	34	26	36	74
Getting lost	7	4	12	16	20	6	17	26
Visuo- spatial problems	7	7	10	46	23	11	22	54

Language	48	100	43	79	82	100	62	89
Word-finding difficulties	31	72	30	79	61	79	47	89
Single word comprehension deficit	18	61	7	0	35	60	14	6
Paraphasias	14	51	3	13	19	64	14	21
Naming difficulties	28	85	21	23	51	87	30	30
Behavioural	95	65	100	42	97	90	100	75
Disinhibition	60	31	81	20	74	82	90	37
Compulsive behaviour	40	35	46	1	71	66	66	9
Apathy or inertia	55	41	75	40	91	61	85	52
Loss of empathy and egocentrism	50	14	55	3	65	47	64	20
Hyper-orality and dietary changes	22	8	50	14	68	37	61	18
Other symptoms								
Motor/ mental slowness	27	15	17	27	70	25	37	34
Hyper-religiosity	1	1	0	0	4	4	0	0
Depression	27	15	4	36	44	23	11	44
Delusions/ hallucinations	7	7	9	7	22	13	10	9
Somatic complaints and aches	15	8	20	14	40	27	27	27
Feeling of anxiety/ panic	11	11	11	28	38	25	18	34

*: Symptoms were collected based on the case notes written by senior neurologists. For further information see supplementary material 1.

rtvFTD: right temporal variant frontotemporal dementia, svPPA; semantic variant primary progressive aphasia, bvFTD; behavioural variant frontotemporal dementia, AD; Alzheimer's disease

Episodic memory problems and prosopagnosia were two of the most common initial symptoms of rtvFTD with a prevalence of 60% and 54%, respectively, increasing to 90% and 70% during follow up. Besides these symptoms, behavioural problems were almost universally present at the initial visit and included behavioural disinhibition (60%), apathy or inertia (55%), loss of empathy and egocentrism (50%), and compulsive behaviour (40%). The latter not only consisted of simple compulsive behaviour, such as clock watching, but also of ritualistic preoccupations, such as dressing each day of the week in a different colour, and repeatedly driving more than one hour to the same shop, to buy objects at a minimal discount. Language problems such as word finding difficulties (31%) and anomia (28%) were relatively less frequent at the first assessment. However, over the disease course, 82% of the cases developed language difficulties. Of note, the characteristic language symptoms of svPPA such as single word comprehension deficits (18%) and paraphasias (14%) were recorded less frequently.

Main differences between diagnostic groups

In order to compare the clinical profiles of rtvFTD, svPPA, bvFTD and AD, the prominent symptoms of the disease groups were displayed against the current diagnostic criteria for bvFTD (2), svPPA (1) and AD (3) on a descriptive spider graph (Figure 1).

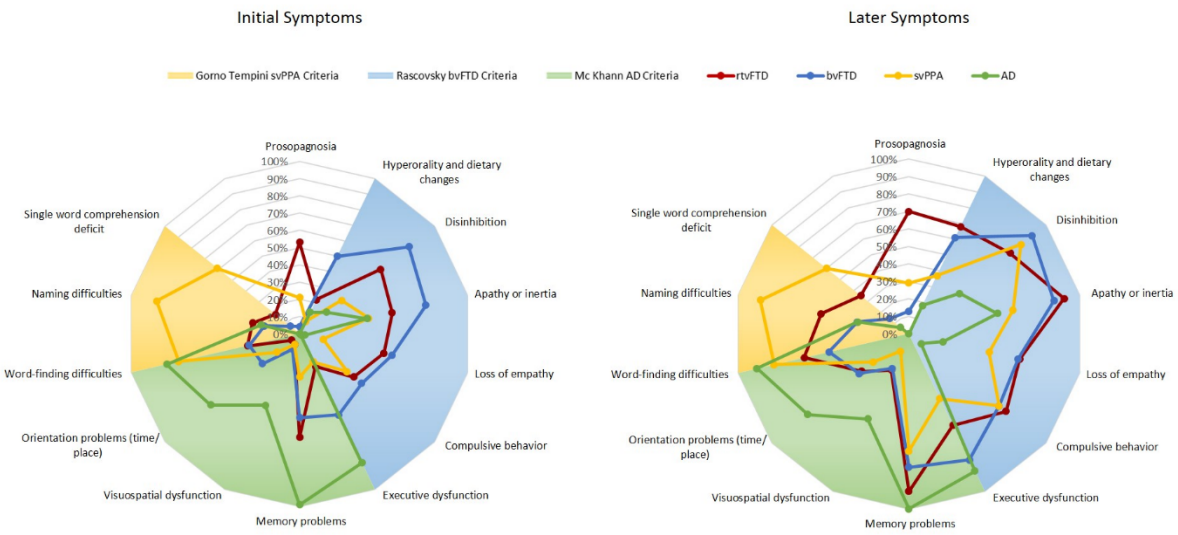

Figure 1: Main differences among disease groups at first assessment (initial symptoms) and at any stage of the disease (later symptoms). The shadow graphs on the background were adapted from current diagnostic criteria (Gorno-Tempini *et al.*, 2011; McKhann *et al.*, 2011; Rascovsky *et al.*, 2011). AD = Alzheimer's disease.

As expected, the pattern of svPPA, bvFTD, and AD clinical symptoms were in line with their respective clinical criteria. RtvFTD cases were characterized by prosopagnosia, behavioural problems, language problems, and episodic memory problems, thereby combining unique features and common features with each of the comparative patient groups. During the disease course, the most prominent clinical features of rtvFTD were still not completely overlapping with one of the other groups, meaning that also during the disease course, rtvFTD kept its own clinical profile. Prosopagnosia was the most unique symptom of rtvFTD. It was not seen in AD, and much less prevalent in svPPA and bvFTD. Memory problems were most commonly present in AD, but not unique, but were also present (to a lesser extent) in rtvFTD and bvFTD, and eventually also in svPPA. Even though all bvFTD patients exhibited behavioural changes at the initial presentation, both rtvFTD (95%) and svPPA (65%) groups initially exhibited behavioural changes as well. However, the characteristics of the behavioural problems were different in rtvFTD. Compulsiveness and apathy-inertia were the most prominent behavioural changes in svPPA, whereas rtvFTD patients exhibited various and more frequent behavioural symptoms such as disinhibition, loss of empathy, as well as compulsiveness and apathy-inertia initially. Although these behavioural problems were also prominent in bvFTD, over the disease course, behavioural symptoms of rtvFTD and bvFTD

showed different progression patterns, where compulsive behaviour, apathy-inertia, and hyperorality and dietary changes evolved most prominently in rtvFTD. In contrast, patients with bvFTD demonstrated greater executive dysfunction than rtvFTD. In addition, depression was more common in rtvFTD (27% initial, 44% later) than bvFTD (4% initial, 11% later). Language disorder was the prominent feature of svPPA. Even though rtvFTD patients demonstrated relatively less frequent language problems initially, at the following visits the majority of patients developed language dysfunction. The two most common language symptoms recorded at the initial visit were word-finding difficulty and anomia for rtvFTD whereas svPPA patients exhibited highly frequent language problems with a wide range of symptom distribution such as single word comprehension deficits, paraphasia, as well as word finding difficulties and anomia. Visuospatial and orientation problems and getting lost were more common in AD than in the FTD groups in both the initial and later stages.

Even though motor/mental slowness was not common in rtvFTD at initial presentation, it became one of the distinguishing symptoms of rtvFTD during follow-up.

Psychiatric features, such as depression, psychotic symptoms, and anxiety evolved during the course of rtvFTD at a higher frequency compared with the other disease groups. Somatic complaints and aches, for which no medical cause was found, were present in 40% of rtvFTD cases, compared to 27% in the other groups. In rtvFTD, these were also associated with beliefs that the body contained valves or tubes that could be influenced from the outside. Hyper-religiosity was less common, but was only observed in the rtvFTD and svPPA groups (Table 2).

Cognitive Test Scores and Neuropsychiatric Inventory

In Table 3 dementia severity and neuropsychological test scores are shown per diagnostic group. Due to change of test protocols over the years, some patients' data were not available. The numbers of data available patients are displayed in the figures and tables.

Table 3: Cognitive test scores of the diagnostic groups

		HC		rtvFTD		svPPA		bvFTD		AD		One-Way ANOVA	
Cognitive domain	**Test**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**p**	**Group Differences**
Disease Severity	**CDR**	-	-	49	0.6 ± 0.35	37	0.9 ± 0.63	54	0.8 ± 0.47	49	0.9 ± 0.43	0.051	NS
Global Cognition	**MMSE**	70	28.9± 1.10	70	25.34+ 3.23	59	21.08+ 6.30	67	25.37 + 3.87	67	20.22+ 5.10	**<0.001**	HC>rtvFTD, bvFTD>

													svPPA, AD
Episodic Memory	**VAT-A**	70	11.61 ± 0.71	58	10.05+ 2.64	46	8.37+ 3.73	55	10.38 + 2.52	57	5.19+ 4.06	**<0.001**	HC, rtvFTD, bvFTD, svPPA> AD
	RAVLT delayed recall	70	8.89 ± 2.83	50	4.62+ 3.34	28	2.86+ 2.86	58	5.26+ 3.33	40	1.85+02 .00	**<0.001**	HC> rtvFTD, bvFTD, svPPA> AD
Executive Functioning	**FAB**	70	17.23 ± 1.13	48	15.02+ 3.41	30	12.40+ 3.74	52	12.96 + 4.27	29	11.55+ 3.56	**<0.001**	HC> rtvFTD> bvFTD, svPPA, AD
	Digit span backward	70	13.91± 2.79	59	8.37+ 2.65	46	6.70+ 2.57	58	7.50+ 2.69	56	5.88+ 2.53	**<0.001**	HC> rtvFTD, bvFTD> svPPA, AD
	TMT-B	70	81.54±34.21	54	121.63 + 77.17	41	167.10+97.36	51	138.33+ 72.60	29	220.52+ 155.29	**<0.001**	HC> rtvFTD, bvFTD, svPPA> AD
Language	**VAT Naming**	70	11.89±1.11	60	9.98+ 2.48	43	6.49+ 3.80	55	11.53 + 1.33	55	11.51+ 0.76	**<0.001**	HC, bvFTD, AD> rtvFTD> svPPA
	Animal Fluency	70	23.7 ± 5.72	60	14.30+ 5.33	45	7.58+ 5.53	57	14.88 + 6.03	60	12.37+ 5.01	**<0.001**	HC> rtvFTD, bvFTD, AD> svPPA
Attention	**Digit span forward**	70	15.2±3.12	60	11.72+ 2.91	48	10.21+ 3.05	58	11.22 + 2.93	57	10.70+ 3.34	0.061	NS
	TMT-A	70	48.7±20.39	63	54.60+ 31.42	49	61.55+ 29.67	61	56.59 + 31.95	52	103.54+ 76.91	**<0.001**	HC, rtvFTD, bvFTD, svPPA> AD
Visuospatial Function	**Fragmented letters (VOSP)**	70	19.3 ± 0.84	42	16.62+ 4.83	23	17.39+ 4.34	42	16.62 + 4.83	24	15.46+ 4.86	0.574	NS
	Dot counting (VOSP)	70	9.8 ± 0.51	39	9.74+1.14	20	9.55+ 1.19	39	9.74+ 1.14	22	8.55+ 1.62	**0.018**	HC, rtvFTD, bvFTD, svPPA> AD

HC: Healthy control, rtvFTD: right temporal variant frontotemporal dementia, svPPA; semantic variant primary progressive aphasia, bvFTD; behavioural variant frontotemporal dementia, AD; Alzheimer's disease CDR; Clinical dementia rating, MMSE; mini-mental state examination, VAT; visual association test, RAVLT; Dutch version of the Rey Auditory Verbal Learning Test, FAB; frontal assessment battery, TMT; trial making test, VOSP; Visual objective and space perception

Dementia severity, as measured with the CDR was lower in the rtvFTD group, however, no significant difference was detected between disease groups (p=0.051). MMSE scores were higher in rtvFTD and bvFTD compared to svPPA and AD (p< 0.001). AD patients demonstrated greater memory impairment (VAT-A and RAVLT delayed recall p<0.001), attention deficits (TMT-A p<0.001, digit span forward p= 0.065) and visuospatial dysfunction (Dot counting p=0.020, Fragmented letters p=0.574) than other groups whereas language deficits were most profound in the svPPA group (VAT naming and animal fluency p<0.001). Patients with rtvFTD exhibited similar performance to bvFTD generally, except on the naming test and FAB. The rtvFTD patients demonstrated worse performance than bvFTD on the naming test (p<0.001), whereas bvFTD patients exhibited greater executive dysfunction (FAB p=0.001). As a result, rtvFTD patients exhibited a generally better performance on neuropsychological tests compared to the other diagnostic groups, except on the naming test (Table 3).

On the other hand, rtvFTD patients exhibited worse performance than cognitively normal subjects on global cognition, episodic memory, language and executive functions. NPI results showed that neuropsychiatric symptoms were most severe in patients with bvFTD, as indicated by the overall NPI score and by the scores for aberrant motor behaviour, sleep time behaviour problems, changing eating habits, irritability, aggression and disinhibition. However, a statistically significant difference was observed only in the overall NPI score and the items related with disinhibition and changing eating habits (p<0.05, bvFTD vs other diagnostic groups). Although bvFTD has the highest overall NPI score, the item related with depression was higher in rtvFTD however this difference was not statistically significant (p= 0.101) (Figure 2).

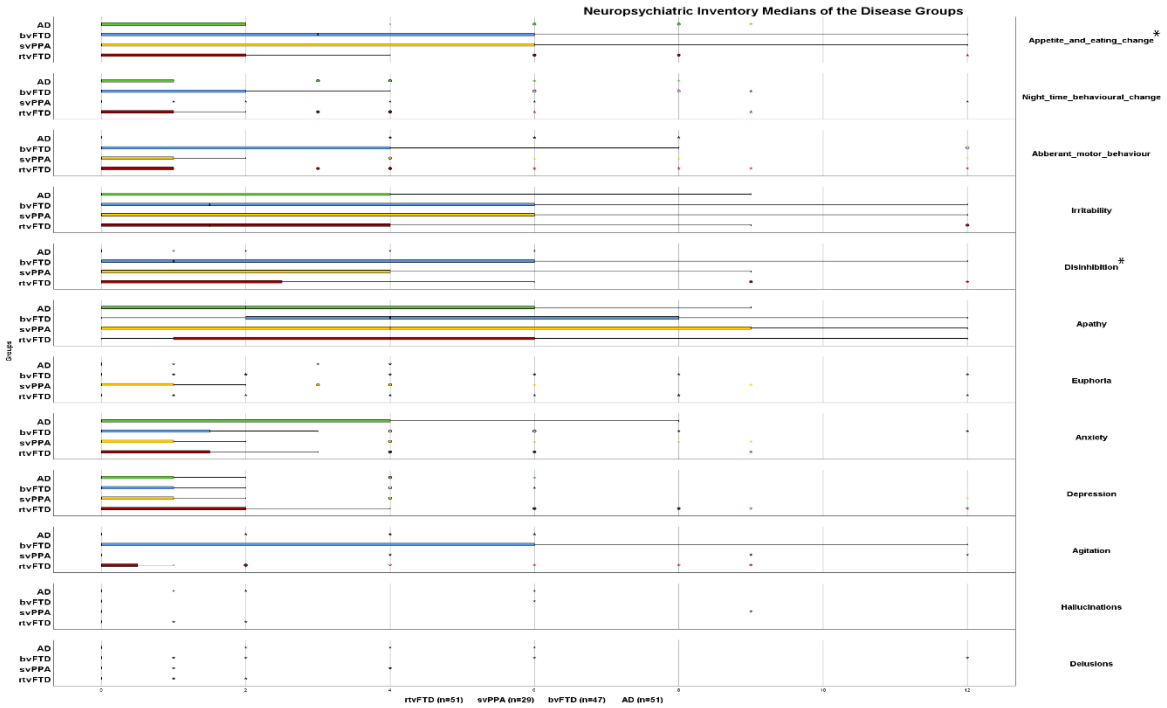

Figure2: Neuropsychiatric inventory medians of the disease groups. AD = Alzheimer's disease. Frequency × Severity scores were analysed. *P < 0.05, bvFTD versus other diagnostic groups.

Radiological characteristics of rtvFTD and comparison with svPPA

VBM analysis revealed that, compared with controls, rtvFTD patients showed bilateral asymmetrical (right > left) grey matter volume loss in the anterior temporal lobes and in the right ventral frontal area. Right-sided grey matter loss was observed in the temporal poles, the superior, medial, and inferior temporal gyri, medial temporal lobe, insula, fusiform gyrus, angular gyrus, and supramarginal gyrus. The same regions were involved in the left temporal lobe, though to a lesser extent. Grey matter loss was also observed in the right inferior frontal gyrus, gyrus rectus, orbitofrontal cortex, with a greater degree of loss observed in the inferior orbitofrontal lobe. SvPPA patients showed a mirrored pattern. Asymmetry index analysis showed that the frontal and temporal lobes were affected almost equally, but in opposite directions in rtvFTD and svPPA. Both in rtvFTD and svPPA, the temporal poles were the most affected areas (Figure 3).

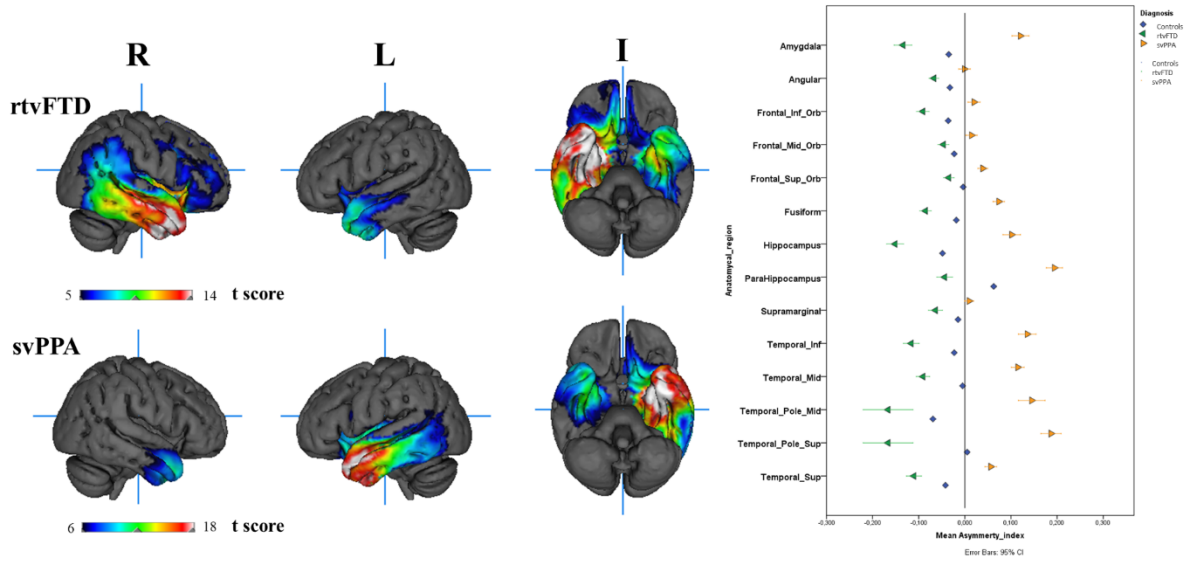

Figure 3: 3D T-maps of the rtvFTD and svPPA and the asymmetry index

Clinico-radiological correlation of prosopagnosia in rtvFTD

Mean symptom duration did not differ significantly between prosopagnosia present (3.4±1.9 years) and absent (2.65±1.5 years) groups (p=0.445). Visual inspection of voxel-wise contrasts between rtvFTD patients with and without prosopagnosia revealed that the patients with prosopagnosia showed more grey matter loss bilaterally in the temporal poles and anterior fusiform gyrus ($p < 0.001$, uncorrected). This association survived family-wise error correction ($p<0.05$) in the left-anterior fusiform gyrus (Supplemental Figure 3).

A diagnostic tree to identify rtvFTD

Based on the combination of the literature review and our data, we summarized the core and supportive symptoms of rtvFTD and prepared a diagnostic tree including clinical and radiological features of rtvFTD and amyloid status (Figure 4). To validate the proposed algorithm, sensitivity and specificity analysis for rtvFTD was performed against the background of the non-rtvFTD syndromes of bvFTD, svPPA, and AD. The sensitivity value of the presence of 2 or more core symptoms (prosopagnosia, memory deficit, and behavioural changes) was 81% whereas the specificity value was relatively low (75%). The core symptoms distinguished rtvFTD from svPPA and AD while approximately half of the bvFTD subjects met the core symptoms. However, when we added the supportive symptoms such as language problems and depression, the specificity value increased to 88% at the cost of sensitivity. Moreover, when the neuroimaging and negative amyloid status were taken into account, we reached a specificity of 100% of the characteristics of rtvFTD (Figure 4).

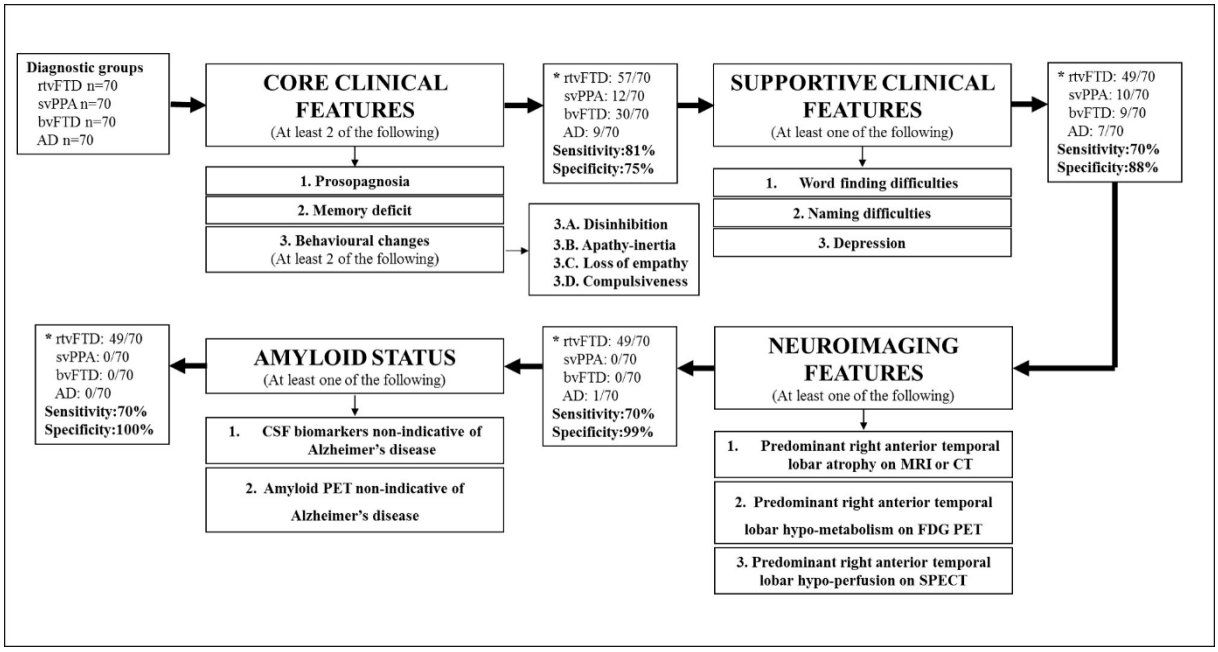

Figure 4: A diagnostic tree to identify rtvFTD. *Number of the subjects who met the proposed criteria. AD = Alzheimer's disease.

DISCUSSION

In this large systematic, retrospective study, we identified a uniquely large cohort of patients with right temporal variant FTD based on brain atrophy pattern and set out to determine their clinical profile. Furthermore, we investigated overlapping and distinguishing clinical features of rtvFTD compared with svPPA, bvFTD, and AD. We also studied the imaging phenotype of rtvFTD in more detail using VBM analysis and compared it with svPPA, the radiological differential diagnosis of rtvFTD. Prosopagnosia, episodic memory impairment and behavioural problems such as disinhibition, apathy, loss of empathy and compulsiveness were the most prominent initial symptoms of rtvFTD, whereas language ability was relatively spared initially, unlike in svPPA. During the progressive disease course, language problems such as word finding difficulties and anomia became the main features of the disease. None of the current diagnostic criteria for bvFTD or svPPA fitted rtvFTD. VBM analysis revealed, apart from predominant right anterior temporal atrophy, involvement of the left temporal and the right ventral frontal areas. Notably, it exhibited a radiological mirror image of svPPA. Additionally, the temporal poles and the anterior fusiform gyrus – especially on the left-side – were associated with prosopagnosia in rtvFTD.

Prosopagnosia was the most unique symptom of rtvFTD. This result is consistent with expectations, as the relationship between prosopagnosia and right temporal lobe involvement has been described frequently (5,6,8,12,14,37,38). Thompson et al. (2003) reported

prosopagnosia in 10 out of 11 cases with a right> left temporal atrophy (4), whereas Chan et al (2009) reported prosopagnosia in 60% (12 out of 20 cases) of patients with rtvFTD (5). A possible explanation for this discrepancy is that impaired face recognition may not be mentioned as a specific problem by the patients and caregivers and specific tests for face recognition are usually not performed in general practice. Since it is not a clinical feature in one of the current diagnostic criteria for svPPA, bvFTD, and AD, it might also easily be neglected by physicians.

Over the last 20 years, the general view has been that episodic memory processing is relatively intact in FTD (1,2). However, episodic memory deficit was one of the prominent presenting symptoms of rtvFTD, and its frequency increased up to 90% later on. Although Thompson et al. (2003) found memory problems in only 27.3% of the rtvFTD patients (4), episodic memory deficit has been highlighted as an initial symptom of rtvFTD in a number of clinical studies and case reports (5,7,8,12,38-40). Since the presence of amnesia remains a diagnostic exclusion criterion for FTD (1,2), the amnestic/prosopagnostic presentation of rtvFTD might easily be confused with AD in the early stages of the disease. It should be noted, however, that even though episodic memory deficit was one of the most common symptoms of rtvFTD, in the line with previous studies (41), we found that they showed better performance on memory tests than AD patients, however worse than healthy controls (RAVLT $p<0.001$). Whereas episodic memory processing in SD and bvFTD has been studied previously (42,43), the mechanism of episodic memory deficits in rtvFTD is still unknown.

Although disinhibition and apathy were the most common behavioural symptoms in both rtvFTD and bvFTD, in accordance with the findings of Kamminga et al. (2015), who compared clinical features between rtvFTD and bvFTD, we also found prominent language dysfunction and prosopagnosia in the rtvFTD group versus more severe executive dysfunction in bvFTD. Contrary to that study, revealing dietary changes as common in both disorders, in the present study these were initially less frequent in rtvFTD than in bvFTD. Compulsiveness was a distinct symptom observed frequently in both svPPA and rtvFTD. Another important result of our study was the loss of empathy, that was common in both rtvFTD and bvFTD, while it was relatively rare as a presenting feature in svPPA. This finding supports the argument that empathy is associated with the right frontotemporal areas (10,44,45). One of the striking results of our study was that at both initial and later stages, depression was observed more commonly in rtvFTD, with higher depression scores on the NPI than bvFTD.

In addition, in the line with previous studies, somatic complaints were observed prominently in rtvFTD at the follow-up visits as well as depression (5,6,8,14).

Overall, rtvFTD patients were more depressive, compulsive, somatic and they demonstrated pronounced deficits in face recognition and language, whereas patients with bvFTD exhibited disproportionate disinhibition, apathy and greater executive dysfunction. Nevertheless, the initial behavioural changes in rtvFTD can be a diagnostic issue, particularly in the early stages of the disease. Prosopagnosia and language problems distinguish rtvFTD from bvFTD and we suggest that the presence of predominant depression at the initial visit might also be helpful in differentiating the behavioural symptoms of rtvFTD and bvFTD.

Language disorder was one of the important features of rtvFTD. However, unlike svPPA, language problems in rtvFTD were not prominent in the early stages of the disease. Similar to other studies, the most common language problems were word-finding difficulties and anomia in rtvFTD (6,7,12,15,37) whereas the characteristic svPPA symptom such as single-word comprehension deficit was relatively infrequent in the rtvFTD versus the svPPA. The svPPA is traditionally seen as inherently tied to language and current diagnostic criteria have been updated from this perspective (1). Even though it has been acknowledged that language abilities are relatively spared in rtvFTD (5,7,8,15), the syndrome is still classified as the right sided semantic variant of progressive aphasias based on its atrophy pattern1. From a clinical perspective, this is incorrect, since language abilities can in fact be spared, in the context of prominent clinical features like behavioural abnormalities, memory and face recognition deficits.

Besides these core symptoms, hyper-religiosity (5,7-9,46), getting lost (5,7) and delusions (5) have been reported as symptoms associated with rtvFTD. Hyper-religiosity was a symptom reported by 4% of rtvFTD patients in our study. Even though this symptom has been described as almost pathognomonic in case reports (8,9,46), it has been reported only around 5-15% in the clinical studies (5-7) and it has also been observed in svPPA patients (4). In our study, hyper-religiosity was observed in both rtvFTD and svPPA, whereas neither bvFTD nor AD patients presented it. Chan et al. (2009) reported that getting lost was observed in 65% of patients in contrast to the low frequency (18%) of our study (5). An explanation of this discrepancy could be the exclusion of patients with positive amyloid pathology. Regarding delusions and visual hallucinations, although their prevalence increased during the disease course of rtvFTD, it was not a distinct symptom of rtvFTD as was suggested by Chan et al., (2009) (5).

On the other hand, motor/ mental slowness was a symptom in rtvFTD which was not recorded to the same extent in svPPA, bvFTD and AD. Since clinical studies and case reports have often focused on initial symptoms, “slowness” might not be mentioned as a symptom associated with rtvFTD in previous literature. However, a post mortem-based study has revealed that over the disease course, 35% of the rtvFTD patients developed parkinsonism (7). In addition, some studies have pointed out the relationship between rtvFTD and motor neuron disease as well as parkinsonism (47-52). Although some authors have suggested that rtvFTD and svPPA reflect the same pathophysiological process and converge clinically within 3 years from symptom onset (15), one longitudinal study has revealed the divergent progression pattern of these two related syndromes (17). Our results also show that rtvFTD patients might exhibit a different progression pattern than svPPA. As symptom duration at presentation and follow-up duration were comparable in rtvFTD and svPPA, this finding cannot be attributed to a hypothesised later presentation of rtvFTD.

Radiological characteristics of rtvFTD and comparison with svPPA

One of the key questions is whether these distinct clinical presentations have a distinct underlying atrophy pattern. To our knowledge, only three studies have assessed the atrophy pattern of rtvFTD systematically and the number of patients has been limited (n= 6-20) in these studies (5,16,17). In line with those studies predominant anterior temporal atrophy with a greater degree on the right side was the characteristic imaging pattern of rtvFTD. However, different from those studies we found that the ipsilateral ventral frontal areas were also affected in both rtvFTD and svPPA initially. On the other hand, one longitudinal study has found that atrophy in the later stages of rtvFTD can be observed in right orbitofrontal areas (17) whereas another study has argued that initial right anterior temporal atrophy is followed by subsequent involvement of the left temporal lobe to resemble patterns observed in svPPA (16). Although our study is not a longitudinal study, our results for the rtvFTD group showed involvement of both contralateral temporal and ipsilateral ventromedial frontal areas, in particular the inferior orbitofrontal lobe, areas which were also observed to be affected in the svPPA group. Even if rtvFTD and svPPA display a radiological mirror image initially, our results show that even in later clinical stages they do not have the same manifestation. Future studies combining longitudinal clinical and neuroimaging findings will be essential to further understand the disease course and large pathological studies will shed light on the pathophysiological basis of these related syndromes.

Clinico-radiological correlation of prosopagnosia in rtvFTD

There is a general agreement that right hemisphere damage is necessary for the occurrence of prosopagnosia (53,54), but disagreement exists about the role of the left hemisphere (55-57). A recent prospective VBM study has shown that face identification is positively associated with right anterior fusiform gyrus volume in FTD (58). However, in that study, only one patient had the right predominant temporal lobe atrophy characteristic of rtvFTD (58). Another VBM analysis in semantic dementia has revealed that the right anterior temporal pole, the right fusiform gyrus and the right medial temporal lobe were associated with prosopagnosia in patients with semantic dementia (59). Although our results are similar to those earlier findings, we observed that the left temporal lobe, in particular the temporal pole and the fusiform area, was also associated with prosopagnosia in rtvFTD.

Strengths and Limitations

Our study differs from the previous studies in one key aspect; this is the first large clinical case-control study that excludes patients with amyloid pathology and presents a small sample size of patients with genetic/pathologically verified frontotemporal dementia. However, there are some limitations that need to be addressed. First of all, the study was performed retrospectively and although symptoms were recorded systematically in our specialized memory clinic, some symptoms might have gone un-noticed because they were not specifically asked for. This might particularly be the case for the more uncommon symptoms, such as hyper-religiosity. Secondly, the initial visit was not the same moment in every patients' course of the disease. Some patients were referred from another hospital for a second opinion, whereas other patients had only been showing a few symptoms for a few months before the appointment. The other limitations were the lack of a specific cognitive test for face recognition, social cognition and missing data in cognitive tests and NPI ratings, due to change of test protocols in years. Lastly, since we performed a memory-clinic based study, all of the identified cases were symptomatic, and therefore, theoretically our sensitivity and specificity analysis of the clinical characteristics accompanying predominant right temporal atrophy might be an overestimation.

Clinical relevance

Neither the Gorno Tempini diagnostic criteria for PPA (1), nor the Rascovsky diagnostic criteria for bvFTD (2) cover the initial amnestic, prosopagnostic presentation of rtvFTD. RtvFTD is a unique progressive neurodegenerative disorder which has a distinctive cognitive,

behavioural and language profile and a characteristic atrophy pattern. To cover specific symptoms of rtvFTD, we prepared a diagnostic tree including the main characteristics of rtvFTD and tested its distinguishing accuracy among the various patient groups. Even though combining core and supportive symptoms decreased the sensitivity value, accompanying language problems and depression distinguished rtvFTD from bvFTD and this yielded a specificity of 88% of clinical characteristics of rtvFTD. Furthermore, it should be underscored that neuroimaging characteristics of rtvFTD distinguished it from other FTD spectrums whereas negative amyloid status was crucial for differential diagnosis of Alzheimer's disease. Therefore, the combination of amyloid status, clinical and radiological features yielded a 100% specificity. From a clinical point of view, the high specificity value implicates that when a patient presents with behavioural problems, the characteristic symptoms of rtvFTD such as prosopagnosia, depression and language problems should be examined. Following the clinical assessment, the right temporal lobe should be explored on neuroimaging, and diagnoses such as Alzheimer's disease should be rejected unless their amyloid status is highly indicative for Alzheimer's Disease. We hope that our framework will serve as a roadmap to identify these patients in a clinical setting. In the near future, multicentre studies will be needed to define diagnostic criteria for rtvFTD and establish their accuracy in prospective cohorts.

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SUPPLEMENTARY MATERIAL

Supplementary material 1

In this retrospective study, all case records were read and reported complaints were written down. Similar complaints were combined into one umbrella term based on similar meaning and/or cognitive/ behavioural domains and some symptoms were excluded based on authors consensus.

Symptom identification and classification (Based on patient/ caregiver history)

Cognitive	Language	Behavioural	Other	Excluded
Memory Problems; forgetfulness, poor memory, worsening memory, memory deficit, problems remembering dates/ places/ addresses/ events	**Word-finding difficulties;** trouble finding correct words during spontaneous speech, pay more effort to find correct word	**Disinhibition;** social awkwardness, inappropriate behaviour, loss of manners or decorum, agitation, impulsiveness, aggression, rash actions, childish puns and jokes, childishness	**Motor/mental slowness;** parkinsonism, rigidity, spasticity, pyramidal symptoms, extrapyramidal symptoms, mental slowness, mental rigidity, slowness, slow walking, falls	**Personality changes;** since this term covers several behavioural changes and it is not specific for a cognitive domain, we excluded this symptom
Prosopagnosia; poor memory for faces, face recognition deficit, difficulties remembering famous faces or familiar faces, difficulties recognising people on family photo album	**Single word comprehension difficulties;** difficulties understanding words, trouble understanding sentences due to lack of word meaning	**Compulsive behaviour;** obsessiveness, hoarding, storing materials, pacing, counting, touching, ritualistic behaviour, preoccupation, fixed-rigid ideas, repeating the same routine or stories, doing puzzles/jigsaws, obsessive gambling, playing same games, clock watching	**Hyper-religiosity;** increased religious ideas, hyper-spiritualism, excessive piety, changing beliefs with regard to religion, tending to read holy books, increased frequency of church visits	**Loss of insight, problems understanding, spontaneous speech alterations, grammatical mistakes;** since these symptoms are not core diagnostic symptoms of any diagnostic group, we did not display these symptoms
Executive dysfunction; poor judgement, impaired planning and organisation skills, disorganization	**Paraphasias;** literal, verbal, semantic paraphasias, using wrong words, neologisms	**Apathy or inertia;** Loss of interest or initiative, withdrawn, lack of energy or effort, lack of desire to learn new things or meet new people or have new experiences, emotionlessness, loss of creativity, carelessness, becoming introverted, flat affect	**Depression;** sadness, decreased mood, melancholia, suicidal ideas	**Motor restless, spending more/less money, mania, tiredness, sleeping problems, libido changes, utilization behaviour, perseveration, apraxia, concentration problems and concretism;** These symptoms were recorded in less than 20% in rtvFTD and none of them is a significant symptom for either rtvFTD (based on literature review) or one of the control groups. Therefore, they were not displayed.

Orientation problems; problems recognising time or place	**Naming difficulties;** poor memory for names, remembering difficulties the names of objects/ familiar countries/ cities/ streets	**Loss of empathy and egocentrism;** diminished response to other people feelings or needs, interrelatedness, diminished personal warmth, emotion recognition difficulties, selfishness, self-centeredness	**Delusions/ hallucinations;** False beliefs for things that did not happen, incorrect perceptions of objects or events involving the senses, visual or auditory hallucinations	
Getting lost; losing way, loss of knowledge about streets/ buildings/ neighbourhood, navigation problems		**Hyper-orality and dietary changes;** appetite changes, increase in appetite, decrease in appetite, seeks out food between meals, overeats at meal times, requests larger or second portion of food, reports hunger, reports being overfull, binge eating, needs to limit food intake, changing food preference (sweet, salt or obsessed with same food or developed other food fads), drinks more soft drinks/ tea/ coffee/ alcohol, obsessed with eating time/ schedule/ routine, loss of table manners, eating fast, eating with hands, increased smoking, loss of taste/ flavours, hyper-orality	**Somatic complaints and aches;** hypochondria, seeking medical help for headache/ muscle pain or other aches without physiological explanation	
Visio-spatial problems; problems in discriminating form and colour, inability to perceive contrast, difficulties in visual spatial orientation and motion detection, difficulties in developing visual strategies, inability to process visual sensory information			**Feeling of anxiety/ panic;** feeling anxious, scared, insecure and panic	

rtvFTD: right temporal variant frontotemporal dementia

Supplementary material 2

Validation of the purposed diagnostic tree

To validate proposed diagnostic features, sensitivity and specificity analysis was conducted in the diagnostic groups for each step (Table 1, 2, 3, 4). Details of the cases and diagnostic symptoms were displayed in table 5.

Table 1. Core symptoms (At least 2 of 3 core symptoms**)**

	rtvFTD Positive	**rtvFTD Negative**
Criteria Positive	81% (n=57)	24% (n=51)
Criteria Negative	18% (n=13)	75% (n=159)
Statistic	**Value**	**95%CI**
Sensitivity	81%	70.34% to 89.72%
Specificity	75%	69.34% to 81.35%
Positive predictive value	53%	46.19% to 59.27%
Negative predictive value	92%	88.16% to 95.26%

Table 2. Combination of core and supportive symptoms (At least 2 of 3 core symptoms and at least 1 of 3 supportive symptoms**)**

	rtvFTD Positive	**rtvFTD Negative**
Criteria Positive	70% (n=49)	12% (n=26)
Criteria Negative	30% (n=21)	88% (n=184)
Statistic	**Value**	**95%CI**
Sensitivity	70%	60.02% to 78.76%
Specificity	88%	79.98% to 93.64%
Positive predictive value	65%	54.56% to 76.10%
Negative predictive value	89%	85.60% to 93.90%

Table 3. Combination of clinical and radiological features (At least 2 of 3 core symptoms, at least 1 of 3 supportive symptoms and at least 1 of 3 neuroimaging features**)**

	rtvFTD Positive	**rtvFTD Negative**
Criteria Positive	n=49	n=1
Criteria Negative	n=21	n=209

Statistic	Value	95%Cl
Sensitivity	70%	60.02% to 78.76%
Specificity	99%	97.38% to 99.99%
Positive predictive value	98%	87.33% to 99.71%
Negative predictive value	90%	87.43% to 93.44%

Table 4. Combination of amyloid status, clinical and radiological features (At least 2 of 3 core symptoms, at least 1 of 3 supportive symptoms, at least 1 of 3 neuroimaging features and negative amyloid status**)**

	rtvFTD Positive	rtvFTD Negative
Criteria Positive	n=49	n=0
Criteria Negative	n=21	n=210
Statistic	**Value**	**95%Cl**
Sensitivity	70%	60.02% to 78.76%
Specificity	100%	98.26% to 100.00%
Positive predictive value	100%	
Negative predictive value	90%	87.49% to 93.47%

rtvFTD: right temporal variant frontotemporal dementia

Table 5. Details of the subjects and diagnostic symptoms

Diagnostic group	Core clinical features			Supportive clinical features	Fulfil diagnostic criteria
	Prosopagnosia	Memory deficit	Behavioural Changes		
rtvFTD	1		4	3	+
rtvFTD		1	2		
rtvFTD	1	1	1		
rtvFTD	1	1	2	1	+
rtvFTD		1	4	1	+
rtvFTD	1		2	1	+
rtvFTD		1	2	1	+
rtvFTD		1	2	1	+
rtvFTD		1	2	1	+
rtvFTD		1	2		

rtvFTD			4		
rtvFTD			4		
rtvFTD		1	2	2	+
rtvFTD	1	1	3	1	+
rtvFTD			4	1	+
rtvFTD			2	1	
rtvFTD		1	3		
rtvFTD			3	1	+
rtvFTD	1	1	2	1	+
rtvFTD	1	1			
rtvFTD			3	1	+
rtvFTD	1		3		
rtvFTD		1	1		
rtvFTD		1	2		
rtvFTD		1	1	1	+
rtvFTD		1	1	1	+
rtvFTD	1		4	1	+
rtvFTD	1	1	3	1	+
rtvFTD	1		3	1	+
rtvFTD	1		3		
rtvFTD			2	1	+
rtvFTD	1	1	3	3	+
rtvFTD	1	1	3	1	+
rtvFTD	1	1	3	1	+
rtvFTD	1	1	3	1	+
rtvFTD	1		2	1	+
rtvFTD	1	1	4	1	+
rtvFTD	1	1	2	1	+
rtvFTD	1		1	1	+
rtvFTD			3	1	+
rtvFTD	1	1	2	1	+
rtvFTD	1	1	2	2	+
rtvFTD	1		3	1	+
rtvFTD	1	1	3	2	+
rtvFTD		1	2		
rtvFTD		1		1	+
rtvFTD		1	1	1	+
rtvFTD	1		2		
rtvFTD		1	4	2	+
rtvFTD	1	1	3	1	+
rtvFTD	1			1	+
rtvFTD			2		
rtvFTD	1		3	1	+
rtvFTD	1	1	3	1	+
rtvFTD	1	1	2	1	+
rtvFTD		1	1		
rtvFTD		1	2		
rtvFTD		1	2		
rtvFTD	1		3	1	+
rtvFTD	1	1	2	1	+

rtvFTD	1		3	2	+
rtvFTD			1		
rtvFTD			3	2	+
rtvFTD	1	1	2		
rtvFTD			4	1	+
rtvFTD			3	1	+
rtvFTD	1	1	2		
rtvFTD	1	1	2	2	+
rtvFTD	1	1	2	1	+
rtvFTD	1		2		
svPPA	1		1	1	
svPPA	1			2	
svPPA				2	
svPPA				2	
svPPA	1			1	
svPPA			3	2	
svPPA				2	
svPPA				1	
svPPA				2	
svPPA	1		2	1	+
svPPA			2	1	
svPPA			2	1	
svPPA			1	2	
svPPA				2	
svPPA				1	
svPPA		1	1	2	
svPPA			1	2	
svPPA			3	2	
svPPA			1	1	
svPPA	1		1	1	
svPPA	1		1	1	
svPPA				1	
svPPA		1		1	
svPPA		1	2	2	
svPPA			2	2	
svPPA		1	1	2	
svPPA		1	3	1	
svPPA	1		1	1	
svPPA		1		2	
svPPA	1		1	1	
svPPA			2	2	
svPPA			1	1	
svPPA		1	1	2	
svPPA			2	2	
svPPA			2	1	
svPPA			2	2	
svPPA			2	2	
svPPA			2	2	

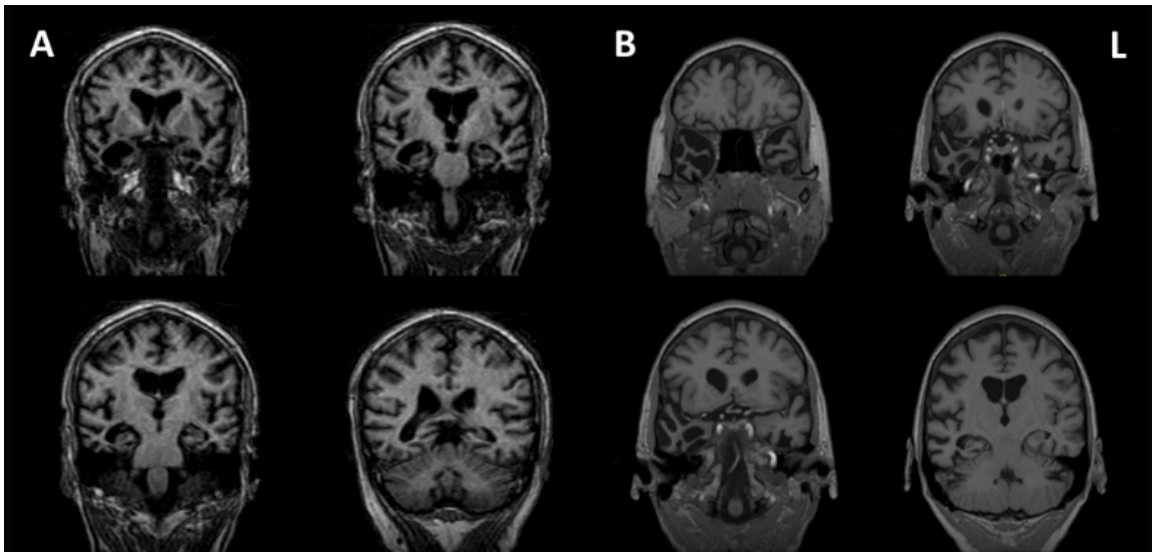
svPPA			1	2	
svPPA			2	1	
svPPA				1	
svPPA	1			1	
svPPA			1	2	
svPPA			2	2	
svPPA		1		2	
svPPA	1	1		2	+
svPPA		1	1	2	
svPPA		1	3	2	
svPPA		1	2	2	+
svPPA			3	1	+
svPPA				2	
svPPA				2	
svPPA			2	2	
svPPA			2	2	
svPPA		1		2	
svPPA		1	3	2	
svPPA	1	1	3	2	+
svPPA	1		4	2	+
svPPA	1	1		2	+
svPPA	1		1	1	+
svPPA			3	2	
svPPA			3	2	
svPPA			4	2	
svPPA		1	2	2	
svPPA	1	1	2	2	+
svPPA				2	+
svPPA				1	
svPPA				2	
svPPA				2	
bvFTD		1	2		
bvFTD			1	2	
bvFTD		1	1		
bvFTD			2	1	
bvFTD			4	1	
bvFTD		1	2		
bvFTD			2		
bvFTD			1		
bvFTD		1	4		
bvFTD		1	1	1	
bvFTD			3	1	
bvFTD			4	2	
bvFTD		1	2		
bvFTD			1		
bvFTD		1	3		
bvFTD			1	1	
bvFTD			1	1	
bvFTD		1	2		
bvFTD		1	2		
bvFTD			2	2	

bvFTD	1	1	2	1	
bvFTD		1	1		
bvFTD		1	3		
bvFTD		1	1	2	
bvFTD		1	1		
bvFTD			2		
bvFTD			3		
bvFTD			1		
bvFTD			3		
bvFTD		1	4	1	
bvFTD		1	3		+
bvFTD		1	1		
bvFTD			2		
bvFTD	1	1	3	1	
bvFTD		1	3		+
bvFTD		1	4		
bvFTD			2		
bvFTD			4		
bvFTD			2		
bvFTD		1	2	1	
bvFTD			2		
bvFTD			1	2	
bvFTD		1	2	2	
bvFTD			1	2	
bvFTD		1	2	1	+
bvFTD		1	3		+
bvFTD			4	2	
bvFTD		1	2		+
bvFTD			3		
bvFTD			2		
bvFTD			2	1	
bvFTD			3	1	
bvFTD			3		
bvFTD		1	2	1	
bvFTD			2		
bvFTD		1	2	2	
bvFTD			3	2	
bvFTD			4		+
bvFTD	1	1	3	1	
bvFTD		1	2		+
bvFTD			3	1	
bvFTD			3	2	
bvFTD		1	3		
bvFTD		1	3	1	
bvFTD			3	1	+
bvFTD		1	3	1	
bvFTD		1	3		+
bvFTD		1	2		
bvFTD			2		
bvFTD			2		

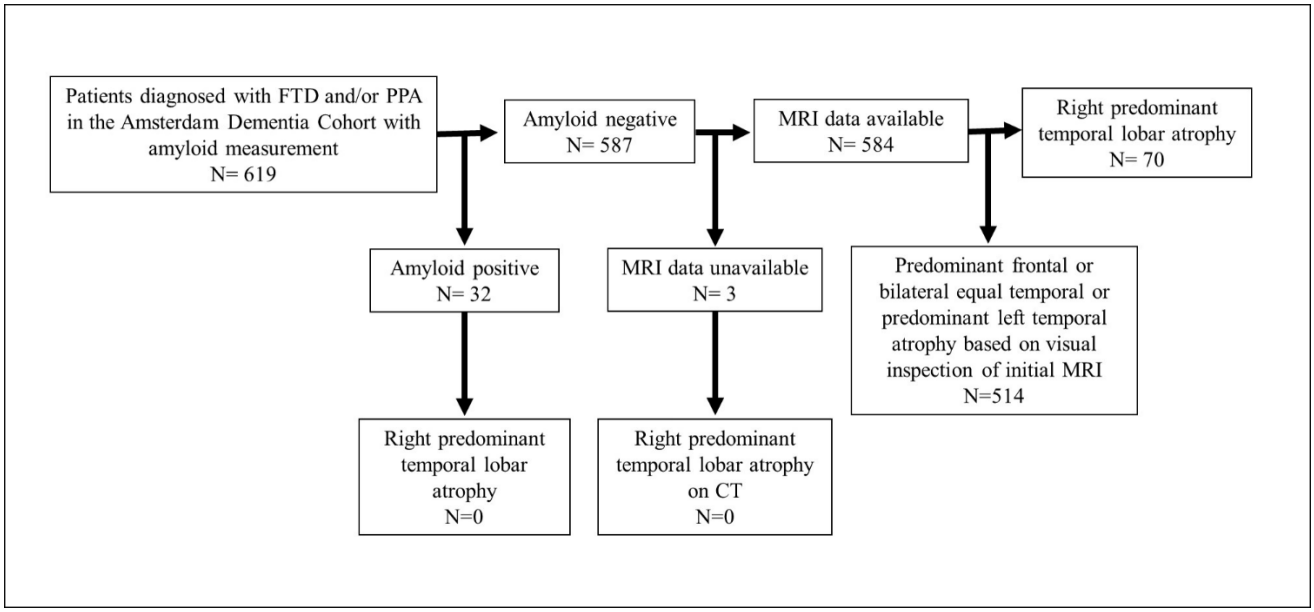
AD		1	1	3	
AD		1	1	3	
AD		1		2	
AD		1	2	2	+
AD		1	1	1	
AD		1			
AD		1			
AD			1	2	
AD		1	2	2	+
AD		1	1		
AD		1			
AD		1	1	1	
AD		1		1	
AD		1	1	2	
AD		1	1		
AD		1		2	
AD		1	1	3	
AD		1	1	2	
AD		1	2	2	+
AD		1		1	
AD		1		1	
AD		1	1	2	
AD		1	2		
AD		1		1	
AD		1	2	2	
AD		1		1	
AD		1	2	2	+
AD		1		3	
AD		1	1	3	
AD		1	2	2	+
AD		1	1	1	
AD		1		1	
AD		1	2		+
AD		1		1	
AD		1		1	
AD		1	2	2	+
AD		1	1	1	
AD		1		2	
AD		1	1	1	
AD		1		1	
AD		1		1	
AD		1		2	
AD		1		1	
AD		1		1	
AD		1	1	1	
AD		1	1	1	

AD		1		2	
AD		1			
AD		1			
AD		1		1	
AD		1		3	
AD		1			
AD		1		1	
AD		1		1	
AD		1		1	
AD		1	1	2	
AD		1		1	
AD		1		1	
AD		1		2	
AD		1	1	3	
AD		1	1	1	
AD		1		2	
AD		1		2	
AD		1		2	
AD		1		1	
AD		1		2	

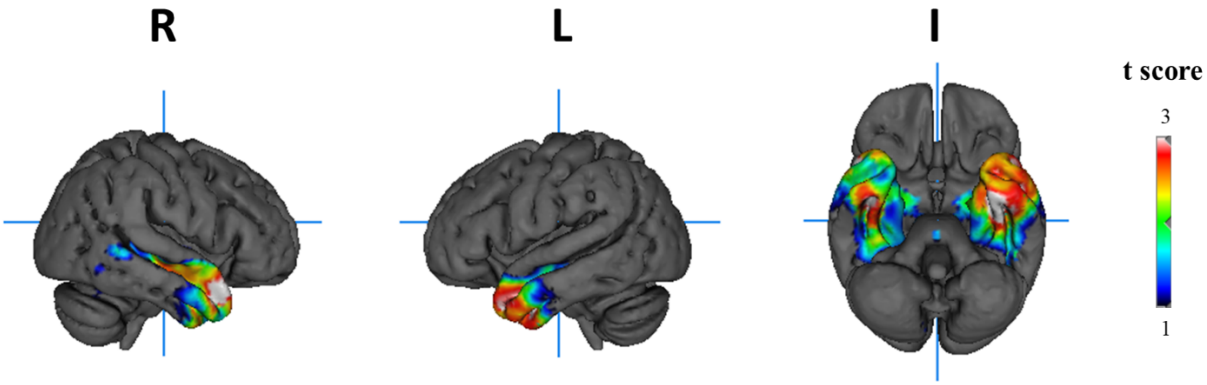
AD: Alzheimer's disease; bvFTD: behavioural variant frontotemporal dementia; rtvFTD: right temporal variant frontotemporal dementia; svPPA: semantic variant frontotemporal dementia



Supplemetary Figure 1: Right predominant temporal lobe atrophy, Not only mesial temporal atrophy (A) but also cortical temporal atrophy (B) was considered at visual inspection. L; Left



Supplementary Figure 2: Patient selection scheme. FTD: frontotemporal dementia; PPA: primary progressive aphasia



Supplementary Figure 3: 3D T-Maps of the radiological correlation of prosopagnosia in rtvFTD. R: right; L: left; I: inferior

CHAPTER 6

THE RIGHT TEMPORAL VARIANT OF FRONTOTEMPORAL DEMENTIA IS NOT GENETICALLY SPORADIC: A CASE SERIES

THE RIGHT TEMPORAL VARIANT OF FRONTOTEMPORAL DEMENTIA IS NOT GENETICALLY SPORADIC: A CASE SERIES

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Abstract

Right temporal variant frontotemporal dementia (rtvFTD) has been generally considered as a right sided variant of semantic variant primary progressive aphasia (svPPA), which is a genetically sporadic disorder. Recently, we have shown that rtvFTD has a unique clinical syndrome compared to svPPA and behavioral variant frontotemporal dementia.

We challenge the assumption that rtvFTD is a sporadic, non-familial variant of FTD by identifying potential autosomal dominant inheritance and related genes in rtvFTD.

We collected all subjects with a diagnosis of FTD or primary progressive aphasia who had undergone genetic screening (n=284) and subsequently who had a genetic variant (n=48) with a diagnosis of rtvFTD (n=6) in 2 specialized memory clinics.

Genetic variants in FTD related genes were found in 33% of genetically screened rtvFTD cases; including MAPT (n=4), GRN (n=1), and TARDBP (n=1) genes, whereas only one svPPA case had a genetic variant in our combined cohorts. Additionally, 4 out of 6 rtvFTD subjects had a strong family history for dementia.

Our results demonstrate that rtvFTD, unlike svPPA, is not a pure sporadic, but a heterogeneous potential genetic variant of FTD, and screening for genetic causes for FTD should be performed in patients with rtvFTD.

Keywords: Dementia, frontotemporal dementia, frontotemporal lobar degeneration, genetic, GRN, MAPT, right temporallobe, TARDBP

INTRODUCTION

Frontotemporal dementia (FTD) is a syndrome, caused by degeneration of the frontal and/or temporal lobes [1]. Patients with predominant behavioural disturbances and frontotemporal atrophy on neuroimaging are classified as behavioural variant FTD (bvFTD) [2] whereas the language predominant subtypes of FTD are classified under the umbrella of primary progressive aphasia (PPA) and have been associated with left hemisphere atrophy [3].

Over the years, the genetics of FTD have been broadly explored. The autosomal dominant inheritance pattern has been found higher in bvFTD, whereas semantic variant PPA (svPPA) is typically a non-familial sporadic disease [4-7]. Pathogenic variants are most common in the microtubule associated protein tau gene (MAPT), the progranulin gene (GRN) and a hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 gene (C9orf72), whereas a variety of rare pathogenic variants has been described as well [5].

Currently, diagnostic criteria for a variant of FTD presenting with behavioural changes, memory deficit and prosopagnosia in the presence of right temporal atrophy (rtvFTD) are lacking [8]. Because of the atrophy pattern, theoretically, rtvFTD is considered a right variant of svPPA [3, 9, 10] and the general assumption is that it is also a sporadic disease.

Only one study focusing on the underlying genetic and pathological features in rtvFTD, showed a positive family history in 45% of the patients with post-mortem diagnostic confirmation [11]. Thus, we set out to investigate whether rtvFTD could be potentially a genetic disorder.

METHODS

In this report, out of 636 patients from the Amsterdam dementia cohort (ADC) with a clinical diagnosis of bvFTD (n=450), non-fluent variant PPA (n=32), logopenic variant PPA (n=18), svPPA (n=65) and rtvFTD (n=71) (January 2000- November 2019)[12], we included 148 cases who had undergone genetic screening. Additionally, 136 FTD/ PPA patients with genetic screening from the Istanbul University dementia cohort (IUDC), (November 1999-January 2020)[13] were included (total genetically screened patients, n=284). Genetic screening was offered in case of a positive family history or when this was requested by the patient / caregiver. All included patients were screened for a variant in the GRN and MAPT genes. Additionally, a subset of patients was screened for the hexanucleotide repeat expansion in the C9orf72 gene (n=189) and/or the variants in other dementia genes with whole-exome

sequencing (WES) (n=77) (Supplementary material 1). In 48 patients, pathogenic variants or variants of unkown significance (VUS) [14] in the FTD related genes were identified and six out of them met the clinical and the radiological characteristics of rtvFTD [8] (Supplementary figure 1). Of note, in all subjects, the atrophy scores of the right temporal lobe [15-17] were higher (at least 1 grade) than the left temporal lobe and the frontal lobes that were assessed by a well experienced neuroradiologist who was blind to the clinical diagnosis (FB). Additionally, in our sample, the frontal atrophy scores were less than grade-1[16] and none of the subjects met the diagnostic criteria of svPPA [3], while all of the fulfilled at least 2 symptoms out of prosopagnosia, episodic memory impairment, and behavioural change [8], even if they had an accompanying left temporal atrophy on the initial MRI. All subjects gave their written informed consent for the use of their clinical and genetic data for research purposes. Details of the genetic and pathological assessment are reported in supplementary material 1.

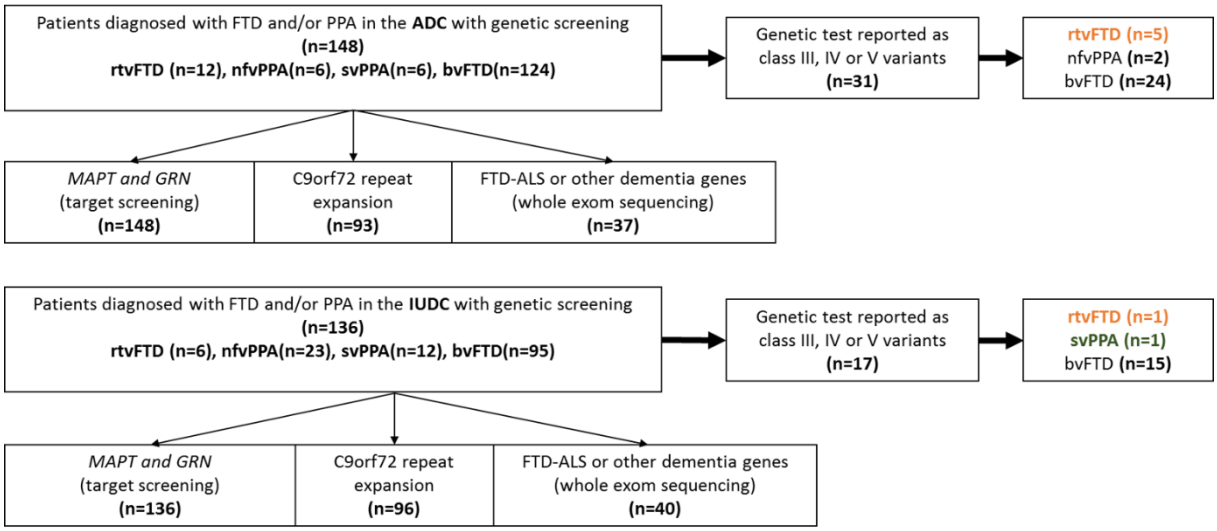

Figure 1: Patient selection

RESULTS

Demographic, clinical features are displayed in table 1 and detailed case histories are reported in supplementary material 2.

Table 1 Demographic and clinical data

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Institution	ADC	ADC	ADC	ADC	IUDC	ADC
Age (years)	59	64	58	53	63	58

Sex	Male	Female	Male	Female	Male	Female
Handedness	Right	Right	Right	Right	Right	Right
Symptom duration (years)	2	8	4	1	1	11
MTA (Right/Left)	4/1	4/2	2/1	3/2	4/2	3/1
PET	N.A.	N.A.	Right temporal hypo-perfusion	N.A.	N.A.	N.A.
Gene	GRN	MAPT	MAPT	MAPT	MAPT	TARDBP
Variant	Gln130Serfs*125	Ser305Thr	Ser352Leu	Arg406Trp	Pro301Leu	Ile383Val
Pathogenicity	Pathogenic [37]	Likely pathogenic [38]. *Other variants in this codon reported as pathogenic*[39-42]	Unknown significance [43]. *Heterozygous in our patient, homozygous in the reported patient*	Pathogenic [44].	Pathogenic [45].	Unknown significance [28-30]. *No data about pathogenicity in the reported patients*
Pathological confirmation	N.A.	N.A.	Suggestive for primary TAU mutation	N.A.	N.A.	N.A.
Modified Goldman Score	2	1	4	1	1	3
APOE	E3E3	E3E3	E3E4	E3E4	N.A.	N.A.
CSF, pg/mL*						
Aβ42	1073	1101	716	1270	N.A.	1574
Tau	326	353	717	512	N.A.	311
P-tau	38	54	70	80	N.A.	37
Cognitive Tests						
MMSE	26/30	28/30	23/30	28/30	29/30	29/30
FAB	16/18	-	14/18	18/18	N.A.	18/18
VAT-A				4/12	N.A.	10/12

RAVLT delayed recall	-	-	-	8/30	N.A.	22/30
VAT naming	12/12	12/12	10/12	12/12	N.A.	10/12
TMT A	41'' (A)	77,6'' (LA)	-	52'' (A)	N.A.	32" (A)
TMT B	88'' (A)	192,7'' (LA)	-	71'' (A)	N.A.	70" (A)
VOSP-Dot Counting	10/10	10/10	10/10	10/10	N.A.	10/10
VOSP-FL	20/20	20/20	-	19/20	N.A.	-

ADC: Amsterdam Dementia Cohort; IUDC: Istanbul University Dementia Cohort; MTA: Mesial temporal atrophy; PET: positron emission tomography; APOE: Apolipoprotein E; CSF : Cerebrospinal fluid; Aβ42: Amyloid βeta 42; P-tau: Phospho Tau; MMSE: Mini mental state examination; FAB: Frontal assessment battery; TMT: Trail making test; VAT: Visual association test; RAVLT: Dutch version of the Rey Auditory Verbal Learning Test; VOSP: Visual objective and space perception; FL: Fragmented letters; L: Low; VL: Very low; HA: High average; LA: Low average; A: Average. *: Cutoff value for CSF Aβ42 indicating Alzheimer's Disease pathology is < 550 pg/mL, Tau> 375 pg/mL, P-tau> 52 pg/mL.

In our combined cohorts, genetic variants in FTD related genes were found in 33% of genetically screened rtvFTD subjects (6 out of 18 genetically screened rtvFTD), whereas only one svPPA (1 out of 18 genetically screened svPPA) subject had a genetic variant.

Summary of the cases

Case 1: A 59-year-old male presented with behavioural problems, memory deficit, depression, topographagnosia and developed swallowing problems and mutism. The modified Goldman score[4] for family history was 2. We identified a heterozygous pathogenic variant in the GRN gene (NM 002087.3) c.388_391del, p.(Gln130Serfs*125).

Case 2: A 64-year-old female presented with prosopagnosia, behavioural changes, memory deficit, depression and developed topographagnosia and motor restless. The modified Goldman score[4] for family history was 1. We identified a heterozygous likely pathogenic variant in the MAPT gene (NM 005910.5) c.914G>C, p.(Ser305Thr).

Case 3: A 58-year-old male presented with behavioural changes, depression, memory deficits and developed prosopagnosia and atypical parkinsonism. The modified Goldman score[4] for family history was 4. We identified a heterozygous VUS in the MAPT gene (NM 005910.5) c.1055C> T, p.(Ser352Leu). In addition, extensive 3R and 4R tauopathy was reported in his autopsywhich is suggestive for a pathogenic mutation in the MAPT gene[18] (Fig. 2).

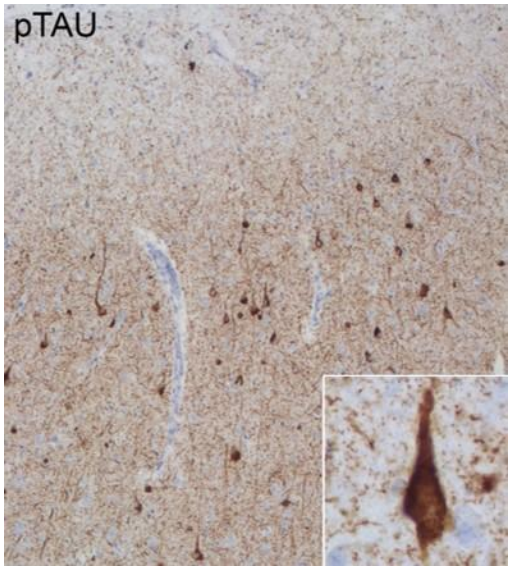

Figure 2: Pathological features of Case 3. Anterior cingulate cortex stained with phospho-tau (p-tau) monoclonal antibody (AT8: Pierce Biotechnology, Rockford, IL, USA). Extensive 3R and 4R tauopathy which is characteristic for *MAPT* related frontotemporal lobar degeneration is observed in neurons across all layers.

Case 4: A 53-year-old female presented with memory deficits, depression, apathy and developed anomia and several behavioural problems. The modified Goldman score[4] for family history was 1. We identified a heterozygous pathogenic variant in the MAPT gene, (NM 005910.5) c.1216C> T, p.(Arg406Trp).

Case 5 : A 63-year-old male presented with behavioural changes, prosopagnosia, anomia and single word comprehension deficit and developed topographagnosia. The modified Goldman score[4] for family history was 1. We identified a heterozygous pathogenic variant in the MAPT gene, (NM 005910.5) c.902C>T p.(Pro301Leu).

Case 6: A 58-year-old female presented with somatic and behavioural problems, memory deficit and motor restless. The modified Goldman score[4] for family history was 3. We identified a heterozygous VUS in the TARDBP gene, (NM007375.3) c.1147A>G, p.(Ile383Val).

DISCUSSION

RtvFTD and svPPA are generally considered sporadic, non familial variants of FTD. In our combined cohorts we can confirm that in svPPA rarely (~5%) class III-V genetic variants in FTD related genes are found. However, 33% of rtvFTD patients that were screened for genetic mutations in FTD genes had a genetic variant. Moreover these variants were in three different genes (MAPT, GRN and TARDBP). This demonstrates that rtvFTD patients, unlike svPPA, are a heterogenous group that should be screened for genetic mutations.

The genetic diagnosis of four out of six rtvFTD cases was FTLD-MAPT. Previous clinico-radiological studies have shown that FTLD-MAPT links to bilateral anterior temporal atrophy [19], which might include rtvFTD. Moreover, the relationship between rtvFTD and MAPT mutations has been previously reported [11].

Besides the MAPT gene, the association between rtvFTD with variants in the GRN gene has been confirmed in separate case reports [20-23]. In many cases with a variant in the GRN gene, the asymmetric atrophy extends to the parietal lobe, which was not the case in our patient. Our finding underscores the observation that a pathogenic variant status in the GRN gene may be associated with an asymmetric atrophy pattern [24, 25], which can also involve uniquely the temporal lobe.

Although TARDBP gene mutations have been described in sporadic and familial ALS in early studies [26, 27], it has subsequently been associated with FTD without ALS [28-33]. Additionally, the heterozygous variant of Case 6 has been reported in subjects with temporal variant FTD without ALS [28-30].

In our study, four out of six patients had a strong family history for dementia. In the literature, a positive family history was reported in 37.5% (15 out of 40) of patients with rtvFTD [combined Chan et al.[34] and Josephs et al. [11]]. This percentage is quite high compared to svPPA in which a suggestive family history is identified in less than 5% of patients [6, 35]

Nonetheless, it is still unknown whether rtvFTD and svPPA share the same pathophysiology. A recent GWAS metadata analysis [36] has revealed that the svPPA gene network is uniquely associated with TAR DNA binding protein 43 metabolism. From this perspective, accompanying tauopathy in rtvFTD resembles the heterogeneous pathophysiology of bvFTD, rather than svPPA. On the other hand, although C9orf72 is the most common worldwide cause of genetic FTD [5], it should be noted that this variant was not found either in our study or other rtvFTD cohorts [11, 34]. Therefore further research into the pathophysiological background of rtvFTD and how this relates to the other FTD subtypes is warranted.

In conclusion, currently, there is no consensus on whether rtvFTD is a mirror variant of svPPA or should be lumped with svPPA. Although reminiscent of svPPA, our findings show that rtvFTD, unlike svPPA, often has a genetic basis and the genetic variants are found in multiple genes. Therefore genetic screening is essential in patients with rtvFTD.

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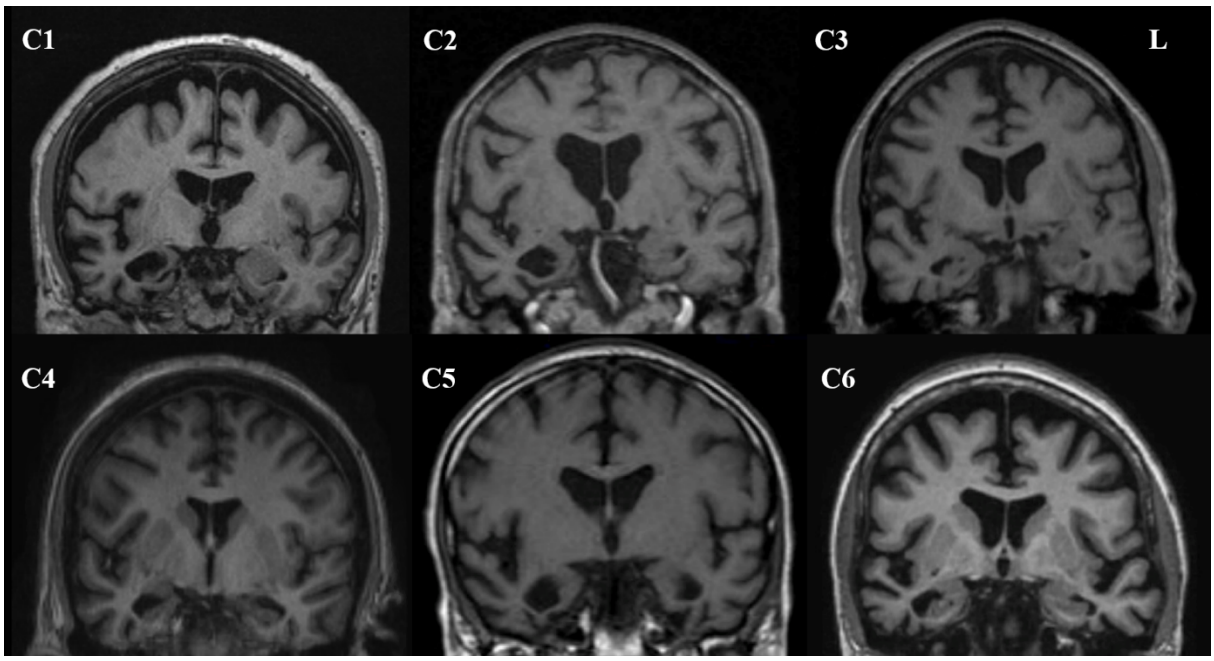
SUPPLEMENTARY MATERIAL



Supplementary Figure 1: Coronal sections of structural T1 weighted MRI scans of the patients. Right predominant temporal lobe atrophy. C1, C2, C4, C5, C6 show prominent right predominant temporal atrophy whereas C3 shows only marginal right sided temporal atrophy. L: Left

Supplementary material 1

Genetic Assessment

Amsterdam Dementia Cohort: Genomic DNA was extracted from peripheral-blood leukocytes according to standard procedures.

WES was performed. DNA was enriched using the SeqCap capturing kit for Illumina Paired-End Sequencing library (version 2.0.1; NimbleGen). The captured fragments were purified, and sequenced on an Illumina Hiseq4000 platform using 100 bp paired-end reads. The average coverage of the exome is ~50x with a minimum depth of >30 reads. Duplicate reads were excluded. Data were demultiplexed with bcl2fastq Conversion Software from Illumina. All sequence reads were mapped to GRCh37/hg19 reference genome using Burrows-Wheeler Aligner (BWA) Tool. GATK was used for variant calling and quality control according to best practice [46]. Population database frequencies (gnomAD v2.1.1), functional and impact-score annotations were assigned to variants using ANNOVAR [47]. The WES data was analysed with Alissa Interpret software from Agilent. Additionally, Multiplex Ligation-dependent Probe Amplification (MLPA) analysis was performed for APP (SALSA P170 APP; MRC Holland) and PSEN1 (SALSA P254 PSEN1; MRC Holland). For C9orf72 a repeat expansion test was performed (commercial kit Asuragen® AmplideX PCR/CE).

Istanbul University Dementia Cohort: Genomic DNA was isolated from the collection of 2 ml venous blood in K3EDTA tubes by kit (MagNA Pure Compact Nucleic Acid Isolation Kit-Large Volume; Roche). Primers were designed to cover all coding exons and exon-intron boundaries of MAPT (NM_005910.5), GRN (NM_000512.4). Sequencing primers are available from the authors upon request. Sanger sequencing reaction was performed on

capillary electrophoresis (ABI 3130) and analyzed using SeqScape software version 2.7 (Applied Biosystems, Bedford, MA, USA).

Pathological assessment- Amsterdam Dementia Cohort

Pathological assessment was available for only one case (Case 3). Comprehensive neuropathological assessments were performed following previously described standard procedures for the evaluation of frontotemporal dementia [48]. The neuropathological diagnosis of FTLD [49] and FTLD-MAPT [18] was made using standard criteria.

List of genes causing or associated with FTD, FTD-ALS or other early-onset dementias, investigated by whole exome sequencing or targeted high-throughput panel sequencing (Alzheimer Dementia Cohort)

ALS2: Amyotrophic lateral sclerosis 2

ANG: Angiogenin

APOE: Apolipoprotein E

APP: Amyloid Beta Precursor Protein

ATP7B: ATPase activity, 7 distinct domain, and B class for second P-type ATPase copper binding pump

C19orf12: Chromosome 19 Open Reading Frame 12

C9orf72: Chromosome 9 open reading frame 72

CCNF: Cyclin F

CHCHD10: Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10

CHMP2B: Chromatin-modifying protein 2B

CLN3: Ceroid Lipofuscinosis Neuronal Protein 3

CLN5: Ceroid Lipofuscinosis Neuronal Protein 5

CSF1R: Colony Stimulating Factor 1 Receptor

CTSD: Cathepsin D

EIF4G1: Eukaryotic Translation Initiation Factor 4 Gamma 1

ERBB4: Tyrosine-protein kinase erbB-4

GRN: Progranulin

FUS: Fused in sarcoma

HNRNPA1: Heterogeneous nuclear ribonucleoprotein A1

HNRNPA2B1: Heterogeneous Nuclear Ribonucleoprotein A2/B1

HTRA1: HTRA serine peptidase 1

ITM2B: Integral membrane protein 2B

MAPT: Microtubule associated protein tau

NOTCH3: Notch homolog 3

NPC1: Intracellular cholesterol transporter 1

NPC2: Intracellular cholesterol transporter 2

OPTN: Optineurin

PDGFB: Platelet derived growth factor subunit B

PPT1: Palmitoyl-protein thioesterase 1

PSEN1: Presenilin 1

PSEN2: Presenilin 2

SOD1: Superoxide dismutase 1

SQSTM1: Sequestosome

TARDBP: TAR DNA binding protein

TIA1: T-cell-restricted intracellular antigen-1

TBK1: TANK binding kinase 1

TREM2: Triggering Receptor Expressed On Myeloid Cells 2

UBQLN2: Ubiquilin 2

VCP: Valosin-containing protein

VPS13A: Vacuolar protein sorting-associated protein 13A

XPR1: Xenotropic And Polytropic Retrovirus Receptor 1

List of genes causing or associated with FTD, FTD-ALS or other early-onset dementias, investigated by whole exome sequencing or targeted high-throughput panel sequencing

(Istanbul University Dementia Cohort)

APOE: Apolipoprotein E

APP: Amyloid Beta Precursor Protein

C9orf72: Chromosome 9 open reading frame 72

CHCHD10: Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 10

DCTN1: Dynactin Subunit 1

GRN: Progranulin

MAPT: Microtubule associated protein tau

PSEN1: Presenilin 1

PSEN2: Presenilin 2

SNCA: Synuclein Alpha

SNCB: Synuclein Beta

SOD1: Superoxide dismutase 1

TREM2: Triggering Receptor Expressed On Myeloid Cells 2

UBQLN2: Ubiquilin 2

TUBA4A: Tubulin Alpha 4a

VPS13A: Vacuolar protein sorting-associated protein 13A

Supplementary material 2

Case 1: A 59-year-old, right-handed male presented with a 2 years history of progressive personality change including sadness, losing initiative and aggressiveness. He was unaware of his mental symptoms and denied them. Moreover, he had developed memory problems and started getting lost in routine surroundings.

A year after the initial visit he did not feel the urge to finish projects like translations for his work and became less empathic. He had signs of disinhibition such as getting angry about the smallest things and drinking alcohol at the same speed as lemonade. His short- term memory was getting worse, he was disoriented in time and place, and lost his overview for administration and his self-care.

His father and maternal grandfather were diagnosed with vascular dementia at the age of 83 and 74, respectively. His mother had dystonia of her feet and she was suffering from memory deficits at the age of 76. Both his mother and maternal grandfather had behavioural problems. The patient's 32 years old son had memory deficits and disorientation problem and his 31 years old daughter also had memory deficits, additionally she consumed alcohol excessively (Table 1).

The neurological examination was normal, and the neuropsychological examination showed deficits in memory and learning ability at the initial visit. Levels of CSF amyloid-beta 42, total tau and phospho-tau were within normal limits [50] (Table 1). The MRI revealed asymmetric cortical atrophy of the temporal lobes including strongly asymmetric right over left MTA [15] (Table 1). No vascular abnormalities were detected (Fig. 1). Genetic testing

showed a heterozygous pathogenic variant in the GRN gene (NM 002087.3) c.388_391del, p.(Gln130Serfs*125).

Approximately 5 years after from the initial visit he became bedridden. He had severe mutism and swallowing problems.

Case 2: A 64-year-old, right-handed female presented with a 8 years history of behavioural changes and memory deficit. Since the death of her husband eight years before, she had suffered from a headache that grew worse over the years and it made her dominantly sad. She sold their own restaurant one year after the death of her husband because she couldn't manage it. She gradually showed less initiative and became more depressive. Subsequently, her self-care concerning clothing diminished. After a few years, memory problems emerged, while she started to exhibit compulsive eating, disinhibition, and changes in social conduct. The patient presented also compulsive symptoms such as living with a fixed time schedule and walking several miles every day. She had difficulty recognizing family members with some additional problems recognizing objects.

Her brother and aunt were diagnosed with FTD and 4 sisters were diagnosed with presenile dementia (Table 1).

At the initial visit the neurological examination was normal, except for remarkable aprosodia. The neuropsychological examination revealed mild deficits in cognitive functions. She had a high distractibility and less overview. CSF amyloid-beta 42, total tau and phospho-tau were normal (Table 1). Her MRI showed asymmetric atrophy of the temporal lobes in both cortical and mesial temporal areas (Table 1, Fig. 1). Additionally, partly confluent white matter hyper-intensities were reported on T2 and FLAIR scans. Genetic testing showed a heterozygous predicted likely pathogenic variant in the MAPT gene (NM 005910.5) c.914G>C, p.(Ser305Thr).

Upon clinical follow up her symptoms gradually declined. She got lost in her neighbourhood with orientation problems. She did not know how to set the table and ate quickly without manners. She had stereotypical speech, echolalia and apraxia. Her cognitive problems worsened in 10 years after the initial symptoms and she was taken to a nursing home.

Case 3: A 58-year-old, right-handed male, presented with a 4 years history of depression, panic, aggression, social withdrawal and progressive memory problems. At the initial visit, loss of initiative and excessive daytime sleepiness were prominent as well. Over the next year, he became obsessed with schedules. Moreover, he played golf every day and he was obsessive to become the best golf player in the Netherlands. Over the consecutive months, his cognitive decline progressed. He had periods with excessive money spending. His self-care declined, and he lived for 12 days without showering. He became more childish, disinhibited, egocentric and he was not aware of his symptoms. He was suffering from a various physical pains that was interpreted as hypochondria and he developed prosopagnosia.

The family history showed no dementia, but his mother attempted suicide.

His neurological examination was normal, whereas the neuropsychological tests showed episodic memory problems at the initial visit (Table 1). The MRI showed marginal atrophy in the parietal and frontal areas as well as in the temporal lobes. Even though the initial MRI

showed marginal atrophy on the right side, (Table 1, Fig. 1) the 18F-FDG PET showed isolated hypo-metabolism in the right temporal lobe. Genetic analysis revealed a heterozygous variant of unknown significance in the MAPT gene (NM 005910.5) c.1055C> T, p.(Ser352Leu). This variant has previously only been described in homozygous state in two siblings with FTD. Because no second (pathogenic) variant was found in the MAPT gene, the clinical significance of this (heterozygous) variant in our patient is unclear.

Three years after his initial symptoms he was completely dependent in daily living activities, had less spontaneous speech and he progressed with a neuroleptic related tremor and tardive dyskinesia. He died 8 years after the initial visit. Post-mortem pathological examination revealed distinct asymmetric right-sided frontotemporal atrophy and extensive 3RD and 4RD taupathy, also in glial cells. There were no Pick bodies. The pathological features were suggestive for a pathogenic variant in the MAPT gene (Fig. 2).

Case 4: A 53- year-old, right-handed, female, presented with a 1-year history of episodic memory deficit. Mainly, she had problems with remembering names and events. She was working as a speech therapist and she did not concern herself as a patient. According to her colleagues and her husband, she became more depressive and less initiative. At the first year follow up, her short-term memory was reduced, and she became stubborn to go outside and cycle faster and faster every day. Her colleagues complained about her behavioural changes. Due to conflict of labour, she became unemployed which made her more depressive. Over the consecutive months, her memory deficit progressed, and naming problems occurred. At the following visit, she was less emphatic, insecure and fixed in time and schedule.

Her family history was positive for dementia. Her mother and 4 brothers were diagnosed with dementia between the age of 50 and 60. Additionally, her cousin and niece were diagnosed with dementia at the early ages.

Except left sided torticollis, her neurological examination was normal. Cognitive tests revealed a moderate learning and memory deficit at the initial visit. CSF amyloid-beta 42, total tau and phospho-tau were normal (Table 1). MRI showed bilateral temporal atrophy; right greater than left (Fig. 1, Table 1). Genetic analysis revealed a pathogenic variant in the MAPT gene, (NM 005910.5) c.1216C> T, p.(Arg406Trp).

Her follow-up continues and currently, she is relatively independent in her daily activities.

Case 5: A 63-year-old, right-handed male was referred to our clinic due to a 1-year history of behavioural changes. These consisted of mainly socially inappropriate behaviour. He had become rude and argumentative in the family and social settings. He was neglectful towards the feelings of his family members and showed no accustomed restraint in dealing with unfamiliar people. He had become gluttonous, indulging in sweet fads, and consuming an excessive amount of jam. One year after his initial symptoms, he developed prosopagnosia and experienced language problems, such as single-word comprehension deficit and object naming.

His family history was positive for dementia. He was the third of the five children of non-consanguineous parents. His father was demented when he died in his early 60s. No further information was available about the dementia profile. A nephew was reported to suffer from an early onset behavioural and memory impairment, and one niece died at the age of 57 after the clinical onset of similar symptoms at the age of 50.

Neurologic examination revealed subtle motor signs, such as Myerson's sign, mild axial rigidity, and reduced left-arm swing. His MMSE score was 29/30. His initial mental status examination showed problems in complex attention, as evidenced by reduced digit span, impaired serial recitations, and increased Stroop interference time, and he gave concrete interpretations to several common proverbs. His linguistic skills were intact, including single-word comprehension and visuoperceptual skills were also intact, including famous face recognition. Otherwise, he had no problems with memory, language, and navigational skills, and his usual activities of daily living (ADLs) were mostly intact.

The MRI showed marked anterior temporal atrophy; right greater than left (Fig. 1). Genetic analysis revealed a pathogenic variant in the MAPT gene (NM 005910.5) c.902C>T p.(Pro301Leu).

The patient had a 4 years follow-up in our clinic up until shortly before his death. Over the years, as the behavioural problems worsened, familiar face recognition, and single-word comprehension problems appeared in parallel. Once, his wife was astonished to hear the patient asking what a “ball” could mean. These problems were reflected in the patients' declining performance in tests of confrontation naming, verbal fluency, semantic memory, and familiar face recognition. During the second part of his follow-up, his navigational skills started to be impaired, and he was lost several times in the environment as he attempted to wander around in inappropriate times and with inappropriate attire. He was incontinent, and behavioural disinhibition stood as the major problem disrupting the ADLs towards the end. Initial motor signs did not evolve any further.

Case 6: A 58-year-old, right-handed, female presented with behavioural problems and memory deficit. According to patient’s husband, the problems started 11 years ago. She had withdrawn socially and had increasingly focused on physical complaints. There had been several therapies and diagnoses like fibromyalgia, but no one really could help her and no real diagnosis had been made inspite of her excessive medical help seeking. Ten years after her initial problems, she became more egocentric and she started to repeat same routine, for instance cooking the same food three times a week and obsessed with baking. She was still suffering from severe pain and she had to lie down, even this happens in the middle of the street. Preoccupation with her body and health was continuing and she had several treatments such as supplements and ozone therapy. She was no longer able to remember the recent events easily and had problems to manage and organise her life. Over the consecutive months, she became addicted with jigsaw puzzles and had difficulties sleeping and sitting due to motor restless.

Family history was not strong for dementia. Her grandfather was diagnosed with dementia at the age of 72 however the type of dementia is unknown. Her brother was diagnosed with autism spectrum disorder and had drugs and alcohol abuse.

The neurological examination was normal. Cognitive tests revealed a moderate memory deficit. CSF amyloid-beta 42, total tau and phospho-tau were normal (Table 1). MRI showed bilateral temporal atrophy; right greater than left (Fig. 1, Table 1). Genetic analysis revealed a heterozygous variant of unknown significance in the TARDBP gene, (NM007375.3) c.1147A>G, p.(Ile383Val).

She has been diagnosed with FTD recently and she is still under our follow-up. Currently, she is relatively independent in her daily activities.

CHAPTER 7

RIGHT TEMPORAL VARIANT FRONTOTEMPORAL DEMENTIA IS PATHOLOGICALLY HETEROGENEOUS: A CASE-SERIES AND A SYSTEMATIC REVIEW

RIGHT TEMPORAL VARIANT FRONTOTEMPORAL DEMENTIA IS PATHOLOGICALLY HETEROGENEOUS: A CASE-SERIES AND A SYSTEMATIC REVIEW

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Abstract

Although the right temporal variant frontotemporal dementia (rtvFTD) is characterised by distinct clinical and radiological features, its underlying histopathology remains elusive. Being considered a right-sided variant of semantic variant primary progressive aphasia (svPPA), TDP-43 type C pathology has been linked to the syndrome, but this has not been studied in detail in large cohorts. In this case report and systematic review, we report the autopsy results of five subjects diagnosed with rtvFTD from our cohort and 44 single rtvFTD subjects from the literature. Macroscopic pathological evaluation of the combined results revealed that rtvFTD demonstrated either a frontotemporal or temporal evolution, even if the degeneration started in the right temporal lobe initially. FTLD-TDP type C was the most common underlying pathology in rtvFTD, however, in 64% of rtvFTD, other underlying pathologies than FTLD-TDP type C were present, such as Tau-*MAPT* and FTLD-TDP type A and B. Additionally, accompanying motor neuron or corticospinal tract degeneration was observed in 28% of rtvFTD patients. Our results show that in contrast to the general assumption, rtvFTD might not be a pure FTLD-TDP type C disorder, unlike its left temporal counterpart svPPA. Large sample size pathological studies are warranted to understand the diverse pathologies of the right and left temporal variants of frontotemporal dementia.

Keywords: dementia; frontotemporal lobar degeneration; frontotemporal dementia; right temporal lobe atrophy; semantic dementia; pathology; FTLD-TDP; tauopathies

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder that predominantly affects the frontal and/or temporal lobes. It is subdivided into three different prototypic subtypes; semantic dementia (SD), progressive non-fluent aphasia (PNFA) and behavioural variant frontotemporal dementia (bvFTD) [1]. In 2011, consensus clinical diagnostic criteria were revised and FTD was classified as behavioural variant [2] whereas SD, PNFA and logopenic variant primary progressive aphasia (PPA) were classified under the umbrella of PPA [3]. On the other hand, a number of studies reported a separate syndromic variant that predominantly affects the right temporal lobe (rtvFTD), usually accompanied by behavioural changes, memory deficit and prosopagnosia [4-9]. While rtvFTD cannot formally be considered a PPA variant due to the absence of aphasia, there have been reports of rtvFTD presenting with non-verbal semantic deficits[10] and neuro-radiological studies have shown mirror image findings, suggesting that they might reflect the same pathophysiological process, albeit on opposite sides [3, 11-13]

Pathological examination plays a key role in understanding the nature of the diseases. Unsurprisingly, the neuropathology underlying clinical FTD is also heterogeneous [14]. The term frontotemporal lobar degeneration (FTLD) is used to encompass pathological conditions that present as clinical FTD. FTLD has been classified into four main groups based on the major proteins accumulation in the brain: tau protein (FTLD-tau); TAR DNA-binding protein 43 (FTLD-TDP); ubiquitin positive, TDP-43 negative and immunopositive for the fused in sarcoma protein (FTLD-FUS); and a remaining group encompassing the few cases characterized by inclusions that label only for markers of the ubiquitin proteasome system (FTLD-UPS) or no inclusions [15]. Based on the morphology and cortical distribution of the accumulation, the two main groups (FTLD-tau and FTLD-TDP) have been subdivided; Pick's disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP),

argyrophilic grain disease (AGD), globular glial tauopathy (GGT) and FTD caused by microtubule association protein tau (MAPT) for FTLD-tau [15-18] and the subtypes A, B, C, D and E for FTLD-TDP [19]. These pathological subgroups and their specific pathologies are linked to a number of clinical syndromes. Whereas clinico-pathological concordance is generally weak, particularly for bvFTD, a strong clinicopathological concordance with the underlying FTLD-TDP type C pathology is present in svPPA [20-22].

Since rtvFTD is sometimes considered a type of svPPA [3, 11, 12], FTLD-TDP type C pathology has been linked to the syndrome [13]. Recently, we have described the different clinical progression patterns of rtvFTD and svPPA [9], leading to the question whether their underlying pathologies may differ. To our knowledge, only one post-mortem study has focused on the pathological characteristics of rtvFTD, highlighting the possible association of rtvFTD with underlying tau-pathology [7]. Therefore, we aimed to determine the range of FTLD molecular pathologies underlying the clinical syndrome of rtvFTD based on a combination of clinico-pathological data from the Amsterdam Dementia Cohort and a review of the literature.

METHODS

1. Patient selection

We identified all subjects diagnosed with FTD and/or PPA from the Amsterdam Dementia Cohort [23] recruited between 1994 and 2019 (n=669) who had a pathological confirmation of their clinical diagnosis (n=32) (Ethical approval protocol no: 2016.061). From this group, patients were selected who had a predominant right temporal lobar atrophy on the initial neuroimaging (n=5) (Supplementary Fig.1). In all rtvFTD subjects, the atrophy scores of the right temporal lobe [24-26] were higher (at least 1 grade) than the left temporal lobe and the frontal lobes, as assessed by an experienced neuroradiologist, blinded to the clinical diagnosis (FB). The visual rating scores are displayed in the results section (Table 1. Additionally, in

our sample, the frontal atrophy scores were less than grade-1[25] and none of the subjects met the diagnostic criteria of svPPA [3], while all fulfilled at least 2 symptoms out of prosopagnosia, episodic memory impairment, and behavioural change [9], and their clinical profile was in line with the previously reported rtvFTD case series [4, 7, 8], even if they had accompanying left temporal atrophy on the initial scan (Supplementary figure 1). Additionally, isolated right temporal lobar hypo-perfusion was reported in Case 1 on perfusion SPECT and isolated right temporal hypometabolism in Case 3 on FDG-PET imaging, in other centres before being referred to us.

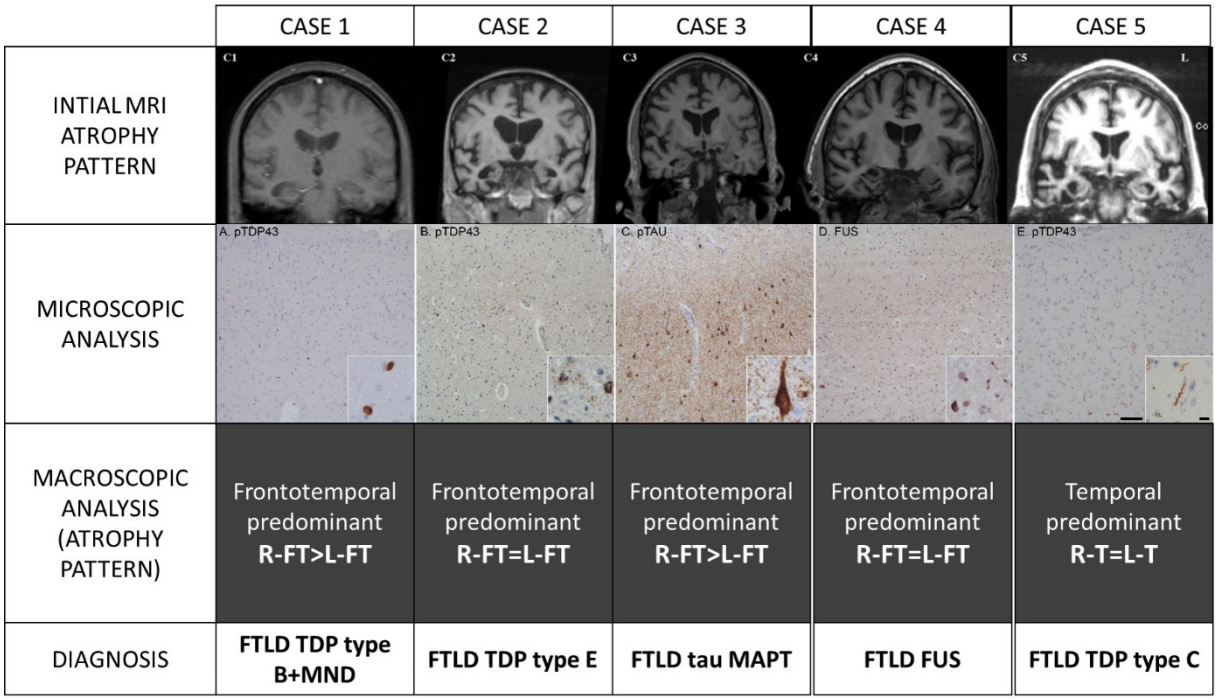

Figure 1: Different pathological diagnoses in donors with rtvFTD. The cases with rtvFTD displayed pathology from different pathological molecular subclasses in FTD. Although all pathological accumulations started from the right temporal lobe, according to the initial MRI atrophy pattern, over time the patients exhibited heterogeneous progression patterns. Case 1 showed FTD-TDP-B pathology with predominant neuronal inclusions throughout the cortical layers in right temporal lobe (a). Clinically, motor neuron disease developed over the disease course. Case 2 showed FTD-TDP-E pathology characterised by granulofilamentous neuronal inclusions (insert) and grains in right temporal lobe (b). The pathology spread to bilateral fronto-temporal areas. Clinically, this was accompanied by severe behavioural and language problems. Case 3 had tau-pathology with threads and tangles and some plaques (Anterior cingulate cortex: C, adapted from Ulugut Erkoyun et al.,2021, JAD, CC BY-NC 4.0). At the end stage of the disease, right predominant frontotemporal atrophy was observed based on the

macroscopic pathological examination. The clinical evolution involved the development of atypical Parkinsonism. Case 4 had large FUS-positive neuronal inclusions and FUS-positive threads (D: right frontal lobe), developed severe global atrophy at a clinical picture of becoming mutistic and bedridden in 4 years after diagnosis. Lastly, case 5 showed long dystrophic neurites characteristic for FTD-TDP-C (E: insular cortex) and developed bilateral temporal atrophy at the end stage of the disease, based on the pathological examination. This patient's clinical features were relatively benign, presenting with verbal and non-verbal semantic impairment and without the development of any motor disturbances and a disease duration of 12 years. Scalebar is 100 μm, scalebar insert is 10 μm

Table 1 Reclassification of the reported molecular neuropathologies

	Publications	**N**	**Reported molecular neuropathology**	**Adapted diagnosis**
1	(Miki *et al.*, 2019)	1	FTLD- TDP type C+ CTD	FTLD- TDP type C+ CTD
2	(Snowden *et al.*, 2019)	1	FTLD- tau-PSP+ TDP type A	FTLD- tau-PSP+ TDP type A
3	(Caplan *et al.*, 2018)	9	FTLD- tau-PiD (n=1) FTLD- TDP type C (n=8)	FTLD-tau-PiD (n=1) FTLD- TDP type C (n=8)
4	(Kim *et al.*, 2018)	1	FTLD- TDP type C+ tau- PSP	FTLD- TDP type C+ tau- PSP
5	(Kuuluvainen *et al.*, 2017)	1	FTLD- TDP type A	FTLD-TDP type A
6	(Koriath *et al.*, 2017)	1	FTLD- TDP type A	FTLD- TDP type A
7	(Wood *et al.*, 2016)	1	FTLD- tau-PiD	FTLD- tau-PiD
8	(Moreno *et al.*, 2015)	1	TDP-43 pathology in all cortical layers. NCI, with crescentic, round, skein-like and granular types. Short threads accompanied the NCI. Due to the admixture of neuronal cytoplasmic inclusion subtypes seen in FTLD-TDP type A and type B, presence of type A threads, but involvement of all cortical layers (type B), the pattern of TDP-43 inclusions is unclassifiable. Skein-like inclusions in lower motor neurons, producing the neuropathological diagnosis of motor neuron disease. Thal amyloid plaque stage 4, Braak 1. 4R-only atypical tauopathy	FTLD- TDP type A-B +AD+ 4R tau
9	(Clark *et al.*, 2015)	1	FTLD- tau-GGT	FTLD- tau-GGT

10	(Josephs *et al.*, 2013)	7	FTLD- TDP type C (n=1) FTLD- TDP type C+ CTD (n=6)	FTLD- TDP type C (n=1) FTLD- TDP type C+ CTD (n=6)
11	(Coon *et al.*, 2012)	2	FTLD- TDP Mackenzie type 3+ MND (n=1) TDP Mackenzie type 3+ MND+ AD (n=1)	FTLD TDP type B+ MND* FTLD TDP type B+ MND*+AD
12	(Lee *et al.*, 2012)	1	FTLD-FUS	FTLD- FUS
13	(Ostberg and Bogdanovic, 2011)	1	FTLD-TDP Mackenzie type 3+ MND	FTLD- TDP type B+ MND*
14	(Kelley *et al.*, 2010)	1	FTLD-TDP-43 pathology with NII	FTLD- TDP type A-B
15	(Kobayashi *et al.*, 2010)	1	FTLD- TDP Cairns type 2+ MND	FTLD- TDP type B+ MND*
16	(Kuwahara *et al.*, 2010)	1	Immunohistochemistry using antibodies to ubiquitin showed NCIs, some of these inclusions were also immunoreactive for phosphorylated TDP-43 antibodies. We identified no DN, but a few NCI, which were positive for both ubiquitin and phosphorylated TDP-43	FTLD- TDP type A-B+ MND*
17	(Chan *et al.*, 2009)	1	Mixed Alzheimer and cortical Lewy body disease (n=1)	AD+ DLB (n=1)
18	(Josephs *et al.*, 2009)	8	FTLD- tau- PiD (n=1) FTLD-tau-MAPT (n=7)	FTLD- tau- PiD (n=1) FTLD- tau-MAPT (n=7)
19	(Kelley *et al.*, 2009)	1	TDP-43 pathology with NII	FTLD- TDP type A-B
20	(Yoshida, 2009)	1	Tau-negative, TDP-43-positive neuronal cytoplasmic inclusions and dystrophic neurites were found. Numerous NFTs and senile plaques with amyloid angiopathy indicated advanced Alzheimer disease.	FTLD- TDP type A-B+ AD
21	(Davion *et al.*, 2007)	1	TDP43 pathology with NII+ MND	FTLD- TDP type A-B+ MND*

TDP: TAR DNA-binding protein 43; TAU: tau protein; MND: motor neuron disease; MAPT: microtubule associated protein; FUS: fused in sarcoma protein; PiD: Pick's disease; PSP: progressive supranuclear palsy; FTLD-U: frontotemporal lobar degeneration with tau-negative, ubiquitin-immunoreactive pathology; AD: Alzheimer's disease; DLB: dementia with Lewy bodies; NII: neuronal cytoplasmic and intranuclear inclusions.

*: Clinically diagnosed with MND

2. Clinical and neuropsychological assessment

All 5 rtvFTD subjects had been followed throughout their disease course by an experienced behavioural neurologist. The case notes of all rtvFTD subjects were scrutinized retrospectively. All initial and annual follow-up reports were reviewed by a senior behavioural neurologist (Y.P.) blinded to pathological information. Initial clinical symptoms were collected and family history of any neurodegenerative or psychiatric disease was recorded. The emergence of motor deficits (pyramidal or extrapyramidal) and progression to different clinical syndromes over the disease course was recorded. The following data were extracted of all subjects at the time of initial visit: Clinical Dementia Rating Scale (CDR) [27] and Mini Mental State Examination (MMSE) [28] as global measures, episodic memory [visual association test (VAT) A [29] and the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT)] [30], executive functions [Frontal assessment Battery (FAB) [31], trail making test (TMT) B [32] and digit span backward [33]], language [VAT naming [29]], attention [digit span forward [33] and TMT A [32]] and visuospatial functions [Visual Objective and Space Perception (VOSP)- Dot counting [34]].

3. Neuropathological analysis

Subjects were included from the Netherlands Brain Bank and department of pathology, Amsterdam UMC, location Vumc, where tissue was collected according to the local legal and ethical guidelines. All histological slides were re-examined according to the current classification system (A.A.D.) [15, 19]. All pathological examinations were conducted by an expert neuropathologist (A.R.) The pattern of FTLD-TDP pathology was classified into the five following subtypes; A, B, C, D and E [19, 35]. The pattern of FTLD-tau pathology was classified into the six following categories; PiD, PSP, CBD, GGT, AGD and FTD caused by MAPT mutations (tau-MAPT) [15, 18]. Co-existing pathological features such as Alzheimer's

disease (AD) [36], Motor neuron degeneration (MND) [37], corticospinal tract degeneration (CTD) [38] and dementia with Lewy bodies (DLB) [39] were recorded.

Details of the pathological examination are presented in supplementary material 1.

4. Systematic review

We conducted a systematic review following PRISMA guidelines [40] to identify the papers reporting pathological features of rtvFTD patients with available clinical and neuroimaging data (Supplementary material 2). The search was completed in December 2019 on two electronic databases; Pubmed and Embase. The following terms were used for the search: ("frontotemporal lobar degeneration" OR "frontotemporal dementia" OR "right temporal " OR "semantic dementia") AND ("pathology") NOT ("epilepsy" OR "tumor"). No filter was employed in the search. Titles and abstracts of the papers were screened according to the following eligibility criteria:

1. Original research, including case series and individual case reports.

2. Exclusion of review articles and animal studies.

3. Exclusion of reports with insufficient information.

Disagreements on eligibility were resolved through discussion among the authors (Supplementary material 3).

After detailed screening, 34 studies were eligible for systematic review. Patients with the following diagnoses "right temporal variant FTD", "right temporal variant semantic dementia", "right temporal variant svPPA", "bvFTD presenting with right temporal atrophy", "right temporal variant bvFTD", "FTD patient with right temporal atrophy", "right predominant semantic dementia" were included. Therefore, non-FTD clinical diagnoses such as amyotrophic lateral sclerosis (ALS) or atypical Parkinsonism were excluded. Of note, all

case notes and neuroimaging features were also re-assessed. If the left temporal or frontal atrophy was equal or higher than the right temporal atrophy, the subjects were not included. Furthermore, all studies were examined in detail to remove cases without TDP-43 staining and when case duplication occurred in, we selected the study from a particular institution/ cohort over a given period of time with the largest sample size. Thirteen studies were excluded based on the criteria mentioned above following author consensus (Supplementary material 3). This yielded a sample of 21 studies (n=44) which have defined the molecular pathology in the patients with predominant right temporal atrophy and a consistent clinical syndrome[4, 8, 9] (Table 2). The data from all 44 subjects were combined with our 5 rtvFTD subjects to analyse clinico-pathological associations in rtvFTD.

Table 2 Initial clinical features of the rtvFTD subjects

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
Age	58	68	59	59	63
Sex	male	male	male	male	female
Handedness	Right	Right	Right	Right	Right
Symptoms					
Prosopagnosia	√		√		√
Memory deficit	√	√	√	√	√
Disinhibition	√	√	√	√	
Apathy- inertia	√	√	√	√	√
Alexithymia			√	√	√
Bizarre preoccupations	√	√	√	√	√
Lack of logical reasoning	√	√	√	√	√
Pathological dwelling on one activity	√	√	√	√	√
Change of personal taste		√	√		
Nicotine/alcohol abuse		√			
Hyperalgesia			√	√	
Over sleeping during the day	√			√	
Word finding difficulties	√	√		√	√
Naming difficulties	√				√
Single word comprehension deficit					√
Depression	√	√	√	√	√
Slowness	√	√	√	√	

Motor restless				√	
Hyper-orality					
Diagnosis prior to autopsy	FTD+MND	FTD	FTD+ atypical parkinsonism	FTD	FTD
Family History	Father had psychiatric symptoms, sister had paranoid disorder	Two brothers and mother had dementia at the age of 70s with behavioural problems	Mother had psychiatric symptoms and attempt a suicide, uncle (maternal) had dementia at the age of 85	Father and brother had depression, son had ADHD	Mother attempt a suicide
MRI anterior temporal R/L	2/0	3/2	2/0	3/1	4/3
MRI mesial temporal R/L	3/0	4/3	2/1	4/0	3/2
MRI frontal R/L	1/0	1/1	1/0	1/1	1/0
SPECT/PET	Right temporal hypo-perfusion	N.A.	Right temporal hypo-perfusion	N.A.	N.A.
Genetic analysis	N.A.	N.A.	MAPT (+) Ser352Leu	N.A.	*MAPT* (negative) *PRGN* (negative) *C9orf72* (negative)
CDR	0.5	0.5	0.5	0.5	1
MMSE	27/30	25/30	23/30	22/30	25/30
FAB	N.A.	N.A.	14/18	18/18	14/18
VAT-A	N.A.	6/12	4/12	4/12	7/12
RAVLT delayed recall	N.A.	0/15	N.A.	12/15	N.A.
VAT naming	N.A.	N.A.	10/12	12/12	6/12
Digit span forward	N.A.	N.A.	12/16	13/16	8/16
Digit span backward	N.A.	N.A.	8/16	7/16	8/16
TMT A	N.A.	N.A.	57'' (A)	69'' (A)	49'' (A)
TMT B	N.A.	N.A.	169'' (LA)	166'' (LA)	102'' (A)
VOSP- Dot Counting	N.A.	N.A.	10/10	8/10	9/10

rtvFTD: right temporal variant frontotemporal dementia; bvFTD: behavioural variant frontotemporal dementia; svPPA: semantic variant primary progressive aphasia; MND: motor neuron disease; ADHD: attention deficit hyperactivity disorder; FTD; frontotemporal dementia, CDR; Clinical dementia rating, MMSE; mini-mental state examination, VAT; visual association test, RAVLT; Dutch version of the Rey Auditory Verbal Learning Test, FAB; frontal assessment battery, TMT; trial making test, VOSP; Visual objective and space perception, A; Avarage, LA; low average, N.A.; not available

Since the classification of the molecular neuropathology of FTD has been updated over the years, we adapted all reviewed pathology reports based on the current classification system and the subtype nomenclature used was that of the more recent harmonized classification system; FTLD-TDP type A = Mackenzie type 1/Sampathu type 3, type B = Mackenzie type 3/Sampathu type 2, type C = Mackenzie type 2/Sampathu type 1, type D = type 4 with VCP mutations [15, 35]. There was no correction for the FTLD-TDP type E diagnosis [19]. In a subset of cases, however available pathological data were insufficient to identify either TDP type A or B. These cases were denominated as TDP- A-B (Table 2).

RESULTS

1. Demographic and clinical data of our cohort

All Amsterdam cases were right-handed. The rtvFTD group comprised 4 male and 1 female patients. Demographic data, detailed clinical symptoms and cognitive test results are displayed in Table 1. All subjects had behavioural problems, depression and memory deficits. While 3 of them had prosopagnosia, 4 of them had word finding difficulties. Additionally, they became negativistic, non-flexible, sensitive to pain, very fixated on certain thoughts or activities, and they lost their logical reasoning. For instance, due to drinking while driving, Case 2's driver's license was withdrawn, which means that he could no longer be a volunteer for the Red Cross. Interestingly, while he did not care for his driving licence, he became obsessed with working in the Red Cross. On the other hand, Case 3 decided to be the golf champion in the Netherlands and spent his entire time and money for this sport, even though he became extremely stingy regarding other daily life activities, including costs for showering. Other cases also displayed bizarre rituals such as walking/cycling for miles in the same route every day or repeating the same eating/drinking routine etc. Change of personal taste (food, colours, music etc) was another prominent feature. Importantly, their behavioural profile was quite different from bvFTD [2], and they had several non-verbal semantic deficits

that might cause those behavioural-psychiatric problems. Furthermore, unlike svPPA, aphasia was not the most prominent feature and neither svPPA diagnostic criteria covered their initial symptom distribution [3] , however their clinical phenotypes were in line with the published rtvFTD literature [4, 8, 9]. Although rtvFTD cases had fairly similar initial clinical presentations, over the years, they exhibited a different progression pattern. While the clinical diagnosis of three of the cases remained FTD, one of the cases (Case 1) developed concomitant MND, whereas another patient carrying a heterozygous *Ser352Leu* mutation in the MAPT gene developed atypical parkinsonism (Case 3) (Table 1). The underlying genetics of this case have been published recently [41].

2. Pathological features of our cohort

Details of the pathological results of the Amsterdam subjects are displayed in table 3.

Table 3 Pathological features of rtvFTD cases

		Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
Macroscopic Analysis	Brain weight	1117 gr.	1410 gr.	1260 gr.	1010 gr.	975 gr.
	Atrophy	FT- Right	FT	FT- Right	FT	T
	Substantia nigra	Normally pigmented	Normally pigmented	Slightly pale	Pale	Slightly pale
	Locus coeruleus	Visible	Visible	Right<Left	Not visible	Visible
	Atherosclerosis	No	Moderate	Severe	Mild	No
Microscopic analysis	Plaque and tangles	Negative	Negative	Thal 3	Negative	Negative
	Congo red	Negative	Negative	Negative	Negative	Negative
	Alpha synuclein	Negative	Negative	Negative	Braak 3	Negative
	Tau	Negative	Negative	Positive	Negative	Negative
	Pick Bodies	No	No	No	No	No
	TDP-43	Positive	Positive	Negative	Negative	Positive
	FUS	Negative	Negative	Negative	Positive	Negative
	Accumulation	All layers	Predominantly layer 2	3R+ 4R	FUS	Several long threads
	Frontal	++	++	+++	+++	+
	Temporal	+++	+++	+++*	+++	+++
	Motor cortex	+++	-	-	n/a	-
	Corticospinal tract	+++	-	-	-	-

	Parietal	-	-	++	n/a	+
	Occipital	-	-	+	-	-
	Hippocampus	+++	+++	+++	+++	+++
	Amygdala	+++	+++	+++	+++	+++
	Caudate, putamen	-	++	+++	+++	++
	Thalamus	-	++	++	+++	++
	Brain stem	-	-	+++	+++	-
	Cerebellum	-	-	-	-	-
	Cervical cord	+++	-	-	-	-
Diagnosis		**FTLD-TDP type B+MND**	**FTLD- TDP type E**	**FTLD-MAPT**	**FTLD-FUS**	**FTLD-TDP type C**

rtvFTD: Right temporal variant frontotemporal dementia, FTLD: Frontotemporal lobar degeneration, MAPT: Microtubule associated protein tau, TDP-43: TAR DNA-binding protein 43, n/a: not available, F: Frontal, T: Temporal, R: Repeat

*: Extensive tau positivity indicates a primary tauopathy. Pathological results are suggestive for tau mutation.

+++: Severe, ++: Moderate, +: Mild, -: Normal

The rtvFTD group exhibited a heterogeneous underlying pathology, including FTLD- TDP type B with motor neuron degeneration, FTLD-TDP type E, FTLD- MAPT, FTLD-FUS, and FTLD-TDP type C (Fig. 1). The macroscopic analysis revealed that except Case 5, who had an underlying TDP- C pathology and a predominant bilateral temporal atrophy, all rtvFTD cases had either right predominant or bilateral frontotemporal involvement at the end stage of the disease. (Table 4).

Table 4 Pathological features of diagnostic groups

Case	Diagnosis	Macroscopic analysis (Atrophy pattern)	Microscopic analysis
1	rtvFTD	Frontotemporal predominant R-FT>L-FT	FTLD-TDP type B +MND
2	rtvFTD	Frontotemporal predominant R-FT=L-FT	FTLD- TDP type E
3	rtvFTD	Frontotemporal predominant R-FT>L-FT	FTLD- tau- MAPT
4	rtvFTD	Frontotemporal predominant R-FT=L-FT	FTLD- FUS
5	rtvFTD	Temporal predominant R-T=L-T	FTLD- TDP type C

rtvFTD: right temporal variant frontotemporal dementia; svPPA: semantic variant primary progressive aphasia; R: right; L: left; F: frontal; T: temporal; TDP: TAR DNA-binding protein 43; TAU: tau protein; MND: motor neuron disease; MAPT: microtubule associated protein; FUS: fused in sarcoma protein; PiD: Pick's disease.

3. Systematic review

The pathological data of 21 studies from 13 centres could be pooled and various molecular neuropathological associations were observed (Table 5). The combination of our results and the results of the systematic review revealed that the underlying pathology of rtvFTD (n=49) was heterogeneous (Fig. 2). The two most common underlying pathologies in rtvFTD were FTLD-TDP (67.3%) and FTLD-tau (26.5%). The observed FTLD-TDP subtypes were FTLD-TDP type C (36.7%), type B (10.2%), type A (4.1%), type E (2%), whereas 16.3% of cases were labelled as FTLD-TDP type A-B. Despite the relatively high frequency of FTLD-TDP type C pathology, 7 out of 18 FTLD-TDP type C subjects had a CTD co-pathology and one subject diagnosed with FTLD-TDP type C had a tau-PSP co-pathology. In other FTLD-TDP sub-groups, co-pathologies such as MND, tau and AD also occurred (Fig. 2). The observed FTLD-tau subtypes were tau-MAPT (16.3%), tau-PiD (6.1%), tau-GGT (2%) and tau-PSP (2%). The minority of the subjects was diagnosed with FTLD-FUS (4.1%) and only one subject had concomitant AD and DLB pathology.

Table 5 Outcomes of the included studies

	Publications	N	Institution	Country	Macroscopy (Atrophy pattern)	Microscopy
1	(Miki *et al.*, 2019)	1	UCL	UK	Frontotemporal predominant R-FT=L-FT	TDP type C+ CTD
2	(Snowden *et al.*, 2019)	1	MCCN	UK	Temporal predominant R-T=L-T	Tau-PSP+ TDP type A
3	(Caplan *et al.*, 2018)	9	UCSF	USA	Frontotemporal predominant R-FT=L-FT (n=1) TDP-C : N.A.	Tau-PiD (n=1) TDP type C (n=8)
4	(Kim *et al.*, 2018)	1	UCSF	USA	N.A.	TDP type C+ Tau- PSP
5	(Koriath *et al.*, 2017)	1	UCL	UK	Temporal predominant R-T=L-T	TDP type A
6	(Kuuluvainen *et al.*, 2017)	1	Helsinki University	Finland	Frontotemporal predominant R-FT=L-FT	TDP type A
7	(Wood *et al.*, 2016)	1	Cambridge Brain Bank	UK	Temporal predominant R-T=L-T	Tau-MAPT
8	(Clark *et al.*, 2015)	1	UCL	UK	Frontotemporal predominant R-FT>L-FT	Tau-GGT
9	(Moreno *et al.*, 2015)	1	UCSF	USA	Frontotemporal predominant R-FT>L-FT	TDP type A-B +AD+ 4R tau
10	(Josephs *et al.*, 2013)	7	Mayo Clinic	USA	Individual data N.A. Overall, temporal predominant	TDP type C (n=1) TDP type C+ CTD (n=6)
11	(Coon *et al.*, 2012)	2	Mayo Clinic	USA	N.A.	TDP type B+ MND* (n=1) TDP type B+ MND*+AD (n=1)
12	(Lee *et al.*, 2012)	1	UCSF	USA	Striatal predominant	FUS
13	(Ostberg and Bogdanovic, 2011)	1	Uppsala University	Sweden	Temporal predominant R-T> L-T	TDP type B+ MND*
14	(Kelley *et al.*, 2010)	1	UCL	UK	N.A.	TDP type A-B
15	(Kobayashi *et al.*, 2010)	1	Tokyo IP	Japan	Temporal predominant R-T>L-T	TDP type B+ MND*

16	(Kuwahara *et al.*, 2010)	1	Tokyo IP	Japan	Temporal predominant R-T>L-T	TDP type A-B+ MND*
17	(Chan *et al.*, 2009)	1	UCL	UK	N.A.	AD+ DLB (n=1)
18	(Josephs *et al.*, 2009)	8	Mayo clinic	USA	N.A.	Tau- PiD (n=1) Tau-MAPT (n=7)
19	(Kelley *et al.*, 2009)	2	UCL	UK	N.A.	TDP type A-B (n=2)
20	(Yoshida, 2009)	1	Aichi University	Japan	Frontotemporal predominant R-FT=L-FT	TDP type A-B+ AD
21	(Davion *et al.*, 2007)	1	Northwestern University	USA	N.A.	TDP type A-B+ MND*

TDP: TAR DNA-binding protein 43; TAU: tau protein; CTD: corticospinal tract degeneration; MND: motor neuron disease; MAPT: microtubule associated protein; FUS: fused in sarcoma protein; PiD: Pick's disease; PSP: progressive supranuclear palsy; FTLD-U: frontotemporal lobar degeneration with tau-negative, ubiquitin-immunoreactive pathology; AD: Alzheimer's disease; DLB: dementia with Lewy bodies; UCL: University College London; UCSF: University of California San Francisco; FTD: frontotemporal dementia; MCCN: Manchester Centre for Clinical Neurosciences; IP: institute of psychiatry; VAPSHCS: Veterans Affairs Puget Sound Health Care System

*: Clinically diagnosed with FTD+MND

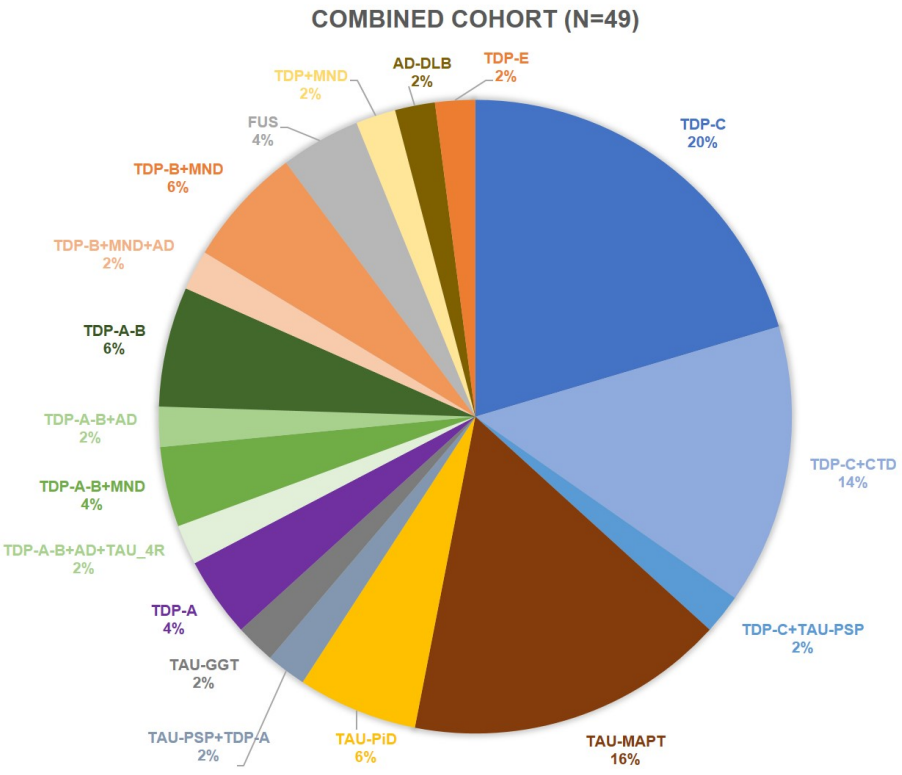

Figure 2: Molecular pathological features of right temporal variant frontotemporal dementia. TDP: TAR DNA-binding protein 43; TAU: tau protein; MND: motor neuron disease; CTD; corticospinal tract degeneration; MAPT: microtubule associated protein; PiD: Pick's disease; PSP: progressive supranuclear palsy; GGT: globular glial taupathy; FUS: fused in sarcoma protein; DLB: dementia with Lewy bodies; AD: Alzheimer's disease

Macroscopic findings were reported in 14 out of 21 studies. The combination of our results and the literature (n=25) revealed that the macroscopic atrophy pattern was again heterogeneous in rtvFTD. Frontotemporal predominant involvement was reported in 11 out of 25 subjects whereas 14 exhibited a temporal predominant atrophy pattern. One FUS case had a striatal predominant atrophy pattern alongside frontotemporal atrophy. Whereas 8 out of 9 TDP type C cases had temporal predominant atrophy in the macroscopic examination, other subtypes such as FTLD-tau or TDP type A-B had either temporal predominant atrophy at the end stage of the disease. Of note, macroscopic atrophy results were available only in 4 tau and 9 TDP type A or B cases (Fig 3).

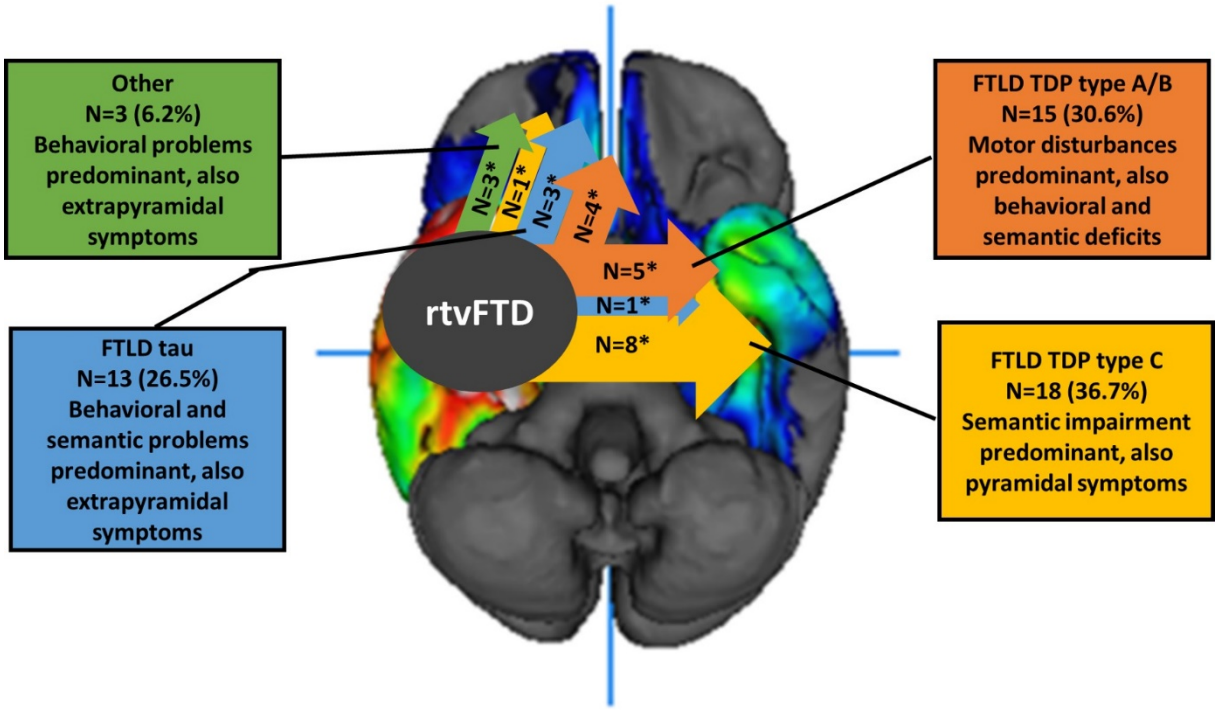

Figure 3: A schematic summary on the FTLD pathologies and symptoms related with rtvFTD. Adapted from Ulugut Erkoyun et al., 2020, Brain, CC BY-NC 4.0. The most common pathological accumulations in rtvFTD were FTLD-TDP type C, FTLD-tau and FTLD TDP type A or B. Since the pathology starts in the right temporal area, initial clinical features were right temporal lobe related symptoms. However, the progression pattern was heterogeneous in rtvFTD. While FTLD-TDP type C mostly spread to the contralateral temporal lobe and the clinical features were related with semantic impairment, FTLD-tau tended to spread to frontal areas, and patients developed more behavioural problems. FTLD-TDP type A/B had a

strong relationship with pyramidal impairment. However, in rtvFTD, corticospinal tract impairment was common in FTLD-TDP type C pathology as well and atypical Parkinsonism might be expected in FTLD-tau cases. *: number of cases that have macroscopic atrophy pattern data

DISCUSSION

In this case series and systematic review, we ascertained the heterogeneous underlying molecular neuropathology of rtvFTD, showing that it cannot be considered a pure FTLD-TDP type C syndrome. In rtvFTD, the most common underlying pathologies were FTLD-TDP type C, tau-MAPT as well as TDP type A and B, whereas its left temporal counterpart; svPPA links to the TDP type C pathology. Moreover, accompanying MND or CTD was prominent in rtvFTD, whereas this has not been reported in larger studies on svPPA [20-22]. Furthermore, the macroscopic descriptions revealed that although neurodegeneration started in the right temporal lobe according to initial neuroimaging, atrophy spread to either the frontal areas or left temporal area which might be the explanation of the heterogeneous clinical progression pattern in rtvFTD.

The systematic review showed that TDP type C pathology was the most common underlying pathology of rtvFTD. Still in the combined dataset, it was observed in only a third of rtvFTD patients and approximately half of them had a co-pathology such as CTD and tau-PSP

Following the FTLD-TDP type C diagnosis, the second most common pathological diagnosis of rtvFTD was FTLD-*MAPT*. This result might be expected because the association between tau mutations and anterior temporal atrophy is well known [42-45] and genetic studies have shown the relationship between *tau* mutations and rtvFTD [7, 41]. However, the relationship between specific right temporal atrophy and tau mutations is still unknown. According to previous studies, FTLD-*MAPT* exhibits a symmetrical atrophy pattern, despite the fact that clinically, the most common tau mutations produce behavioural symptoms and later semantic impairment [42, 44] which resembles the clinical profile of rtvFTD [9]. Additionally, the

association between svPPA and *MAPT* mutations is quite rare [22, 46-48]. Moreover, a recent GENFI paper reported that in the pre-symptomatic carriers of the *MAPT*, *GRN* and *C9orf72* genes, there was significant evidence of atrophy in the right anterior insula and they suggested that there may be some distinct regions in which the disease process starts [49]. This may explain the pathological diversity between two temporal lobe disorders; rtvFTD and svPPA. Future studies combining neurodevelopmental, embryonic, clinical, genetic and pathological findings will be required to further understand the biological basis of selective and lateralized neurodegeneration.

It has previously been suggested that rtvFTD can be divided into two major subtypes; the semantic clinical phenotype associated with temporal atrophy and TDP type C pathology and the behavioural type associated with frontal atrophy and FTLD-*MAPT [7].* Even though our study confirms the observation of two anatomical rtvFTD variants, we argue that the motor component of the syndrome should not be neglected. However, due to low case numbers, we cannot derive associations with specific types of underlying pathology. Future larger dataset studies are warranted to elucidate the underlying pathology specific clinical presentation and progression pattern in rtvFTD.

In contrast to the previous argument, Borghesani et al., (2020) suggested that the left and the right temporal variant of FTD should be considered the same disease based on their similar neuroanatomical progression patterns within the temporal and contralateral temporal regions[50]. However, the limitation of that study is that only subjects with TDP type C pathology were included, thereby potentially excluding other underlying pathologies with a different progression pattern. Additionally, it must be noted that most neuropathological studies taking into account the underlying neuropathology of rtvFTD were based on svPPA cohorts[20, 50], hence reports of underlying pathology of rtvFTD diagnosed with bvFTD are lacking.

One of the important results of our study is the relationship between rtvFTD and co-existing MND or CTD features. Co-existing CTD or MND was observed in 28.6% of rtvFTD subjects in our combined dataset. The general assumption is that ALS links to either bvFTD or nfvPPA while the association with svPPA is rare [51]. In addition, although previous pathological studies have revealed that those accompanying pathologies are mostly related with either FTLD-TDP type B or A- B subtypes [35], our results point out that CTD might accompany FTLD-TDP type C, in particular in rtvFTD. This association was also suggested by Josephs and colleagues (2013) [7]. Of note, some authors have reported the combination of left predominant temporal atrophy and CTD [52, 53]. Recently, we described the clinical profile of rtvFTD and reported that slowness is a distinctive symptom of rtvFTD in particular in the later stages of the disease [9].Underlying tau pathology and MND form a potential explanation of this clinical observation.

One of our cases was found to harbour FTLD-FUS pathology. Consistent with the literature [15], FUS pathology is rare, and we show that the phenotype can also present as rtvFTD. In addition, another rtvFTD subject was diagnosed with FTLD-TDP type E in our cohort. TDP type E has been recently identified based on a small number of case series, and links to prominent behavioural and movement disturbances that was also consistent with our case [19].

This is the first study that systematically collected the underlying molecular neuropathology of rtvFTD, which challenges the assumption that rtvFTD is an FTLD-TDP type C disorder by reporting heterogeneous FTLD pathologies in the patients with rtvFTD. However, there are some limitations that need to be addressed. First of all, the number of our subjects was limited and the results mostly rely on the literature review. Secondly, current neuropathological criteria for FTLD could not be applied in all rtvFTD cases described in the literature.

The right temporal lobe plays a key role in memory, social cognition, verbal and especially non-verbal semantic cognition. Therefore, rtvFTD can present with combination of psychiatric features and multi-domain cognitive impairment. Our results show that heterogeneous FTLD pathologies can initially cause right temporal lobe neurodegeneration and present with rtvFTD clinical features. To date, due to the lack of separate diagnostic criteria, rtvFTD has been relatively neglected in the large clinicopathological studies, although our findings of highly heterogeneous underlying pathologies in rtvFTD might have consequences for individualised patient management.

Our findings suggest that rtvFTD might be a separate pathological entity and future large scale studies are warranted to shed light on whether the presentation, disease course and associated pathology provide the evidence for this.

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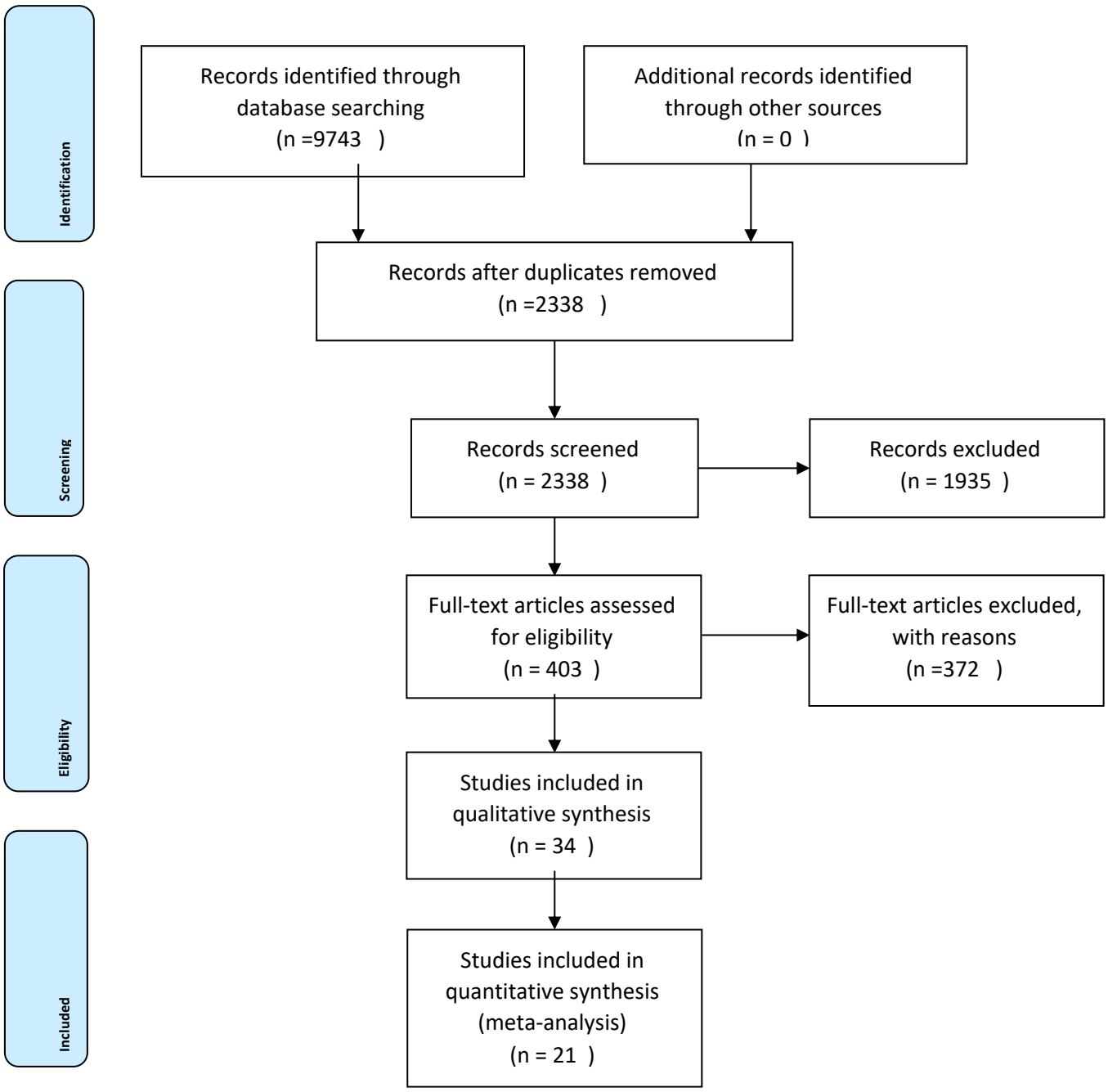
SUPPLEMENTARY MATERIAL

Supplementary material 1

Pathological examination

Brain autopsy was carried out within 4 h of death according to the Legal and Ethical Code of Conduct of the Netherlands Brain Bank. Tissue blocks taken from all cortical areas, hippocampus, amygdala, basal ganglia, substantia nigra, pons, medulla oblongata, cerebellum and cervical spinal cord were embedded in paraffin blocks, and underwent routine staining with haematoxylin–eosin, Bodian, methenamine-silver and Congo red. Tissue blocks were taken from the right hemisphere in each case. Immunohistochemistry was performed using primary antibodies against hyperphosphorylated tau (AT8, Innogenetics; 1:40), ubiquitin (anti-ubiquitin, Dako; 1:500, following 80°C antigen retrieval), β-amyloid protein (anti-beta amyloid, Dako; 1:100, following formic acid pretreatment), α-synuclein (anti-α-synuclein, Zymed Laboratories; undiluted, following formic acid pretreatment), p62 (BD Biosciences Pharmingen; 1:200, following 80°C antigen retrieval), TDP-43 (Biotech; 1:100, following pressure cooking), TDP-43 phosphorylated at serine 409/410 (Cosmo Bio; 1:8000), fused in sarcoma (Sigma-Aldrich anti-fused in sarcoma; 1:25–200 with initial overnight incubation at room temperature, following pressure cooking). Primary antibodies were incubated overnight at 4°C. Endogenous peroxidase activity was inhibited by incubation in phosphate buffered saline–hydrogen peroxide–sodium azide solution (100 ml 0.1 M phosphate-buffered saline + 2 ml 30% H2O2 + 1 ml natriumazide) for 30 min. The Histostain-Plus broad-spectrum kit DAB (Zymed) was used, and slides were counterstained with Mayer's haematoxylin and mounted in Entellan®. The pathological diagnosis was made by an experienced neuropathologist (A.R.).

PRISMA 2009 Flow Diagram



Supplementary material 3

All reviewed articles were re-reviewed. A number of the studies were excluded based on authors consensus.

	Publications	N	Institution	Country	Status
1	(Miki *et al.*, 2019)	1	UCL	UK	Included
2	(Snowden *et al.*, 2019)	1	MCCN	UK	Included
3	(Kim *et al.*, 2018b)	1	Northwestern University	USA	Excluded: A logopenic variant PPA subject with right hemisphere language dominance
4	(Caplan *et al.*, 2018)	9	UCSF	USA	Included
5	(Irwin *et al.*, 2018)	3	Penn FTD Center	USA	Excluded: Insufficient radiological data to identify the right predominant temporal lobar atrophy
6	(Kim *et al.*, 2018a)	1	UCSF	USA	Included
7	(Perry *et al.*, 2017)	9	UCSF	USA	Excluded: Case duplication. Study design; centre/period: UCSF Memory and Aging Center/ from 1998 to 2012. Caplan *et al.,* (2018) covers these patients
8	(Koriath *et al.*, 2017)	1	UCL	UK	Included
9	(Kuuluvainen *et al.*, 2017)	1	Helsinki University	Finland	Included
10	(Wood *et al.*, 2016)	1	Cambridge Brain Bank	UK	Included
11	(Clark *et al.*, 2015)	1	UCL	UK	Included
12	(Moreno *et al.*, 2015)	1	UCSF	USA	Included
13	(Henry *et al.*, 2014)	1	UCSF	USA	Excluded: Case duplication. Study design; centre/ period: UCSF Memory and Aging Center/ 2006. Caplan *et al.,* (2018) covers this patient
14	(Cannon *et al.*, 2013)	1	Mayo Clinic	USA	Excluded: A case with right temporal atrophy, however, clinical features are suggestive for ALS rather than FTD
15	(Josephs *et al.*, 2013)	7	Mayo Clinic	USA	Included
16	(Coon *et al.*, 2012)	2	Mayo Clinic	USA	Included
17	(Lee *et al.*, 2012)	1	UCSF	USA	Included
18	(Laforce *et al.*, 2012)	1	UCSF	USA	Excluded: Frontal atrophy scores are equal or higher than right temporal atrophy scores
19	(Mahoney *et al.*, 2012)	1	UCL	UK	Excluded: Individual pathological data are not available
20	(Rohrer *et al.*, 2011)		UCL	UK	Excluded: Individual clinical and radiological data are not available
21	(Ostberg and Bogdanovic, 2011)	1	Uppsala University	Sweden	Included
22	(Mimuro *et al.*, 2010)	1	Aichi University	Japan	Excluded: Patient is cognitively normal
23	(Kelley *et al.*, 2010)	1	UCL	UK	Included
24	(Kobayashi *et al.*, 2010)	1	Tokyo IP	Japan	Included
25	(Kuwahara *et al.*, 2010)	1	Tokyo IP	Japan	Included
26	(Rohrer *et al.*, 2010)	4	UCSF	USA	Excluded: Case duplication. Study design; centre/ period: UCSF Memory and Aging Center/ unknown. Caplan *et al.,* (2018) covers these patients
27	(Chan *et al.*, 2009)	2	UCL	UK	1 case included, 1 case excluded (lack of TDP-43 staining)
28	(Josephs *et al.*, 2009)	11	Mayo clinic	USA	8 cases included, 3 cases excluded (case duplication). Study design; centre/ period: Mayo Clinic Alzheimer Disease Research Center or Alzheimer Disease

					Patient Registry/ from January 1992 to December 2008. Josephs *et al.,* (2013) covers these 3 cases with TDP type C pathology
29	(Kelley *et al.*, 2009)	2	UCL	UK	Included
30	(Yoshida, 2009)	1	Aichi University	Japan	Included
31	(Beck *et al.*, 2008)	3	UCL	UK	Excluded: Frontal atrophy scores are equal or higher than right temporal atrophy scores
32	(Leverenz *et al.*, 2007)	1	VAPSHCS	USA	Excluded: Frontal atrophy scores are equal or higher than right temporal atrophy scores
33	(Davion *et al.*, 2007)	1	Northwestern University	USA	Included
34	(Davies *et al.*, 2005)	2	University of Cambridge and University of Sydney	UK, Australia	Excluded due to lack of TDP-43 staining

UCL: University College London; UCSF: University of California San Francisco; FTD: frontotemporal dementia; MCCN: Manchester Centre for Clinical Neurosciences; IP: institute of psychiatry; VAPSHCS: Veterans Affairs Puget Sound Health Care System; ALS: amyotrophic lateral sclerosis; TDP-43: TAR DNA binding protein 43.

CHAPTER 8

SUMMARY, KEY FINDINGS, GENERAL DISCUSSION, AND FUTURE PERSPECTIVES

SUMMARY

The primary aim of this thesis was to provide a new approach to better understand the concept of FTD and its subtypes. Our results showed that FTD is an area of neurology where it had been written about centuries before yet forgotten by most of the medical community and re-born in the past four decades. From a poorly recognized entity, it is now accepted worldwide as a major cause of young-onset dementia with the seminal contributions of the early FTD researchers. They brought the disorders as a neurological entity with profound psychiatric features to the forefront of the neurology community despite the resistance to the idea that FTD is a separate entity and different from AD. The split between neurology and psychiatry delayed the recognition of FTD because neurologists ignored the behavioral features whereas psychiatrists did not have a biological approach. Currently, the biggest limitation is the lack of biological biomarkers which cause diagnostic confusion between FTD; a neurodegenerative disorder, and PPD, which are considered non-neurodegenerative disorders. However, our results reported in **chapter 3** showed that the distinction between FTD and PPD is not black and white, and there is an anatomical overlap as well. We found that gray matter volume alterations in the prefrontal and anterior cingulate cortex, temporal lobe, amygdala, and insula comprise the trans-diagnostic brain anatomical alterations in bvFTD and PPD. Our meta-analysis of structural alterations in gray and white matter in bvFTD and PPD revealed a significant overlap of involved brain regions which paves the way for future investigations of shared pathophysiological pathways between bvFTD and psychiatric disorders and potential trans-diagnostic therapies. Although diagnostic challenges seem to be relatively less in PPA compared to bvFTD, our results reported in **chapter 4** showed that within 5 years (IQR = 2.5) after clinical onset, 65.6% of the PPA patients additionally fulfilled the clinical criteria for another neurodegenerative syndrome (PPA-plus). Fourteen out of 24 (58%) svPPA patients additionally met the diagnostic criteria of bvFTD (5.1 years, IQR = 1.1), whereas the clinical features of 15/18 (83%) lvPPA patients

were consistent with AD (4.5 years IQR = 3.4). Furthermore, 12/22 (54%) of the subjects with the nfvPPA progressed to meet the diagnostic criteria of the corticobasal syndrome, progressive supranuclear palsy, or motor neuron disease (5.1 years IQR = 3.4). However, despite those limitations mentioned above, it should be addressed that the modern diagnostic criteria for bvFTD and PPA are used widely and they helped to recognize those patients who have behavioral and language problems in combination with frontal and/or left temporal atrophy. However, the degeneration may start from the right temporal lobe and none of the diagnostic criteria of FTD covers this specific presentation. Perhaps the ignorance of rtvFTD might be the biggest limitation of the modern diagnostic criteria. In **chapter 5**, we reported the clinical and the radiological characteristics of 70 FTD patients with predominant right temporal atrophy and revealed that prosopagnosia, episodic memory impairment and behavioural changes such as disinhibition, apathy, compulsiveness and loss of empathy were the most common initial symptoms, whereas, during the disease course, patients developed language problems such as word-finding difficulties and anomia. Distinctive symptoms of rtvFTD compared to the other groups (age and sex-matched 70 svPPA, 70 bvFTD, 70 AD) were depression, somatic complaints, and motor/mental slowness. Aside from right temporal atrophy, the imaging pattern showed volume loss of the right ventral frontal area and the left temporal lobe, which represented a close mirror image of svPPA. Although the symptom distribution of rtvFTD cases was unique and none of the current diagnostic criteria catch the rtvFTD specific symptoms, the radiological results were in line with the existing literature. Given the mirror image of svPPA, we could speculate that the nature of the temporal variants of FTD is similar. In other words, rtvFTD is also a sporadic, FTLD TDP type C disorder, just like svPPA. This argument opened new doors to study the genetic and pathological background of the syndrome. In **chapter 6,** we reported the genetic mutations and inheritance patterns of rtvFTD patients and compared them to svPPA. Genetic variants in FTD related genes were found in 33% (n=6) of genetically

screened rtvFTD cases (n=18); including MAPT (n = 4), GRN (n = 1), and TARDBP (n = 1) genes, whereas only one svPPA case (out of 18 screened) had a genetic variant. Additionally, 4 out of 6 rtvFTD subjects had a strong family history for dementia. And we concluded that rtvFTD is genetically heterogeneous. The results of **chapter 7** were in line with **chapter 6**. Our results confirmed that rtvFTD is pathologically heterogeneous as well. In this case report and systematic review, we reported the autopsy results of five subjects diagnosed with rtvFTD from our cohort and 44 single rtvFTD subjects from the literature. Macroscopic pathological evaluation of the combined results revealed that rtvFTD demonstrated either a frontotemporal or temporal evolution, even if the degeneration started in the right temporal lobe initially. FTLD-TDP type C was the most common underlying pathology in rtvFTD, however, in 64% of rtvFTD, other underlying pathologies than FTLD-TDP type C were present, such as Tau-*MAPT* and FTLD-TDP type A and B. Additionally, accompanying motor neuron or corticospinal tract degeneration was observed in 28% of rtvFTD patients. Our results showed that in contrast to the general assumption, rtvFTD might not be a pure sporadic and FTLD-TDP type C disorder, unlike its left temporal counterpart svPPA.

KEY FINDINGS

1. The concept of FTD is an old and a new story at the same time. Seminal work was done almost 2 centuries ago, however, because of the split between neurology and psychiatry, the research on cognition and behavior slowed down until the new generation of behavioral neurologists brought it to the forefront of neurology communities at the end of the 1980s. Whereas in the past, the main problem was the acceptance of FTD as a separate entity, currently, the focus is on biologically oriented behavioural neurology/psychiatry.
2. Leading experts consider that developing the biological diagnostic biomarkers and disease-modifying treatments as the most urgent needs in FTD research. Additionally,

to facilitate FTD research and better conceptualize behavioral neurology education, they underscore that instead of traditional department systems such as neurology or psychiatry, independent specialized multidisciplinary centers should be established.

3. The prefrontal areas, anterior cingulate cortex, temporal lobe, amygdala, and insula are the overlapping anatomical areas between bvFTD and PPD which might explain the clinical overlap of those social brain disorders.
4. PPAs are not limited to aphasia. Each subtype has a unique profile and progression pattern. Behavioral disturbances might arise in svPPA, whereas global cognitive decline and broad language problems due to underlying AD pathology should be expected for lvPPA. nfvPPA patients may be least affected on the behavioral and cognitive domains initially, but show a progression to other neurodegenerative syndromes, particularly those associated with a motor impairment which might cause a high mortality risk
5. rtvFTD is the mirror image of svPPA and presents with prosopagnosia, memory deficits, and behavioral problems such as disinhibition, apathy, and loss of empathy. Additionally, it has some specific symptoms such as depression, hyper-religiosity, complex preoccupations, and somatization that are not parts of current diagnostic criteria.
6. Despite the radiological mirror image pattern, the underlying genetic risk factors and pathology might be different in rtvFTD and svPPA. FTD-related genetic mutations such as *MAPT*, *TARDBP*, and *GRN* may cause rtvFTD which highlights the importance of genetic screening in rtvFTD in daily practice. Additionally, in contrast to the general assumption suggesting FTLD-TDP type C is the only cause of the temporal variants of FTD, the underlying pathology might differ between the right side variant and the left side variant. FTLD-tau, FTLD-TDP type A and B as well as FTLD-TDP type C should

also be expected especially in rtvFTD. Furthermore, accompanying motor neuron disease or corticospinal tract degeneration is common on the right side.

GENERAL DISCUSSION

The wall between neurology and psychiatry

FTD is a field of neurology that has perhaps the strongest relationship with psychiatry. Due to the lack of specific biological biomarkers, approximately 50% of FTD patients have been diagnosed with a prior psychiatric diagnosis [1]. For instance, a young case presenting with emotional and behavioral problems, declining psychosocial functioning might be easily considered as a PPD case. However, over time, when the frontotemporal atrophy is observed on the neuroimaging, the revision of the diagnosis turns to FTD; based on the retrospective conclusion that the patient was not a "real" PPD. It is important because, given the general assumption that PPD are non-degenerative, there is growing evidence that family members of *C9orf72* mutation carriers have a higher prevalence of schizophrenia and bipolar disorder, whereas *C9orf72* related FTD can present with schizophrenia, bipolar disorder or autism spectrum disorders symptoms [2-4]. Moreover, young cases with a diagnosis of schizophrenia and bipolar disorder may have underlying FTLD neuropathology [5]. Based on this empirical overlap, a potential shared neurobiological background between bvFTD and schizophrenia [5-8], bipolar disorder [9] and autism spectrum disorders [2] has been postulated by independent authors. Their hypotheses, however, remain to be tested.

It should be noted that the prevalence of the FTLD pathologies/ genes are not common in the large PPD cohorts and the nature of the pathophysiology in PPD is different [10]. Additionally, due to the complex heterogeneous etiological background of PPD, it is still unknown whether all PPD are neurodegenerative [11]. Regardless of the discussion

whether PPD are neurodegenerative or neurodevelopmental or functional, our results in Chapter 3 showed that structural changes are observed in PPD as well, more importantly, the brain volumetric alterations are similar to the atrophy pattern of bvFTD. Not surprisingly, in line with the discussion in Chapter 2, there is a big body of literature from the 17th century to date, suggesting prefrontal, insular and amygdalar areas are associated with the behavioural/psychiatric symptoms [12-34]. It is conceivable that through various mechanisms of action, these social brain disorders affect the same neuro-anatomical networks [35-36]. Our radiological approach is pertinent because neuroimaging studies may offer clues about the effects of the potential shared etiology. Recent ENIGMA-GWAS collaborations have hypothesized that if some brain regions show volumetric case-control differences and others not, these areas may be more vulnerable to the genetic and environmental risk factors, and they have termed it "selective brain region vulnerability" [37]. To conclude, we found considerable neuroanatomical overlap between 2 diagnostic groups classified as neurodegenerative (bvFTD) and non-neurodegenerative (PPD) pointing to shared genetic or environmental selective brain region vulnerability that can explain their clinical overlap. We believe that such a cross-disorder point of view might allow identification of shared disease mechanisms and development of analogous treatments.

Our approach is important not only for dementia but also for other types of neurological disorders. As we discussed in Chapter 2, because of the separation between neurology and psychiatry, neurologists have paid little attention to cognition and behaviour. On the other hand, psychiatrists are not trained in neurological examination, they would not be in a position to detect associated signs such as parkinsonism, eye movement disorder or motor neuron disease. They also have little training in neuroimaging interpretation. Therefore, the behavioural features of epilepsy, multiple sclerosis, even Parkinsonism

have not been examined by clinicians and couldn't have found room in their diagnostic criteria. Moreover, the neurological examination has been oversimplified to cranial nerves, pyramidal, extrapyramidal, sensorial systems, and reflexes. It is clear that the lack of the assessment of cognition and behaviour is one of the biggest gaps in neurology education and practice which must be closed by further effort.

The limitations of the current diagnostic criteria

The most recently established diagnostic criteria for bvFTD[38] and PPA [39] have now been in use for a decade. They definitely increased the awareness of the syndrome and opened the doors to study each subtype in detail. Although representing an important effort at further definition and classification, the current diagnostic criteria have several limitations. The sensitivity value has been found 85% for the possible bvFTD and 75% for the probable bvFTD criteria in the original article [38]. Harris et al., [40] have also found high values (95% sensitivity and 82% specificity of the possible and 85% sensitivity and 95% specificity of the probable bvFTD criteria) in presenile dementia patients whereas Vijverberg et al., [41] have reported quite a low specificity value (27%) in the late-onset frontal lobe syndrome. This result highlights that the significant clinical overlap between bvFTD and PPD causes diagnostic challenges even in the elderly population and current diagnostic criteria do not differ FTD from other disorders characterized by social cognition impairment such as PPD whereas it differs FTD from AD. Although the diagnostic criteria of bvFTD have high sensitivity, the current diagnostic criteria for PPA do not cover all PPA patients and one-third to one-half of PPA syndromes are unclassifiable [42-43]**.** Moreover, our results in chapter 4 showed that even the patients who perfectly fulfil the PPA diagnostic criteria had additional symptoms even at the initial visit that would become more eminent over time. More importantly, each subtype has a unique progression pattern. Emphasizing the evolution

of new symptoms that lead to a secondary, parallel diagnosis might facilitate the recognition of the various PPA subtypes. Additionally, our results support the recent argument, suggesting that FTLD syndromes are not discrete in the clinical features of their respective clinical criteria, but instead exist as a multidimensional spectrum [44]. As we discussed in chapter 2, FTD is a complex disorder that is hard to understand easily. However, as underscored in Chapter 2, we need to keep in mind that all FTLD pathologies may cause heterogeneous syndromes, in parallel, all FTD syndromes may have heterogeneous underlying pathologies [45,46]. Therefore, diagnostic criteria might also have a global approach to increase the sensitivity and a detailed description of distinctive symptoms to increase the specificity with the combination of a biological framework such as supportive anatomical, genetic and pathological features.

Perhaps the most critical one of those limitations is that there was no mention of the patients with right temporal atrophy. Interestingly, the very first diagnostic criteria for FTD; Lund-Manchester criteria classified the syndrome under 3 canonical subtypes such as FTD, semantic dementia and progressive non-fluent aphasia. In the semantic dementia subsection, they subdivided it into 2 categories; the language variant (currently known as svPPA) and the "perceptual variant" which is related to the right side [47]. While the behavioural variant, progressive non-fluent variant of FTD, and language variant of semantic dementia took a place in the modern diagnostic criteria [38,39], this perceptual variant of semantic dementia that consists of prosopagnosia, bizarre preoccupations, and parsimonia was mentioned in one paragraph under the svPPA diagnostic criteria as a rare variant and couldn't have separate diagnostic criteria [39]. Associating rtvFTD with a primary aphasic disorder, however, may contribute to the neglect of early behavioral and psychiatric symptoms, memory, and non-verbal semantic deficits, leading to misdiagnosis. In Chapter 5, we proposed a diagnostic

framework to detect those patients earlier. The core clinical features of the syndrome that we proposed were memory deficit, prosopagnosia, and behavioural problems such as disinhibition, apathy, and loss of empathy. While the core symptoms differed rtvFTD from AD and svPPA substantially, approximately half of the bvFTD sample met the core criteria as well (the sensitivity of the core symptoms: 81%, the specificity of the core symptoms: 75%). Therefore, we added the "supportive" clinical symptoms such as depression, naming, and word-finding problems to distinguish rtvFTD patients from bvFTD patients (the sensitivity of the core+supportive symptoms:70%, the specificity of the core+supportive symptoms: 88%). However, there were a group of symptoms related to rtvFTD based on the published literature [48-54] that are quite rare in our dataset. These symptoms such as changes in taste (music, color, food), hyper-religiosity, somatization might be rtvFTD specific symptoms and might be overlooked in a retrospective design if they had not been asked specifically. Therefore, a further international effort is needed to characterize this unique form of FTD.

Mismatched twins; the differences of the temporal variants of FTD

As its name suggests, FTD describes a group of disorders that includes frontal and temporal variants. At presentation, patients with temporal variant FTD show atrophy predominantly of the anterior temporal cortex as well as the amygdala, anterior insula, posterior ventromedial frontal cortex, and the temporooccipital gyri [55,56]. The anterior temporal atrophy is often asymmetric. From the radiological point of view, in line with our results in chapter 5, there is a large body of literature suggesting that they are mirror images of each other [55,56]. However, from the clinical point of view, it is hard to classify these twin sisters into one category. Earlier studies have reported that patients with dominant hemisphere disease lose semantic knowledge, whereas non-dominant degeneration is characterized by prominent emotional and behavioral changes

[48,56,57]. However, a group of scientists has suggested that the clinical features of both sides can be explained by semantic impairment [53,58,59]. It presents with a verbal semantic deficit if it is on the left side, whereas non-verbal semantic deficits cause behavioural problems in rtvFTD [53, 58, 59]. In theory, this explanation is quite clear and easy to sum up all symptoms, however, in practice, it is hard to associate all behavioural/ psychiatric symptoms with semantic impairment. In daily clinical practice, due to the lack of cognitive tests to assess non-verbal semantic impairment, these symptoms are classified as behavioural/psychiatric symptoms since they cause behavioural/psychiatric problems. For instance, if a patient loses the semantic meaning of his/her bodily sensations (alexisomia), the clinical symptom would be somatization or hyperalgesia which has been mostly considered as a psychiatric problem. Another example, loss of empathy in rtvFTD might also be considered as a semantic impairment which has been termed as "alexithymia" (emotion reading problem, loss of the meaning of emotions) [60]. On the other hand, alexithymia has been considered as a social cognition deficit by several authors [61,62]. Therefore, the current debate on rtvFTD is whether it is a semantic disorder [53] or a social cognition disorder [62] . It is a bit hard to reconcile these two points of view; one pointing towards a role of the anterior temporal lobe as a semantic hub [53,63], the other towards some underdetermined role of the right temporal lobe in social processing [61,62]. On the other hand, the role of the temporal lobes in episodic memory has been neglected in this debate. Because episodic memory deficit has been highlighted as an initial symptom of rtvFTD in a number of clinical studies and case reports as we reported in chapter 5 [48, 51, 52, 64, 65]. However, the mechanism of the memory deficit in rtvFTD is not clear yet. Previous dementia-centered studies have associated the temporal variants of FTD with autobiographical memory deficits [66,67]. However, neuroscientific studies focusing on

social cognition have shown that the right anterior temporal lobe is more sensitive to social stimuli than other types of stimuli that have been tested [68,69] and explained the memory deficit related with anterior temporal lobes by “social knowledge related memory problems". Moreover, they have suggested that the prosopagnosia in rtvFTD is also a memory problem by terming it as “visual-person-memory dysfunction” [69]. Another explanation is that the anterior temporal lobes are a store for personal semantic and episodic memories that are essential in social interactions [70,71]. On the other hand, the right temporal lobe is also linked to the representation of beliefs [72], reading statements about physical appearance, bodily sensations [73], person's emotions and perceptions [74]. In sum, one possibility is that rtvFTD contains functional subdivisions, each separately concerned with aspects of semantics, episodic and emotional knowledge that are linked to each other.

Furthermore, our results in chapter 5 have shown that slowness was a symptom in rtvFTD, which was not recorded to the same extent in svPPA, bvFTD, and Alzheimer’s disease. Since clinical studies and case reports have often focused on initial symptoms, ‘slowness’ might not be mentioned as a symptom associated with rtvFTD in previous literature [48,62]. However, a post-mortem-based study has revealed that over the disease course, 35% of the rtvFTD patients developed Parkinsonism [51]. In addition, some studies have pointed out the relationship between rtvFTD and motor neuron disease as well as parkinsonism [51, 75-78]. Although some authors have suggested that rtvFTD and svPPA reflect the same pathophysiological process and converge clinically within 3 years from symptom onset [56], one longitudinal study has revealed the divergent progression pattern of these two related syndromes [62]. This argument raised a new question of whether rtvFTD patients might exhibit a different progression pattern than svPPA, in other words, the nature of those twin sisters might be different.

In order to find an answer to this question, in chapter 6 and 7, we focused on the underlying pathologies and the genetic risk factors in rtvFTD, and we found a heterogeneous neurobiological background in rtvFTD, unlike its left temporal counterpart svPPA that is almost a pure sporadic FTLD TDP type C disorder. In chapter 5, we collected all subjects with a diagnosis of FTD or primary progressive aphasia who had undergone genetic screening (n = 284) and subsequently who had a genetic variant (n = 48) with a diagnosis of rtvFTD (n = 6) in 2 specialized memory clinics; Amsterdam dementia cohort and Istanbul dementia cohort. In our combined cohorts, as reported in the previous literature [46], we can confirm that in svPPA rarely (∼5%) class III-V genetic variants in FTD-related genes are found. However, 33% of rtvFTD patients that were screened for genetic mutations in FTD genes had a genetic variant and 4 out of 6 patients had a strong positive family history for dementia. Moreover, these variants were in three different genes (*MAPT, GRN*, and *TARDBP*). In chapter 7, we reported the autopsy results of five subjects diagnosed with rtvFTD from our cohort and 44 single rtvFTD subjects from the literature. Macroscopic pathological evaluation of the combined results revealed that rtvFTD demonstrated either a frontotemporal or temporal evolution, even if the degeneration started in the right temporal lobe initially. FTLD-TDP type C was the most common underlying pathology in rtvFTD, however, in 64% of rtvFTD, other underlying pathologies than FTLD-TDP type C were present, such as Tau-*MAPT* and FTLD-TDP type A and B. Additionally, accompanying motor neuron or corticospinal tract degeneration was observed in 28% of rtvFTD patients.

The genetic etiology and associated pathologies may influence disease presentation and progression worth exploring further. Despite the overall similarities of clinical features, previous studies have shown that each genetic or pathological protein might have a characteristic progression pattern. This argument might explain the differences between

rtvFTD and svPPA. Irwin et al., (2018) [79] have found that the FTLD-Tau group has right greater than left orbitofrontal grey matter tau pathology, and the FTLD-TDP group has right greater than left orbitofrontal white matter TDP-43 pathology. There was a trend for increased left greater than right ventral lateral temporal lobe grey matter pathology in the FTLD-TDP subgroup and FTLD-Tau subgroup, however, no subtype-specific data has been reported in this article [79]. Studies focusing on the atrophy/progression pattern of the familial and sporadic FTD variants have shown that *MAPT* carriers tend to have more anterior temporal atrophy [80] and exhibit earlier disease onset [81], *GRN* carriers have more white matter impairment and asymmetric gray matter atrophy most in the temporoparietal areas [80], *C9orf72* is associated with symmetric atrophy predominantly involving dorsolateral, medial and orbitofrontal lobes, with additional loss in anterior temporal lobes, parietal lobes, occipital lobes and cerebellum whereas sporadic cases have frontal and anterior temporal atrophy suggesting that the disease trajectories may differ depending on etiology [80]. Our results reported in chapter 6 and 7 confirm this argument also in the rtvFTD subgroup. The clinical picture might be heterogeneous in rtvFTD depending on the underlying pathology. From the pathophysiological point of view, the question must be: what is the reason of this region-specific pathological accumulation? Whereas, from the clinical point of view, the question that we have: why the right variant of the temporal variant of FTD is genetic/pathologically heterogeneous whereas the left variant is homogeneous? Before trying to answer this question we need to be careful about the terminology and our inclusion criteria. Since rtvFTD does not have seperate clinical diagnostic criteria, our inclusion criteria were radiological in chapter 6 and 7 whereas clinical diagnostic criteria were used for svPPA in all studies regarding the underlying genetic and pathology in semantic dementia. This nuance is imporant, because the

genetic and pathological features are unknown in the patients with left anterior temporal atrophy who do not fulfill the clinical diagnostic criteria for svPPA. Although, svPPA (as a clinical diagnosis) is a pure sporadic TDP type C disorder, perhaps the left temporal variant FTD (as a radiological diagnosis) might be heterogeneous just like its right temporal counterpart.

These two questions are waiting to be tested. Future collaborative large sample size studies would answer this question and close one of the gaps in the field. Hereby, we should emphasize the importance of the large pathologically confirmed FTD cohorts in the world, and collaboration of different disciplines such as embryology, pathology, physiology, clinical and evolutionary science.

FUTURE PERSPECTIVES

The side effect of science is that studies raise more questions than they answer. However, the good thing is that they provide new sights and new directions to work on.

The lesson that we have learned from our history paper is that behavioural neurologists must focus on how the brain works instead of focusing on one disorder. It is almost impossible to understand the function of the entire cerebral cortex by ignoring the part related to the psychiatric/behavioural features. Therefore, more collaborative studies are warranted to understand this complex puzzle. Our meta analysis on the anatomical overlap between FTD and PPD might play a wake-up call role for future multidisciplinary studies on behavioural/ social cognition problems onset disorders.

The limitations of the current diagnostic criteria must be reconsidered and revised based on multicultural and multilingual data.

One of the important results of this thesis is increasing the awareness of rtvFTD. Since our results are based on single-center data, we initiated an international multicenter project to establish consensus diagnostic criteria for rtvFTD which should be validated in a prospective design.

Other unresolved questions further down the nature of the temporal variants of FTD are why the underlying genetic mutations and pathological accumulations are heterogeneous in the right temporal lobe degeneration whereas the left side is quite homogeneously sporadic and related with FTLD TDP type C. Future embryological studies with evolutionary perspectives will be crucial to understand the mysteries of the lateralization of the human brain.

From another perspective, our results in chapter 4 show that the clinical features of PPA are more than aphasia. Since we use aphasia centered diagnostic criteria for PPA in all PPA related studies, we don't know the pathological and genetic features of the patients with the left anterior temporal atrophy who do not meet the current diagnostic criteria for svPPA. Although, svPPA (as a clinical diagnosis) is a pure sporadic TDP type C disorder, perhaps the left temporal variant FTD (as a radiological diagnosis) might be heterogeneous just like its right temporal counterpart. This nuance should be taken into account in the future studies related FTD pathophysiology.

Our results reveal that a large body of work needs to be done on the temporal variants of FTD. Still, we do not know the role of the temporal lobes in memory, behaviour, social cognition and language as well as their interactions. We should also focus on the white matter connections and resting state activities as well as the gray matter atrophy. In that regard, one of our next projects will be mapping the semantic appraisal network.

It is clear that FTD studies have provided us a new way of thinking about human behaviour and have unearthed a new question; where is the line between normal and abnormal behaviour? It is impossible not to agree with Bruce Miller on one issue; “The philosophers of the next century are going to be neuroscientists” [82].

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82. https://www.youtube.com/watch?v=gQGI5yIMsfw

APPENDIX

List of publications

List of theses of the Alzheimer Center

Acknowledgements

LIST OF PUBLICATIONS

In this thesis

Ulugut Erkoyun **H,** Groot C, Heibron R, Nelissen A., Van Rossum J, Rutten RJ, Koene T, Van der Flier WM, Wattjes MP., Scheltens P, Ossenkoppele R, Barkhof F, Pijnenburg YAL. (2020) A clinical-radiological framework of the right temporal variant of frontotemporal dementia. Brain. DOI: https://doi.org/10.1093/brain/awaa225

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Ulugut H, Trieu C, Groot C, Van 't Hooft J, Tijms BM, Scheltens P, Ossenkoppele R,Barkhof F, Van den Heuvel OA, Pijnenburg YAL. (2021) Overlap of neuro-anatomical involvement in frontotemporal dementia and primary psychiatric disorders; a meta-analysis. Biological Psychiatry. DOI:https://doi.org/10.1016/j.biopsych.2022.05.028

Ulugut H, Mesulam MM, Snowden J, Neary D, Miller B, Pijnenburg YAL. (2022) Frontotemporal Dementia; past, present, future. (Ready for submission))

OTHER PUBLICATIONS

Ulugut Erkoyun **H,** Beckmann Y, Bülbül NG, İncesu TK, Kanat NG, Ertekin C. (2017) Spontaneous yawning in patients with multiple sclerosis: A polygraphic study. Multiple Sclerosis and Related Disorders. DOI: http://dx.doi.org/10.1016/j.msard.2017.06.012

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Arıcı Ş**, Ulugut** Erkoyun **H**, Özer B, Peker Ş. (2015) Postiktal Psikoz ile Seyreden Bir Epilepsi Olgusu. Türkiye Klinikleri Nöroloji Dergisi. doi: 10.5336/neuro.2014-42329

Ulugut H, Erkoyun E**.** `I forgot everything` The Frequency of Subjective Cognitive Decline in a Secondary Care Neurology Clinic in Izmir, Turkey. (2022) Balıkesir Health Sciences Journal

LIST OF THESES OF THE ALZHEIMER CENTER

1. L. Gootjes: Dichotic Listening, hemispheral connectivity and dementia (14-09-2004)
2. K. van Dijk: Peripheral Nerve Stimulation in Alzheimer's Disease (16-01-2005)
3. R. Goekoop: Functional MRI of cholinergic transmission (16-01-2006)
4. R. Lazeron: Cognitive aspects in Multiple Sclerosis (03-07- 2006)
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