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Premorbid personality in the frontotemporal dementia - amyotrophic lateral sclerosis (FTD-ALS) spectrum: behavioral and imaging correlates

Tutor:

Prof. Giovanna Zamboni

PhD Coordinator:

Prof. Michele Zoli

Doctoral Thesis of:

Giulia Vinceti

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A Emanuele

SUMMARY

ABSTRACT

Background: Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are generally considered to be two clinical expressions of the same neurodegenerative continuum (FTD-ALS spectrum) with common underlying pathology and genetic background. Patients can present with pure behavioral/cognitive (FTD), pure motor (ALS) or mixed (FTD-ALS) forms. What determines the development of one rather than the other phenotype is still unknown. However, with reference to this issue it has been observed that patients' personality differs between the phenotypes: ALS patients tend to display a prosocial behavior characterized by kindness and agreeableness; FTD patients tend to present with disinhibition, anti-social behaviors and lack of empathy. These traits are often described by patients' relatives as having always characterized their personality. We therefore aimed at testing if FTD and ALS patients had different personality profiles in their premorbid life, with the hypothesis that premorbid personality is associated with specific vulnerability to damage of brain networks related to social behavior and motor function.

Method: We prospectively recruited a cohort of eligible FTD and ALS patients who consecutively presented to outpatients Neurology Clinics of the Modena University Hospital, Italy, as well as a group of healthy controls. Patients' personality was assessed through the NEO Personality Inventory 3 (NEO-PI-3), which analyses the five main personality factors (Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness). The NEO-PI-3 questionnaire was administered to patients' caregivers with reference to the patient's personality at two timepoints: at diagnosis and 15 years prior to symptoms onset. Patients who did not have contraindication also underwent MRI scan of the brain that included high resolution T1-weighted and resting state functional MRI (rsfMRI) sequences. Imaging data were analyzed with FSL tools including voxel-based morphometry (VBM) and probabilistic independent component analysis (ICA).

Result: 50 patients (30 FTD, 17 ALS, and 3 FTD-ALS assigned to the FTD group, based on their first symptom) were recruited. A significant difference in premorbid

personality emerged in the Openness domain, showing that years before symptoms onset ALS patients had been more open to new experience, ideas and emotions than FTD patients (150 vs 133, p=0.020). The two groups also differed in the Extraversion domain, with ALS patients being characterized, in premorbid life, by higher sociability, loquacity, and optimism (150 vs 134, p=0.006). VBM analysis showed, in addition to the expected differences in gray matter atrophy between groups, a positive correlation between premorbid Neuroticism and gray matter (GM) volume in the areas of left hippocampus-parahippocampal gyrus and right hippocampus across all patients. Between-group comparisons of fMRI data showed that -in the Salience resting state network (RSN)- ALS patients had greater functional connectivity than both FTD patients and control subjects in the right insula, dorsal striatum and nucleus accumbens, and left thalamus. In the correlation analysis between functional connectivity and premorbid personality scores, a positive correlation between functional connectivity (FC) in Salience RSN and premorbid Openness emerged across all patients.

Conclusion: premorbid personality profile differs in FTD and ALS patients in at least two domains, Openness and Extraversion. Also, ALS showed higher functional connectivity in key areas of Salience RSN compared to FTD and controls, and a positive correlation between FC in the Salience RSN and Openness emerged across the whole group. These results support the hypothesis that premorbid personality may represent a vulnerability marker to the development of specific phenotypes, the behavioral or motor form, along the FTD-ALS spectrum.

1. INTRODUCTION

1.1.The FTD-ALS continuum

Frontotemporal dementia (FTD) is a neurodegenerative syndrome characterized by impairment of personality, behavior, executive functions and language, with relative sparing of memory function. Three main clinical phenotypes are recognized: a clinical behavioral variant (behavioral FTD, bvFTD), with prevalent behavioral and cognitive alterations of frontal type[1], and two language variants, the non-fluent variant of Primary progressive aphasia (nfvPPA), characterized by non-fluent and agrammatic speech and apraxia of language, and the semantic variant of Primary progressive aphasia (svPPA), characterized mainly by anomic disorder and impairment of the semantic system[2]. Amyotrophic lateral sclerosis (ALS) is also a neurodegenerative disease characterized by progressive paralysis of skeletal muscles, leading to death from respiratory failure or internal complications 2-5 years after clinical onset[3]. It constitutes the most frequent form belonging to the group of motor neuron disease (MND).

Both the clinical definitions of ALS and FTD subtend a heterogeneous group of sporadic and familial neurodegenerative diseases, with different etiology, neuropathology, and biochemical features. From a clinical perspective, symptoms and signs specific to each of the two clinical entities frequently coexist. Indeed, an association between FTD and ALS has been observed as early as in the 1990, when cases of rapidly progressive dementia in association with clinical features of motor neuron disease were described[4]. The growing number of similar observations and the discovery in recent years of convergent genetic and pathological substrates for both diseases reinforce the hypothesis that the two diseases are different expressions of the same neurodegenerative spectrum, thus delineating a continuum ranging from pure forms of MND with exclusive motor involvement, to pure forms of FTD with exclusive cognitive involvement, passing through hybrid forms of ALS-MND with involvement of both systems, motor and cognitive[5, 6]. It has been shown that about 10-15% of patients with ALS meet the diagnostic criteria for a diagnosis of FTD, and milder cognitive impairment not severe enough to reach criteria for dementia might be detected in up to 50% of them[7-9]. More specifically, impairment in executive functions can be detected in 20-25% of cases while other cognitive deficits (i.e., language or memory deficit) are present in 5-10% of ALS patients. Cognitive involvement in ALS is associated with worse prognosis and more rapid progression of the disease, particularly in the case of established FTD diagnosis. Moreover, behavioral disturbances are detected in up to 75% of ALS patients, depending on the scale used to measure them (ALS-cognitive behavioral screen[10], the ALS-frontotemporal dementia-Q[11], Motor Neuron Disease behavioral Instrument[12]). Behavioral symptoms in ALS overlap with those noted in FTD: they typically involve impaired social cognition, theory of mind (ToM) and emotional processing. They do not affect survival, but greatly increase the burden for caregivers.

Conversely, it has been shown that nearly 15% of patients with FTD develop motor neuron signs and a further 30-40% show subtle clinical or electrophysiological evidence of motor dysfunctions[13]. As expected, when ALS-related signs are present, survival is shorter, and decline is more rapid. These findings underline the importance to assess both cognitive/behavioral and motor signs and symptoms in patients who are diagnosed with FTD or ALS, especially if there is family history in the pedigree.

1.2. Neuropathology

The population of susceptible neurons differs substantially in ALS and FTD, involving, respectively, upper/lower motor neurons and prefrontal/temporal neurons. The clinical phenotype best reflects the specific pattern of neuronal loss. Nonetheless, the recognition that ubiquitin-positive intracellular inclusions were the most frequent finding in susceptible regions in both diseases suggested a common pathological mechanism for FTD and ALS. When the phosphorylated form of TAR-DNA binding protein (TDP-43) was subsequently recognized as the principal compound of these ubiquitinated inclusions, the term FTLD-TDP was introduced[14]. While TDP-43 inclusion pathology underlies the greatest proportion of ALS cases, it constitutes the pathological substrate of about 50% of FTD cases.

1.3. Genetics

For many decades it has been observed that there are familiar clusters of FTD, ALS and FTD-MND. Associations with loci on chromosome 17 and 9q and subsequent causative genes for both diseases were identified (TARDBP gene, FUS gene). But the most important discovery was the identification of the chromosome 9 open reading frame 72 (C9orf72) hexanucleotide GGGGCC repeat expansion in 2011, which was rapidly recognized as the major cause of both familial FTD and familial ALS[15, 16] and the most frequent mutation associated with FTD-ALS cases, since it can be detected in up to 50-80% of familial forms and up to 15-20% of sporadic forms[17]. Rarer causes are mutations in the *SOD1*, *FUS*, *TARDBP*, *TBK1, NEK1*, *MAPT* and *GRN* genes. The presence of C9orf72 expansion is associated with a specific type of FTLD-TDP pathology, indicated as type B FTLD-TDP subgroup[18]. In these cases, the intracellular inclusions present with a peculiarity, since they stain negative for TDP-43 but positive for p62, a marker of the ubiquitin proteasome system. Thus, the presence of p62 pathology is a highly distinctive feature of C9orf72-associated FTLD[15].

The mechanisms underlying neurodegeneration in genetic FTD-ALS, as well as in FTD and ALS separately, are largely unknown, and how C9orf72 repeat expansion causes such various phenotypes is a matter of debate. Epigenetic phenomena or disease modifier polymorphisms have been suggested, but more studies are needed[6, 19].

1.4. Imaging

The anatomical distribution of the neurodegenerative lesions that gives rise to the FTD syndrome, and particularly the bvFTD core symptoms, typically involves specific interconnected brain regions, known as the Salience network (SN), that are involved in the representation of the homeostatic relevance (i.e. salience) of ambient internal and external stimuli so that appropriate visceral-emotional-autonomic, behavioral, and cognitive responses can be deployed[20]. For success in social contexts, these diverse brain resources must be mobilized in a dynamic, timesensitive manner that is tuned in response to rapidly evolving conditions[21]. These regions include the anterior cingulate cortex (pregenual and subgenual), anterior insula (ventral [i.e. fronto-insular] and dorsal), striatum, amygdala, hypothalamus, and thalamus. Also, these are the earliest[22] and most consistently[23] atrophic regions in bvFTD on structural neuroimaging studies, regardless of the underlying neuropathological etiology[24].

Imaging features, i.e. a frontal and/or anterior temporal atrophy or hypoperfusion/hypometabolism on MRI or PET/SPECT respectively, were added to the revised research criteria for bvFTD, according to which a "probable bvFTD" diagnosis requires a supportive imaging[1]. Indeed, an anterior-predominant pattern, which almost always includes the anterior insula and anterior cingulate cortices, usually suggests underlying FTLD pathology. The involvement of additional structures, like frontal, temporal, parietal, limbic, subcortical, or brainstem, can assist in formulation of the pathologic differential diagnosis.

Structural and functional neuroimaging techniques have become a well-established diagnostic and research tool also in the ALS field, as it has demonstrated to provide a reliable biological marker of disease in ALS[25-27].

Recent MRI applications to ALS have focused on the analysis of structural changes in T1-weighted images assessed by automatic analysis approaches. Also, great attention has been recently posed to implementation of diffusion MRI, and specifically of diffusion tensor imaging (DTI) for assessment of white matter (WM) integrity in ALS and for the analysis of microstructural connectivity changes. The main finding of these studies is a decreased fractional anisotropy (FA) and increased mean diffusivity (MD) of the cortico-spinal tracts. These parameters are also associated with disease severity and rate of progression[28].

Kalra et at. documented that progressive WM degeneration in ALS is most prominent in the cortico-spinal tracts and frontal lobes and, to a lesser degree, in the corticopontine-corticorubral tracts and corticostriatal pathways[29].

Regarding functional neuroimaging in ALS, FDG-PET has been extensively used at the group level, and it has allowed the detection of a specific metabolic signature of ALS: a distribution pattern of hypometabolism in prefrontal, frontal, precentral, and postcentral regions, bilaterally, associated with hypermetabolism in posterior occipital and middle temporal cortices, cerebellum, midbrain, and cortico-spinal tracts[30, 31].

When the concept of FTD-ALS continuum emerged, neuroimaging techniques were used, in single modality or combined, to identify imaging signatures common to both diseases within the spectrum. Indeed, a combination of cortical atrophy and white matter tract degeneration characterizes both diseases[32]. Gray matter and white matter changes partially overlap between FTD, ALS and FTD-ALS patients, specifically in the right medial orbital and bilateral anterior cingulate cortex, in the corticospinal tract and in corpus callosum, supporting the idea of a common dissemination of the neurodegenerative process through specific brain regions. As expected on the basis of the clinical features of the two diseases, FTD patients show a higher degree of atrophy in orbitofrontal and fronto-medial areas, while the degeneration of motor pathways is prominent in ALS patients, consistent with clinical presentation.

Resting state fMRI (rsfMRI) studies have shown changed connectivity between cortical and subcortical structures[33] or changes in the activity of the Default Mode network and other networks in patients with frontotemporal dementia-motor neuron disease[34].

Trojsi et al. used rsfMRI in a cohort of ALS and bvFTD patients in early stages of disease, and found, compared to controls, a decreased functional connectivity within sensorimotor, right frontoparietal, Salience, and executive networks in both patient groups; conversely, they found divergent connectivity patterns within the Default mode network, with rsfMRI signals in the posterior cingulate cortex enhanced in bvFTD patients and suppressed in ALS patients[35].

1.5. Phenotypic variability and etiologic factors in FTD-ALS spectrum

In keeping with the profound clinical variability of the syndromic complex and with the wide range of the involved genetic and pathological factors, what affects and determines the development of one rather than the other clinical phenotype is still largely unknown.

Recently, some authors have hypothesized a role of neuroinflammation in determining the many different clinical presentations along the spectrum.

M. Otto et al. in a recent study that included patients with either genetic and sporadic forms of ALS and FTD, non-symptomatic carriers of mutations, and healthy controls showed that neuroinflammation is associated with the symptomatic phase of ALS and FTD, and that different neuroinflammatory profiles could be one reason for the disparate presentations[36]. Specifically, they found that levels of neuroinflammatory markers were increased in both ALS and FTD patients, but the patterns differed. In ALS, levels of CHIT1 and YKL40 were increased relative to those in controls, but levels of GFAP were unaffected. In FTD, levels of YKL40 and GFAP were increased, but levels of CHIT1 were barely affected. These patterns were consistent between the genetic and sporadic forms of the conditions. The authors concluded that more severe macrophage/microglia activation was a hallmark of ALS forms, while astrocytosis was specific for FTD. Also, they proposed GFAP determination in CSF as an additional tool to improve identification of FTD in patients with ALS.

Besides differences at the molecular level, in clinical practice several authors have anecdotally described some recurrent features in the personality profile of ALS compared to FTD patients, which seem to be present even many years before disease onset.

More precisely, neurologists caring for ALS patients commonly describe them as ''pleasant and friendly''[37, 38], ''sympathetic'', “nice”[39], emphasizing their active involvement in medical care and their remarkable resilience in coping with their inexorably progressive disease. The typical behavioral presenting features of FTD are instead opposite to the personality traits described above: FTD patients show disinhibition, loss of manner, socially inappropriate behaviors and impulsive actions, or apathy and loss of empathy. Indeed, when facing with patients with a suspected diagnosis of FTD, it becomes essential to discern whether these behavioral aspects constitute a normal age-dependent accentuation of pre-existing personality traits or instead represent the prodromal-early symptoms of a neurodegenerative disease. This can be particularly challenging since patient's caregivers frequently describe these behavioral traits as having somehow always characterized - although significantly attenuated - the personality of their relative along all their life, long before the symptoms that prompted medical attention. This observation is at the basis of the main research question of the present thesis: do patients with FTD have, during their pre-morbid life, a specific personality profile that makes them vulnerable, if affected by a neurodegenerative disease of the FTD-ALS spectrum, to the development of the frontal/behavioral clinical phenotype, rather than the motor phenotype?

1.6. Personality: definition and neurobiology

Personality can be defined as a set of constant patterns of perceiving, relating, and thinking about the environment and oneself, which the subject exhibits in a wide range of social and personal contexts[40].

Many efforts have been made to describe and classify personality; nowadays the predominant approach rely onto the Five-Factor Model (FFM), according to which personality results from the combination of five key traits, often called the "Big Five": Neuroticism, which corresponds to emotional instability, with a general tendency to have negative feelings, such as fear, sadness, embarrassment, anger and disgust, and poor capacity to cope with stress; Extraversion, that is characteristic of sociable, assertive, optimistic, dynamic individuals; Openness, which is defined by curiosity towards internal and external experiences, artistic sensibility, great imagination, non-judging attitude; Agreeableness, that corresponds to altruism, trust in others' intentions, empathy, tendency to collaboration; Conscientiousness, which represents determination, resolution, sense of duty, and self-control. Each dimension can be further divided in 6 facets, that allow for a more refined analysis (Table 1)[41,42].

Domains	*Neuroticism facets*	*Extraversion facets*
N: Neuroticism	N1: Anxiety	E1: Warmth
E: Extraversion	N2: Angry Hostility	E2: Gregariousness
O: Openness	N3: Depression	E3: Assertiveness
A: Agreeableness	N4: Self-Consciousness	E4: Activity
C: Conscientiousness	N5: Impulsiveness	E5: Excitement Seeking
	N6: Vulnerability	E6: Positive Emotions
Openness facets	*Agreeableness facets*	*Conscientiousness facets*
O1: Fantasy	A1: Trust	C1: Competence
O2: Aesthetics	A2: Straightforwardness	C2: Order
O3: Feelings	A3: Altruism	C3: Dutifulness
O4: Actions	A4: Compliance	C4: Achievement Striving
O5: Ideas	A5: Modesty	C5: Self-Discipline
O6: Values	A6: Tendermindedness	C6: Deliberation

Table 1. Domains and facets of the Big Five Model [43]

Several recent studies aimed at clarifying the neural correlates of personality by investigating its anatomical and functional basis through various neuroimaging techniques. They have focused either on morphological aspects, such as the amount of local gray matter volume or white matter tracts integrity measured with structural MRI, or on functional aspects, by studying the interaction between individual traits and stimulus processing with functional MRI (fMRI)[44].

Bjørnebekk et al. administered the NEO-PI-3 questionnaire to 265 healthy individuals to investigate their brain correlates with multimodal neuroimaging techniques, and found that higher Neuroticism, in particular in its facets reflecting anxiety, depression and vulnerability to stress, was associated with smaller total brain volume, widespread decrease in white matter (WM) microstructure, and smaller frontotemporal surface area; higher scores on Extraversion were associated with thinner inferior frontal gyrus, and Conscientiousness was negatively associated with the temporoparietal junction area; no reliable associations between brain structure and Agreeableness and Openness, respectively, were found[45].

DeYoung et al. used structural MRI to examine the covariance between the Big Five factors and local gray matter volume and found associations that supported their biological interpretation of four out of the five tracts. In particular, Extraversion covaried with volume of medial orbitofrontal cortex, which is involved in processing reward information; Neuroticism covaried with volume of brain regions associated with threat, punishment, and negative affect – with reduced volume in dorsomedial prefrontal cortex and left medial temporal lobe including hippocampus, and with increased volume in the midcingulate gyrus; Agreeableness covaried with volume in regions linked to empathy, theory of mind, and other forms of social information processing that enable and motivate altruistic behavior – i.e. reduced volume in posterior left superior temporal sulcus, and increased volume in posterior cingulate cortex; Conscientiousness covaried with volume in lateral prefrontal cortex, a region involved in planning and following rules[46].

Xu et al. investigated the neural correlates of the five-factor model personality factors (Neuroticism, Extraversion, Openness to experience, Agreeableness, and Conscientiousness) by analyzing the relationships between white matter (WM) integrity and personality traits among 51 healthy participants using diffusion tensor imaging (DTI) and the revised NEO Personality Inventory (NEO-PI-R); they found that Neuroticism correlated positively with DTI mean diffusivity (MD) in the corona radiata and superior longitudinal fasciculus, tracts that interconnect prefrontal cortex (PFC), parietal cortex, and subcortical structures, conversely Openness and Agreeableness correlated negatively with the same areas. Furthermore, Neuroticism correlated positively with MD in the anterior cingulum and uncinate fasciculus, tracts that interconnect PFC and amygdala. Openness correlated negatively with MD of WM adjacent to the dorsolateral PFC in both hemispheres. Based on these results, they suggested that greater Neuroticism associates with worse integrity of WM interconnecting extensive cortical and subcortical structures, including the PFC and amygdala, and that greater Openness associates with better integrity of WM interconnecting extensive cortical and subcortical structures including the dorsolateral PFC[47].

Canli et al. conducted a fMRI study that showed a correlation between differences in brain activity in response to emotional stimuli and the personality traits Extraversion and Neuroticism[48].

Moreover, some studies focused on the relationship between personality traits and resting-state networks (RSN) that can be measured with fMRI acquired at rest, such as the Default mode network and the Salience network. As an example, harm avoidance, which is an index of Neuroticism, has been shown to negatively correlate to the Salience network's information exchange efficiency, whereas Conscientiousness was linked to higher functional connectivity in the left fronto-parietal and Default mode networks[49, 50].
Despite the great interest that has been shown towards this topic, findings are often inconsistent, and a univocal and comprehensive model of the neuroanatomical correlates of personality is not yet available.

1.7. The role of personality in diseases development and progression

In the last few years, the idea that individual personality may play a role in the development and progression of different diseases, including neurodegenerative diseases, has gained increasing attention and has been investigated in both the psychiatric and neurologic fields.
Personality traits have been studied as potential risk factors for the development of dementia, in particular Alzheimer's disease (AD). A number of studies outlined that higher Neuroticism predicts a substantial increased dementia risk, while higher Conscientiousness confers protection against dementia. Openness may also have a protective effect, but results are inconsistent[51]. Among these investigations, a study that compared personality traits in AD patients and asymptomatic individuals who had AD neuropathology at autopsy is of relevance. In fact, it found lower Neuroticism and higher Conscientiousness in asymptomatic subjects, suggesting that a resilient personality profile may play a role in the relationship between neuropathological processes and clinical manifestations of dementia, postponing the onset of symptoms in people with underlying AD neurodegeneration[52].
The role of personality has been investigated also in relation to different symptoms in dementia patients. First, premorbid personality traits have been implicated as risk factors for the development of behavioral and psychological symptoms of

dementia (BPSD), which are a heterogeneous group of neuropsychiatric symptoms commonly present in patients with neurodegenerative diseases and include, among others, depression, anxiety, disinhibition, agitation, aggression, and apathy. Even though studies investigating this relationship are limited and heterogeneous in both the type of patients investigated and the adopted methodologies, there are some common results. High premorbid Neuroticism has consistently been associated to the development of BPSD, probably due to increased susceptibility to stress. In contrast, high premorbid Conscientiousness, Extraversion, Openness and Agreeableness resulted more commonly as protective factors[53]. Second, it has been suggested that personality traits, in particular Neuroticism and Openness, may modulate cognitive abilities in patients with early AD. This finding is consistent with the notion that Neuroticism is associated with lower gray matter volume and connectivity in frontal cortex even in healthy controls, suggesting that neurodegeneration in AD could potentiate a pre-existing vulnerability[54].

Finally, and more specifically of interest for the purposes of the present study, some previous studies analyzed the relationship between the FTD-ALS spectrum disorders and personality. As already mentioned, since the 1970s several authors have described the possible presence of a peculiar personality profile in patients with ALS and have hypothesized a possible relationship between this personality profile and the etiological factors involved in motor neuron disease[55]. Peters and collaborators compared the personality profile of 21 men and 17 women who had amyotrophic lateral sclerosis (ALS) with the profiles of 50,500 general medical patients by means of the Minnesota Multiphasic Personality Inventory profiles, and found no evidence for a distinct personality profile in ALS[56]. Grossman and colleagues used the NEO-PI questionnaire (administered to the caregiver) to compare the personality profiles of patients with ALS with a control sample of patients with a diagnosis of other chronic, progressive non-neurodegenerative diseases, obtaining lower values for patients with ALS compared with controls with regard to the variable "Openness to experience", which is related to imagination, aesthetic sensitivity, attention to emotions and feelings, preference for variety and innovation and intellectual curiosity[57]. This trait of "Openness to experience" could contribute to the tendency of these patients, when faced with the diagnosis of the

disease and its progressive course, not to emphasize its emotional implications, trying to remain compliant with expectations even in the acceptance of doctors' recommendations, being strongly adherent to prescriptions.
Mehl et al. compared ALS patients with controls and found that the former scored significantly higher in the dimension of Agreeableness, which can be interpreted as representative of patients' attitude[38]. Similarly, Kullman et al. showed that male ALS patients scored higher for Extraversion and Conscientiousness, while female patients scored higher for Agreeableness, Conscientiousness, and Extraversion, and lower for Neuroticism[58].

1.8. Cognitive and behavioral reserves

In recent years, the concept of brain or cognitive reserve, which is the brain's resilience to neuropathology, has evolved and explicated in both terms of anatomical reserve (i.e. amount of nerve tissue) and functional reserve (i.e. neural networks integrity and efficiency). The idea of a cognitive reserve against brain damage originates from the observation that there is not always a direct relationship between degree of brain pathology – both in neurodegenerative diseases and other forms of brain damage, such as stroke – and clinical manifestations. Thus, reserve can be defined as the brain resilience that allows some individuals more than others to maintain adequate cognitive functions at a given level of pathology. It can be separated into two main features: brain reserve, which refers to anatomical differences in terms of amount of nervous tissue, and cognitive reserve, which refers to functionality of brain networks that allows some individuals to cope better with brain damage[59], although this distinction has been criticized since function ultimately also depends on structural elements such as neurons and synapses. The concept of reserve has been widely demonstrated in AD, where patients with higher cognitive reserve, measured with various proxies such as years of education or type of occupation and leisure activities, have been shown to require more brain damage to exhibit the same level of clinical decline[60].
Accordingly, there are conditions in which weakness of a specific function or neural network confers a greater vulnerability to the development of a certain neurological

deficit or symptom. An example is the finding of a significantly higher incidence of anamnestic dyslexia in people with the logopenic variant of primary progressive aphasia (lvPPA) than in the healthy reference population: this can be interpreted as a greater vulnerability of the anatomical area of the parieto-temporal junction and therefore early symptomatic manifestation in the face of the presence of pathological insult[61]. In a similar way, mathematical and visuospatial learning disabilities showed a higher prevalence in patients with posterior cortical atrophy (PCA) – a form of dementia with selective impairment of visuospatial circuits – than in other form of dementia and general population. Consequently, it can be argued that neurodevelopmental differences in specific brain networks may be associated with specific clinical phenotypes of later-life neurodegenerative diseases[62].

As a parallel to the cognitive reserve concept, Premi and colleagues hypothesized the existence of a "behavioral reserve" that would confer protection, within a group of patients with bvFTD, against the development of a particular phenotype, defined as "disinhibited"[63].

Transposing this concept, we can then ask whether interindividual variability in "pro-social" behavior and in the ability to identify the mental and emotional states of others plays a role in determining the specific clinical phenotype along the FTD-MND spectrum. That is, in this study we question if the specific type of pre-morbid personality constitutes a *locus minoris resistentiae* or, on the contrary, a strength that contributes and influences the type of symptomatic manifestation once the subject is affected by the neurodegenerative process. Our research questions are therefore the following:

1. Are subjects with a poor pro-social personality profile at risk of developing early symptoms of disease in the brain areas most responsible for behavior (the fronto-temporal areas), thus leading towards the cognitive-behavioral form of disease (bvFTD)?
2. Viceversa, are subjects with a robust pro-social and empathic personality profile more resilient to the development of the cognitive-behavioral form of the disease, in favor of the motor manifestation of disease (ALS)?

2. AIM OF THE STUDY

Although it is now recognized that FTD and ALS are part of the same neurodegenerative spectrum, the clinical variability among the phenotypic manifestations of such FTD-ALS spectrum is wide. Which etiologic factors most contribute to the development of one rather than the other phenotype remain still largely unknown.

In our clinical practice, we have frequently observed and collected preliminary data (unpublished) suggesting that ALS patients tend to adhere to the personality profile described in several previous reports as particularly prosocial and empathic.

The recently established concept of the FTD-ALS continuum led us to the hypothesis that personality may have a role in modulating or influencing the phenotypic expression of the neuropathologic process along such spectrum. Specifically, the main hypothesis of the present study is that patients with opposite FTD and ALS phenotypic manifestations of the FTD-ALS spectrum have different premorbid personalities, and that the variability of premorbid personality modulates the functional reorganization of the brain once the neurodegenerative process begins.

In addition, we tested the following secondary hypotheses: (i) the scarcely prosocial and empathic premorbid personality in FTD patients reflects a specific vulnerability of brain networks related to social behavior, predisposing to the development of behavioral disturbances; (ii) on the contrary, the pleasant and nice premorbid personality in ALS patients reflects a relative integrity of these circuits, protecting patients from the occurrence of behavioral symptoms, but a specific vulnerability of brain networks related to motor control.

To investigate these hypotheses, we tested the premorbid personality of FTD and ALS patients through the administration of personality inventories. We also investigated if these potential differences could reflect differences in brain organization in terms of structure or functional connectivity by using voxel-based morphometry (VBM) and resting state functional Magnetic resonance imaging (rsfMRI) analysis, respectively.

3. MATERIALS AND METHODS

3.1.Participants

All eligible FTD and ALS patients seen at the Memory and Motor Neuron Disease Clinics of the Neurology Unit, Ospedale Civile Baggiovara, Azienda Ospedaliero Universitaria di Modena in the period January 2018 – October 2021 were prospectively recruited.

Inclusion criteria consisted in:

- Diagnosis of FTD and/or ALS according to existing diagnostic criteria[1, 2, 64];
- Presence of a reliable caregiver;
- Ability to read and speak Italian in order to allow the administration of questionnaires and neuropsychological tests;
- Sufficiently intact visual and hearing function to allow the administration of questionnaires and neuropsychological tests.

Exclusion criteria comprised:

- Diagnosis of stroke, head trauma, epilepsy or neurodegenerative disease other than FTD and ALS;
- Withdrawal of consent at any time of the study.

The study was conducted under ethical approval of the Local Ethics Committee (Number 247/18, approved on January 8th, 2018) and all subjects gave written informed consent before recruitment.

Each patient underwent a cognitive and behavioral assessment. A subset of patients underwent a blood test to search for genetic mutations known to be associated to FTD-ALS spectrum (MAPT, GRN, C9orf72, SOD1, TARDBP, FUS, VCP, PFN1, TUBA4A, OPTN, UBQLN2, SQSTM1, TBK), and a lumbar puncture to screen for CSF biomarkers of neurodegeneration. Patients who did not have contraindications also underwent an MRI scan. Patients and caregivers were asked to fill in questionnaires to evaluate patients' premorbid and current personality.

3.2. Clinical and neuropsychological assessment

Demographic and clinical data were collected including gender, age, education, time of onset, duration of disease, clinical features at onset and at follow-up, neuropsychological profile. The neuropsychological assessment consisted of a standardized battery of cognitive tests (Bedside Battery), developed by the University of California San Francisco (UCSF) Memory and Aging Center, and adapted from the English version to Italian[65-67].

For general functioning and cognition, the Mini-Mental State Examination (MMSE) was performed. The California Verbal Learning Test (CVLT) was used to evaluate verbal memory. Visuospatial abilities were assessed through the Number Location Test from the Visual Object Space Perception Battery (VOSP). Modified-Trails Making Test (M-TMT), Modified Five-Point Test (MFPT), M&N Alternation, F-words per minute, Couples of words and Proverb Interpretation, Calculation, Stroop Test and Digit Span assessed short-term memory, attention, working memory, abstraction, and executive functions.

Language function was tested with specific subtests, including: the abbreviated Boston Naming Test (15 items) (BNT) for confrontation naming; animals per minute to evaluate semantic fluency; the Peabody Picture Vocabulary Test revised (PPVT-R) for single word comprehension; the syntax comprehension subtest of the Curtiss-Yamada Comprehensive Language evaluation-Receptive test (CYCLE-R) for syntactic comprehension; the word reading section of the Wide Range Achievement test-4 (WRAT-4) and reading of irregular words to evaluate single-word reading and surface dyslexia; multiple repetitions of multisyllabic words and repetition of sentences from the Motor Speech Evaluation (MSE) for repetition and verbal agility. Finally, faces concordance and emotions recognition of the Comprehensive Affect Testing System (CATS) were used to evaluate emotion perception abilities.

Behavioral symptoms were assessed through the Neuropsychiatric Inventory (NPI)[68], a questionnaire administered to caregivers which rates frequency and severity of twelve neuropsychiatric disturbances which are common in dementia.

In addition, both patients and caregivers were asked to complete the Frontal Systems Behavior Scale (FrSBe)[69], a 46-item questionnaire designed to provide a measure of behavior before and after the onset of a neurological disorder. The subject must rate on a five-point Likert scale (1 = almost never; 5 = almost always) the frequency of 46 behaviors, divided into three subscales that evaluate three frontal syndromes: apathy, disinhibition, executive dysfunctions. Ratings are collected for two timepoints, before the illness and at present time. Compared to NPI, FrSBe is particularly useful to evaluate FTD patients, since it separates different behavioral dysfunction profiles. Moreover, the discrepancy between caregivers' FrSBe total score and patients' FrSBe total score is used as a reliable measure of anosognosia.

Depression symptoms were evaluated with the Beck Depression Inventory-II (BDI-II)[70] and cognitive reserve with Cognitive Reserve Index questionnaire (CRI-q)[71].

Finally, the ALS Functional Rating Scale-Revised (ALSFRS-R)[72] was used to evaluate severity of disease and functional status in patients with ALS. It is a validated instrument for monitoring the progression of disability, which considers twelve areas of daily living activities (speech, salivation, swallowing, handwriting, feeding, dressing, turning, walking, climbing, dyspnea, orthopnea, respiratory insufficiency) rated from 4 (normal) to 0 (completely impaired), with a maximum score in fit patients of 48.

3.3.Personality evaluation

Patients' personality was assessed with NEO Personality Inventory 3 (NEO-PI-3)[73], which is one of the most commonly used questionnaires in the scientific literature to describe personality according to FFM[41].

In its latest version, it consists of 240 items which are statements describing various situations of daily: the respondent must answer to each item on a five-point Likert scale (1 = completely disagree; 5 = completely agree). It is adapted in an Italian version and takes 30-40 minutes to be completed.

The analysis of all the responses combined allows to obtain a score for each of the five dimensions – Neuroticism, Extraversion, Openness, Agreeableness and

Conscientiousness – and the thirty subcategories or facets. Altogether, they provide a detailed picture of subject's personality.

There is not a cut-off of normality for each score, but the higher the score, the stronger the representation of that dimension in the subject's personality. Also, normative data from an Italian neutral reference sample (RS) of 727 individuals are provided in the NEO-PI-3 Manual.

Patients were required to fill the questionnaire once, referring to their current situation. Caregivers were asked to complete the questionnaire twice, referring to the patient's personality at two timepoints: referring to the patient's current time (after disease onset, i.e. current personality) and referring to 15 years before (before disease onset, i.e. premorbid personality). In this setting, caregivers' compilation is essential, since patients' cognitive deficits, behavioral disturbances, and anosognosia (especially for FTD patients) do not always allow to obtain reliable data from self-administered questionnaires.

3.4.Statistical analysis

Analysis of demographic, neuropsychological and behavioral data were performed with Stata 16.1. Parametric and non-parametric analysis, as appropriate, were made for comparisons between diagnostic groups. A p value < 0.05 was considered statistically significant. Differences in personality factors between groups at each timepoint were tested with repeated-measures ANOVA. Analysis of association between variables were performed with Pearson's correlation.

3.5.Imaging analysis

Patients underwent a multimodal MRI protocol at the Ospedale Civile Baggiovara, Azienda Ospedaliero Universitaria di Modena on a 3T GE scanner equipped with a 48-channel-array head coil. The imaging protocol included, among other sequences, high-resolution T1-weigthed 3D BRAVO structural images (TR 2.15 sec; TE 3.1 msec; FOV 328x512x340; voxel dimension 1mm isotropic) and single-shot gradient echoplanar imaging (EPI) T2*-weighted images acquired along the transverse plane, parallel to the anterior to posterior commissural line, while the subject rested for fMRI (TR 1.7 sec; TE 31.0 msec; slice thickness 3 mm including a 0.3 mm gap; voxel dimension 3 mm isotropic; 200 volumes).

Images were analyzed using FSL (FMRIB Software Library) v6.0 software (https://fsl.fmrib.ox.ac.uk/fsl).

Structural data were analyzed with FSL-VBM[74], an optimized VBM protocol[75] carried out with FSL tools[76].

First, single-subject structural images from 10 normal controls and 28 patients (21 FTD and 7 ALS) were brain-extracted and grey matter-segmented before being registered to the MNI 152 standard space using non-linear registration[77]. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template (made of 21 subjects, 7 from normal controls, FTD and ALS respectively). Second, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

Voxelwise General Linear Modelling (GLM) was applied using permutation-based non-parametric testing ('randomise' command in FSL, with 5000 permutations), correcting for multiple comparisons across space, to perform comparison analyses exploring differences in GM volumes between groups (FTD, ALS and controls). Age of patients was also mean centered and entered as covariate of no interest to control for its potential effect.

We then examined the relationship between GM volume and each of the five dimensions of NEO-PI-3 referred to premorbid personality with separate independent GLM models, performing one-tailed t-test for each direction of correlation across all sample. In all these GLM models, age of patients, MMSE scores and NEO-PI-3 scores for current personality (as assessed by caregivers) were also mean centered and entered as covariates of no interest.

Results were first explored at a Threshold-Free Cluster Enhancement (TFCE) correction of $p < 0.05$. However, they were also explored at the threshold of $p < 0.001$, uncorrected.

Resting fMRI data were analyzed using probabilistic independent component analysis (ICA) as implemented in the Multivariate Exploratory Linear Optimized Decomposition into Independent Components FSL tool (MELODIC)[78, 79]. Noise components were manually classified using criteria developed by Griffanti et al.[80], and denoised data of all patients were temporally concatenated and decomposed into 25 components using ICA to identify large-scale networks of covariation during rest. Pre-processed and denoised functional data from an equal number (N=7) of participants randomly selected in each group (controls, bvFTD and ALS) were used for this purpose to avoid bias towards the larger group (total number of data sets included was therefore 21). The concatenated 21 fMRI data sets were decomposed using ICA to identify large-scale patterns of functional connectivity in the whole sample. In this analysis data set was decomposed into 25 components in line with previous studies[81]. Biologically valid, non-artifactual RSNs were identified both by visual inspection and by using spatial correlation (i.e., $r>0.49$) against a set of previously defined maps. Dual regression was then used to generate subject-specific versions of the RSN maps as described in Filippini et al[82].

Voxel-wise statistics were then performed using permutation-based non-parametric testing ('randomise' in FSL, with 5000 permutations) to compare diagnostic groups on the RSNs on which we had a priori hypothesis, i.e. those involved in social cognition and executive functions (Salience, fronto-parietal, Default mode RSNs) and motor control (sensory motor RSN), plus a control network on which we did not expect significant changes (visual RSN). Gray matter values obtained from VBM were entered in all the GLM as covariate of no interest to control for the potential effects of regional atrophy on fMRI comparisons, as in Zamboni et al[81].

Results were considered significant at $p < 0.05$, fully corrected with threshold-free cluster enhanced (TFCE) correction. After observing significant results, parameter estimates of functional connectivity were extracted from the significant resulting regions (functional ROIs) and from the whole RSN of interest and correlated with premorbid NEO-PI-3 scores.

4. RESULTS

4.1.Cases characterization and selection

Fifty-five consecutive patients (mean age 68.1, 19 females), along with their caregivers, were recruited between December 2018 and October 2021.

Among them, 35 had a diagnosis of FTD, 3 had a mixed FTD-ALS phenotype, and 17 had a diagnosis of ALS. Among the 35 FTD patients, 30 were classified as bvFTD, 3 as svPPA, and 2 as nfvPPA. The 3 FTD-ALS patients were classified as bvFTD-ALS; in all three FTD-ALS patients the first symptoms of disease were cognitive/behavioral, while motor and language symptoms developed later. These 3 bvFTD-ALS patients were assigned to FTD group, based on their first symptom, since their group was too small to be considered and analyzed independently.

We decided to exclude the 5 cases with language presentation from further analysis, since PPA are known from the literature to be characterized by a very different neuropsychological and behavioral phenotype, as well as specific pattern of brain atrophy, which is substantially different from bvFTD patients. Also, in our clinical experience, we have not noticed common traits of personality in PPA patients as we have for bvFTD patients.

Genetic testing resulted in 1 MAPT gene mutation (bvFTD patient) and 4 C9orf72 repeat expansions (2 bvFTD-ALS patient, 1 bvFTD, 1 ALS).

4.2.Demographic and neuropsychological characteristics

Demographic and neuropsychological characteristics of the FTD and ALS group, and their comparison, are reported in Table 2.

The groups did not differ significantly in terms of sex balance and education. There was almost a significant difference in age, with FTD patients older than ALS patients at time of enrollment ($p=0.054$). Also, FTD patients showed a longer disease duration (5.38 vs 2.30 years; $p < 0.001$) at time of enrollment.

ALS patients performed better than FTD in most cognitive tests, consistently with the fact that they did not complain of major cognitive deficits. The only exception was the verbal agility task, in which FTD patients performed slightly better than ALS patients (4 vs 3.33), even without reaching statistical significance ($p = 0.382$).

As expected, patients with FTD had significantly more behavioral disturbances than patients with ALS measured with NPI (25.72 vs 3.60; $p < 0.001$). This result was confirmed by caregivers' FrSBe scores for apathy, disinhibition, and executive dysfunctions. The FrSBe discrepancy score (patients' total scores subtracted from caregivers' total scores) for FTD patients resulted positive (mean = 37.06), indicating unawareness of disease (or anosognosia), while for ALS patients it resulted negative (mean = -4.10), meaning that they tended to perceive greater impairment than caregivers. Mean difference between the discrepancy score in FTD and ALS patients was statistically significant ($p = 0.035$).
Both groups showed low scores for depression at BDI-II. The median score for ALS patients was slightly lower than for FTD patients (12.38 vs 14.91).
Finally, cognitive reserve measured with Cri-q questionnaire (which evaluates education, work, and free time activities) appeared significantly higher in ALS patients (120 vs 100. 95; $p = 0.013$).

	All patients	FTD	ALS	FTD vs ALS
Demographic characteristics				
Number	50	33	17	-
Gender M:F	32:18	22:11	10:7	p = 0.424
Age (y)	67.95 (10.01)	69.5 (10.5)	63.4 (11.2)	p = 0.054
Education (y)	10.54 (4.42)	10.21 (4.68)	11.50 (3.60)	p = 0.196
Disease duration (y)	4.45 (3.64)	5.38 (3.49)	2.30 (3.12)	p < 0.001*
Neuropsychological characteristics				
MMSE	25.33 (3.85)	24.48 (3.73)	27.80 (3.19)	p = 0.010**
CVLT free recall (10')	4.41 (2.75)	3.46 (2.40)	7.50 (0.93)	p < 0.001**
VOSP	7.54 (3.03)	6.92 (3.27)	9.33 (0.87)	p = 0.073
M-TMT correct lines	9.64 (5.48)	8.39 (5.63)	14 (0)	p = 0.008**
MFPT correct figures	5.14 (3.71)	4.68 (3.08)	7 (5.51)	p = 0.281
MFPT repeated figures	3.31 (5.24)	3.82 (5.74)	1.29 (1.25)	p = 0.479
M&N Alternation	0.86 (0.91)	1.07 (0.90)	0 (0)	p = 0.008*
Abstraction	2.80 (1.88)	2.12 (1,56)	4.78 (1,20)	p < 0.001**
Calculation	3.50 (1.65)	3.21 (1.73)	4.50 (0.76)	p = 0.064
Stroop 3	31.53 (18.18)	23.85 (12.71)	56.50 (6.95)	p < 0.001**
Direct span	5.14 (1.11)	4.93 (1.02)	5.78 (1.20)	p = 0.068
Reverse span	3.43 (1.35)	3.07 (1.15)	4.56 (1.33)	p = 0.008**
BNT	11.34 (2.56)	10.58 (2.44)	13.56 (1.33)	p = 0.001**
Phonemic fluency	9.44 (5.03)	8.08 (3.95)	13.88 (5.87)	p = 0.008**
Semantic fluency	12.65 (6.46)	10.04 (4.46)	21.13 (4.26)	p < 0.001**
PPVT-R	12.89 (2.18)	12.38 (2.30)	14.33 (0.71)	p = 0.007**
CYCLE-R	4.20 (1.28)	3.96 (1.40)	4.89 (0.33)	p = 0.093
Reading	73.18 (4.90)	72.32 (5.48)	75.56 (0.53)	p = 0.009**
Verbal agility	3.83 (1.45)	4 (1.36)	3.33 (1.66)	p = 0.382
Repetition	4.33 (0.93)	4.15 (0.99)	4.89 (0.33)	p = 0.026**
CATS face concordance	10.29 (1.99)	9.69 (1.99)	12 (0)	p < 0.001**
CATS emotions recognition	10.57 (3.57)	9.62 (3.66)	13.33 (0.87)	p = 0.004**
NPI	22.03 (16.01)	25.72 (14.85)	3.60 (4.98)	p < 0.001*
FrSBe apathy	44 (13.94)	49.82 (11.80)	31.20 (8.90)	p < 0.001*
FrSBe disinhibition	31.22 (9.26)	34.86 (8.89)	23.20 (2.57)	p < 0.001*
FrSBe executive dysfunctions	52.66 (18.99)	62.50 (13.07)	31 (9.29)	p < 0.001*
FrSBe discrepancy	22.36 (39.84)	37.06 (42.01)	-4.10 (14.76)	p = 0.035*
BDI-II	13.84 (10.66)	14.91 (11.36)	12.38 (10.17)	p = 0.717
CRI-q	105.89 (18.53)	100.95 (17.33)	120 (14.96)	p = 0.013**

Table 2. Demographic and neuropsychological characteristics of patients. Reported values are means with standard deviation values in parenthesis. The last column on the right reports the results of the comparison between diagnostic groups (level of statistical significance p < 0.05). * FTD > ALS, ** ALS > FTD. Abbreviations: MMSE: Mini-Mental State Examination; CVLT: California Verbal

Learning Test; VOSP: Visual Object Space Perception Battery; M-TMT: Modified-Trails Making Test; MFPT: Modified Five-Point Test; BNT: Boston Naming Test; PPVT-R: Peabody Picture Vocabulary Test revised; CYCLE-R: Curtiss-Yamada Comprehensive Language evaluation-Receptive test; WRAT-4: Wide Range Achievement test-4; CATS: Comprehensive Affect Testing System; NPI: Neuropsychiatric Inventory; FrSBe: Frontal Systems Behavior Scale; BDI-II: Beck Depression Inventory; CRI-q: Cognitive Reserve Index questionnaire.

4.3.Analysis of personality profiles

NEO-PI-3 scores were collected from caregivers' ratings of patients' personality for 40 patients (25 bvFTD, 2 FTD-ALS and 13 ALS). Table 3 shows scores at the two different timepoints: before disease onset (premorbid personality) and after disease onset (current personality). When comparing each patient group (FTD and ALS) with the mean of the reference sample (RS) of the Italian population, we found some relevant differences. Regarding premorbid personality, FTD scored low in Neuroticism (126.88 vs 136.19, $p=0.04$), Extraversion (136.55 vs 152.69, $p < 0.001$) and Openness (133.92 vs 162.66, $p <0.001$). ALS scored low in Openness (149.84 vs 162.66, $p=0.02$) while they scored high in Conscientiousness (174.76 vs 162.21, $p=0.02$). Considering current personality (after disease onset), FTD still scored low in Extraversion and Openness, but also in Conscientiousness at present time (142.68 vs 162.21, $p=0.005$). Conversely, ALS still scored low in Extraversion and Openness, with the adjunction of Agreeableness in which they scored higher compared to the RS (166.27 vs 156.64, $p=0.005$).

	FTD	ALS	RS	p (FTD vs RS)	p (ALS vs RS)	p (FTD vs ALS)
Premorbid personality						
Neuroticism	126.88(22.69)	127.53(22.08)	136.19 (22.10)	0.04*	0.18	0.93
Extraversion	136.55(22.29)	150.53(11.34)	152.69(20.37)	<0.001*	0.50	0.04*
Openness	133.92(18.46)	149.84(18.10)	162.66(23.07)	<0.001*	0.02*	0.01*
Agreeableness	160.40(23.17)	163.38(16.44)	156.64(16.89)	0.40	0.16	0.68
Conscientiousness	166.81(27.41)	174.76(17.78)	162.21(23.66)	0.39	0.02*	0.34

	FTD	ALS	RS	p (FTD vs RS)	p (ALS vs RS)	p (FTD vs ALS)
Current personality						
Neuroticism	160.40(23.17)	163.38(16.44)	136.19 (22.10)	0.15	0.28	0.68
Extraversion	119.54(28.40)	132.36(25.46)	152.69(20.37)	<0.001*	0.02*	0.21
Openness	127.09(21.63)	142.09(21.33)	162.66(23.07)	<0.001*	0.009*	0.06
Agreeableness	158.45(16.34)	172.90(15.33)	156.64(16.89)	0.60	0.005*	0.02*
Conscientiousness	142.68(29.68)	166.27(33.31)	162.21(23.66)	0.005*	0.69	0.04*

Table 3. Personality profile in the FTD and ALS groups. Reported values are means with standard deviation values in parenthesis, and are shown for FTD, ALS and the reference sample (RS). The last three columns on the right report the results of the comparison between each diagnostic groups (FTD and ALS) and the RS, as well as between FTD and ALS, respectively (level of statistical significance $p < 0.05$).

4.4. FTD and ALS patients' premorbid and current personality: comparison between groups

Table 3 also reports the comparison between the two diagnostic groups, FTD and ALS, with reference to both premorbid and current personality.

When comparing premorbid personality, a significant difference between groups emerged in the Extraversion domain, with ALS scoring higher than FTD (150.53 vs 136.55, p=0.04).

The Openness domain also revealed a significant difference between groups, again with ALS scoring higher FTD patients (149.84 vs 133.92, p=0.01).

No other significant differences emerged in the remaining domains.

With reference to current personality, the difference between ALS and FTD in the Openness domain persisted with a trend to statistical significance (142.09 vs 127.09, p=0.06), while the difference in Extraversion domain disappeared.

Parallelly, in both Agreeableness and Conscientiousness domains a significant difference between ALS and FTD emerged (172.90 vs 158.45, p=0.02 for Agreeableness; 166.27 vs 142.68, p=0.04 for Conscientiousness).

4.5. Premorbid Domains' facets: comparison between groups

The NEO-PI-3 scores for the five domains' facets in premorbid personality were analyzed and are shown in Table 4.

Regarding Extraversion, one facet, Positive emotions, was higher in ALS compared to FTD (27.30 vs 23.29, p=0.013); the facet Activity showed a trend of significance in the same direction (26.23 vs 22.74, p=0.061).

The description of Activity implies that a high Activity score is seen in rapid tempo and vigorous movement, a sense of energy, and a need to keep busy; active people lead fast-paced lives. Conversely, low scorers are more leisurely and relaxed in tempo, though they are not necessarily sluggish or lazy.

In the Openness domain, two facets differed between FTD and ALS. Fantasy resulted significantly lower in FTD compared to ALS (24.92 vs 21.07, p=0.031). Individuals who are open to fantasy have a vivid imagination and an active fantasy life, they daydream not simply as an escape, but as a way of creating an interesting inner world for themselves. They elaborate and develop their fantasies and believe that imagination contributes to a rich and creative life. Low scorers are more prosaic and prefer to keep their minds on the task at hand.

Also, the facet Feelings appeared to discern ALS from FTD (27.46 vs 24.22, p=0.031). Openness to feelings implies receptivity to one's own feelings and emotions and the evaluation of emotion as an important part of life; high scorers experience deeper and more differentiated emotional states and feel both happiness and unhappiness more keenly than others do. Conversely, low scorers have somewhat muted affects and do not believe that feeling states are of much importance.

Five domains' facets	FTD	ALS	p
Neuroticism			
N1: Anxiety	23.40(4.29)	26.38(5.78)	0.07
N2: Angry Hostility	18.85(5.67)	19.69(4.51)	0.64
N3: Depression	19.55(5.04)	19.84(4.99)	0.86
N4: Self-Consciousness	20.33(5.51)	18.46(6.33)	0.34
N5: Impulsiveness	23.74(4.42)	24.15(5.71)	0.80
N6: Vulnerability	20.96(6.17)	19(3.10)	0.28
Extraversion			
E1: Warmth	28(5.65)	31(3.24)	0.084
E2: Gregariousness	19.33(5.56)	21.61(3.42)	0.18
E3: Assertiveness	22.07(6.33)	24.15(3.48)	0.277
E4: Activity	22.74(5.82)	26.23(4.18)	0.061
E5: Excitement Seeking	21.11(5.00)	20.23(6.22)	0.63
E6: Positive Emotions	23.29(5.09)	27.30(3.14)	0.013*
Openness			
O1: Fantasy	21.07(5.38)	24.92(4.42)	0.031*
O2: Aesthetics	21.22(5.01)	24.38(5.99)	0.087
O3: Feelings	24.22(4.28)	27.46(4.31)	0.031*
O4: Actions	23.33(4.85)	25.15(4.59)	0.266
O5: Ideas	20.18(5.51)	22.38(5.48)	0.243
O6: Values	23.85(4.20)	25.53(3.84)	0.229
Agreeableness			
A1: Trust	25.51(6.17)	25.92(4.53)	0.83
A2: Straightforwardness	28(6.00)	28.07(3.94)	0.96
A3: Altruism	29(5.83)	31.30(4.92)	0.22
A4: Compliance	23.37(4.66)	20.69(5.31)	0.11
A5: Modesty	26.07(4.99)	27.46(4.73)	0.40
A6: Tendermindedness	28.44(5.02)	29.92(3.40)	0.34
Conscientiousness			
C1: Competence	27.70(5.80)	29(2.97)	0.45
C2: Order	27.44(6.18)	27.92(6.51)	0.82
C3: Dutifulness	31.03(5.00)	31.92(4.15)	0.58
C4: Achievement Striving	26.33(5.47)	28.23(5.35)	0.30
C5: Self-Discipline	29.25(6.34)	31(3.74)	0.36
C6: Deliberation	25.03(5.82)	26.69(4.15)	0.36

Table 4. Five domains' facets.

4.6.Evolution of personality traits over time

To evaluate changes over time between premorbid and current personality in the two diagnostic groups, we performed repeated-measures ANOVAs for each personality domain.

There was a significant effect of time on Neuroticism (p=0.005), since it tended to increase from premorbid to current personality in both groups. However, there was no significant interaction between time and diagnostic group (p=0.59), meaning that FTD and ALS patients behaved similarly over time.

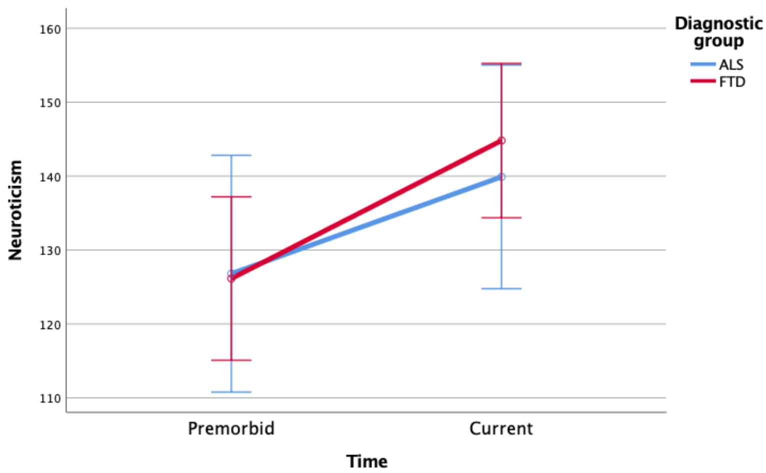

Figure 1. Evolution of Neuroticism over time between diagnostic groups.

Similarly, in both Extraversion and Openness there was a significant effect of time (p=0.027, p=0.004), in that they tended to decrease in both FTD and ALS patients, but there was no interaction time-by-group (p=0.595, p=0.693). As previously mentioned, there was a significant effect of diagnostic group.

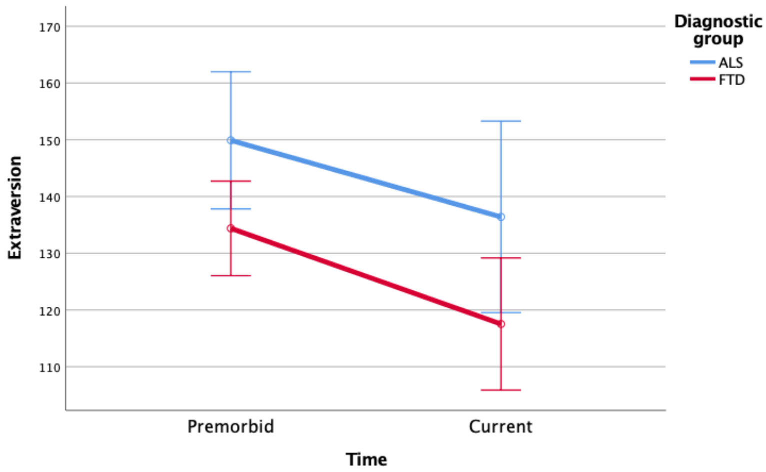

Figure 2. Evolution of Extraversion over time between diagnostic groups.

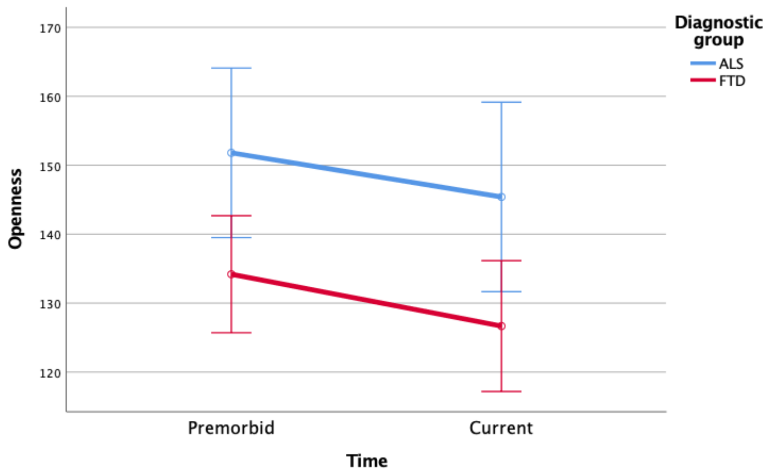

Figure 3 Evolution of Openness over time between diagnostic groups.

Conversely, the two groups behaved differently in the Agreeableness domain, with a significant interaction between time and diagnostic group (p=0.02). In fact, they were similar in premorbid life, but became different in current time, since FTD patients decreased their Agreeableness scores and ALS patients increased them. There was no significant effect of time or diagnosis alone (p=0.305, p=0.2).

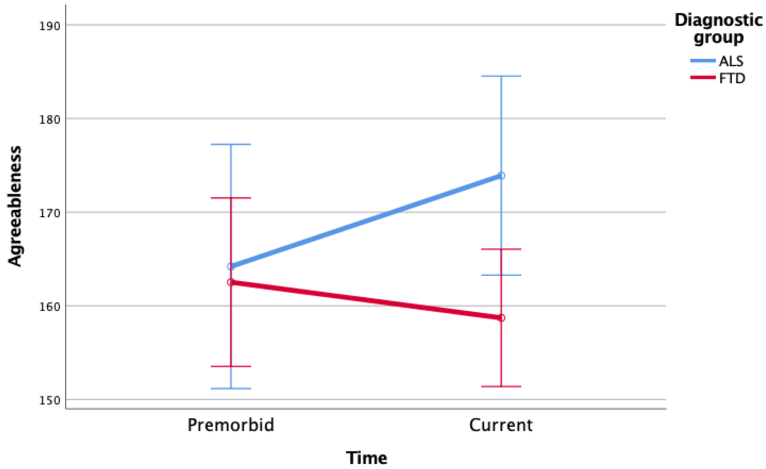

Figure 4. Evolution of Agreeableness over time between diagnostic groups.

Finally, there was a significant effect of time (p=0.004) and an almost significant interaction time-by-group (p=0.06) in the Conscientiousness domain. In fact, both groups decreased their score during time, but while the reduction was mild for ALS patients, it appeared extremely marked for FTD patients. The effect of diagnostic group also resulted significant (p=0.04).

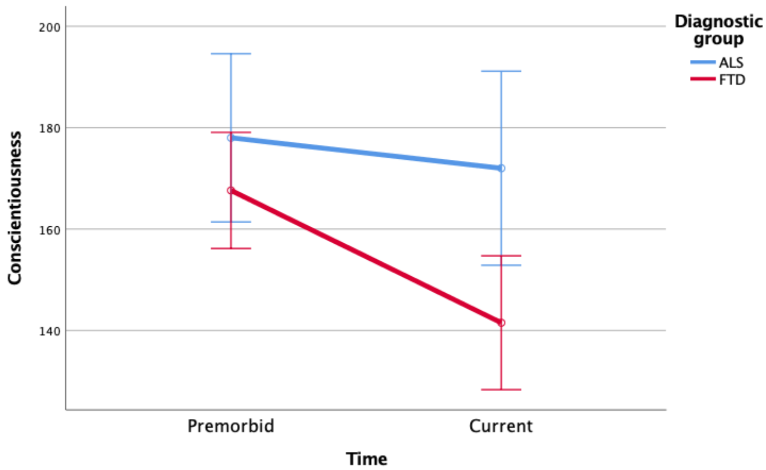

Figure 5. Evolution of Conscientiousness over time between diagnostic groups.

4.7. Imaging results

4.7.1. VBM results

Among the 50 patients recruited, 28 patients (21 FTD and 7 ALS) performed the MRI protocol, and high-resolution T1-weighted images were used for VBM as previously described. Also, a group of 10 healthy subjects were included in the analysis as healthy controls.

4.7.1.1. GM volume comparison between groups

We compared GM density between FTD and ALS patients and controls (Fig.6).
No results survived at corrected threshold of $p < 0.05$.
At uncorrected threshold of $p < 0.001$, FTD showed greater atrophy in bilateral frontal as well as temporal and parietal areas compared to controls.
ALS showed greater atrophy in bilateral primary motor cortex, left greater than right, compared to controls.
The direct comparison between FTD and ALS showed greater atrophy in ALS compared to FTD in the bilateral premotor cortex, left greater than right.

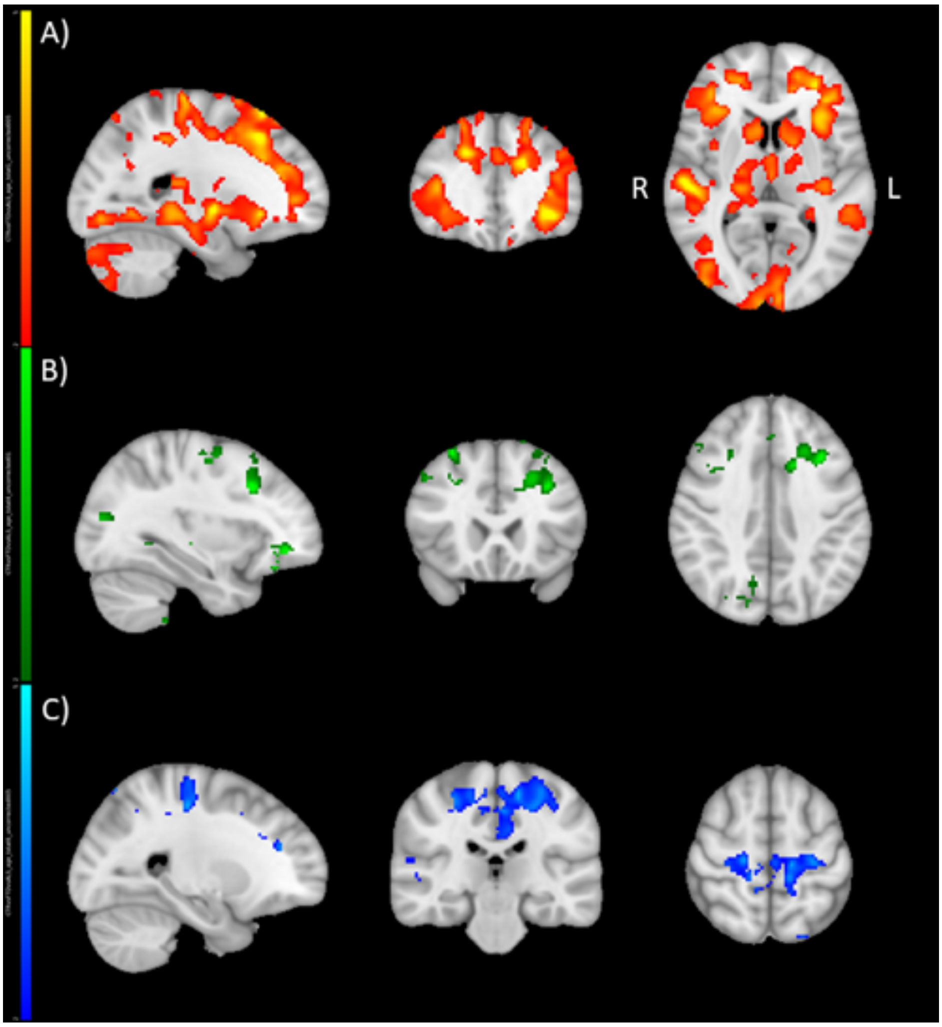

Figure 6. Results of VBM analysis, comparison between groups. A) In red-yellow, areas of decrease gray matter volume in FTD patients relative to controls. B) In Green, areas of decrease gray matter volume in FTD relative to ALS patients. C) In blue-light blue, areas of decrease gray matter volume in ALS patients relative to controls). Results are shown at $p_{uncorr} < 0.005$ for visualization purposes.

4.7.1.2. Correlation between GM volume and personality traits across all subjects

The VBM correlational analysis with premorbid NEO-PI-3 scores assessed by caregivers (which also included age, MMSE and current NEO-PI-3 scores as covariates of no interest) showed a significant positive correlation between GM volume and Neuroticism in bilateral hippocampus for left more than right (TFCE corrected $p < 0.05$) (Fig.7). In detail, the lowest the premorbid score on Neuroticism the greater the atrophy in both hippocampi, left parahippocampal gyrus, and right and left temporal fusiform gyri.

A significant positive correlation (TFCE corrected $p < 0.05$) was also found between GM volumes and Conscientiousness in the right angular gyrus. In the same region, also Extraversion and Openness were found to be positively correlated, but at $p<0.005$ uncorrected.

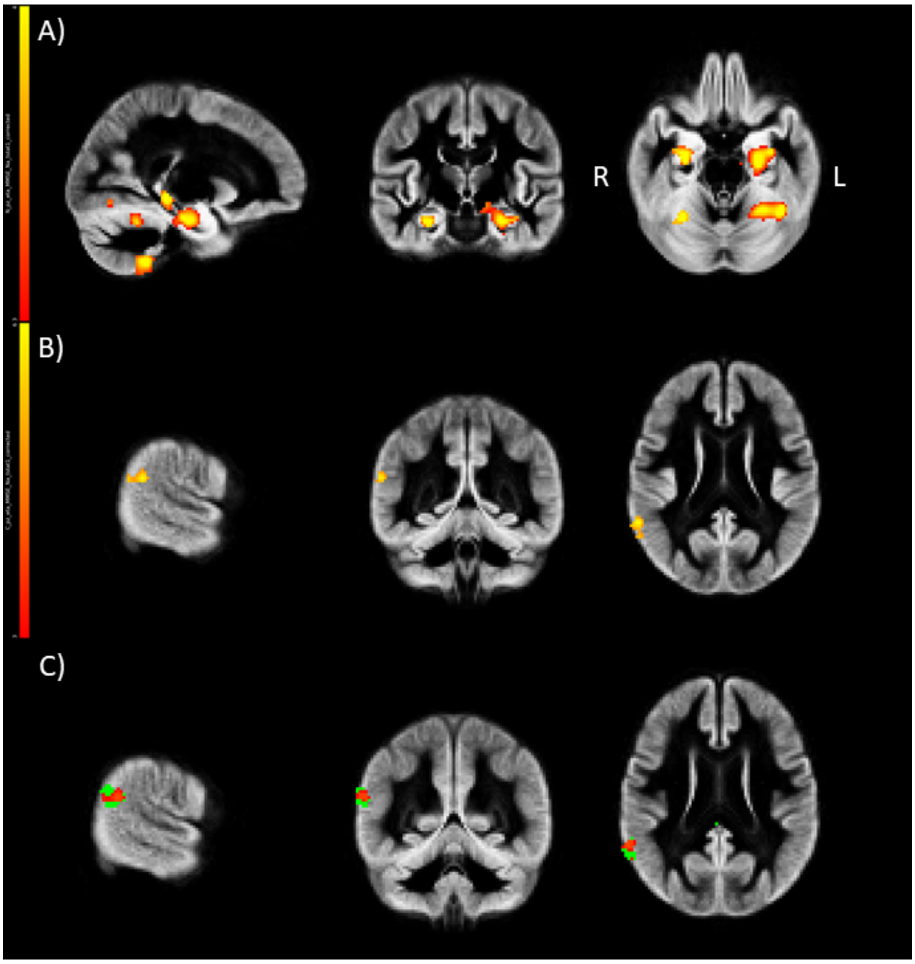

Figure 7. Results of the VBM correlational analysis between GM and the five NEO-PI-3 domains across all patients. A) Areas of significant correlation between GM and Neuroticism (TFCE corrected $p<0.05$). B) Areas of significant correlation between GM and Conscientiousness (TFCE corrected $p<0.05$). C) In red, overlay of areas of positive correlations between GM and Extraversion, Openness and Conscientiousness at $p_{uncorr} < 0.005$, superimposed on areas of significant correlation between GM and Conscientiousness shown in B (here in green).

4.7.2. fMRI results

Eight of the 25 group-ICA spatial maps were identified as biologically valid, non-artifactual resting state networks (RSNs). These RSNs identified were:

1. The Default mode network (DMN): this network includes the posterior cingulate cortex and angular gyrus;
2. The visual cortical network: it includes the occipital lobes and it extends laterally towards the occipito-temporal junction;
3. The right frontoparietal network: it has complementary pattern to the previous network, including the bilateral intraparietal activation;
4. The anterior sensory-motor network: it includes activation in pre- and post-central gyri;
5. The posterior sensory-motor network: it includes activation in pre- and post-central gyri;
6. The left frontoparietal network: it shows activation in left inferior parietal cortex, bilateral intraparietal sulcus, and left middle and superior frontal gyri;
7. The Salience network (SN): it includes the frontal lobe, anterior cingulate and insula;
8. The anterior Default mode network (DMN): it includes the anterior medial and lateral prefrontal cortex.

4.7.2.1. Functional connectivity comparison between FTD and ALS patients

Within the Salience network, ALS showed greater functional connectivity compared to both Controls and FTD in the right insula, putamen and nucleus accumbens, and in the left thalamus (Fig.8).

Compared only to the FTD group, ALS also showed greater connectivity in the left anterior cingulate cortex, left frontal pole and middle frontal gyrus, right angular gyrus.

No significant differences were found between groups in the other RSNs.

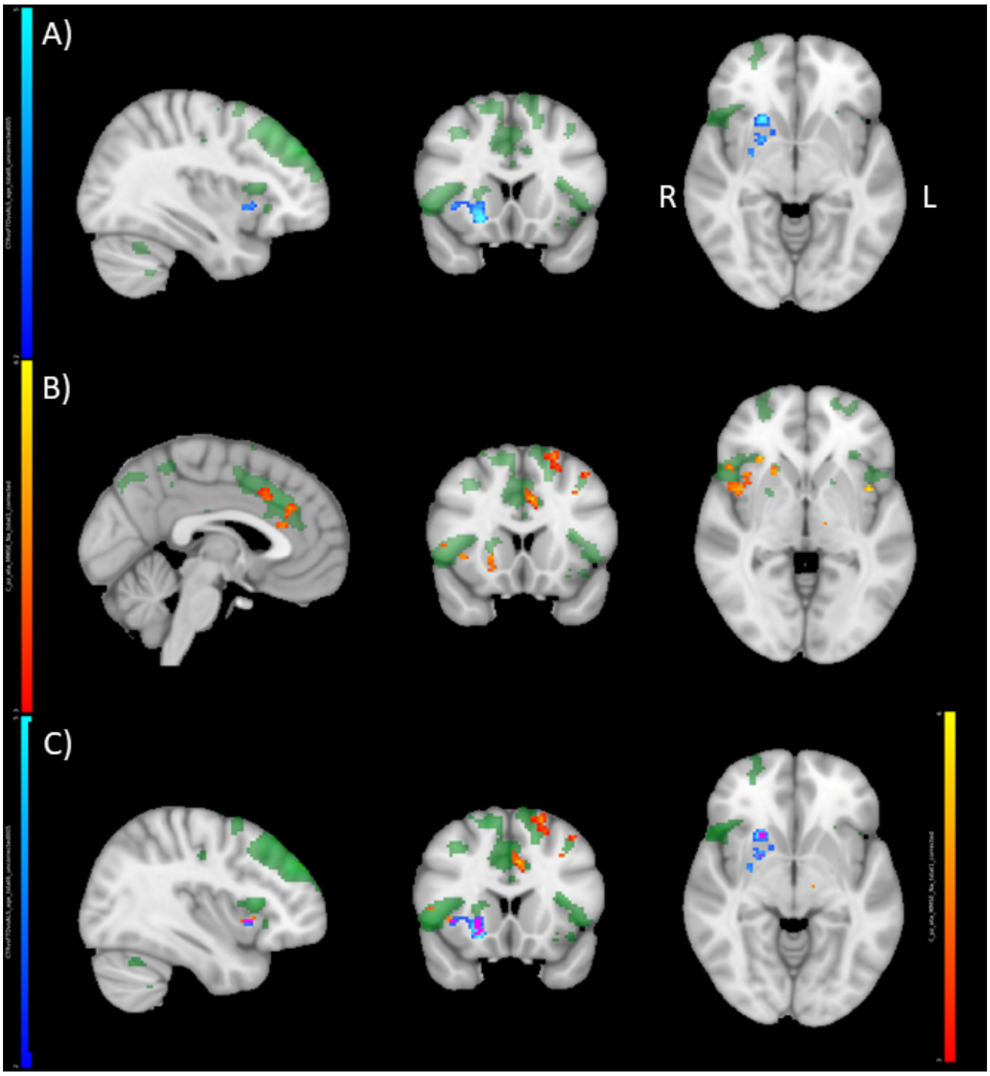

Figure 8. Results of between-group comparisons of rsfMRI connectivity within the Salience Network (SN), shown in transparent green in all the images. A) In blue-light blue, regions of significant greater SN functional connectivity in ALS relative to controls. B) In red-yellow, regions of significant greater SN functional connectivity in ALS relative to FTD. C) overlay of A and B, with common areas shown in purple. Results are shown at TFCE corrected $p < 0.05$.

4.7.2.2. Correlation between functional connectivity and premorbid personality

Since we found significant between-group differences in functional connectivity within the Salience network, we explored if they were associated with scores of premorbid personality.

A significant positive correlation emerged between parameter estimates of functional connectivity extracted from the regions of significant difference between ALS and FTD in the Salience network and premorbid scores of Openness ($r = 0.37$, $p = 0.0312$) across all patients (FTD and ALS altogether).

A similar significant positive correlation ($r = 0.358$, $p = 0.0372$) emerged between mean parameter estimates of functional connectivity extracted from the whole Salience network and the premorbid Openness scores (fig.4).

A significant positive correlation was also found between mean parameter estimates of functional connectivity extracted from the whole Sensory-motor network and premorbid Openness ($r = 0.32$, $p = 0.05$).

A positive correlation at the trend level emerged between parameter estimates of functional connectivity extracted from the regions of significant difference between ALS and FTD in the Salience network and premorbid scores of Extraversion ($r = 0.30$, $p = 0.08$).

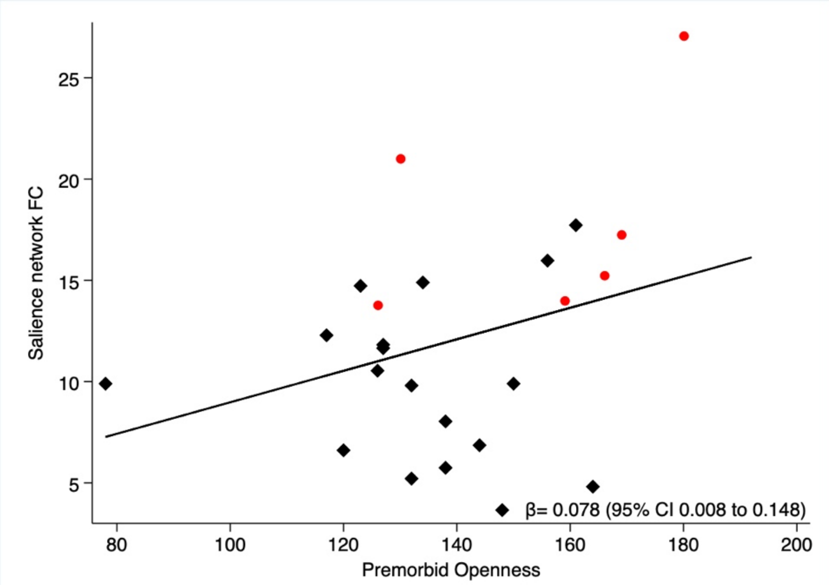

Figure 9. Correlation between Functional Connectivity (FC) in the Salience Network and NEO-PI-3 premorbid Openness scores. Red dots represent ALS patients, black squares represent FTD patients.

Voxel-wise correlational analyses between premorbid personality scores and current functional connectivity across all patients give no significant results in any of the RSNs of interest.

5. DISCUSSION

In this study, we aimed at testing the hypothesis that, along the FTD-ALS continuum, patients with the two different phenotypes bvFTD and ALS are characterized by a different premorbid personality. In addition, we wanted to investigate if different premorbid personality profiles are associated with subsequent differences in brain structure and function across the continuum.

5.1.Premorbid personality

We found that FTD and ALS patients differed in two domains of premorbid personality, Extraversion and Openness. Specifically, FTD showed lower scores compared to both ALS and to the reference sample for the NEO-PI-3 test, as rated by their caregivers. This means that individuals who subsequently developed the behavioral/cognitive form of the disease (bvFTD) were originally characterized by a less open and extravert personality than people who subsequently developed the motor phenotype of the disease (i.e. ALS). This is the key and most novel finding of the present study, concerning a topic very rarely investigated. In fact, the literature on personality and neurodegeneration is scarce and generally contradictory. To the best of our knowledge, only one study investigated ALS patients' premorbid personality, finding higher levels of Extraversion, Agreeableness, and Conscientiousness in ALS patients relative to healthy controls[58]. Our findings show some consistency with these results, even if, based on our results, we could assert that FTD, rather than ALS, deviate from the reference mean in Extraversion, showing lower scores not only compared to ALS but also to the reference norm sample. Conversely, both FTD and ALS deviated from the reference mean in Openness, with absolute low values compared to the norm sample. Also, a difference in Openness emerged between the two group, with FTD scoring lower than ALS. Another study on current personality carried out in ALS patients detected lower scores in the Openness domain, as compared with patients with other chronic and progressive non-neurologic diseases[57]. However, there are no studies directly comparing premorbid personality between FTD and ALS patients.

5.2.Premorbid Extraversion

The Extraversion-Introversion axis describes a dimensional personality trait associated with qualities including sociability, assertiveness and cheerfulness. The low pole of the dimension is associated with introverted qualities such as being quiet and reserved. Therefore, individuals who score low in Extraversion are tendentially introvert, reserved, independent, and even-paced, generally preferring to be alone, even if this is not synonymous with social anxiety. Although they are not given to the exuberant high spirits of extraverts, introverts are not unhappy or pessimistic. In some ways, introvert attitude might be best described as absence of Extraversion more than its opposite. Conversely, individuals that are high in Extraversion are sociable; they like people and prefer large groups and gatherings. Extraverts tend to be assertive, active, and talkative. They like excitement and stimulation and tend to be cheerful in disposition. They are upbeat, energetic, and optimistic.

Research on the cognitive neuroscience of Extraversion has gained much attention in the last decades, and several psychobiological theories of this domain have been formulated[83-85], all sharing the assumption of the feed-forward model[86]. It assumes that personality traits are encoded in DNA as a set of genetic polymorphisms in genes coding for brain development; then, the genetic influence, in conjunction with environmental factors, feed forward into brain functioning and behavior, leading to individual differences in brain functioning which in turn generate individual differences in measured phenotypic traits. Several theories identify the mesolimbic dopamine system as the primary mechanism underlying individual differences in Extraversion[87]. Specifically, they implicate a neuroanatomical network and modulatory neurotransmitters in the processing of incentive motivation. This corticolimbic-striatal-thalamic network integrates the salient incentive context in the medial orbital cortex, amygdala, and hippocampus; encodes the intensity of incentive stimuli in a motive circuit composed of the nucleus accumbens, ventral pallidum, and ventral tegmental area dopamine projection system; and creates an incentive motivational state that can be transmitted to the motor system[87].

Individual differences in the functioning of this network are thought to arise from functional variation in the ventral tegmental area dopamine projections, which are directly involved in coding the intensity of incentive motivation. Reward-reactivity has been linked with dopamine function in behavioral neuroscience research[88-90] and with Extraversion in psychometric[91] and behavioral research.

Also, several neuroimaging studies have been conducted to test the prediction of these theories. Among functional MRI studies, Cohen and colleagues[92] have shown with a fMRI experiment that individual differences in Extraversion and the presence of the A1 allele on the dopamine D2 receptor gene predict activation magnitudes in the brain's reward system during a gambling task, thus adding evidence to a possible link between differences in personality, genetics, and brain functioning. Kennis et al.[93] reviewed fMRI studies on the topic and concluded that Extraversion correlates consistently with increased activity in response to positive stimuli in several areas associated with dopaminergic pathways, including the ventral and dorsal striatum and ventral prefrontal cortex.

Among structural MRI studies, Wacker and Smillie[94] reviewed several studies that investigated associations between Extraversion and the volume and morphology of the medial orbitofrontal cortex, a crucial area in the mesocortical dopaminergic pathway. Positive associations between Extraversion and volume of this structure have been reported, but they have proved difficult to replicate.

In our study, we found a greater FC of ALS patients compared to FTD and to controls within the Salience network, specifically in the right insula, right putamen and right nucleus accumbens, and the left thalamus. This finding might be interpreted as in line with the previously cited studies, and creates a link between the behavioral difference in Extraversion trait found between ALS and FTD in premorbid personality and the current state of functional connectivity in the Salience network, that includes the corticolimbic-striatal-thalamic dopaminergic pathway so strongly connected to Extraversion in the literature. Thus, we can speculate that an individual modulation of Extraversion can be reflected in different brain structural and functional organization, which in turn could influence the manifestation of a subsequent neurodegenerative process when occurring in the brain, by modulating the pattern of spreading of the disease along some preferential, already vulnerable neural circuits. More precisely, we can speculate that subjects with higher degrees of Extraversion might have become resilient to the bvFTD phenotype, which is known to specifically affect the Salience network[95], because they had premorbidly developed stronger functional connectivity in regions of the Salience network that are also part of the mesolimbic pathway. Thus, when the neurodegenerative process begun, these subjects may have been paradoxically more vulnerable to the motor presentation of the disease, thus developing ALS.

5.3.Premorbid Openness

We also found a marked difference in premorbid Openness between ALS and FTD.
Openness is a personality trait reflecting a broad range of cognitive–affective styles such as absorption in sensory experience, preference for novel experiences, curiosity, and creativity[73]. Open people are typically described as highly "permeable" and receptive to salient stimuli and strongly motivated to "enlarge" their sensory experience. At the brain level, some authors have proposed that Openness is associated with mesocortical networks (i.e., midbrain–prefrontal cortex (PFC) dopaminergic circuits)[46], and therefore Openness and Extraversion have been associated with dopaminergic function. Indeed, dopamine (DA) plays a key role in encoding, maintaining, and updating information relevant for adaptive behaviors and, more generally, in orienting attention towards salient stimuli. DeYoung have also hypothesized that two distinct dopaminergic pathways underlie Openness and Extraversion: the mesocortical and mesolimbic pathways, respectively[96].
So, it is not surprising that we found similar result for both the domains across groups. Of note, we found in both FTD and ALS lower scores for Openness compared to the reference sample, outlining that both FTD and ALS patients were characterized by a relatively low tendency to curiosity towards internal and external experiences, artistic sensibility, great imagination.
We also found that the functional connectivity within the Salience network correlated with premorbid Openness, suggesting that also Openness could play a role in modulation of the Salience network functional connectivity.

Considering all these results, we could speculate that low levels of Openness, which seem to characterize both FTD and ALS, might represent a "risk factor" for the whole FTD-ALS spectrum of disease, and that different level of Openness could influence phenotypic manifestation of the disease, with very low degrees of Openness pushing towards clinical phenotypes that specifically targets the Salience network, i.e. FTD.

5.4.Premorbid Conscientiousness

We also found that ALS patients were high scorers in Conscientiousness compared to the reference population, while FTD patients scored in the normal range, even if the difference in the direct comparison between ALS and the FTD groups did not reach statistical significance.

Individuals who are high in Conscientiousness are purposeful, strong-willed, and determined. They are typically involved in planning, organizing, and carrying out tasks, and this explain why high Conscientiousness is often associated with academic and occupational achievement. High scorers are scrupulous, punctual, and reliable. Conversely, low scorers are less exacting in applying moral principles, and more lackadaisical in working toward their goals. During the individual development, a person learns how to manage his impulses, and the inability to efficiently control them is generally a marker of high Neuroticism. Nonetheless, self-controls can also refer to a more specific and active planning process, including organization and performance of tasks; individual differences along this trajectory constitute the theoretical basis of Conscientiousness[97]. However, a tight relation between Conscientiousness and Neuroticism exists, since at least in the NEO-PI-3 all six facets of Neuroticism are negatively correlated with Conscientiousness. This observation was confirmed in our study population, since both FTD and ALS seemed to display a relatively low level of premorbid Neuroticism, and a relatively high, but still in the normal range, Conscientiousness level for FTD while ALS showed significantly high level of Conscientiousness.

We found a significant positive correlation of this domain with GM volume in the right temporo-parietal junction (TPJ) and angular gyrus across the whole group of patients, i.e. FTD and ALS altogether. The same positive correlation with the right TPJ emerged with Extraversion and Openness premorbid scores, even if not reaching statistical significance. Also, we also found that the TPJ showed higher functional connectivity in the ALS compared to FTD, but not compared to controls, in the Salience network.

Several studies have implied the TPJ, and particularly the right TPJ, as a key area among those involved in ToM[98]. Recently, Bitsch et at. conducted a fMRI experiment to test the hypothesis that the rTPJ-activity is involved in social decision-making situations. They found that the rTPJ and the posterior–medial prefrontal cortex showed higher activity during competitive versus a cooperative social interaction, and specifically the rTPJ showed a high response during an early interaction phase. Tei et al. also used fMRI experiments to test the role of temporoparietal junction (TPJ) in flexible behavior and found that it plays a crucial role, combined with the dorsolateral-prefrontal cortex (DLPFC) in flexibility, and particularly moral flexibility, which can be related to some aspects of Conscientiousness.

Mai et al.[99] used non-invasive transcranial direct current stimulation (tDCS) of the rTPJ and showed that accuracy of both ToM and cognitive empathy decreased after receiving inhibitory stimulation, suggesting that altering the cortical excitability in the rTPJ could influence human's socio-cognitive abilities.

Also, many studies have related personality factors with parietal activity: Extraversion, Openness, Conscientiousness and Agreeableness were found to be positively correlated with parietal activity, specifically the precuneus, during rsfMRI[100].

Based on these literature findings and our results, we can speculate that in our group of patients the rTPJ seem to play an important role in at least Conscientiousness, and premorbid level of this personality trait could influence structural integrity and functional connectivity of this area within other regions of the Salience network, which in turn is considered to represent the functional correlate of ToM brain regions.

Thus, according to the Five Factor Model, individuals who have a high level of Extraversion are typically described as prosocial and friendly, they appreciate being with other people and are prone to joy and optimism. High level of

Conscientiousness indicates self-control, rules following, hard-working, resolution, determination, and reliability [43]. All these domains, in which ALS patients scored higher than FTD in our study group, can reasonably be interpreted as an expression of the nice and prosocial personality that is often described by caregivers and physicians in reference to ALS patients.

5.5.Premorbid Neuroticism

Finally, we found a positive correlation between premorbid Neuroticism and GM volume in both hippocampi, left parahippocampal gyrus, and right and left temporal fusiform gyri across the whole group. This means that individuals with neurotic traits well before disease onset show a higher preservation of these structures once the disease is diagnosed, whereas subjects characterized by more emotional stability in their premorbid life show today more GM atrophy in the same areas.

Neuroanatomical correlates of Neuroticism are a debated topic in literature, since several studies have found different results over the years, and so a univocal model has not yet been established. As general notion, Neuroticism is positively corelated with activation in the amygdala, the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC) and hippocampus. DeYoung et al., who conducted an extensive VBM study on the correlation between NEO-PI-3 personality traits and GM volume, found that higher Neuroticism is associated to greater atrophy in medial temporal lobe, including the hippocampus[46]. Similarly, other studies linked mood disorders, which are frequently considered an expression of neurotic personality, to greater atrophy of hippocampus and amygdala[101, 102].

However, a meta-analysis of VBM studies that considered different personality theories revealed instead an increased GM volume in the left amygdala and parahippocampal gyrus in individuals with high levels of negative emotionality related traits – that's to say Neuroticism in FFM model[103].

Moreover, a study that investigated neural correlates of depression and negative automatic thoughts, which again can be considered an expression of high Neuroticism, found a correlation between these elements and increased GM volume of parahippocampal gyrus[104].

Hippocampus, parahippocampal gyrus, and amygdala are important structure of the limbic system and have been long recognized as central nodes for regulation of stress responses[105]. In particular, it has been shown that individuals with mood disorders have a more sustained limbic activity during emotional processing, in particular towards negative stimuli[105, 106]. From this perspective, it could be speculated that highly neurotic subjects have greater GM volume in these limbic regions as a consequence of plastic changes occurred for following their greater use. Once the neurodegenerative disease develops, these same regions may therefore result resilient to GM loss relative to other structures.

5.6.Current personality

When looking at the current personality scores, the difference in Openness persisted also at present time, even if slightly attenuated.

In the Extraversion domain, no significant difference appeared to persist at present time, since both groups displayed an important decrease in the domain's scores, significantly low compared to the reference norm sample.

Finally, differences between the two groups also appeared in Agreeableness and Conscientiousness domains, and this could be partially explained in terms of adaptation to disease. For the Agreeableness domain, the difference in current personality was driven by the sharp increase in Agreeableness scores at present showed by ALS. Conversely, the marked difference in current Conscientiousness was driven by the sharp decline of FTD, which also ALS showed even if much more restrained.

As expected, FTD patients appeared less pleasant after the development of dementia, probably due to the dementia itself. Actually, loss of empathy and disinhibition strictly characterize bvFTD, and they could be the effect of neurodegeneration directly impacting on the specific behavioral neurocircuits known to be selectively involved in the disease.

On the contrary, ALS patients manifested even higher level of kindness at the present moment compared to the premorbid state, which already showed scores in the upper normal reference range. This is in line to what experienced by those, clinicians or caregivers, who take care of ALS patients, who are often perceived as inexplicably resilient throughout their difficult disease and in spite of their inevitably poor prognosis, showing themselves collaborative to clinicians and prone to follow recommendations and treatment[37]. Again, these change along time in Agreeableness could be explained in term of response to neurodegeneration, which in this case could exacerbate an already present personality tract. A different longitudinal trajectory appeared to be followed by Conscientiousness domain, which in ALS group was characterized by absolute high scores in the past, that decreased over time and fitted in the normal range at the disease timepoint.

Changes in personality traits during life have been extensively studied, although with inconsistent results. A recent study, which examined a broad sample of individuals at different ages, showed that Extraversion and Openness tend to decrease during lifetime, Conscientiousness is stable or increases through early and middle adulthood, but decreases in older adulthood, and Neuroticism decreases through most of adulthood but begins to increase again in older age. Agreeableness seems to remain relatively stable over time[107].

Our results are generally in line with these findings, in particular for Extraversion, Openness and Conscientiousness. As regards Neuroticism, it is interesting that some authors have suggested increasing Neuroticism in older adulthood as a reflection of increasing level of anxiety regarding onset of terminal diseases and approaching mortality[108]. This could be a reasonable explanation for the substantial increase in Neuroticism that we found for both FTD and ALS patients. In particular, despite their relatively younger age, ALS patients have to face a diagnosis of an incurable, disabling and rapidly progressive condition of which they are completely aware, this being a markedly different situation compared with FTD patients. As mentioned above, differences in overtime changes in the Agreeableness domain between FTD and ALS patients can be probably explained in terms of consequence of the disease rather than in terms of changes in personality during the lifespan.

Thus, personality seems to greatly vary along time and, for most of the personality tracts, these changes can be seen as a consequence of aging combined with the effect of the neuropathological process itself.

5.7.Limitations and future directions

A limitation of our study is that our sample was rather small, especially the subsample of patients that underwent the MRI scan, and the asymmetry between the FTD and ALS group, thus limiting the statistical precision of our estimates. Another limitation of the study is that personality evaluation of premorbid and current personality was based on caregivers' ratings: this approach was chosen as an obliged alternative to self-compiled questionnaires, that in case of patients affected by neurodegenerative disease could not be a reliable methodology. Nonetheless, caregivers' evaluation is not immune to bias, since it could be less precise for recall difficulties or influenced by individual attitude and caring role itself.

Also, caregivers were instructed to compile the "premorbid" form of the NEO-PI-3 referring to the patient 15 years before. However, we know that neurodegenerative diseases start many years before first symptoms, and even retrospectively it is not possible to date precisely when the disease started in a specific individual. So, we cannot be certain that the collected data on premorbid personality reliably reflect the premorbid state, thus indicating the need of studies with prospective design on this issue.

In addition, imaging analysis have been performed with MRI scans acquired at the time of the disease, therefore the correlation between historical behavioral data and current MRI findings must be interpreted with caution.

6. CONCLUSIONS

In this study, we found a remarkable difference in premorbid personality of FTD patients compared with ALS patients, the former being characterized by lower Extraversion and Openness many years before the disease onset. We also found differences in functional connectivity between ALS and FTD in a specific brain network, the Salience network, which includes key areas known to be associated with the Extraversion and Openness personality traits and known to be specifically involved in FTD neurodegeneration. Finally, we found a correlation, across the whole group of patients, between functional connectivity in the Salience network and premorbid Extraversion and Openness, suggesting a possible association, with a potential causative role, between premorbid personality and disease phenotype, i.e. ALS vs FTD.

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