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A review on shared clinical and molecular mechanisms between bipolar disorder and frontotemporal dementia

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Abstract

Mental disorders are highly prevalent and important causes of medical burden worldwide. Co-occurrence of neurological and psychiatric symptoms are observed among mental disorders, representing a challenge for their differential diagnosis. Psychiatrists and neurologists have faced challenges in diagnosing old adults presenting behavioral changes. This is the case for early frontotemporal dementia (FTD) and bipolar disorder. In its initial stages, FTD is characterized by behavioral or language disturbances in the absence of cognitive symptoms. Consequently, patients with the behavioral subtype of FTD (bv-FTD) can be initially misdiagnosed as having a psychiatric disorder, typically major depression disorder (MDD) or bipolar disorder (BD). Bipolar disorder is associated with a higher risk of dementia in older adults and with cognitive impairment, where a subset of patients presents a neuroprogressive pattern during the disease course. No mendelian mutations were identified in BD, whereas three major genetic causes of FTD have been identified. Clinical similarities between BD and bv-FTD raise the question whether common molecular pathways might explain shared clinical symptoms. Here, we reviewed existing data on clinical and molecular similarities between BD and FTD to propose biological pathways that can be further investigated as common or specific markers of BD and FTD.

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Keywords

bipolar disorder; frontotemporal dementia; neuropsychiatric symptoms; neurodegeneration; biomarkers

1. Introduction

The World Health Organization estimates that approximately 15% of adults worldwide aged 60 years or over currently suffer from some form of mental disorder (WHO, 2018). Data from the same source show that mental disorders are responsible for 6.6% of all disability (disability adjusted life years-DALYs) in this age group. Dementia and depression are the most common forms of mental and neurological disorders in the elderlies. With the older population growing rapidly (Alzheimer's, 2016), physical and mental health challenges will need to be recognized. Unfortunately, mental health issues are still under-identified by older subjects themselves and their family members, as well as by health-care professionals (Alzheimer's, 2016; WHO, 2018). There is also a stigma attached to these conditions, which makes sufferers reluctant to seek medical care. Even when receiving medical care, challenges remain concerning diagnosis and treatment, since neurological and psychiatric symptoms can co-occur in the same patient (Choi et al., 2017; Woolley et al., 2011).

Co-occurrence of cognitive and psychiatric symptoms in elderlies is particularly typical in Alzheimer's disease (AD) (Lanctot et al., 2017), and has been also observed in less frequent types of dementia. In frontotemporal dementia (FTD), for instance, behavioral or language disturbances can manifest in the absence of cognitive symptoms at early stages of the disease (Chare et al., 2014; Liscic et al., 2007; Mendez et al., 2007; Miller et al., 1995; Nyatsanza et al., 2003; Woolley et al., 2011; Woolley et al., 2007; Zamboni et al., 2008). Although depression is a symptom presentation typically seen in AD (Lanctot et al., 2017), patients with the behavioral subtype of FTD (bv-FTD) can be initially diagnosed with a psychiatric condition significantly more often than patients with AD or other FTD subtypes (Woolley et al., 2011). bv-FTD patients were more likely to be misdiagnosed as having major depressive disorder (MDD), bipolar disorder (BD) or schizophrenia (SCZ). Interestingly, BD is associated with a significantly higher risk of dementia in older adults (Diniz et al., 2017), and cognitive impairments have been consistently found in this disorder (Cullen et al., 2016). Moreover, the course of BD may follow a progressive pattern, as observed in a subgroup of patients (Bauer et al., 2017; Kapczinski et al., 2014; Magalhaes et al., 2012). This progression includes the presence of cognitive impairment later in the disease course (Elshahawi et al., 2011; Martinez-Aran et al., 2004), a feature also characteristic of bv-FTD (Chare et al., 2014).

Clinical similarities between BD and bv-FTD have been a focus of research past decade (Dols et al., 2016; Kerstein et al., 2013; Lopes and Fernandes, 2012; Masouy et al., 2011; Rubino et al., 2017; Woolley et al., 2011; Woolley et al., 2007), raising the question whether the same molecular pathways might explain shared clinical symptoms. No mendelian mutations have been identified in BD, whereas three major genetic causes of FTD have been identified so far: microtubule-associated tau protein (MAPT) (Hutton et al., 1998;

Wilhelmsen et al., 1994), progranulin (GRN) (Baker et al., 2006; Cruts et al., 2006), and in the hexanucleotide expansion in chromosome 9 (C9ORF72) (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Interestingly, FTD patients caring mutation in the C9ORF72 gene present the majority of psychiatric symptoms, and this mutation has been associated with familial BD (Galimberti et al., 2014; Meisler et al., 2013). The presence of different misfolded proteins in the brain, as well as genetic mutations (associated or not to these misfolded proteins or otherwise) are hallmarks in the pathology of FTD (Lowe, 2011; Mackenzie and Neumann, 2016; Takada, 2015, 2017), but these features has not been consistently explored in BD. In BD, other molecular pathways, such as inflammation, neuroprotection and oxidative stress have been further investigated (Muneer, 2016). Here, we reviewed the existing data on clinical and molecular similarities between BD and FTD (with a focus on bv-FTD whenever possible) to propose potential biological pathways that can be further investigated as common or specific markers of BD and FTD. This is important to better understand the pathophysiology of these diseases and also for diagnostic purposes.

2. Clinical symptoms of bipolar disorder relevant to neurology

2.1 Clinical features and cognitive impairment in bipolar disorder

Bipolar disorder is characterized by recurrent episodes of mania and depression, interspersed with periods of normal mood, energy and behavior (euthymia). During manic episodes, patients experience racing thoughts, disinhibition, impulsivity, elevated mood, grandiosity and low need for sleep, while episodes of depression are characterized by sadness, thoughts of guilt, and incapacity to feel pleasure or interest in daily activities (anhedonia). Additionally, some degree of cognitive impairment can often be found in patients with BD, even during euthymia (Burdick et al., 2010).

Although cognitive impairments are present in various psychiatric disorders, they can be especially prominent in BD (Cullen et al., 2017; Vohringer et al., 2013). The trajectory of BD can be highly variable, and progressive worsening of cognitive functions can occur in a subgroup of these patients (Burdick et al., 2015; Van Rheenen et al., 2017). In a meta-analysis, different rates of impairment in multiple cognitive domains of euthymic BD patients were found in cross-sectional studies: executive function 5.3–57.7%, attention/working memory 9.6–51.9%, speed/reaction time 23.3–44.2%, verbal memory 8.2–42.1% and visual memory 11.5–32.9% (Cullen et al., 2016). The high prevalence and evidence of impairments in multiple cognitive domains suggest cognitive decline is an endophenotype of at least a subgroup of BD patients. Trait-related cognitive deficits are present at BD onset and become more severe at later stages of the disease (Rosa et al., 2014). Another systematic review included 39 studies found a positive association between cognitive decline and poor clinical outcome in BD (Cardoso et al., 2015). Furthermore, evidence from the review suggest that cognitive function may be associated with clinical course of the disease such as number of mood episodes, hospitalizations, and duration of illness. Meta-analytical data on cognitive impairment among non-demented patients in remission from acute episodes of BD showed that executive and verbal memory were the most commonly impaired domains (Balanza-Martinez et al., 2010). Recent studies have demonstrated that executive function, working memory, and verbal memory are the domains especially affected in BD patients

(Bourne et al., 2013; Cardoso et al., 2015; Ospina et al., 2018; Vrabie et al., 2015). Memory impairment could explain functionality problems in patients, even during euthymic periods (Cullen et al., 2016; Mann-Wrobel et al., 2011; Martinez-Aran et al., 2004). Several studies have shown that BD patients may exhibit cognitive decline during the disease course. However, these results vary with regard to the cognitive domains affected, as well as the associated risk factors (Arts et al., 2008; Bora et al., 2009; Cullen et al., 2017; Gildengers et al., 2007). The number of manic episodes seems to be the clinical marker most strongly associated with neuroprogression in BD, as described in recent reviews (Passos et al., 2016). Other reviews involving adults associated greater cognitive impairment with more severe or longstanding illness and with use of antipsychotic medication (Cullen et al., 2016). A meta-analysis including data from 31 studies and 2876 subjects showed that BD patients had impairments in all cognitive domains evaluated (executive function, attention, verbal memory, and learning and response inhibition), even after adjusting for confounding factors, such as age, gender and IQ (Bourne et al., 2013).

The presence of cognitive dysfunction is particularly noteworthy given the evidence that some patients with BD start out cognitively intact or even with superior cognitive functioning relative to healthy controls (MacCabe et al., 2010). However, more recent data collected through systematic review and meta-analysis indicate that cognitive deficits can be present in early stages of BD (Daglas et al., 2015; Lee et al., 2014). A meta-analysis on cognitive performance in first-episode BD (any phase: depression, hypomania, mania, mixed or psychosis), indicated deficits with small to large effects for processing speed, attention, verbal learning, memory and executive functions compared to healthy controls (Lee et al., 2014). A systematic review of cognitive functioning in the early stages of BD showed deficits in working memory as the most consistent finding (Daglas et al., 2015). Further longitudinal studies may help elucidate the longitudinal trajectory of cognitive impairment from first-episode.

BD in older adults is associated with increased risk of dementia over the long-term (Diniz et al., 2017; Rise et al., 2016). This finding appears to be correlated with the number of major affective episodes throughout the clinical course of the disease, particularly those requiring hospitalizations (Kessing and Andersen, 2004). However, there is limited data on the cognitive profile of older adults with BD that develop dementia. Additionally, biological mechanisms underlying cognitive decline and dementia in BD are still poorly understood. The e4 allele of apolipoprotein E (APOE*4) is a well-established risk factor for dementia in AD. APOE*4 was not associated with BD diagnostic and appeared not to impact the occurrence of dementia in BD (Kerr et al., 2016). Also, cognitively impaired patients with BD do not display the so-called AD bio-signature in the cerebrospinal fluid (CSF - i.e., low beta-amyloid and high hyperphosphorylated tau protein levels) (Forlenza et al., 2016). Given the distinct clinical and biological features of cognitive impairment in BD, dementia in BD seems to be unrelated to AD pathological mechanisms (Kerr et al., 2016). These findings suggest that cognitive deterioration in BD may not be associated with the classical pathophysiological mechanisms observed in AD (Forlenza et al., 2016). Other mechanisms may underlie the cognitive deficits in older adults with BD, such as residual mood symptoms (Ferrier et al., 1999; Goswami et al., 2006), structural brain abnormalities (Beyer et al., 2004; Brooks et al., 2009; Cao et al., 2016), long-term side effects of medications and

adverse psychosocial conditions (Aprahamian et al., 2014). Additionally, medical comorbidities, such as diabetes can also contribute to this scenario (Aprahamian et al., 2014; Hajek et al., 2014), although this issue has yet to be fully elucidated. For example, subjects witht late-stage BD had a decreased hippocampal volume and worse verbal memory recall but no correlation between these two variables was found (Cao et al., 2016). As mentioned above, further longitudinal research on cognitive performance after the onset of BD is needed to determine the extent to which cognitive deficits progress over time (Daglas et al., 2015). In a five-year follow-up of older adults, the group with BD exhibited worse cognitive performance in comparison to healthy older subjects at baseline, but they did not have greater cognitive decline during the follow-up. Interestingly, subclinical manic symptoms at baseline predicted a decline in memory (Schouws et al., 2016). Similar results were also found in a 9-year follow-up of bipolar euthymic patients at baseline and during the follow-up. Cognitive impairment remained stable over several clinical evaluations, except for a worsening of executive function, which was associated with the disease duration and with subsyndromal depressive symptoms (Torrent et al., 2012).

2.2 Neuroprogression in bipolar disorder

Considering the cognitive impairments observed in a subset of BD patients, different authors have proposed that the clinical course of BD may follow a progressive path (Duffy et al., 2014; Muneer, 2016). Other clinical findings, such as higher number of spontaneous mood episodes and hospitalizations, increased risk of suicide, and poor response to treatment during the disease course corroborate the neuroprogressive hypothesis of the disease (Passos et al., 2016; Tidemalm et al., 2014). Biological findings have also corroborated with this hypothesis through neuroimaging, as well as neurocognitive studies (Bora et al., 2010; Lin et al., 2013). For example, bipolar patients with poor clinical evolution were found to have worse cognitive performances and smaller hippocampal volumes than subjects with better outcomes (Cao et al., 2016). Both, clinical and biological factors have indicated the progressive nature of BD. The concept of neuroprogression postulates that different mood episodes could promote cumulative damage in neural cells (neurons and glia), affecting the neural activity, and ultimately, causing brain vulnerability to subsequent episodes (Vieta et al., 2013). This process involves dysfunctions in several systems, potentially affecting cellular resilience and neural plasticity (Berk et al., 2011; Grande et al., 2016; Vavakova et al., 2015). This vulnerability seems to be related to increased inflammation, where cytokines seems to play a role, as well as a number of modifications caused by increased oxidative stress, mitochondrial dysfunction and a decrease in neurotropic factors (Cunha et al., 2006; Fernandes et al., 2011; Gigante et al., 2011; Kapczinski et al., 2010; Kapczinski et al., 2008; Nery et al., 2016).

3. Clinical symptoms of frontotemporal dementia relevant to psychiatry

Unlike other types of dementia, such as AD, cognitive decline is not a hallmark symptom observed in the early stages of FTD. The term frontotemporal dementia includes different clinical syndromes preferentially affecting the frontal and temporal lobes. For this reason, the term encompasses heterogeneous clinical syndromes. According to the prevalence of symptoms at earlier stages, FTD is divided in three different clinical subtypes: behavioral

variant, semantic variant, and non-fluent progressive aphasia (Gorno-Tempini et al., 2011; McKhann et al., 2001b). In all clinical subtypes, cognitive decline typically occurs at more advanced stages, while behavioral or language disturbances are the first symptoms to manifest (Chare et al., 2014; Liscic et al., 2007).

The most common form of FTD is the behavioral subtype (bvFTD). This form is highly relevant to psychiatry, since early bvFTD symptoms overlap with primary psychiatric disorders. Several behavioral and personality changes observed in BD patients during manic episodes are also observed in bv-FTD, such as changes in dietary habits, loss of social awareness, disinhibition, and stereotypical behaviors (Mendez et al., 2007; Miller et al., 1995; Nyatsanza et al., 2003; Zamboni et al., 2008).

Psychosis is one of the psychiatric symptoms seen in FTD patients that has attracted increased attention in the past few years. In a review, the prevalence of psychosis in FTD patients reached as high as 50% of the cases (Hall and Finger, 2015). In addition, delusion was found in 25% of the patients in large cases series (Leger and Banks, 2014; Schoder et al., 2010). In the biggest case series of neuropathologically confirmed FTD patients (n=97), 32% exhibited psychotic symptoms (21% with delusions and 18% with hallucinations) (Landqvist Waldo et al., 2013). Further studies involving large case series should be performed in order to better characterize the most frequent psychiatric symptoms that are more frequent in FTD patients.

4. Clinical aspects common to bipolar disorder and frontotemporal dementia

The neuroprogression of BD seen in a subset of cases is characterized essentially by the presence of recognized mood swings at all stages of the disease, and also cognitive decline that, although sometimes present initially, are more pronounced in advanced stages. A similar clinical picture is observed in FTD. Thus, increasing research in the field has highlighted common clinical characteristics common to BD and dementia, and to FTD and psychiatric symptoms (Dols et al., 2016; Kerstein et al., 2013; Lopes and Fernandes, 2012; Masouy et al., 2011; Rubino et al., 2017; Woolley et al., 2007). Review studies have investigated the clinical similarities between FTD and BD (Lopes and Fernandes, 2012; Masouy et al., 2011), as have case reports (Kerstein et al., 2013; Rubino et al., 2017; Woolley et al., 2007) and case series (Dols et al., 2016), all of them published by independent groups. Generally, case report studies present the clinical history of FTD patients initially misdiagnosed with late-onset BD based on predominant behavioral changes consistent with manic episodes. However, clinical follow-up, in addition to neuroimaging findings showing severe degeneration of the pre-frontal lobe, led to a change in final diagnosis to FTD (Kerstein et al., 2013; Woolley et al., 2007). One case report, for instance, described a patient with late-onset BD subsequently diagnosed as having bv-FTD (Rubino et al., 2017). This patient also had a mutation in the progranulin gene (GRN), which is a type of monogenic cause of bvFTD. On the other hand, the case series reported four BD cases that gradually developed into a clinical syndrome, including apathy, disinhibition, loss of empathy, stereotypical behavior, and compulsiveness, that fulfilling criteria for possible bv-

FTD. These cases were followed up for 10 years and, unexpectedly, imaging findings showed no evidence of severe neurodegeneration. These results suggest that bv-FTD symptoms may also be present in late-stage BD, making differential diagnosis difficult in specific cases. Evidence from original articles also supports the clinical overlap between BD and FTD. A number of findings show that bv-FTD cases were initially misdiagnosed as BD, major depression disorder (MDD) and other psychoses (Kerstein et al., 2013; McKhann et al., 2001a; Mendez et al., 2007; Passant et al., 2005; Woolley et al., 2011). A systematic retrospective blinded chart review showed that 51% of bv-FTD patients had received an initial diagnosis of mood disorder. The most frequent diagnosis was MDD (60% of the cases), followed by BD (18% of the cases) (Woolley et al., 2011). This raises the question whether the clinical similarities between BD and early FTD could be underpinned by specific alterations in the cognitive network and at molecular levels. We can speculate that in the initial stages of FTD and BD, similar molecular, cellular, and possibly network dysfunctions may be pivotal in the development of clinical manifestations.

4.1 Differential diagnosis of BD and FTD

The differential diagnosis between of mood disorders and bv-FTD remains a challenge (Ducharme et al., 2015; Lanata and Miller, 2016). Executive dysfunction tests provide relative specificity in distinguishing bv-FTD from psychiatric disorders (Ducharme et al., 2015). There is a relative specificity of executive dysfunction tests to distinguish bvFTD from psychiatry disorders (Elderkin-Thompson et al., 2004). Tests for social cognition and executive dysfunction have been shown to be more sensitive than standard neuropsychological tests for specifically distinguishing bv-FTD cases from controls (Torralva et al., 2009), and also for differentiating bv-FTD from primary psychiatric disorders (Bertoux et al., 2012). Tests offering better specificity for diagnosing bv-FTD include the Social Cognition and Emotional Assessment (Funkiewiez et al., 2012), and the Executive and Social Cognition Battery, especially the Mind in the Eyes (Baron-Cohen et al., 1997) and Faux Pas (Stone et al., 1998). These tests proved better able to differentiate bv-FTD from MDD, even at its earlier stages, possibly because they were initially used to identify early executive and social cognitive impairments (including emotional processing dysfunctions) caused by prefrontal lesions (Gregory et al., 2002; Torralva et al., 2007). However, tools to differentiate bvFTD from manic states in BD are still lacking (Lanata and Miller, 2016).

Selective neuroimaging evaluation, focusing on frontal and temporal regions using magnetic resonance imaging (MRI) or hypometabolism positron emission transmission (PET), was also tested to improve the differential diagnosis of bv-FTD and mood disorders (Ducharme et al., 2015; Panegyres et al., 2007). However, in the initial stages of the disease, these imaging findings may be inconclusive.

Genetic tests for the genes encoding tau *(MAPT)*, progranulin (*GRN*), and chromosome 9 open reading frame 72 (C9ORF72*)* are indicated when family history of early onset dementia, or psychosis and mania are reported (Galimberti et al., 2013; Wood et al., 2013). Although the molecular etiology of FTD has not been fully elucidated, the molecular and genetic tools currently indicated for differential diagnosis between bvFTD and primary

psychiatric conditions, are based on the knowledge acquired by the clinicopathological studies in FTD. This is due to the lack of biological validation corresponding to clinical findings in BD. The scenario reveals the need for further investigation of biological factors that could improve the diagnosis of primary psychiatric diseases.

5. Biological aspects of bipolar disorder and frontotemporal dementia

5.1 Connectivity and neuroanatomical studies in frontotemporal dementia and bipolar disorder

Hypoconnectivity of the salience network, particularly in the frontoinsular and anterior cingulate cortex, is well established in the early stages of bv-FTD (Seeley, 2017). In BD, however, the evidence of salience network dysfunction is limited. A recent systematic review has found no differences in resting state functional connectivity in the salience network between euthymic BD patients and controls, but the phenomenon has been less studied in maniac and depressive episodes (Syan et al., 2018). Nonetheless, regions in the medial prefrontal regions (including the insula and anterior cingulate cortex) – that are also part of the salience network - are considered relevant in emotion regulation and hence in the pathophysiology of BD (Syan et al., 2018).

Two recent studies compared imaging findings of FTD and BD patients (Baez et al., 2017; Delvecchio et al., 2018). Delvecchio et al (2018) used, for the first time, magnetic resonance imaging (MRI) and positron emission tomography (PET) techniques to investigate common and distinct neural substrates of BD and bv-FTD. This study showed that bv-FTD and BD patients exhibit distinct localization of grey matter reduction, with bv-FTD showing grey matter reductions in the dorsolateral prefrontal cortex as well as unique grey matter and metabolic alterations within the orbitofrontal cortex, whereas BD patients showed grey matter decrease in the ventrolateral prefrontal cortex. Also, bvFTD unique volumetric shrinkage in network temporo-parietal within regions was observed, together with greater metabolic impairments within the temporal cortex and more extensive volumetric and metabolic abnormalities in the limbic lobe (Delvecchio et al., 2018). The BD group displayed higher grey matter volumes in caudate nucleus, while bvFTD subjects displayed lower metabolism in this brain region. A different approach was perceived by Baez et al (2017), where they combined neuroimaging and clinical data to assess neuropsychological and neuroanatomical differences between bv-FTD and elderly BD patients. bv-FTD patients displayed a significant decrease in grey matter volume in frontal, temporal and parietal regions, when compared to BD patients (Baez et al., 2017). Additionally, clinical data demonstrated that bvFTD patients exhibited higher executive function and theory of mind impairments than BD patients. Taken together, these findings shed light on the differential diagnostic of bv-FTD and elderly BD. Dorsolateral prefrontal and temporal cortices being more affected in bv-FTD and relates to executive functions, and ventrolateral prefrontal cortex more associated to BD, although further studies are needed to translate the use of imaging as a diagnostic tool to distinguish bv-FTD and BD.

5.2 Neuropathology of frontotemporal dementia

While the term “frontotemporal dementia” refers to the clinical syndromes, the term “frontotemporal lobar degeneration” (FTLD) describes a heterogeneous group of neurodegenerative diseases commonly associated with the clinical syndrome of FTD, and show predominantly involvement of frontal and temporal lobes (Lowe, 2011; Lowe and Kalaria, 2015; Mackenzie and Neumann, 2016). Non-specific findings of chronic degeneration, including superficial cortical vacuolization, neuronal loss and gliosis are observed in affected neocortex of these cases (Cairns et al., 2007; Lowe, 2011). A series of discoveries in the last 15 years has helped to redefine our understanding about FTLDs. Although a pathological entity defined as FTLD is based on the abovementioned cortical changes, subcortical degeneration including amygdala, basal ganglia and brainstem is a universal finding (Brettschneider et al., 2013; Cairns et al., 2007; Grinberg et al., 2009). Pathological groups of FTLD are based on the most striking molecular defect, reflecting the underlying pathogenic process (Figure 1). The first group to be recognized was FTLD with tau inclusions (FTLD-tau), tau is a microtubule-associated protein, and it is one of the most common pathological forms of FTD. Tau-negative FTLD cases with ubiquitin inclusions were included in FTLD-TDP after the of the presence of transactive response DNA-binding protein (TDP-43) in the majority of these cases (Neumann et al., 2006). FTLD-TDP represents the most common FTLD molecular subtype (Mackenzie and Neumann, 2016). Based on the presence of TDP-43 inclusions with distinct morphologies and patterns of cortical laminar distribution, four pathological subtypes of FTLD-TDP were recognized with clinical and genetic correlations (Lowe and Kalaria, 2015; Mackenzie and Neumann, 2016). Third FTLD group to be recognized was the subset of FTD subjects who present inclusions of the fused in sarcoma DNA-binding protein (FUS) (Cairns et al., 2007; Mackenzie et al., 2011). Although quite rare, studies have shown that most of the inclusions of the tau and TDP-negative FTLD cases are immunoreactive to antibodies against FUS protein (Neumann et al., 2011). FUS belongs to a family of RNA-bindings proteins (RBPs) named FET (Svetoni et al., 2016). Recently, studies showed that these FUS-positive inclusions also contain Ewing’s sarcoma (EWS) and TATA-binding protein-associated factor 15 (TAF15), that also belong to the FET protein family (Svetoni et al., 2016). In view of these findings, this FTLD subtype is now grouped under the designation of FTLD with FET inclusions (FTLD-FET) (Neumann et al., 2011). Very few FTLD cases are characterized by the presence of ubiquitin-positive inclusions only, without a disease-specific protein. There cases are classified as FTLD-U.

It is important to emphasize that misfolded tau and TDP-43 are not exclusively found in FTLD cases. Aggregates formed by these proteins are also present in other neurodegenerative diseases, such as AD (Josephs et al., 2014; Josephs et al., 2016), chronic traumatic encephalopathy (McKee et al., 2016), argyrophilic grain disease (Rodriguez et al., 2016) and hippocampal sclerosis of aging (Nelson et al., 2011). These protein aggregates are also found in the brains of cognitively normal older adults (Kovacs et al., 2013; Nascimento et al., 2018; Nascimento et al., 2015). Protein malformation is a process inherent to aging. For example, ubiquitination is a regular mechanism of cell protection indicating that a certain misfolded protein must be degraded, by either proteasome or autophagy pathways (Lilienbaum, 2013; Nedelsky et al., 2008). During aging, the mechanisms of clearance might

not be sufficed to cope with the amount of misfolded proteins that are being produced (Kovacs et al., 2013). The question is, given these proteins are present during normal aging, how do we know the threshold for their aggregates to cause clinical manifestation? The relationship between the presence of misfolded proteins, clinical manifestations, as well as the molecular pathways by which these protein aggregates would lead to neurodegeneration, is not fully understood. Neurodegeneration is caused by a combination of factors, including not only the presence of misfolded proteins, but also synaptic alterations, neuroinflammation (characterized by reactive astrocytosis and activated microglia), and selective neuronal loss (Soto and Estrada, 2008).

Strong clinicopathological associations are observed in topographic distribution of protein aggregates in the brain. These observations led to the proposal of neuropathological staging models for different neurodegenerative disease (Braak and Braak, 1991; Brettschneider et al., 2013; Josephs et al., 2014; Josephs et al., 2016). The relationship between the presence of misfolded proteins and cell death in neurodegenerative diseases was further investigated in AD, but to a lesser degree in FTD patients. It was initially hypothesized that neuronal loss was the problem in neurodegeneration. Indeed, some observations in post-mortem brains corroborated to this hypothesis (Anderson et al., 2000; Kimura et al., 2010; Lassmann et al., 1995; Selznick et al., 1999; Su et al., 2000). However, further studies failed to reproduce the same findings and synaptic dysfunctions showed better temporal and topographic correlation with clinical symptoms (Haass and Selkoe, 2007).

One of the theories in neurodegeneration holds that misfolding and aggregation result in the acquisition of a neurotoxic function by the misfolded proteins. Different pathways may operate depending on where the proteins accumulate, i.e. which cell type, cellular compartments (intracellularly or extracellularly) or brain region (Soto, 2003; Soto and Estrada, 2008). Because cell types and brain regions are affected differently in neurodegenerative diseases, it is unlikely that the same molecular mechanisms underlying AD would explain what is occurring in FTD.

In FTD, besides gain of toxic function, loss of function may also play a role. Genetically modified animals (i.e. with mutations in the genes encoding these misfolded proteins e.g. TDP-43) provide a model of loss of function, and have significantly greater cognitive impairments when compared to wild-type animals (Caccamo et al., 2012; Tsai et al., 2010). Interestingly, a transgenic mice model mimicking pathological FTLD showed impairment in protein degradation pathways (Caccamo et al., 2015), and therapeutic strategies designed to improve protein quality control mechanisms were able to restore learning/memory impairment (Shahheydari et al., 2017). TDP-43 aggregates are the most common forms of neuropathological abnormalities in FTD, and animal models with mutation in the gene encoding this protein (*TARDBP*) are important tools to help understand the role of this protein in behavioral symptoms of FTD. Indeed, TDP-43 was found to co-aggregate with the disrupted in schizophrenia 1 (DISC1) protein in the cytosol of neurons in brains of both FTLD mouse model and patients (Endo et al., 2018). Examination of the animal data revealed that, co-aggregation of TDP-43/DISC1 reduced synaptic protein expression by disrupting activity-dependent dendritic local translation. As a result, mutated animals showed TDP-43 aggregation, synaptic dysfunction and behavioral deficits. Because these

findings were verified *in vivo*, the evidence suggests that TDP-43 participates in the regulation of local translation, which, in turn, affects aberrant behaviors that are relevant to psychiatric symptoms. Ultimately, this data connects the presence of misfolded TDP-43 with behavioral symptoms.

5.3 Neuropathology of bipolar disorder

Neuropathological abnormalities have also been described in postmortem samples from brains of BD patients. Cortical thinning is observed mainly in temporal, frontal, orbitofrontal and pre-frontal cortices (Elvsashagen et al., 2013; Hanford et al., 2016; Maller et al., 2014; Rimol et al., 2010). Glial deficits, thinning of grey matter in the anterior cingulate, reduced density of neurons in some layers of dorsolateral prefrontal cortex were significant on meta-analysis (Harrison et al., 2018). However, the conclusion of the study was that the data published to date has insufficient robustness, magnitude or specificity, to be of clinical or diagnostic value. This is due to the small sample sizes in neuropathological studies. Hundreds of brains are included in genetic studies yet neuropathological research lack this support. The presence of misfolded proteins in postmortem brains of BD patients has not been consistently explored. Only three studies have analyzed the presence of tau and TDP-43 abnormal aggregates in BD patients (Shioya et al., 2015; Velakoulis et al., 2009a; Velakoulis et al., 2009b). However, these studies involved only small sample sizes of individuals with BD. This may be because there are few brain banks worldwide comprising tissue from psychiatric subjects, particularly BD (de Oliveira et al., 2012). One of these studies analyzed abnormal distribution of TDP-43 in patients with late-onset psychosis, including nine patients with SCZ and three with BD. The authors found an absence of normal nuclear staining of TDP-43, without presence of protein inclusions, in three subjects, one of which was diagnosed with BD type I. Also, the alterations were associated with a positive family history of psychiatric illnesses (Velakoulis et al., 2009a). Another study by the same group focused on analyzing TDP-43 aggregates in postmortem brain of younger-onset FTD subjects. Retrospective analysis of patient clinical files revealed that a subset of these cases was initially diagnosed as having a psychiatric disorder, including one bipolar and four schizophrenic diagnoses. All five patients that had been previously diagnosed with a psychiatric disorder tested positive for misfolded TDP-43. The third study investigated the presence of a tauopathy called argyrophilic grain disease (AGD) in BD subjects. The incidence and extent of AGD pathology seemed to be more severe in the BD group compared to controls, although the low number of BD cases (n=11 versus n=1240 controls) precluded further statistical analyses (Shioya et al., 2015).

Other studies have investigated the presence of misfolded proteins in post-mortem brains from patients with psychiatric symptoms. The first one was published in 2010 and comprised 72 schizophrenics and 11 schizophrenics with an additional affective component (depression or bipolar disorder) (Geser et al., 2010). The authors found no associations between the control and mental disorder groups. By contrast, a recent study investigated patients with a clinical history of AD together with psychosis and found that the presence of abnormal aggregates of TDP-43 in the hippocampus was associated with a tendency for a reduced likelihood of psychosis (Vatsavayi et al., 2014). These findings contradict results of a study showing TDP-43 neuropathological alterations in patients with psychiatric

conditions (Velakoulis et al., 2009a). This could be because different pathways related to these neuropathological alterations may be disrupted across psychiatric and neurological conditions.

Taken together, the study of protein aggregates in psychiatric disorders may indicate that neuropathological findings of TDP-43 and tau are not well-structured characteristics of these conditions. The presence of these protein aggregates in BD may, for example, represents a clinical misdiagnosis in life or an overlap between BD and bv-FTD. In addition, since the presence of these neuropathological changes occurs during the aging process (Kovacs et al., 2013; Nascimento et al., 2018), the presence of misfolded proteins in the brains of older adults with psychiatric conditions can also be expected. To better address these questions, a detailed and well-structured neuropathological investigation of TDP-43 and tau protein aggregates in the brain of subjects with BD, with other psychiatric conditions, comparing these with age-matched non-psychiatric subjects is needed. This same study design could also be employed for an investigation of protein levels (of TDP-43 or tau) in post-mortem brain or blood samples of psychiatric cases. Clarification on the role of these proteins will further understanding of the biological mechanisms underlying psychiatric and cognitive symptoms in mental disorders.

5.4 Molecular genetic studies in frontotemporal dementia

FTD has an important genetic component, since a substantial percentage of the cases (30 to 50%) have at least one first-degree relative with FTD and about 10 to 15% have a family history of FTD with autosomal dominant pattern of inheritance (Goldman et al., 2005; Rohrer et al., 2009; Takada, 2017; Takada et al., 2016). The most common genetic forms of FTD are due to mutations in *C9orf72*, *MAPT* and *GRN* genes (Galimberti et al., 2015; Sieben et al., 2012), explaining 17% of the familial FTD (Sieben et al., 2012). Among these three most common genetic causes, the majority of psychiatric symptoms are present in carriers of the FTD with mutations in *C9orf72* and to a lesser extent in GRN carriers (Galimberti et al., 2015; Woollacott and Rohrer, 2016). Psychotic and obsessive-compulsive symptoms are among the commonest psychiatric symptoms verified in FTD *C9ORF72* (Calvo et al., 2012; Floris et al., 2012; Galimberti et al., 2015; Snowden et al., 2012). Symptoms include delusion with visual and auditory hallucinations, in the absence of neurologic symptoms and brain atrophy (Arighi et al., 2012). A systematic review on the C9orf72 in neurological disorders showed that intermediate repetitions within this gene are associated with psychiatric symptoms (Ng and Tan, 2017). Findings from this review showed that intermediate allele sizes associated more frequently with neuropsychiatric phenotypes. Furthermore, these intermediate sizes were detected in subjects with personal or family history of FTD and/or psychiatric illness. Stretching the association between C9orf72 and psychiatric symptoms, presence of late-psychosis (>40 years) and non-response to neuroleptics raise the suspicion of FTD due to the C9ORF72 (Galimberti et al., 2015). In to a lesser extent, GRN mutations FTD patients were also associated with personality changes, sexual disinhibition, ritualistic behaviors, and paranoia (Le Ber et al., 2008).

Because molecular genetics explains a high percentage of these cases, the interest in the study of molecular causes of FTD has increased greatly in the past two decades. Increasing

research in this field found less common and rare genes have linked to monogenic causes of FTD. Table 1 shows the genes, chromosome location and molecular function of genes linked to FTD, including common and rare genetic causes. Molecular function of all genes was retrieved from the gene bank of The National Center for Biotechnology Information (NCBI, U.S. National Library of Medicine, Bethesda MD, USA). Besides these genes that were primarily associated with FTD, mutations in presenilin-1, which are causative of familial AD, have also been associated with a clinical FTD syndrome (Bernardi et al., 2011).

Although a high percentage of cases exhibit a monogenic pattern, it is important to notice that there are still a substantial number of FTD cases that have not been linked to single genetic mutations (Woollacott and Rohrer, 2016). This suggests there are causative genes are yet to be discovered, and/or that this FTD subtype might also have a polygenic or oligogenic pattern, characterizing a multifactorial disease, in which environmental conditions may also play a role. A large genome-wide association study (GWAS) conducted on 3526 FTD patients and 9402 healthy controls identified three novel single-nucleotide polymorphisms associated with FTD for all its clinical subtypes (rs9268877, rs9268856 rs1980493) at locus 6p21.3, site comprising the human leukocyte antigen (HLA) gene (Ferrari et al., 2014). Interestingly, a sub-analysis including only patients with the behavioral subtype (n=1377 FTD and 2754 controls) identified a potential novel SNP (rs302668) at locus 11q14, which encompasses transcripts related to lysosomal biology (RAB38/CTSC). These findings suggest that immune system disturbances (link to 6p21.3) and possibly lysosomal and autophagy pathways (link to 11q14) may be potentially involved in FTD.

5.5 Molecular genetic studies in bipolar disorder

Molecular picture of BD is very different from what it is observed in FTD. The role of a genetic component is unarguably present in BD, since the heritability based on twin studies has been estimated at 60% to 80% (Smoller and Finn, 2003). However, no individual monogenic mendelian heritance pattern has been discovered for BD up to date (Gratten et al., 2014; Kerner, 2014). Several studies focusing on individual genes have failed in the attempt to be replicated across different cohorts (Craddock and Forty, 2006; Hayden and Nurnberger, 2006). Here, we only give some examples of genetic mutations found in BD patients that are associated to known impaired biological aspects of the disorder. For example, mutation in genes related to codification/production of neurotransmitters, serotonin transporter (*5-HTT, SERT*), tryptophan hydroxylase (*TPH*), catechol-O-methyltransferase (*COMT*), and D-amino acid oxidase activator (*DAOA*) (Anguelova et al., 2003; Cho et al., 2005; Rotondo et al., 2002). Genes related to production of neurotrophic factors, brain-derived neurotrophic factor (*BDNF*), and glycogen synthase kinase 3 beta (*GSK3beta*) (Neves-Pereira et al., 2002; Ortega et al., 2010; Sklar et al., 2002), and genes involved in the controlling of circadian rhythm, aryl hydrocarbon receptor nuclear translocator-like (*ARNTL*) and circadian locomotor output cycles kaput (*CLOCK*) (Nievergelt et al., 2006; Shi et al., 2008). However, the lack of reproducibility across studies make the interpretation of these genetic findings in BD very difficult, impacting clinical practice.

Non-genetic risk factors (such as, alcohol/drug dependence and physical/sexual abuse) has been also shown to contribute to the manifestation of BD (Aas et al., 2014). Taken together,

lack of contribution of individual genes that could explain high heritability, as well as, strong contribution of non-genetic risk factors, characterizes BD as polygenic and complex multifactorial disorder. With the advance in technology in the genomic era, it has been possible to better dissect the molecular mechanisms behind complex disorders (Ikeda et al., 2018; Orru and Carta, 2018). Combining data from different GWAS studies, more than 40 SNPs have been associated to increased risk for BD (Chen et al., 2013; Cichon et al., 2011; Green et al., 2013; Ikeda et al., 2018; Muhleisen et al., 2014; Psychiatric, 2011). Different SNPs were found by each of these studies. Also, slightly lower estimates of genetic risks have been suggested based on family studies and large population cohorts (Wray and Gottesman, 2012). Thus, it has been suggested that susceptibility to BD is most likely influenced by many genetic risk factors with small to moderate effect (Gratten et al., 2014; Ikeda et al., 2018; Kerner, 2014; Orru and Carta, 2018).

Although there is a high variation in the SNPs found by the different GWAS studies, variants in six different genes (Table 2) were recently highlighted due to their biological relevance observed trough animal models, neuronal cell cultures or using functional/structural brain imaging data (Ikeda et al., 2018).

5.6 Molecular genetic findings common to bipolar disorder and frontotemporal dementia

Since brain biopsy is highly invasive, peripheral measurements offer an important tool for improving diagnosis and treatment of mental illnesses. In the case of FTD, mutation-detections rates of the genes associated with the disease have important implications for genetic counseling and testing in clinical settings (Wood et al., 2013). Plasma and CSF levels of proteins encoded by the genes associated with genetic forms of FTD have been studied as biomarkers (Ghidoni et al., 2012). Progranulin, a protein encoded by the *GRN* gene, has been consistently found to be lower in affected and unaffected *GRN* carriers (Galimberti et al., 2018; Ghidoni et al., 2008; Takada et al., 2016). Furthermore, it was possible to establish a cut off among mutation carriers and non-carriers with at least 97% sensitivity (Galimberti et al., 2018; Ghidoni et al., 2008; Takada et al., 2016). The fact that unaffected *GRN* carriers also show decrease in circulating progranulin levels suggest that this molecular feature precedes clinical symptoms. A more recent article in this field found lower levels of peripheral progranulin in *GRN* carriers that did not show clinical symptoms or brain atrophy, which reinforces measurement of progranulin as a biomarker for FTD (Galimberti et al., 2018). Based on these findings, a large-scale screening of levels in dosage of carriers with the progranulin mutation could represent a useful, quick and inexpensive approach for monitoring future treatments, since the progranulin levels should increase during the treatment (Ghidoni et al., 2012). Tau protein, encoded by the *MAPT* gene, has also been investigated as a biomarker of FTD in plasma. Higher levels of plasma tau concentrations were found in bvFTD (1.96 pg/mL SD ±1.07), compared to controls (1.67 pg/mL SD ±0.50) (Foiani et al., 2018), but its importance as a diagnostic tool has yet to be established. Considering the clinical similarities between BD and FTD, researchers have investigated molecular genetic findings of FTD in patients with BD. Interestingly, two different studies showed that progranulin plasma levels were significantly decreased in BD patients, when compared to controls (Galimberti et al., 2012; Kittel-Schneider et al., 2014). In the line with these results, a recent case-report of an Italian male presenting with late-

onset BD that developed into bv-FTD over time, and found that this patient carried the mutation in the *GRN* gene (Rubino et al., 2017). Another case report described a BD proband presenting *C9ORF72* gene expansions. Interestingly, the father also carried the *C9ORF72* expansion and a postmortem analysis of the brain confirmed FTLD (Meisler et al., 2013). Studies involving larger samples should be conducted to confirm these initial case-report findings.

6. Common biological pathways may underlie both BD and FTD

Given the complex polygenic and multifactorial etiology of BD, molecular genetics studies have failed in identifying a single gene as the cause of the disorder (Gratten et al., 2014; Kerner, 2014). Therefore, the investigation of downstream biological events, rather than BD genetic etiology, has allowed advances in the understanding of the neurobiology of BD. To date, inflammation, oxidative stress and neurotrophic factors are the three downstream biological changes consistently explored and associated with BD pathophysiology and progression (Frey et al., 2013; Muneer, 2016). In Table 3, several clinical characteristics, as well as specific molecules related to the biological pathways that are fundamental in BD are presented, and compared with the same aspects detected in similar studies on FTD. Clinical characteristics included age at onset (Snowden et al., 2002; Yassa et al., 1988), disease duration (Medeiros et al., 2016; Young et al., 2018; Zhang et al., 2017) and progression (Grande et al., 2016; Young et al., 2018). For the molecules, due to the large volume of published data regarding inflammation, oxidative stress, and decreased neurotropic factors in BD, we included findings from meta-analytic studies were included (Andreazza et al., 2008; Brown et al., 2014; Fernandes et al., 2015; Ghidoni et al., 2008; Goldsmith et al., 2016; Modabbernia et al., 2013; Rao et al., 2017; Tseng et al., 2016; Wang and Miller, 2018). For BD, original articles were retrieved using the following search terms: “bipolar disorder AND inflammation”, “bipolar disorder AND oxidative stress”, “bipolar disorder AND neurotrophic factor”. The same search strategy was used for FTD, where “bipolar disorder” was replaced by “frontotemporal dementia” (Atagi et al., 2015; Blasko et al., 2006; Bossu et al., 2011; Galimberti et al., 2012; Galimberti et al., 2008; Galimberti et al., 2009; Hu et al., 2010; Kittel-Schneider et al., 2014; Martinez et al., 2008; Miller et al., 2013; Rainero et al., 2009; Rentzos et al., 2006a; Rentzos et al., 2006b; Ventriglia et al., 2013). For both diseases, findings of studies measuring inflammatory biomarkers and neurotrophic factors in human the peripheral tissue or CSF were included (Atagi et al., 2015; Blasko et al., 2006; Bossu et al., 2011; Fernandes et al., 2015; Galimberti et al., 2008; Galimberti et al., 2009; Goldsmith et al., 2016; Hu et al., 2010; Kittel-Schneider et al., 2014; Miller et al., 2013; Modabbernia et al., 2013; Rainero et al., 2009; Rao et al., 2017; Rentzos et al., 2006a; Rentzos et al., 2006b; Tseng et al., 2016; Ventriglia et al., 2013; Wang and Miller, 2018). Concerning oxidative stress markers, investigations measuring these alterations in human post-mortem brains were also included (Andreazza et al., 2008; Brown et al., 2014; Martinez et al., 2008).

Inflammation is the widely-recognized condition implicated in BD that has been most explored in FTD. However, we found more isolated findings that were not consistently tested across independent groups. The inflammatory markers found, common to both BD and FTD, were interleukin-6 (IL-6), Tumor Necrosis Factor Alpha (TNF-α) and progranulin. IL-6 and TNF-α were increased in BD (Goldsmith et al., 2016) and FTD

compared to controls (Bossu et al., 2011; Rainero et al., 2009). IL-6 is an inflammatory cytokine not only implicated in inflammation and infection responses, but also in the regulation of metabolic, regenerative, and neural processes (Scheller et al., 2011). Interestingly, increased levels of IL-6 are associated with neuroprogression in BD (Jacoby et al., 2016; Wiener et al., 2017). Increased IL-6 levels have also been associated with functional impairment in BD patients (Wiener et al., 2017). In FTD, a specific polymorphism in the promoter of the IL-6 gene (174G>C, substitution of a guanine by a cytosine at the position 174) significantly modified the scores on the Frontal Assessment Battery, suggesting that this interleukin has particular effect on the clinical aspects of FTD (Rainero et al., 2009). TNF-α is a key component of neuroinflammation processes and physiologically it plays an important role in neural function, such as synaptic plasticity, learning and memory, sleep and food intake (Olmos and Llado, 2014). In patients with BD, TNF-α is considered a trait marker of the disease, since higher levels of this molecule are found not only during mood episodes, but also during euthymia (Soczynska et al., 2009). In FTD, TNF-α mediates protein aggregates of TDP-43 (Picher-Martel et al., 2015), and the role of progranulin in the cell (Alquezar et al., 2016; Krabbe et al., 2017). Mutation in the progranulin gene is a common genetic cause of FTD, and leads to decreased progranulin protein levels and accumulation of TDP-43 protein. A decrease in progranulin protein is associated with increased levels of TNF-α (Alquezar et al., 2016; Krabbe et al., 2017). Interestingly, progranulin levels were decreased in both BD and FTD (Galimberti et al., 2012; Ghidoni et al., 2008; Kittel-Schneider et al., 2014). Taken together, these findings suggest that IL-6, TNF-α, and progranulin may be biological markers common to both diseases. Genetic variations in HLA (human leukocyte antigen) genes have also been associated with both BD and FTD, and indicated that HLA-related inflammation mechanisms are also present in both disorders (Broce et al., 2018; Tamouza et al., 2018). Although we found shared inflammatory factors, several interleukins and chemokines have differently associations with BD and FTD. In BD, we found IL-1, IL-beta1, IL-4, IL-10, soluble IL-2 receptor (sIL-2R) and sLL-6R and the soluble tumor necrosis factor receptor 1 (sTNFR1) were identified, while in FTD, IL-11, IL-12, IL-15, IL-17, IL-14 and the chemokines tumor necrosis factor (TNF) receptor-associated factor NF-κB activator (TANK)-binding kinase 1 (TBK1), monocyte chemoattractant protein 1 (MCP-1) and triggering receptor expressed on myeloid cells 2 (TREM2) were found. This means that specific panels of interleukins and chemokines may be used to distinguish BD and FTD.

Levels of neurotrophic factors have been less explored in the peripheral tissue in FTD patients than inflammation markers. However, decreased levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) were found in both BD (Fernandes et al., 2015; Rao et al., 2017) and FTD (Blasko et al., 2006; Ventriglia et al., 2013). The role of BDNF in psychiatric conditions and neurodegenerative processes has been extensively explored. BDNF is the most investigated and well characterized neurotrophin and major regulator of synaptic plasticity, neuronal survival and differentiation (Koshimizu et al., 2009). The BDNF Val66Met polymorphism has been suggested as a risk factor for both, BD (Li et al., 2016) and FTD (Borroni et al., 2012). Clinically, this polymorphism may influence stress sensitivity trait, personality trait, glucocorticoid-induced corticohippocampal remodeling, and behavioral despair (Notaras et al., 2017; Wei et al.,

2017). This would explain why individuals carrying BDNF Val66Met polymorphism are more susceptible to diseases highly influenced by environmental conditions. At the molecular level, this variant is associated with altered protein intracellular and dendritic trafficking (Chen et al., 2004; Chiaruttini et al., 2009), which could impair synaptic activity. NGF is another neurotrophin of interest in both diseases. Higher NGF levels have been associated with increased anxiety, obsessive-compulsive behavior and more impaired functionally status (Salles et al., 2017). In neurodegenerative diseases, higher levels of NGF were associated with increased markers of neurodegeneration (as expressed by the ratio P-tau181/Abeta42). This suggests that NGF could be a potential marker for disease progression in both BD and FTD (Blasko et al., 2006). However, research is lacking on factors that may be triggering increased of NGF in both diseases. Specific neuroprotective factors, such as neurotrophins 4/5 (NT-4/5) and 3 (NT-3), as well as the insulin growth factor 1, that were found decreased only in BD, have not been investigated in FTD.

Meta-analytic studies in BD have focused on oxidative reactive factors, such as thiobarbituric acidic reactive substances and nitric oxide activity, and in oxidative stress-related damages to macromolecules, such as lipid peroxidation, protein nitration and DNA/RNA damage. Levels of lipid peroxidation, DNA/RNA damage, thiobarbituric acidic reactive substances and nitric oxide were significantly higher in BD patients (Andreazza et al., 2008; Brown et al., 2014). There is little evidence supporting increased lipoxidation-derived protein damage in brain tissue of FTD patients (Martinez et al., 2008). Further research focusing on measuring other types of oxidative stress damages in FTD human brain samples could elucidate new pathways implicated in this disease. In this context, recent evidence, using system biology analysis, has shown that DNA damage, oxidative stress and calcium/cAMP may be homeostasis-associated biomarkers in frontotemporal dementia (Palluzzi et al., 2017). Although in FTD studies of human samples there is little evidence of the same types of OS damage found in BD, several articles report the implication of oxidative stress in FTD based on animal and cellular models. These models show a direct link between causative mutations of FTD and oxidative stress damage caused by mitochondrial dysfunction (Esteras et al., 2017; Lopez-Gonzalez et al., 2016), which is a hallmark of BD (Kato, 2017). Mitochondria are not cellular organelle exclusively related to damage in macromolecules and oxidative stress. Recently, research has focused on the role of endoplasmic reticulum stress in psychiatry and neurodegenerative disorders (Bengesser et al., 2016; Hetz and Saxena, 2017). Endoplasmic reticulum stress triggers a signaling reaction known as the unfolded protein response (Hetz and Saxena, 2017). This reaction is an adaptive response to improve protein folding and promote quality control mechanisms and degradative pathways. However, under conditions of prolonged stress, this adaptive response is insufficient, leading to an accumulation of misfolded proteins and cell death. Aggregation of misfolded protein, as previously discussed here (see subtopics 5.1 and 5.2”), is a hallmark characteristic observed in post-mortem brain tissue of FTD subjects (Cairns et al., 2007). Although, the contribution of these protein aggregates in the pathophysiology of BD requires further investigation, evidence shows that unfolded protein response plays a role in the neuroprogression of the disease (Pfaffenseller et al., 2014). Besides protein aggregates and neuronal loss, endoplasmic reticulum chronic stress also represses synthesis of synaptic proteins (Hetz and Saxena, 2017). This could explain the link between endoplasmic

reticulum stress and behavioral/cognitive symptoms in FTD and BD (Cisse et al., 2017; Trinh et al., 2012).

7. Hypothetical model of shared molecular mechanisms shared by bipolar disorder and frontotemporal dementia

A fact that might explain this conjunction of cellular alterations together, including inflammation, oxidative stress and neurotropic factors, as well as endoplasmic reticulum stress response, is brain aging (Dominguez and Barbagallo, 2016). Brain aging is the main a risk factor for the development of dementia (Alzheimer's, 2016). Even in FTD cases with underlying monogenic causes, patients will manifest symptoms only later in life (Chare et al., 2014). Biological evidences have supported the theory of accelerating aging in BD (Fries et al., 2017; Vasconcelos-Moreno et al., 2017). This evidence includes the association between accelerated epigenetic aging and lower global functioning in BD patients (Fries et al., 2017). The fact that BD is associated with higher risk of dementia in old age supports the accelerating ageing hypothesis in BD. In addition, BD has been strongly associated with metabolic syndrome (Bai et al., 2016). In Figure 2, we propose a scheme showing how these molecular changes might interact and affect the clinical symptoms of FTD and BD.

Cautious is required when interpreting this hypothetical model, for instance, differences in disease progression between FTD and BD should be considered. In the case of FTD, variation in the levels of molecules (increased or decreased) would be expected to follow a more rapid progressive pattern, when compared to BD. In BD, these molecular changes may hypothetically be occurring at a slower pace during life-time, with variations probably dependent on the progression of the disease, including number of mood episodes, especially psychotic ones. This would also impact the final consequences in the cascade, where we consistently find the presence of misfolded proteins in FTD (Cairns et al., 2007; Mackenzie et al., 2011), but possibly with a lower burden in BD (Shioya et al., 2015; Velakoulis et al., 2009a). The cause of decreased progranulin levels in BD remains unknown, since monogenic mutations in the *GRN* gene are not associated with this disorder. Also, the trigger of decreased in NGF levels in both, FTD and BD has yet to be investigated. *C9orf72* gene expansions were found in BD proband, as well as family history of BD (Meisler et al., 2013), however, further investigation should be conducted to better characterize the related downstream molecular alterations.

Currently, research on psychiatric and neurological diseases (specifically dementia) is based on the clinical instruments available for detection of patterns of symptoms in order to classify diseases into a specific group, namely, BD or SCZ, and FTD or AD (Association, 2013; Rascovsky et al., 2011). As a consequence, psychiatric and neurological diseases have been treated as separated conditions, not only in research, but also in clinical settings. However, the high heterogeneity of clinical symptoms observed in psychiatric conditions and dementia syndromes, together with the overlapping symptoms, indicate that clinical data collected through semi-structured interviews alone may not suffice as a proxy for electing the best treatment for patients. In this context, biological factors may be a key aspect for improving the diagnosis and treatment of FTD and BD. Decreased progranulin plasma

protein levels in both FTD and BD is one example of how subjects clinically classified into different disease groups can present the same biological aspects (Galimberti et al., 2012; Ghidoni et al., 2008; Kittel-Schneider et al., 2014). Here, we present a hypothetical model showing biological aspects potentially shared by FTD and BD (Figure 2). Future investigation comparing the same molecules (particularly inflammation and neurotrophic factors) in cohorts of bv-FTD and BD patient may promote fresh insights in the treatment and diagnosis of these diseases. We need not only to understand the role of these molecules in each of these diseases by studying the potentially shared mechanisms, but also to discover molecular changes that could differentiate psychiatric conditions from dementia (for instance, types of chemokines). The latter could help in early detection, which is crucial for a better prognosis, especially among pre-senile subjects suffering from behavioral changes.

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Highlights

- Differential diagnosis of psychiatric and neurological disorders remains a challenge.
- Clinical similarities between bv-FTD and BD can lead to misdiagnosis.
- Specific inflammatory and neuroprotective changes may underlie both bv-FTD and BD.
- Further molecular studies can provide translational insights with therapeutic implications.

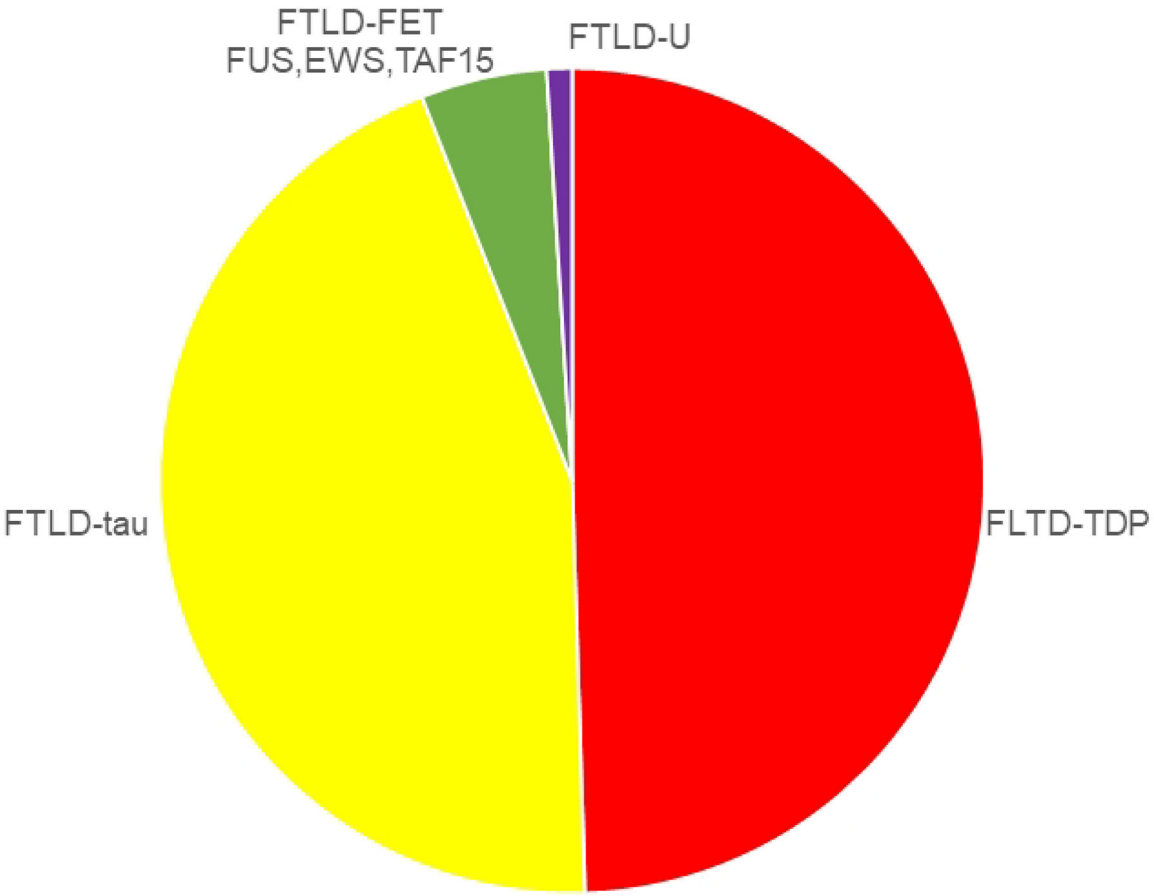

Figure 1.

Molecular classification of frontotemporal lobar degeneration (FTLD). Approximately 50% of FTLD cases are TDP-positive and tau-negative (red) and 40% are tau-positive (yellow). Tau and TDP43-negative cases with FET-positive inclusions (green) are estimated to represent 5–10% of all FTLD. Minority of FTLD cases present only ubiquitin-positive inclusions without any disease-specific protein identified (purple). Abbreviations: TDP, transactive response DNA binding protein; FET, protein family, FUS, fused in sarcoma; EWS, Ewing's sarcoma; TAF15, TATA-binding protein-associated factor 15; U, ubiquitin proteasome system.

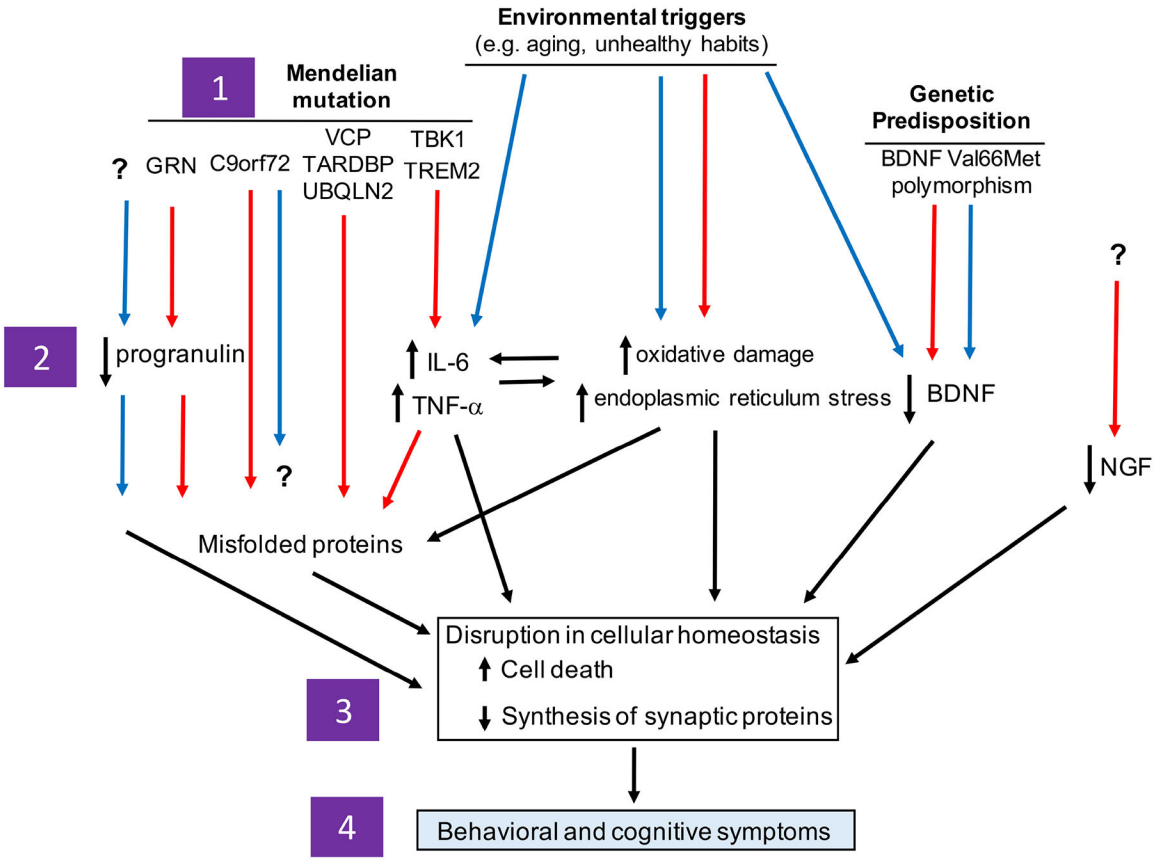

Figure 2.

Hypothetical model of molecular mechanisms shared by bipolar disorder (BD) and frontotemporal dementia (FTD). Triggers, molecular and cellular changes, as well as downstream clinical changes are labeled in purple as 1, 2, 3 and 4, respectively. Red arrows represent evidence-based mechanisms in FTD, blue arrows evidence-based mechanisms in BD, while evidence-based general findings in both BD and FTD are represented by black arrows. Abbreviations: GRN, progranulin; VCP, vasolin-containing protein; *TARDBP*, transactive response DNA-binding protein; *UBQLN2*, ubiquilin 2; *C9orf72*, chromosome 9 open reading frame 72; TNF-α, tumor necrosis factor; TBK1, tumor necrosis factor (TNF) receptor-associated factor NF-κB activator (TANK)-binding kinase 1; TREM2, triggering receptor expressed on myeloid cells 2.

Table 1.

Symbol, name, chromosome location and molecular functions of the common and rare genes associated with monogenic forms of frontotemporal dementia.

	symbol	name	Chromosome location	Molecular function	Findings in BD
Common	C9orf72	Chromosome 9 Open Reading Frame 7	9p21.2	Autophagy and endocytic traffic	Yes (Meisler et al., 2013)
	MAPT	Microtubule Associated Protein Tau	17q21.31	Microtubule assembly and stability, establishment and maintenance of neuronal polarity	no
	PGRN	Granulin Precursor	17q21.31	Cytokine-like activity, inflammation, wound repair, and tissue remodeling	Yes (Rubino et al., 2017)
Rare	ANG	Angiogenin	14q11.2	RNA synthesis. Synthesis and triggers the assembly of stress granules (SGs). Vascularization. Angiogenic activity.	no
	TARDBP	TAR DNA Binding Protein	1p36.22	Regulates transcription and splicing, microRNA biogenesis, apoptosis and cell division.	no
	VCP	Valosin Containing Protein	9p13.3	Ubiquitination and endoplasmic reticulum-associated degradation (ERAD), proteasome degradation	no
	UBQLN2	Ubiquilin 2	Xp11.21	Ubiquitin-proteasome system (UPS), autophagy and the endoplasmic reticulum-associated protein degradation (ERAD) pathway.	no
	OPTN	Optineurin	10p13	Maintenance of Golgi complex, membrane trafficking, in exocytosis.	no
	ATXN2	Ataxin 2	12q24.12	Trafficking and endocytic internalization Epidermal Growth Factor Receptor	no
	CHMP2B	Charged Multivesicular Body Protein 2B	3p11.2	Lysosome functioning	no
	TREM2	Triggering Receptor Expressed on Myeloid Cells	6p21.1	Immune responses in macrophages and dendritic cells, chronic inflammations	no
	TBK1	NF-kappa-B activator (TANK)-binding kinase 1	12q14.2	Inflammatory responses	no

BD= bipolar disorder; p= short arm; q= long arm

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2020 July 13.

Table 2.

Single nucleotide polymorphism, risk allele, gene symbol, gene name, chromosome location and molecular functions of genetic risk variants associated with bipolar disorder.

SNP	risk allele	symbol	name	Chromosome location	Molecular function
rs10994415	C	ANK3	Ankyrin 3	10q21.2	Structural constituent of cytoskeleton and protein binding, bridging
rs1006737	A	CACNA1C	Calcium Voltage-Gated Channel Subunit Alpha1 C	12p13.33	Voltage-gated calcium channel activity
rs12576775	A	ODZ4	Teneurin Transmembrane Protein 4	11q14	Neuronal connectivity during development
rs1064395	A	NCAN	Neurocan	19p13.11	Cell adhesion, extracellular matrix organization and central nervous system development
rs9371601	T	SYNE1	Spectrin Repeat Containing Nuclear Envelope Protein 1	6q25	RNA, actin and protein binding
rs9834970	C	TRANK1	Tetratricopeptide Repeat and Ankyrin Repeat Containing 1	3p22	No gene ontology molecular function found for this gene

SNP= single nucleotide polymorphism; BD= bipolar disorder; p= short arm; q= long arm

Table 3.

Comparison of clinical and biological variables between bipolar disorder and frontotemporal dementia.

	BD	FTD
Age of onset	20 to 40 (Yassa et al., 1988)	45 to 65 (Snowden et al., 2002)
Duration (years)	3.2 to 10.4 (Medeiros et al., 2016; Zhang et al., 2017)	Average of 6 (Young et al., 2018)
Progression	Varies widely according to recurrent mood episodes (Grande et al., 2016)	Fast (Young et al., 2018)
Inflammation	Cytokines and Cytokines receptors: IL-1, IL-4, IL-6, IL-10 sIL-2R, IL-1β, and sIL-2R, sIL-6R (Goldsmith et al., 2016; Wang and Miller, 2018; Modabbemia et al, 2013)	Cytokines: IL-6, IL-11, IL12, IL-15, IL-17, IL-23(Rentzos et al. 2006; Galimberti et al. 2008; Rainero et al. 2009; Hu et al. 2010; Bossù et al., 2011)
	Chemokines: TNF-α, sTNFR1 (Modabbernia et al, 2013)	Chemokines: TBK1, TNF-α, MCP-1 (Miller et al 2013; Blasko et al. 2006)
	Others: progranulin (Galimberti et al., 2012; Kittel-Schneider et al., 2014)	Others: progranulin, TREM2 (Ghidoni et al., 2008; Atagi et al. 2015)
Neurotrophic factors	BDNF, NGF, IGF-1, NT-3 and NT-4/5 (Fernandes et al., 2015; Tseng et al., 2016; Tu et al., 2016; Rao et al., 2017)	BDNF and NGF (Ventriglia et al. 2013; Blasko et al. 2006; Galimberti et al. 2009)
Oxidative damage	Lipid peroxidation, DNA/RNA damage, and nitric oxide, TBARS (Andreazza et al., 2008; Brown et al., 2014)	Lipoxidation-derived protein damage (Martinez et al. 2008)

BD= bipolar disorder; FDT= frontotemporal dementia; IL= interleukin; sIL-2R= soluble IL-2 receptor; sIL-6R= soluble IL-6 receptor; TNF-α= tumor necrosis factor; sTNFR1- soluble tumor necrosis factor receptor 1; TBARS = Thiobarbituric acid reactive substances TBK1= tumor necrosis factor (TNF) receptor associated factor NF-κB activator (TANK)-binding kinase 1; MCP-1= monocyte chemoattractant protein 1; TREM2= triggering receptor expressed on myeloid cells 2; BDNF= brain-derived neurotrophic factor; NGF= nerve growth factor; IGF-1= insulin growth factor 1; NT-4/5= neurotrophin-4/5; NT-3= neurotrophin-3