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BIPOLAR DISORDER AND DEMENTIA: A CLOSE LINK

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Abstract

Cognitive impairment in psychiatric disorders plays an important role in patient's social adjustement and global prognosis. Specific cognitive deficits during different phases of mood disorders have been demonstrated by recent meta-analyses. Several imaging data also confirmed progressive brain damages in mood disorders compatible with cognitive symptoms.

Different biological hypotheses have been put forward to explain the association between bipolar disorder (BD) and dementia. Some useful treatments for BD, such as lithium, have demonstrated a great effectiveness in both dementia prevention and BD. Further studies are however needed to assess the possible existence of a characteristic dementia in BD.

Key words: bipolar disorder, dementia, neuroimaging, lithium, amyloid

Declaration of interest: none

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Introduction

Cognitive impairment has been considered for a long time as a secondary feature of psychiatric disorders, while, currently, it is considered an integral part of the clinical picture (O'Brien 2005). In recent years literature focused on cognitive dysfunctions and their impact on psychosocial and occupational functioning mainly in BD (Tsai et al. 2007, Huxley and Baldessarini 2007, Burdick et al. 2010). Indeed, more than 50% of BD elderly patients suffers from cognitive deficits (Gildengers et al. 2004) and about two-third complain of subjective memory complaints (O'Brien 2005). Deficits have been identified in multiple cognitive domains, such as information processing speed (Depp et al. 2007, Gildengers et al. 2007), executive functions (Depp et al. 2007, Gildengers et al. 2007, Clark et al. 2002, Thompson et al. 2005, van Gorp et al. 1998, Zubieta et al. 2001), memory (Clark et al. 2002, Cavanagh et al. 2002, Deckersbach et al. 2004, Martinez-Aran et al. 2004, van Gorp et al. 1999), attention/concentration (Clark et al. 2005, Harmer et al. 2002), and visual-spatial abilities (Clark et al. 1985, Savard et al. 1980). Moreover, a few studies suggested that BD could be a risk factor for developing dementia. Therefore, it has been hypothesized that there might be a common neurobiological basis underlying dementia and BD (Kessing and Andersen 2004). In a study on elderly BD patients fulfilling criteria of dementia, a specific bipolar dementia-type has been proposed (Lebert et al. 2008). By the way, the risk of dementia is less documented in BD than in depressive disorder (Chen et al. 1999, Ownby et al. 2006). Even in depression it remains controversial whether the risk is associated with the number of episodes or with a particular cognitive decline related to late-onset illness (Chen et al. 1999, Ownby et al. 2006). Some authors highlighted the symptomatological, neuropsychological and brain imaging similarities between frontotemporal dementia (FTD) and BD (Masouy et al. 2011). Furthermore, in their concept of bipolar spectrum, Akiskal et al. (2005) proposed a BD of type VI (BD VI), characterized by a clinical picture with overlapping "bipolarity" and dementia. This kind of diagnosis concerns mixed, labile, agitated episodes in the setting of dementia, evident only from the sixth to seventh decade of life and onwards, featured by mood instability that slowly progresses into attention, memory and concentration (or increased distractibility) disturbances, irritability, agitation, irregular circadian rhytms (Akiskal et al. 2005, Dorey et al. 2008). In BD VI patients, premorbid temperament is often described as "strong" (Akiskal et al. 2005). These patients may be classified as hyperthymic or irritable or sometimes cyclothymic and a positive family history of BD or a bipolar diathesis is often detectable (Ng et al. 2008). From a therapeutic

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point of view, behavioral and cognitive symptoms are often refractory to or precipitated by antidepressants and acetylcholinesterase inhibitors, whereas mood stabilizers and/or atypical antipsychotics may be beneficial (Ng et al. 2008).

In this paper we aim to review available literature on neuropsychological, therapeutic and neuroimaging studies investigating the links between BD and dementia.

Neuropsychological features

Recent meta-analyses demonstrated persistent cognitive deficits during all phases of BD involving several domains. Verbal memory and attention show the most severe impairment, while executive functions and visual memory seem to be less compromised (Goldberg and Chengappa 2009, Quraishi and Frangou 2002).

Patients affected by BD of type I (BD I) show the most relevant cognitive impairment amongst all affective patients. This kind of impairment especially involves verbal memory, visual memory and semantic fluency. To date, it is unclear if the severe cognitive profile of BD I is due to the neurotoxic effects of manic episodes, or represents an expression of the basic neurobiological difference between BD I and BD II.

A concomitant history of psychosis in BD I patients represents a risk for severe impairment in verbal memory, working memory and executive functions. Family history of psychosis is also associated with a worse performance in selective attention and visual-motor processing. It is important to highlight the relationship between the polarity of mood episodes and the characteristics of cognitive deficits. Usually, mania provokes deficits in verbal memory and executive functions, while depression affects executive functions, verbal learning, visual and spatial memory (Lopes and Fernandes 2012). Two domains (visual and working memory deficits) show a remission of impairment in euthymic patients (Wingo et al. 2009).

The assessment of a neuropsychological test battery designed and validated for BD should be a primary aim in clinical practice. Moreover, this tool would be very useful to assess the benefits of treatment and to improve our knowledge on natural history of this illness.

Pharmacotherapy effects on cognition: the case of lithium

In the literature there are conflicting findings about lithium effects. Terao et al. (2006) reported that patients with present and/or past history of lithium treatment had significantly better Mini-Mental State Examination (MMSE) scores than patients without it (Terao et al. 2006). This study is in accordance with a case-control data (Nunes et al. 2007) that compared the prevalence of AD in elderly BD patients in euthymic phase who were on chronic lithium treatment with those who were not. Alzheimer's disease was diagnosed in 3 patients of the first group and in 16 patients of the other. Conversely, Dunn et al. (2005) identified from the General Practice Research Database in UK all cases of dementia between 1992 and 2002 and compared the number of lithium prescriptions for dementia patients with a control group, while reporting that dementia patients received more lithium prescriptions (n.47, 0.47%) than control subjects (n.40, 0.43%).

Other studies and meta-regressions reported lithium treatment as associated with impairments in learning, memory and psychomotor performance (Roiser et al. 2009, Latalova et al. 2011), but recent evidence suggests that this effect may be limited to certain subgroups of BD patients. (e.g, lithium non-responders) (Latalova et al. 2011, Kessing and Andersen 2004, Terao 2007).

Taken together this findings do not permit to draw any final conclusion on lithium effect, even because patients with dementia show an increased risk of developing mania and depression (Nilsson et al. 2002) and are thus more likely to receive lithium treatment.

Lithium might indirectly prevent dementia through its prophylactic effects on diminishing acute affective episodes. In fact, every new episode seems to increase the risk of a diagnosis of dementia in depressive disorder by 13% and by 6% in BD respectively, while supporting the hypothesis of cumulative "neurological toxicity" of the affective episodes (Kessing 1998, Kessing et al. 1999, Bearden et al. 2000, Kessing and Andersen 2004, Gildengers et al. 2004, Masouy et al. 2011).

The majority of studies suggest that direct neuroprotective effect of lithium is due to the modulation of multiple mechanisms, like signaling pathway and gene expression in CNS. Indeed, lithium increases the levels of important cytoprotective proteins, such as bcl-2 (Chen et al. 1999) that are involved in the regulation of apoptotic cell death by acting on mitochondria to stabilize membrane integrity and to prevent opening of the permeability transition pore that induces apoptosis (Manji et al. 2000).

Lithium also decreases the levels of specific proapoptotic proteins, such as p53 and Bax (Wei et al. 2000) and reduces glutamate-induced excitotoxicity mediated by NMDA receptors (Nunes et al. 2007). Recently it has been suggested that lithium mechanism of action is perhaps linked to its ability to inhibit the activity of the enzyme glycogen synthase kinase-3 (GSK-3) (Rowe and Chuang 2004, Rowe et al. 2007). This enzyme has two isoforms, α and ß, and plays a key role in the CNS by regulating different processes or transcription factors (tau phosphorylation, regulation of c-jun, pCreb and myocyte enhancer factor (MEF2), nuclear export of the nuclear factor of activated T cells (NF-Atc), nuclear factor kappa B (NFKB) and nuclear translocation of ß-catenin (Rowe et al. 2007, Gould and Manji 2005, Beaulieu et al. 2004). However, the main target involved in lithium's neuroprotective effects still remains the neuronal apoptosis regulation (Aghdam and Barger 2007, Engel et al. 2006, Fornai et al. 2008). Some observations suggest a mechanism for direct and indirect GSK-3 ß inhibition by lithium, which may influence the formation of both amyloid plaques and neurofibrillary tangles, the two neuropathological hallmarks of Alzheimer's disease (Terao 2007, Mendes et al. 2009).

In vitro and in vivo studies have further shown that lithium treatment increases the expression of VEGF (Silva et al. 2007, Yasuda et al. 2009, Guo et al. 2009), perhaps by inhibiting GSK-3 ß and stabilizing ß-catenin signaling in order to prevent stress-induced reductions in VEGF level (Brambilla et al. 2005), and promotes angiogenic and anti-apoptotic signaling in rat ischemic preconditioned myocardium (Kaga et al. 2006). Although GSK-3a and GSK-3ß could play distinct roles in transcriptional regulation and cell survival, these results strongly suggest that they are both involved in the execution of glutamate-induced neuronal death, and that both isoforms are initial targets of lithium-induced neuroprotection (Lian and Chuang 2007, Liang and Chuang 2006).

Lithium action on GSK could account for potential benefits of this treatment in chronic neurodegenerative diseases, such as Huntington disease (HD) and

amytrophic lateral sclerosis (ALS).

Magnetic resonance spectroscopy (MRS) reported a significant increase of total brain N-acetyl aspartate (NAA) (5%) after 4 weeks of lithium treatment in both temporal lobes and in central occipital and left parietal lobes in both patients and healthy control subjects (Moore et al. 2000) and increased grey matter volumes (Moore et al. 2000). A volumetric reduction in left anterior cingulate was found in untreated BD patients compared with healthy subjects, with no difference between lithium-treated and control subjects (Sassi et al. 2004). In addition, lithium administration did not provide any changes in NAA in control subject brains (Brambilla et al. 2004). These findings may suggest that the neuroprotective role of lithium could be region-specific and disease-related.

In any case further studies are needed in this area to clarify the risk/benefit ratio of psychotropic drugs, and lithium neuroprotective efficacy should also be tested in appropriate clinical studies in both neurodegenerative and psychiatric disorders.

Neuroimaging in BD: from structure to symptom

For many years brain damages have been explored in psychiatric disorders. Nowadays, there are no conclusive evidence on localized lesions in BD. Therefore, there is a growing literature on several brain modifications that should be related to symptoms. Kempton et al. (2008) showed that BD patients had a 2.5 deeper white matter (WM) hyperintensities compared with healthy subjects. WM alterations in BD are very heterogeneous and aspecific, although the main affected region seems to be the frontal one (Aikaterini et al. 2011). Moreover, diffusion tensor tractography in BD patients detected white matter fiber bundle abnormalities and disrupted integrity of connecting structures of the anterior limbic network (Benedetti et al. 2011). In addition, fMRI studies showed white matter hyperdensity of periventricular and deep subcortical location associated with cognitive deficits in prolonged illness with a poor prognosis (Bearden et al. 2001).

As far as particular regions of interest (ROI) and volumetric studies of BD brains are concerned, several areas have been deeply studied. Prefrontal cortex dysfunction seems to play a key role in the pathophysiology of BD, correlating with reduced frontal lobe size, neuropsychological deficits (Sax et al. 1999) and loss of bundle coherence in white matter (Adler et al. 2004). Moreover, decreases in volume and grey matter density (Doris et al. 2004, Lyoo et al. 2004) in anterior cingulate cortex (particularly in the left side) have been reported in BD, with subgenual prefrontal cortex (SGPFC) being significantly reduced in patients with a high genetic loading (Hyraiasu et al. 1999). To confirm these data, recent findings show that hemispheric white matter volumes, especially in the frontal region, are significantly reduced in BD I twins, as compared with control twins subjects (Kieseppa et al. 2003).

The temporal lobe, in particular the superior temporal gyrus (STG), the major anatomic substrate for speech, language and auditory processing, does not seem to present differences between BD patients and normal control subjects (Brambilla et al. 2003), nevertheless controversial findings have also been published (Chen et al. 2004). The majority of the studies, except one (Manji et al. 2000) comparing patients with healthy subjects did not detect any difference between the two groups in hippocampal dimension (Strakowski et al. 2002, Hauser et al. 2000).

The same controversial data have been reported also for amygdala volume (Altshuler et al. 2000, Swayze et al. 1992, Blumberg et al. 2003). More agreement exists for a smaller cerebellum and vermis volume in BD patients (Nasrallah et al. 1981) that seems to increase with the progression of the disorder (Del Bello et al. 1999). Increased locus coeruleus neuronal density (Baumann et al. 1999) and enhanced raphe echogenity (Becker et al. 1995) have been also described in BD patients.

Controlled CT scan and MRI studies reported an increased size of the third (Rieder et al. 1983) and lateral ventricles (Pearlson 1984), especially in patients with multiple episodes. Nevertheless, in BD, ventricular enlargement has been considered less important than in schizophrenia (Elkis et al. 1995).

MRS studies highlighted decreased N-acetylaspartate (NAA) levels in adolescent and adult BD (Winsberg et al. 2000; Chang et al. 2003), especially in dorsolateral prefrontal cortex (DLPFC), while suggesting the presence of elevated choline levels, mainly in the basal ganglia (Hamakawa et al. 1998). Further, higher myonositol and glutamine/glutamate levels have been detected in anterior cingulate and medial frontal grey matter and prefrontal cortex, respectively of BD children and adolescents (Castillo et al. 2000, Davanzo et al. 2001).

BD patients also showed abnormal frontal levels of phosphomonoester (PME): enhanced concentrations during affective episodes and decreased levels in euthymia (Deicken et al. 2005).

Moreover, normal PME levels has been found in temporal lobe and basal ganglia of euthymic BD patients (Silverstone et al. 2002, Hamakawa et al. 2004), mostly in those who received lithium or valproate. These findings suggest increased frontal and temporal membrane phospholipid alterated metabolism during affective episodes that would reflect neuronal membrane turnover. Previous studies also reported low intracellular pH in euthymic patients particularly in frontal lobes, basal ganglia and areas of increased WM hyperintensity (Hamakawa et al. 2004).

In conclusion, there exist scattered data of abnormal NAA, myoinositol and phospholipid metabolism in prefrontal cortex and choline concentration in the basal ganglia that need to be sustained by further data.

Genes studies

According to some authors, the severity of prefrontal cognitive deficits in BD and schizophrenic patients could be predicted by mutations in genes related to migration and neurodevelopment (Pavuluri et al. 2009). The most examined genes associated with abnormal cognitive functions are those of the serotonin transporter-linked polymorphic region (5HTTLPR), the polymorphism of cathecol O-methyltransferase (COMT) and the brain-derived neurotrophic factor (BDNF) and its receptor neurotrophic tyrosine kinase of type 2 (NTRK2). In family studies, deficits in executive functions and verbal memory (Ferrier et al. 2004), and also cognitive flexibility and attention shift (Clark et al. 2005) demonstrated in healthy siblings and euthymic patients, suggest a genetic vulnerability of BD patients for both conditions.

BDNF is a protein involved in neuronal support, growth and differentiation of new neurons that has been suggested to be involved in the pathophysiology

of different psychiatric disorders with a particular emphasis on its role on dysfunctions of the hippocampus and related cognitive dysfunction. In fact, BDNF is involved in hippocampal plasticity, hippocampal-dependent memory, activity-dependent increases in synaptic strength (Frodl et al. 2004). Monteggia et al. (2004) showed that selective loss of BDNF expression in the adult mice brain may be linked to reduced hippocampal-dependent learning, hyperactivity and more severe impairments in hippocampal functions. In addition, BDNF acts as a vital trophic protein for neuronal survival and differentiation in CNS development, and modulates cholinergic, dopaminergic and serotoninergic neurons (Poo 2001, Stern et al. 2008, Gallinat et al. 2010).

Moreover, BDNF plays an important role in glutamatergic synapse regulation and glutamate receptor activity (Carvalho et al. 2008), crucial factors involved in memory and other cognitive hippocampus-related functions. The gene encoding human BDNF is localized in chromosome 11, band p3, and it encodes a precursor peptide (pr-BDNF) which is cleaved to form the mature protein via proteolyses. It was shown that the frequent non-conservative amino acid substitution valine to methionine on codon 66 (val66met-polymorphism) in the 5' signal domain of BDNF gene leads to disturbances in the intracellular packaging and regulated secretion of BDNF without affecting mature BDNF protein function (Egan et al. 2003). The role of BDNF in hippocampal functioning is also confirmed by Gruber et al. (2011) who showed a significant effect of BDNF genotype on metabolic markers, specifically in the left hippocampus. In particular, homozygous carriers of the met-allele exhibited significantly lower levels of hippocampal metabolic markers (N-acetyl aspartate [NAA], choline, creatine and glutamate/glutamine) compared with val-val homozygotes. In addition, although not reaching a statistical significance, carriers of the met-allele revealed a reduced overall performances in verbal memory, cognitive performance measured using the German version of the Rey Auditory Verbal Learning Test (VLMT). Other studies showed that individuals who are methionine (met) allele carriers of the BDNF (Valine66Methionine [Val66Met]) polymorphism have decreased hippocampal volumes, compared with individuals homozygous for the val-allele. These reductions were present in both depressed patients and healthy individuals and were independent from age and gender. In depression, Met allele carriers showed bilateral volume reductions (Frodl et al. 2007), while val/val patients displayed left hippocampal reduction (Gonul et al. 2010) and right hippocampal increase (Kanellopoulos et al. 2011).

Pezawas et al. (2004) showed that the met-allele was associated with hippocampal volume reduction in healthy individuals. In both depressed patients and healthy individuals, the presence of at least one met-allele was associated with a significantly decrease of gyrification index in all four quadrants (dorsal and ventral bilaterally), in a period of four years, in comparison with val/val homozygotes (Mirakhur et al., 2009).

As already mentioned the BDNF/NTRK2 signaling pathway plays a critical role in regulation of survival and differentiation of neuronal population (Lin et al. 2009). Therefore, it seems plausible that variations in these genes may impact on vulnerability to mood disorders, and there is a greating interest in defining this relationship. One group described two possible functional single nucleotide polymorphism (SNPs) (rs 1187323, rs1187326) whose minor alleles were associated with less hippocampal Trk protein than the major allele in postmortem brains (Dunham et al. 2009). In agreement with this finding, another study in BD patients described an association between two BDNF SNPs and degree of prophylactic lithium response, while suggesting this pathway may also play a modulatory role in major depressive disorder. Finally in a genetic association study analyzing variants in the BDNF and NTRK genes, one SNP in the promoter region of NTRK2 (rs11140714) was reported to be associated with suicide attempts in a sample of 394 patients with depression after correction for multiple comparison for all tested SNPs (Kohli et al. 2010). A recent finding supported the involvement of NTRK2 in mood disorders and the related anatomical abnormalities (Murphy et al. 2012). A significant interactive effect between NTRK2 polymorphism and depression diagnosis maximally affecting white matter diffusivity in the cingulum was revealed.

Depressed patients homozygous for the A allele of NTRK2 showed significantly reduced fractional anisotropy (FA) compared with patients with at least one copy of the G allele or control patients with either the A/A or G carrier genotypes in certain areas involved in emotional processing and mood regulation. Significantly smaller grey matter volume was also detected in frontal lobe regions in patients homozygous for the allele A. In other words, the polymorphism in NTRK2 gene seems to increase risk for architectural changes in several brain regions involved in emotional and cognitive regulation. These findings could give a new look on the link between BD and cognitive deficits, highlighting a common pathogenesis.

Neurochemical and neurophysiological studies

Progressive and stage-related neuroanatomical changes and cognitive decline are generally caused by progressive biochemical changes (Berk et al. 2010). This occurs not only in the well-documented monoamine and second messenger abnormalities, but also in inflammatory cytokines, corticosteroids, neurotrophins, mitochondrial energy generation, oxidative stress and neurogenesis (Berk et al. 2011).

Nowadays a growing body of evidence from different lines demonstrates that glial and inflammatory response are central in neurodegenerative disorders and cognitive-related dysfunctions. Several studies on AD and other forms of dementia, show an important role of chronic release of pro-inflammatory mediators by microglia cells. Microglia constitutes the main immune defense in the CNS and, in response to neuronal injury, promotes the initiation of immune responses by enhancing the expression of toll-like receptors (TLR), become activated, acquire phagocytic properties and release a wide range of mediators such as tumor necrosis factor-alpha (TNFa) and interleukin (IL)-1 and 6. Activated microglia upregulates expression of the 18KDa translocator protein (TSPO), present at very low levels in normal healthy CNS and detected in vivo by PET. The acute inflammatory response is generally beneficial, as it tends to minimize injury and promotes tissue repair. However, chronic neuroinflammation, could induce detrimental effects by releasing of neurotoxic factors and promoting neuronal death. In fact, there is a plethora of evidence from post-mortem studies in AD patients (Venneti et al. 2009) and animal models (Leung et al. 2011) reporting a high accumulation of pro-inflammatory cytokines, close to

amyloid plaques (Akiyama et al. 2000, Eikelenboom et al. 2002). The increased activated microglia also inversely correlated with the patient's MMSE scores, which is compatible with a role of microglia in neuronal damage (Edison et al. 2008). In addition, elevated levels of activated microglia were also detected in patients with amnestic mild cognitive impairment (MCI) (Okello et al. 2009). Despite the evidence suggestive of pathogenic role of chronic neuroinflammation in AD, it has been hypothesized that the storage of amyloid plaques is actually due to a failure in microglia clearance mechanism that would normally remove protein (Napoli and Neumann, 2009). It has been shown that in the presence of pro-inflammatory cytokines, phagocytic functions of microglia are compromised (Koenigsknecht-Talboo et al. 2005) hence, resulting in aggregating formation (Bolmont et al. 2008). Therefore, the relationship between mood disorders and cognitive decline has been interpreted as the result of a common neuropathological mechanism, or as the expression of a greater vulnerability to the triggering of neurodegenerative phenomena (Aznar and Knudsen, 2011). Most of the studies in AD and MCI reported a reduction of ß amyloid 42 (Aß42), and an increase of Aß40 and Aß40/ Aß42 ratio (Graff-Radford et al. 2007, Van Oijen et al. 2006). Recently, a positive correlation was found between ß-amyloid peptide 40 and 42 plasma levels (Aß40/Aß42) ratio and the number of affective episodes in a sample of 16 bipolar depressed patients (Piccinni et al. 2012), while others detected a positive correlation between the Aß40/Aß42 ratio and subsequent cognitive decline (Okereke et al. 2009, Seppälä et al. 2010, Yaffe et al. 2011). However, although only a few data regarding the relationship between depression and peripheral levels of Aß peptides are now available, nevertheless they supports the hyphothesis that BD may be considered a neurodegenerative illness that probably shares some damage mechanisms with other diseases affecting the CNS.

Neurobiological studies: amyloid metabolism

Amyloid ß (Aß) peptides of 40 or 42 amino acids are formed after sequential cleavage of the amyloid precursor protein (APP) (Zhang et al. 2011). AD is neuropathologically characterized by the extracellular deposition of the Aß and by the intraneuronal generation of neurofibrillary tangles, neuropil threads, and abnormal material in dystrophic nerve cell processes of neuritic plaques.

These changes are also present in post-mortem analysis of a large number of non-demented elderly people, but deposits are restricted to distinct sites (neocortex, allo-cortex, basal ganglia, and diencephalic nuclei) (Thal et al. 2004), while AD patients present widespread lesions occurring in many brain areas (all affected in non-demented patients plus brain stem and cerebellum). Alterations of Aß peptides concentrations in plasma from AD patients (i.e. reduced A42 and an increased A40/A42 ratio) are common findings in recent studies, and this alteration was also found in MDD patients (Sun et al. 2007, Kita et al. 2009). Direct cytotoxic effects of A ß, negative effects on monoaminergic transmission, and functional antagonism between BDNF and Aß, suggest the potential involvement of Aß in the pathophysiology of BD and the neurobiology of dementing processes. Studies suggest that Aß may exhibit functional interference with BDNF, as BDNF stimulates long-term potentiation (LTP) and glutamatergic transmission (Korte et al. 1995, Levine et al. 1998, Lue et al. 1999), while Aß inhibits these phenomena (Snyder et al. 2005). Furthermore, Aß inhibits the synthesis of BDNF and could block the phosphorylation of the transcription factor cAMP response element-binding (CREB) (Tong et al. 2001) and its nuclear translocation (Arancio and Chao 2007, Arvanitis et al. 2007). The hypothesized increase in glutamatergic transmission during mood episodes (Kugaya and Sanacora 2005, Machado-Vieira et al. 2009, Yildiz-Yesiloglu and Ankerst 2006) may play a role in the Aß -mediated neurotoxicity, explaining the relationship between cognitive decline and clinical history of mood disorders (Geerlings et al. 2008, Gualtieri and Johnson 2008, Kessing and Andersen 2004, Torres et al. 2007). It has been suggested that some form of mood disorder may thus represent a prodromal manifestation of AD, or a subtype of amyloid-associate mood disorder characterized by cognitive impairment and risk of dementia (Sun et al. 2007).

Conclusions

The relationship between dementia and BD needs further studies and investigations. To date several data demonstrate a close link between the two conditions probably due to common diathesis in some cases, or to specific brain changes emerging during affective episodes. Imaging, neurobiological and genetic data support the existence of this relationship. Cognitive deficits should be more investigated in order to assess specific cognitive pictures during different phases of BD to explore the possible existence of a specific bipolar dementia subtype that would require specific preventive strategies and therapeutic targets to be developed in the future.

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