Biological and neuropsychological markers of cognitive dysfunction in unipolar vs bipolar Depression: What evidence do we have?

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Abstract

Cognition is a critical aspect of psychopathology. The aim of this review is to evaluate and discuss evidence on the biological and neuropsychological markers of cognitive dysfunction in unipolar and bipolar Depression to improve the differential diagnosis and develop plans of personalized pharmacological treatment. The different use of biological and neuropsychological markers is reviewed and their use to support the clinical process and differential diagnosis is critically examined. While biological markers can help to reduce the risk of misdiagnosis, neuropsychological markers can be assessed more readily and with a less invasive methodology. To this end, additional research on the thresholds differentiating the cognitive dysfunction in unipolar and bipolar Depression should be conducted on specific psychometric tools proposed in this review. Most importantly, future effort should be directed towards the validation of both types of markers specifically for these two populations. Finally, this review contributes to the field by

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focusing on the clinical need of a precise differential diagnosis that, when put in a translational framework, should combine an integration of research and clinical practice allowing for a better understanding of mental health and for evidence-based clinical practice.

Keywords: Cognitive dysfunction; Unipolar Depression; Bipolar Depression; Differential diagnosis; Psychometric assessment.

1. Introduction

Cognitive functioning has become of growing interest and has been investigated in a variety of contexts and applications, among which neuropsychological assessment, social cognition, and education (Bajaj, 2020; Osborne-Crowley, 2020; Parrales, Palma, Álava, & Campuzano, 2020).

The understanding of psychopathology has been enriched especially by the focus on human cognitive processes. Nowadays it is well known that mental illness is characterized by significant cognitive impairments that are firmly associated with other affective and behavioral signs and symptoms (Haywood & Raffard, 2017). In schizophrenia, for example, there are alterations in attention, executive functions, language, processing speed, memory and visuospatial ability (Hedges, Farrer, Bigler, & Hopkins, 2019a), while in Obsessive-Compulsive Disorder, specific cognitive strategies are aimed at the management of a sense of guilt (Mancini & Gangemi, 2018), with a lower cognitive flexibility/set shifting and a higher susceptibility to perseveration (Yazdi-Ravandii, Shamsaei, Matinnia, Shams, Moghimbeigi, Ghaleiha *et al.*, 2018).

Disorders that share a disturbance in mood - defined as *affective disorders* or *mood disorders* (Ellenbroek & Youn, 2016) - show a particular association with cognitive dysfunction, as deficits in cognition often precede or appear during the early stage of those pathologies and persist after the resolution of emotional symptoms, thereby, contributing to the patient's overall disability (Hedges, Farrer, Bigler, & Hopkins, 2019b). As the category of "affective disorders" mainly refers to the different kinds of Depressive Disorders and Bipolar Disorders, cognitive dysfunction is observed both in unipolar/bipolar depressive as well as inmanic/hypomanic states.

According to the World Health Organization, Depression is ranked as the single largest contributor to global disability, it is the major cause of suicide deaths and affects about 4.4% of the global population; moreover, this number is set to increase (WHO, 2017).

There are different depressive phenotypes but two of them - unipolar and bipolar - represent the most challenging in terms of differential diagnosis (Hirschfeld, 2014). Indeed, long-term follow-up studies have demonstrated that people suffering from Bipolar Disorder spend nearly half of their time (about 40%) in a depressive phase, about 50% of the time in an euthymic phase and only 10% of the time in a manic/hypomanic phase (Judd, Akiskal,

Schettler, Endicott, Maser, Solomon *et al.*, 2002). This is particularly true for Bipolar II Disorder (Judd, Akiskal, Schettler, Coryell, Endicott, Maser *et al.*, 2003). Moreover, bipolar patients usually ask for consultation only when they are depressed (Hirshfeld, Cass, Holt, & Carlson, 2005). These factors together result in late diagnosis or mistreatment, with a negative general outcome regarding the patient's quality of life and a high overall burden of the disease (Leyton & Barrera, 2010).

Therefore, differential diagnosis is critical. To this end, research on cognition may significantly help the clinician by describing the cognitive profiles of unipolar and bipolar Depression and efforts should be made to include them as part of the diagnostic process in order to personalize pharmacological treatment. In other terms, collecting and differentiating markers of cognitive dysfunction related to the different depressive phenotypes would increase the specificity of the diagnosis and the appropriateness of an adequate treatment.

Starting by acknowledging that unipolar and bipolar Depression are disorders of the brain, and that behavior is the last step of a cascade that started long before problems manifest themselves, we probably should start with the brain, with its wiring and connections, with its metabolism, and with the way it interacts with its surroundings. A lot of variation exists in how the brain is wired and how it functions, but this variation does not exclude the existence of some possible and predictable set of factors that put bipolar and unipolar depressed patients at a different risk for cognitive problems. When crossing a behavioral, emotional, or cognitive threshold, what underlying different thresholds has each patient crossed that has determined his/her vulnerability? What drives the patient's cognitive dysfunction?

Markers of cognitive dysfunction can be identified either as neuropsychological or as biological, each to be evaluated with their own specific clinical tools.

This review explores the role of neuropsychological and biological markers of cognitive dysfunction in unipolar and bipolar Depression and collects evidence regarding their potential role in strengthening differential diagnosis. Particular attention will be given to the psychometric tools that we might want to include in the assessment of unipolar and bipolar Depression to improve the quality of clinical decision-making and adequately plan the treatment.

2. Depression: Main phenotypes and cognitive dysfunction

The publication of the DSM-5 (APA, 2013) imposed several important changes in the diagnostic categories compared to the previous DSM-IV-TR (APA, 2000), such as, the abolition of the category of "Mood Disorders" (Rodríguez-Testal, Senín-Calderón, & Perona-Garcelán, 2014). In the new Manual, "Bipolar and Related Disorders" and "Depressive Disorders" figure as two distinct categories. The first includes Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder and Disruptive Mood Dysregulation Disorder, while the second includes Major Depressive Disorder (MDD), Persistent Depressive Disorder (Dysthymia), and Premenstrual Dysphoric Disorder.

Given the general aim of this review, it is useful to remind that Bipolar I Disorder must be characterized by a distinct manic episode that may be associated with other periods of Major Depressive Episodes and/or hypomania, whereas Bipolar II Disorder can be diagnosed if there has been at least one episode of hypomania and one episode of Major Depressive Disorder. Major Depressive Disorder, instead, is characterized by a two-week period showing at least either depressed mood or loss of interest or pleasure, associated with other symptoms like changes in appetite, weight, sleep patterns, diminished energy and feelings of worthlessness and excessive guilt. Specifiers and additional criteria of inclusion and exclusion are thoroughly discussed in the DSM-5.

In depressive phenotypes, two fundamental types of cognitive dysfunction can be distinguished: *cognitive biases* and *cognitive deficits* (Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011). The first consist of systematic distortions in the processing of information, in terms of selection, interpretation, encoding and retrieval. They influence the way depressed people view themselves, the world and their future and they are best treated by specific psychotherapeutic approaches (Young, Rygh, Weinberger, & Beck, 2014). Cognitive deficits, instead, can be defined as specific impairments in several domains, among which, attention, executive functions, and memory, which represent the main cognitive domains to be considered. They can be detected, measured, and should be taken into consideration to support the diagnosis and the efficacy of treatment. As discussed before, these deficits are expressed in terms of neuropsychological and biological markers. In the next paragraphs, we will present and critically review the markers of cognitive dysfunction in unipolar and bipolar Depression.

3. Markers of cognitive dysfunction in unipolar Depression

3.1. Neuropsychological markers

According to international and Italian psychiatrists, cognitive symptoms represent a relevant dimension of MDD and are among the residual symptoms affecting the risk for relapse (Albert, Brugnoli, Caraci, Dell'Osso, Di Sciascio, Tortorella *et al.*, 2016). Indeed, unipolar Depression is characterized by several neuropsychological markers, which represent a core feature that needs to become a specific target for treatment. For example, SSRI and SNRI antidepressants improve cognitive symptoms independently from their efficacy related to the affective dimension (Castellano, Ventimiglia, Salomone, Ventimiglia, De Vivo, Signorelli *et al.*, 2016). Neuropsychological changes are so obvious that the term "pseudodementia" has been coined to refer to the impaired cognition given the resemblance with neurodegenerative diseases, but instead here it is due to a psychiatric condition (Brodaty & Connors, 2020). Moreover, the DSM-5 includes the "diminished ability to think or concentrate, as well as indecisiveness" as a criterion for a major Depression episode (APA, 2013).

Moderate deficits in executive functions, memory and attention are altered in depressed patients compared to healthy subjects and research has demonstrated that impairment in executive functions and memory persist even after mood symptoms have remitted (Rock, Roiser, Riedel, & Blackwell, 2014). Also, Castellano and co-workers (2020) reported that neurocognitive performance at baseline influenced long-term psychosocial functioning with a specific role played by verbal memory, which predicted the functional outcome after one year in patients who had a partial response to antidepressants (Castellano, Torrent, Petralia, Godos, Cantarella, Ventimiglia *et al.*, 2020).

According to Austin, Mitchell and Goodwin (2001), in MDD there are deficits in attention, verbal and visual memory, executive processes and psychomotor skills, which sums up decades of research on this topic. Also, verbal fluency and attentional set-shifting are impaired in depressed elderly patients (Beats, Sahakian, & Levy, 1996) whereas younger out-patients show similar symptoms with additional deficits in motor speed (Purcell, Maruff, Kyrios, & Pantelis, 1997). Deficits in the Digits backwards task and perseverative responses characterized a sample of patients with endogenous/melancholic Depression (Austin, Mitchell, Wilhelm, Parker, Hickie, Brodaty *et al.*, 1999).

Taken together, the debate with respect to neuropsychological markers is still open and their role in unipolar Depression, either as endophenotypes or as epiphenomena of the pathology (McInerney, Gorwood, & Kennedy, 2016), warrants a more in-depth evaluation.

3.2. Biological markers

Attention towards biological markers of cognitive dysfunction in unipolar Depression is growing fast. The link between Depression and cognitive impairment is so robust, that a lifetime history of Major Depression can be considered as a risk factor for the development of Alzheimer's disease and as a predictor of the conversion from Mild Cognitive Impairment (MCI) to dementia (Steffens, 2012).

Deficits in neurotrophin signaling are observed in Major Depressive Disorder (MDD): reduced plasma levels of BDNF and TGF-β1 - a growth factor and an anti-inflammatory cytokine with key roles in neuroprotection, synaptic plasticity and the formation of new memories - correlate with Depression severity (Caraci, Spampinato, Morgese, Tascedda, Salluzzo, Giambirtone *et al.*, 2018). Moreover, MDD patients display higher levels of proinflammatory cytokines, such as IL-6 and IL-8, and of the tumor necrosis factor-α (TNF-α), which correlate with circulating mitochondrial DNA (mtDNA) (Kageyama, Kasahara, Kato, Sakai, Deguchi, Tani *et al.*, 2018). Signs of inflammation and oxidative stress have led to the hypothesis that the immune system is involved actively in MDD (Maes, Nowak, Caso, Leza, Song, Kubera *et al.*, 2016). Additional data stem from the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to higher levels of cortisol in depressed patients and is often associated with inflammation (Pariante, 2017). Lower levels of neurotrophins and higher levels of glucocorticoids together with a heightened inflammation increase Aβ toxicity, hippocampal atrophy and, consequently, cognitive deficits (Caraci, Copani, Nicoletti, & Drago, 2010).

These findings are further strengthened by neuroimaging data. The anterior Cingulate Cortex (ACC) is involved in attention, problem solving, motivation and decision-making (Rushworth, Behrens, Rudebeck, & Walton, 2007), while the Dorsolateral Prefrontal Cortex (DLPFC) is considered critical for cognitive functions (Liao, Feng, Zhou, Dai, Xie, Ji *et al.*, 2012). The ACC, DLPFC and Orbitofrontal Cortex (OFC) have been hypothesized to work together to inhibit a negative emotional response and emotional memory thanks to a cognitive control network, within which

emotional response and memory originate from regions, such as the amygdala and the hippocampus. ACC, DLPFC and OFC appear to be critical biomarkers for cognitive dysfunction in unipolar Depression also when considering data from Electroencephalography (EEG) and Positron Emission Tomography (PET) (Lai, 2019). Furthermore, Magnetic Resonance Imaging (MRI) data indicate the presence of structural changes in recurrent depressed patients with a lower volume of grey matter in the left hippocampus (Samann, Hohn, Chechko, Kloiber, Lucae, Ising *et al.*, 2013). Also, mean depressive symptom scores are associated with reductions in brain volume in the cingulate gyrus and in the OFC, as well as with the rate of a decline in volume of the left frontal white matter (Dotson, Davatzikos, Kraut, & Resnick, 2009).

Taken together, the data regarding biomarkers, do not indicate a clear picture on whether cognitive dysfunction in Depression is part of an underlying and stable neurobiological vulnerability, which would support the neurodevelopmental origins of Depression, or whether cognitive dysfunction occurs only during depressive episodes, as outlined by McInerney and colleagues (McInerney, Gorwood, & Kennedy, 2016), which would support a more immediate environment-related hypothesis with a strong contribution of epigenetics.

4. Markers of cognitive dysfunction in bipolar Depression

4.1. Neuropsychological markers

Cognitive impairment and neuropsychological dysfunction are two fundamental characteristics in patients with Bipolar Disorder, especially in the depressive phase, because the resulting deficits compromise the social, relational and professional capacities of these patients and significantly affect their overall functioning and quality of life (Melloni, Poletti, Vai, Bollettini, Colombo, & Benedetti, 2019).

Significant evidence in the literature has highlighted the relationship between the number of episodes related to mood variability and the severity of cognitive deficits, reporting the presence of structural and neuropsychological changes (Hellvin, Sundet, Simonsen, Aminoff, Lagerberg, Andreassen *et al.*, 2012; Cardoso, Bauer, Meyer, Kapczinski, & Soares, 2015; Passos, Mwangi, Vieta, Berk, & Kapczinski, 2016). In fact, in bipolar patient anomalies related to the white matter (WM), to ventricular

enlargement (Birner, Seiler, Lackner, Bengesser, Queissner, Fellendorf *et al.*, 2015) as well as to the loss of the volume and thickness of the total gray matter (GM) have been observed (Hallahan, Newell, Soares, Brambilla, Strakowski, Fleck *et al.*, 2011; Gildengers, Chung, Huang, Begley, Aizenstein, & Tsai, 2014).

From a neuropsychological point of view, the most important cognitive impairment of bipolar patients, in the depressive phase, are deficits in memory and executive function (Martìnez-Aràn, Vieta, Colom, Reinares, Benabarre, Gastó *et al.*, 2000; Bearden, Hoffman, & Cannon, 2001; Borkowska & Rybakowski, 2001), even after remission. This data have been confirmed by several other studies, which, other than the aforementioned dysfunctions, also reported of alterations in episodic memory (Sweeney, Kmiec, & Kupfer, 2000), inattention (van der Meere, Börger, & van Os, 2007; Maalouf, Klein, Clark, Sahakian, Labarbara, Versace *et al.*, 2010; Belleau, Phillips, Birmaher, Axelson, & Ladouceur, 2013) in verbal appeal and fine motor skills (Malhi, Ivanovski, Hadzi-Pavlovic, Mitchell, Vieta, & Sachdev, 2007) and finally of dysfunctions related to visual-mnemonic skills and verbal fluency (Martìnez-Aràn *et al.*, 2000; Harkavy-Friedman, Keilp, Grunebaum, Sher, Printz, Burke *et al.*, 2006; Xu, Lin, Rao, Dang, Ouyang, Guo *et al.*, 2012), which worsen based on the progression of mood-related episodes (Lee, Hermens, Scott, Redoblado-Hodge, Naismith, Lagopoulos *et al.*, 2014; Galimberti, Bosi, Caricasole, Zanello, Dell'Osso, & Viganò, 2020). Furthermore, serious damage is observed in functions of the frontal lobe, which involve visuospatial and visuomotor skills, working memory and, most importantly, executive functioning (Borkowska & Rybakowski, 2001).

Recent research has found a poor performance in verbal memory, working memory, psychomotor coordination and selective assessment in a sample of Bipolar type I depressed patients (Melloni *et al.*, 2019), while marked deficits in episodic memory, in learning and recalling a list of objects, and in encoding information were reported in another study (Dongaonkar, Hupbach, Nadel, & Chattarji, 2019).

As discussed above, the most impaired cognitive function in this phase of Bipolar Disorder, in addition to deficits in memory, seems to be executive functioning: Galimberti and colleagues showed that the centrality of this dysfunction drives the overall cognitive deterioration of the aforementioned patients (Galimberti *et al.*, 2020).

Finally, several authors have explained the relevance of the so-called “suggestive elements” present in the depressive phase of Bipolar Disorder,

which involve psychopathological symptoms and clinical variables and refer to, for example, to psychomotor agitation, emotional lability, irritability, insomnia, hyperphagia and rapid thoughts, which, although not involved in the cognitive aspects, influence the recognition of the disorder (Ghaemi, Sachs, & Goodwin, 2000; Yatham, 2005).

Taken together, many of the neuropsychological markers belonging to the depressive phase of Bipolar Disorder are similar to those observed in Unipolar depressive Disorder, albeit with a minimal distinction. Therefore, it is important to further discuss the differences between the two disorders, in order to improve the differential diagnosis and to choose the appropriate therapy that is best fitted to the clinical phenotype of the patient.

4.2. Biological markers

A similarity exists between the biological markers of Bipolar Disorder in the depressive phase with those of unipolar Depression, which concerns the decrease in levels of brain-derived neurotrophic factor (BDNF) levels (Cunha, Frey, Andreazza, Goi, Rosa, Gonçalves *et al.*, 2006; Bourne, Aydemir, Balanzá-Martínez, Bora, Brissos, Cavanagh *et al.*, 2013). In fact, various mood-related episodes negatively affect the homeostatic balance between inflammatory mechanisms, oxidative processes and neuroprotective substances (such as BDNF) and contribute to neuronal apoptosis (Berk, Kapczinski, Andreazza, Dean, Giorlando, Maes *et al.*, 2011; Fries, Pfaffenseller, Stertz, Paz, Dargél, Kunz *et al.*, 2012; Bauer, Pasco, Wollenhaupt-Aguiar, Kapczinski, & Soares, 2014).

Furthermore, in the case of Bipolar Disorder, especially during the depressive phase, the levels of proinflammatory agents are higher, such as for interleukins (IL-6, IL-2R, IL-1beta), the tumor necrosis factor (TNF-α), cellular TNF-α receptors (TNFR1), and CXCL10 serum levels (Barbosa, Huguet, Sousa, Abreu, Rocha, Bauer *et al.*, 2011; Barbosa, Bauer, Machado-Vieira, & Teixeira, 2014; Barbosa, Machado-Vieira, Soares, & Teixeira, 2014; Bauer *et al.*, 2014). In particular, the levels of the pro-inflammatory markers YKL40, sCD40L and hsCRP are higher and these alter the function of monoaminergic systems, such as dopaminergic and serotoninergic systems, finally affecting the cognitive and affective functions (Rosenblat, Brietzke, Mansur, Maruschak, Lee, & McIntyre, 2015). The role of adiponectin is relevant as well and plays a basic role in metabolic and inflammatory processes: research has demonstrated that low levels of

adiponectin were associated with the depressive state of bipolar subjects (Platzer, Fellendorf, Bengesser, Birner, Dalkner, Hamm *et al.*, 2019).

Additional evidence comes from studies that support the hypothesis that inflammatory diseases, such as autoimmune thyroiditis, psoriasis, Guillain-Barré syndrome (GBS), autoimmune hepatitis, multiple sclerosis (MS), migraine, rheumatoid arthritis (RA), obesity, atherosclerosis, and type II diabetes mellitus, play a significant role in the genesis of Bipolar Disorder (Kupka, Nolen, Post, McElroy, Altshuler, Denicoff *et al.*, 2002; Edwards & Constantinescu, 2004; McIntyre, Konarski, Misener, & Kennedy, 2005; Bachen, Chesney, & Criswell, 2009; Calkin, Van De Velde, Ruzickova, Slaney, Garnham, Hajek *et al.*, 2009; Eaton, Pedersen, Nielsen, & Mortensen 2010; Han, Lofland, Zhao, & Schenkel, 2011; Hsu, Chen, Liu, Lu, Shen, Hu *et al.*, 2014; Perugi, Quaranta, Belletti, Casalini, Mosti, Toni *et al.*, 2015).

As for unipolar Depression, also for bipolar Depression an involvement of inflammation in metabolic dysfunction has been suggested. In particular, enhanced HPA activity may induce central obesity and insulin resistance (Boutzios & Kaltsas, 2000; Rosenblat *et al.*, 2015).

Research conducted in the field of neuroimaging has contributed greatly to the more accurate analyses of the depressive phase in Bipolar Disorder: bipolar subjects in the depressive phase displayed abnormally high levels of amygdala activity, when exposed to mostly neutral or sad facial expressions, while a reduction was observed in the bilateral amygdala-ventromedial prefrontal cortex (vmPFC) when exposed to happy facial expressions (Almeida, Versace, Mechelli, Hassel, Quevedo, Kupfer *et al.*, 2009).

Other studies, however, observed an increased volume of the lateral and third ventricles (Gulseren, Gurcan, Gulseren, Gelal, & Erol, 2006; Beyer, Young, Kuchibhatla, & Krishnan, 2009; Hallahan *et al.*, 2011; Frey, Andreazza, Houenou, Jamain, Goldstein, Frye *et al.*, 2013; Goldstein & Young, 2013), which became evident only after the occurrence of several mood-related episodes (Strakowski, DelBello, Zimmerman, Getz, Mills, Ret *et al.*, 2002).

Several neurobiological models studying emotional dysregulation have also analyzed the anomalies in the fronto-limbic-subcortical structures in bipolar patients, highlighting that they themselves are part of an increase in bottom-up processes and/or a decrease in top-down processes (Savitz & Drevets, 2009; Phillips & Swarts, 2014). This data are supported by functional magnetic resonance imaging (fMRI) studies in which a reduction in activation in the cortical cognitive brain network and an increased

activation in the ventral limbic brain regions was confirmed in subjects with Bipolar Disorder (Houenou, Frommberger, Carde, Glasbrenner, Diener, Leboyer *et al.*, 2011).

Despite the results achieved, novel studies are needed, including neuroimaging studies, in order to distinguish more clearly the structural and functional differences between unipolar and bipolar Depression and to identify those biological markers that reflect the pathophysiological processes underlying these two disorders (de Almeida & Phillips, 2013).

5. Evidence for differential diagnosis

5.1. Comparing unipolar and bipolar Depression

Carrying out a precise and accurate differential diagnosis between unipolar and bipolar Depression represents a great clinical challenge. The main reason for this concerns not only the higher prevalence of depressive symptoms compared to hypomanic symptoms in bipolar Depression, but also the fact that a significant amount of manic symptoms remain below threshold in both unipolar and bipolar Depression (de Almeida & Phillips, 2013).

Hence, it is easy to understand that the consequences of an incorrect diagnosis could lead to severe problems. For example, if a depressed bipolar patient were treated only with antidepressants, their effectiveness would be reduced since antidepressants should be coupled with mood stabilizers to have the desired therapeutical effect (Goodwin & Consensus Group of the British Association for Psychopharmacology, 2009; Yatham, Kennedy, Parikh, Schaffer, Beaulieu, Alda *et al.*, 2013). Furthermore, inadequate treatment could result in an increased risk of suicide, an easier transition to mania, and an increase in health care costs (Hirschfeld, Lewis, & Vornik, 2003; Perlis, Ostacher, Goldberg, Miklowitz, Friedman, Calabrese *et al.*, 2010; Goodwin, 2012).

Along this line, an accurate screening of the two disorders, from a cognitive point of view, would help to avoid an incorrect diagnosis, which is of fundamental importance (Hirschfeld, 2014).

Biological markers are certainly one of the key issues in the management of patients with unipolar and bipolar Depression and many are common to both ailments. A difference in this sense can be found in serum BDNF levels, which are lower in bipolar patients and higher in unipolar patients and in control subjects (.15 ± .08, .35 ± .08 and .38 ± .12, respectively, $p <$

.001) (Fernandes, Gama, Kauer-Sant'Anna, Lobato, Belmonte-de-Abreu, & Kapczinski, 2009). The laboratory cut-off, in fact, equal to .26 pg/ml, is able to sustain the differential diagnosis of the two disorders with an accuracy equal to 88%. Because of this, BDNF could contribute as a predictive marker, as a marker of the presence of the disease or as a surrogate marker (Fernandes, Molendijk, Köhler, Soares, Leite, Machado-Vieira *et al.*, 2015; Polyakova, Stuke, Schuemberg, Mueller, Schoenknecht, & Schroeter, 2015; Sagar & Pattanayak, 2017).

In recent years, the analysis of the neural networks involved in mood disorders, using the neuroimaging data of both structural and functional measures related to the formation of neuronal circuits involved in the processing and regulation of emotions, has been very important (de Almeida & Phillips, 2013).

Thanks to structural magnetic resonance imaging, irregularities in the integrity of the white matter and more specifically of the corpus callosum and the cingulum, characterizing Bipolar Disorder compared to Major Depression, have been observed (Benedetti, Absinta, Rocca, Radaelli, Poletti, Bernasconi *et al.*, 2011; de Almeida & Phillips, 2013; Matsuoka, Yasuno, Kishimoto, Yamamoto, Kiuchi, Kosaka *et al.*, 2017; Repple, Meinert, Grotegerd, Kugel, Redlich, Dohm *et al.*, 2017) and have been associated with alterations in the gray matter volume of the prefrontal cortex and hippocampus (Matsuo, Harada, Fujita, Okamoto, Ota, Narita *et al.*, 2019; Niida, Yamagata, Matsuda, Niida, Uechi, Kito *et al.*, 2019). However, a recent study has shown that depressed bipolar subjects have reduced gray matter volumes in the right hippocampus, in the parahippocampal gyrus, in the fusiform gyrus, in the amygdala, in the insula, in the rolandic and frontal operculum, and in the cerebellum (Vai, Parenti, Bollettini, Cara, Verga, Melloni *et al.*, 2020). Similar results have been reported by Liu and colleagues, who have shown that depressed unipolar patients have an increased ReHo in the right parahippocampal gyrus compared to control subjects. In addition, the ReHo in the right hippocampus of depressed bipolar patients was found to have a larger volume, while the ReHo in the right middle occipital gyrus appeared to be smaller. Finally, bipolar depressed patients displayed a reduction of ReHo in the right inferior temporal gyrus. This suggests that the latter could be considered as an important biological marker in the differential diagnosis of the two disorders (Liu, Li, Zhang, Liu, Sun, Yang *et al.*, 2020). Moreover, as regards regional homogeneity, Liu and colleagues found that subjects with bipolar Depression, compared to unipolar depressed patients, had higher ReHo

values in the right dorsal anterior insular, right middle frontal gyrus, right cerebellum posterior gyrus, and the left cerebellum anterior gyrus (Liu, Ma, Wu, Zhang, Zhou, Li *et al.*, 2013). Liang and colleagues, in contrast, emphasized how bipolar depressed patients displayed higher ReHo values in the thalamus than unipolar depressed patients (Liang, Zhou, Yang, Yang, Fang, Chen *et al.*, 2013).

Other studies, concerning the structural measures of neuroimaging, have contributed to making differential diagnoses more effective, by examining and comparing healthy subjects, unipolar depressed and bipolar depressed patients. These studies helped to discover that bipolar depressed patients present a reduction in fractional anisotropy (FA) in the right uncinate fasciculus (Versace, Almeida, Quevedo, Thompson, Terwilliger, Hassel *et al.*, 2010) as well as an increase in periventricular and deep white matter hyperintensities (DWMH; Silverstone, McPherson, Li, & Doyle, 2003) and a volume reduction in the left habenula (Savitz, Nugent, Bogers, Roiser, Bain, Neumeister *et al.*, 2011). In addition, the anterior cingulate cortex has shown to be a biological marker useful for differential diagnosis: in the depressive phase of Bipolar Disorder, the level of glutamate was higher while in unipolar Depression the level dropped considerably (Yüksel & Öngür, 2010).

Regarding the functional measures of neuroimaging, several studies examined the functionality of the neuronal circuits involved in emotion. Taylor Tavares and colleagues, for example, conducted research with unipolar, bipolar depressed patients and healthy control subjects, in order to analyze whether a reversed learning paradigm could measure the ability to modify a behavior when reinforcement (positive or negative) was changed; unipolar depressed patients reversed their response following negative reinforcement, which appeared to be related to reduced ventrolateral and dorsomedial prefrontal cortical activity, unlike bipolar patients who maintained a normal level of neural activity. In addition, unipolar depressed patients also displayed reduced activity in the ventrolateral prefrontal cortex (VLPFC) during reversal shifting, which was associated with a reduction in the activity of the amygdala in the presence of positive reinforcement (Taylor Tavares, Clark, Furey, Williams, Sahakian, & Drevets, 2008). Another study, which employed an executive control model with emotional distractors and that involved female subjects with bipolar and unipolar Depression, reported that the latter displayed a better developed dorsal anterior mid cingulate cortical activity compared to the other subjects during

the demanding 2-back condition of the model with neutral face distracters (Bertocci, Bebko, Mullin, Langenecker, Ladouceur, Almeida *et al.*, 2012).

Neuropsychological assessment plays a key role in the differential diagnosis between unipolar and bipolar Depression. A number of studies have highlighted the similarity of neuropsychological functioning characterizing both disorders (Sweeney *et al.*, 2000; Gruber, Rathgeber, Bräunig, & Gauggel, 2007; Daniel, Montali, Gerra, Innamorati, Girardi, Pompili *et al.*, 2013). For example, research conducted by Liu and colleagues in a sample of healthy controls, depressed unipolar and bipolar patients showed that the latter two groups had similar impairments in psychomotor speed, working memory, visual memory, verbal fluency and switching of attention with respect to the healthy subjects (Liu, Zhong, Wang, Liao, Lai, & Jia, 2018). The study conducted by Xu and colleagues (2012) showed analogous results. By comparing depressed bipolar I, bipolar II and unipolar patients, a fairly similar cognitive picture emerged regarding dysfunctions in processing speed, visual memory and cognitive functions, although bipolar I patients displayed greater deficits in verbal fluency and executive functions compared to the other patients (Xu *et al.*, 2012). Consistent with these studies, other researchers observed similar clinical and cognitive performances between the two disorders, especially with respect to processing speed (Daniel *et al.*, 2013) and verbal memory (Hermens, Naismith, Redoblado Hodge, Scott, & Hickie, 2010).

In fact, these conclusions are consistent with what has been explained in the previous paragraphs, in which we emphasized that the neuropsychological markers of the two disorders clearly overlap and, in some cases, show the same profile.

In contrast, other studies support the presence of differences in the type of neuropsychological deficits in unipolar and bipolar Depression. Taylor Tavares and co-workers discovered that bipolar depressed people displayed more cognitive deficits than individuals with unipolar Depression (Taylor Tavares, Clark, Cannon, Erickson, Drevets, & Sahakian, 2007). Likewise, the study of Hori and colleagues demonstrated that patients with bipolar Depression had greater deficits in verbal memory and executive functions than patients with unipolar Depression (Hori, Matsuo, Teraishi, Sasayama, Kawamoto, Kinoshita *et al.*, 2012). Furthermore, psychomotor retardation is a particularly clear factor in defining the difference between the two disorders: numerous studies have observed a more evident psychomotor slowdown in bipolar as compared to unipolar Depression (Mitchell, Frankland, Hadzi-Pavlovic, Roberts, Corry, Wright *et al.*, 2011; Motovsky

& Pecenak, 2013). Similarly, attention deficits appear much more marked in depressive Bipolar Disorder (Benazzi, 2006; Mitchell *et al.*, 2011; Gosek, Heitzman, Stefanowski, Antosik-Wójcińska, & Parnowski, 2019).

Borkowska and Rybakowski (2001), on the other hand, analyzed the differences between the two disorders using tools designed to assess the functionality of the frontal lobe. Depressed bipolar patients displayed a higher level of cognitive dysfunction related to the activity of the frontal lobe (in particular, in attention, verbal fluency, spatial planning, and abstract functioning) and presented a significantly reduced performance in non-verbal intelligence compared to unipolar depressed patients. More recent studies (Galimberti *et al.*, 2020) have demonstrated an enhanced mnemonic impairment in subjects with unipolar Depression compared to bipolar Depression, with marked dysfunctions in executive functions being more evident.

Thus far, the nature of the neuropsychological differences between bipolar and unipolar depressed patients is contradictory, which leads to significant difficulties in the differential diagnosis. However, what is certainly known is that subjects with bipolar Depression appear to exhibit greater cognitive impairment than subjects with unipolar Depression.

Consequently, the debate regarding the structure and function of the cognitive and neuropsychological profile between unipolar and bipolar Depression is still open. From a clinical point of view, however, the inclusion of cognitive and neuropsychological analyses should provide valid elements to make a more accurate differential diagnosis between the two described disorders, which up to now have been too often misdiagnosed (Galimberti *et al.*, 2020).

6. Psychometric tools for differential diagnosis

As discussed above, evidence collected thus far is ambiguous and therefore hampers the use of cognitive dysfunction in the differential diagnosis of unipolar and bipolar Depression. If, on the one hand, various authors reported of significant differences between unipolar and bipolar depressed patients regarding cognitive dysfunction, other researchers, on the other hand, observed quantitative and non-qualitative discrepancies, which suggests there is concordance in affirming that the cognitive dysfunctions involved in the two types of Depression are the same, but with a different severity of impairment. Indeed, quantitative differences common to both disorders lead to a lower performance in patients with bipolar Depression.

Based on the accumulating empirical evidence, but more importantly because of the paucity in neuropsychological tests that support a scrupulous differential diagnosis between the two disorders, we suggest the following.

As a first step, we propose to perform research on the calibration and validation of the psychometric tests presented in the next paragraphs and to define the thresholds differentiating unipolar from bipolar depressive cognitive dysfunction. These (domain-specific) cut-off scores will then allow us to distinguish the cognitive deficits framed within a unipolar or bipolar Depression from a quantitative point of view.

A large review of the previous literature has helped us understand which tests detect quantitative differences between patients suffering from one or the other disorder. As a second and last step, we thus suggest to add other psychometric tools to discriminate between the presence or absence of specific neuropsychological deficits. After the suggested calibration mentioned above, these tools should become an essential part of the psychometric strategies in support of the differential diagnosis between unipolar and bipolar Depression.

6.1. Memory

Deficits in memory appear to be a neuropsychological dysfunction common to both unipolar and bipolar Depression although it is more deficient in bipolar depressed patients (Murphy & Sahakian, 2001; Mansell, Colom, & Scott, 2005).

After a careful review of the literature, we have selected several psychometric tools useful for differential diagnosis.

A first important tool is the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). The task is simple: the experimenter reads a list of 16 words (list A), aloud and at intervals of one second, at the end of which the participant will have to repeat the words he/she remembers in any order. The 16 words, which are part of 4 large semantic clusters (tools, fruit, clothing, spices and aromatic herbs), are not consecutive in the same category. Subsequently, list B is presented to the participants. This is a list of "interferences" that contains two categories of list A and two random categories, not shared by the former. Neither list contains words common to both. The repetition of the words contained in list A is requested immediately (short delay) as well as after 20 minutes (long delay). The test ends with a recognition exercise, in which 44 words are presented to the subject that must be categorized by him/her as target words or distractors.

The CVLT has proved to be highly discriminating not only for mnemonic deficits in general but specifically for episodic memory, as well as for dysfunctions related to verbal learning, because the test collectively assesses the encoding, the recall and the recognition of the elements presented. Apart from measuring the number of elements that a subject can learn, it also stresses the strategies and techniques that the subject uses to learn new information.

Another useful tool to analyze deficits related to visual-spatial memory is the Corsi Test (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000). It consists of a wooden tablet on which 9 asymmetrical cubes are glued facing the side of the experimenter. The experimenter first touches the cubes with one finger, forming a standard sequence of increasing length, which the subject will have to reproduce later based on what he/she remembers of the path. The test is useful especially for depressed bipolar patients, who have visual-spatial abilities that are more compromised than unipolar depressed patients.

Regarding deficits involving working memory, the Mini Mental State Examination (MMSE) is a very useful test (Folstein, Folstein, & McHugh, 1975). The MMSE is composed of 30 questions, which, in addition to verifying the dysfunctions in working memory, also analyze problems related to space-time orientation, attention, language and constructive praxis. The MMSE represents an excellent tool for differential diagnosis because once calibrated for unipolar and bipolar Depression, it would offer a wider range of cognitive areas to be evaluated, allowing to assess the differences between the two forms of depression more accurately.

Finally, the Rey Auditory Verbal Learning Test (RAVLT) is an excellent tool to discriminate among mnemonic disorders, especially those related to verbal memory (Rey, 1958; Taylor, 1959). The RAVLT consists of 7 tests. In the first test, the examiner reads a list of 15 words that the subject must immediately repeat, and this is repeated 4 times. In the sixth test, the administrator distracts the subject with visuospatial tasks for 15 minutes, to then make him/her repeat the words read previously. If the subject cannot remember them all, another 45 words will be presented to him (30 distractors together with 15 of the first test) and he/she will be asked to list them again. The test is very useful not only because it discriminates deficits in verbal memory, but also because it analyzes verbal learning, which is strongly compromised in subjects with bipolar Depression and, therefore, useful in a differential diagnosis.

6.2. Executive functions

Executive functions, like memory, seem to be particularly deficient in patients with bipolar Depression (Hori *et al.*, 2012).

The Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000) is a sophisticated test that we suggest to be included in the neuropsychological evaluation of patients with bipolar and unipolar Depression. The test battery is divided into 6 cognitive and behavioral tasks, which are the following: conceptualization of similarities, phonemic lexical fluency, motor programming, response to conflicting instructions, task on inhibitory control (go-no-go) and prehension behavior. The FAB is recommended because it discriminates the overall functioning of all executive functions, thanks to its 6 cognitive tasks.

Another important battery to be included to test executive function is the Behavioral Assessment of the Dysexecutive Syndrome (BADS; Wilson, Alderman, Burgess, Emslie, & Evans, 1996). The BADS is an excellent tool because it is composed of various tests that globally evaluate many aspects of executive functions, using an ecological approach that reproduces contexts and problems similar to those encountered in everyday life. The 6 cognitive tasks to be performed include: test of the rule change of cards, action planning test, key search test, test of cognitive estimates, zoo map test and modified test of the 6 elements.

Finally, an important practical test to be included for the evaluation of the aforementioned functions is the Tower of London Test (Allamanno, Della Sala, Laiacona, Pasetti, & Spinnler, 1987). It consists of a tablet with three vertical rods positioned in ascending order, on which 3 balls of different colors are inserted in a specific order. The rods are long enough to accommodate one, two or three balls. The subject will have to move the balls, one at a time, in order to reach an arrangement previously established by the administrator. This test helps to understand the subjects' abilities regarding strategic decision-making processes and the planning of effective solutions as well as the capacity to inhibit impulsiveness as it has the objective of solving a specific task while being constraint by specific rules.

6.3. Attention

We carefully reviewed the literature and attention was shown to be markedly involved in both unipolar and bipolar Depression. To test attention and attention-related functions, it is essential to carefully choose specific

neuropsychological tests that are able to discriminate the presence or absence of any attention-related deficits.

To this end, we propose the following two tests for the assessment of attention in bipolar and unipolar depressed patients.

The first is the Trail-making Test (TMT-A and TMT-B) (Reitan, 1958), which can be performed on paper or on a computer. In the TMT-A version, the 25 stimuli are numbers that the subject must connect with a line in an increasing manner, in the shortest possible time. Version B (TMT-B), on the other hand, is characterized by stimuli, which are both numbers and letters; in this case the subject, starting from number 1, alternates his/her ability to connect, in an increasing way, a number and a letter. This test not only discriminates deficits related to attention, but it is also sensitive to the detection of dysfunctions related to spatial planning skills. Several studies have used the Trail-making Test to make a differential diagnosis. For example, Xu and colleagues highlighted that bipolar depressed patients presented a poorer attention and visual-motor performance than unipolar depressed patients (Xu *et al.*, 2012). Borkowska and Rybakowski (2001), on the other hand, noticed a tendency in depressed bipolar patients to obtain poorer results on the TMT-B than unipolar patients.

The second test we propose is the Stroop Color Word Interference Test (Golden, 1978). It is a test in which the subject must name the ink color with which the names of different contrasting colors are written. To do this, it is necessary to inhibit the automatic tendency to read the color name rather than focusing on the color of the ink itself. Borkowska and Rybakowski used the Stroop test to analyze differences between the two types of depression regarding attention and observed that also in this case the scores of depressed bipolar patients were lower than those of unipolar patients (Borkowska & Rybakowski, 2001).

6.4. Abstract reasoning

Abstract reasoning, which represents one of the most important cognitive abilities in carrying out activities related to daily life, is compromised in both unipolar and bipolar Depression.

One of the most valid and reliable tests assessing this neuropsychological function is the Wisconsin Card Sorting Test (WCST; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). The WCST uses a deck of cards called “response” cards, which must be combined to the “stimulus” cards, according to an entirely personal criterion that changes from subject to

subject. During the test, the administrator is allowed to give only a (minimal) feedback regarding the strategies used by the patient who, thanks to the feedback, will identify the most correct classification criteria. Among the criteria for one type of classification, the administrator switches to another criterion without informing the subject. The subject's task now is to develop a new classification strategy. The WCST is an excellent test not only because it is able to discriminate deficits related to abstract reasoning, but also because it specifically examines the frontal functions of the subject, which are more compromised in bipolar depressed patients (Borkowska & Rybakowski, 2001). In addition, the WCST helps to evaluate the degree of flexibility of patients towards problem solving and the strategies used in everyday life to cope with difficulties. From this point of view, it would be important to analyze the problem solving skills of unipolar and bipolar depressed people and to include the WCST to help the differential diagnosis of the two disorders: Borkowska and Rybakowski (2001) observed a worse performance on the WCST in depressed bipolar patients as compared to unipolar depressed patients.

6.5. Verbal fluency and processing speed

Finally, the Wechsler Adult Intelligence Scale (WAIS-IV) can turn useful to evaluate dysfunctions in verbal fluidity and processing speed. The WAIS is made up of 15 subtests, divided into 4 dimensions: visual-perceptual reasoning, working memory, verbal comprehension, and processing speed. The last two dimensions are those that are more specifically connected to our purpose.

Verbal comprehension is characterized by the subtests: Similarities, Vocabulary, Information and Understanding. The index of this dimension predicts the results regarding crystallized intelligence (connected to the knowledge acquired in the educational and the school context) and concerns contextualized learning within the social environment.

Processing speed, on the other hand, is characterized by the subtests: Search for symbols and Cipher and Cancellation, whose index mainly measures the speed with which the visual stimuli and the manual motive responses are performed by the subject.

This test offers important advantages because it not only helps to assess the dysfunctions related to verbal fluency and speed of processing, which are both severely compromised in the two types of Depression, but also helps to give a general judgment concerning the patient's intellectual

functioning and allows for the analyses of other possible deficits related to cognitive and intellectual abilities. In the end the results from all the different domains will provide us with the necessary insight into the patients strengths and needs that will lead to the development and planning of individually tailored interventions for the recovery or enhancement of the patient's skills.

7. Conclusions

Depression is a complex disorder causing long-term disability, when not treated adequately. In this review, evidence related to the difference between unipolar and bipolar Depression was collected and presented, with a specific focus on cognitive dysfunction. As the literature suggests, biological markers can help to reduce the risk of misdiagnosis, but neuropsychological markers can be assessed more quickly, more easily and with a methodology that is less invasive. To this end, additional research on thresholds differentiating the cognitive dysfunction in unipolar and bipolar Depression should be conducted on the psychometric tools proposed in this review.

As stated by Cammisuli and Pruneti (2018), the psychopathology of cognition is now focused on how cognitive dysfunction is related to the origin and development of psychiatric conditions, as cognitive processes are intrinsically linked to emotional and relational functioning. The scope of this review was to contribute to the field focusing on the clinical need of a precise differential diagnosis that, when put in a translational framework, should combine an integration of research and clinical practice allowing for a better understanding of mental health and for evidence-based clinical practice.

Including biomarkers is not going to give us a definite answer, but may help to identify risk, not the cause of the cognitive dysfunction. Furthermore, given the extreme complexity of the problem, most biological risk factors may contribute together with other risk factors (pertaining to other dimensions) to a small amount of risk but may help to explain and predict a substantial part of present and future cognitive disability. By using a combination of neurocognitive and biological markers, we may be able to redefine how to think about cognitive dysfunction in unipolar and bipolar Depression.

Patients diagnosed with Depression often develop clinically meaningful deficits in attention, information processing speed, executive functions, such as working memory, and emotional and psychosocial functioning. These

deficits can have a detrimental impact on their quality of life. Failure to comprehensively assess and closely monitor the specific cognitive signs and symptoms of unipolar and bipolar depressed patients may lead to confusion or misattribution surrounding their day-to-day struggles. Therefore, an early detection by combining biomarkers with appropriate neuropsychological indicators and cut offs for cognitive dysfunction may help us to intervene in a timely and appropriate manner using the right treatment for each individual patient. To this end, this review contributes to an empirically founded use of psycho-diagnostic tools in a field that is yet to be fully investigated.

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