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IMPACT OF BIPOLAR DISORDER AND OBSESSIVE-COMPULSIVE DISORDER COMORBIDITY ON NEUROCOGNITIVE PROFILE: A MINI-REVIEW

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SUMMARY

The comorbidity of bipolar disorder (BD) and obsessive-compulsive disorder (OCD) is widely known. The overall rate of association between BD and OCD is very high and varies, depending on the authors, from 11% to 18%, with peaks of 21% in primarily bipolar patients. Vice versa, about 60% of patients with OCD have a second psychiatric diagnosis, which in 23% of cases turns out to be BD. The differences between the BD patients with and without OCD were so numerous and important (e.g., different onset of mood episodes, history of suicide attempts, seasonality, rapid cycling and impulsivity) that the comorbidity between BD and OCD may represent a distinct form of BD, similar to cyclothymic BD for psychopathological features. However, the comorbidity does not seem to have any impact on cognitive performance, such as there is no specific difference between patients who first develop BD and then OCD or vice versa. Anyway, the detection of the neurocognitive profile of these patients at the time of the first clinical evaluation could have clinical implications also in the therapeutic and rehabilitative management of this type of patient. Indeed, it would be desirable to develop a new model of rehabilitation that is less differentiated for both BD and OCD or for their comorbidity, also to make cognitive rehabilitation faster and less expensive. The purpose of this mini-review is to update the knowledge currently available on the impact of BD and OCD comorbidity on neurocognitive profile.

Key words: *bipolar disorder - obsessive-compulsive disorder - OCD - comorbidity - neurocognitive profile*

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INTRODUCTION

Bipolar disorder (BD) is a recurrent chronic disorder characterized by frequent mood fluctuations and changes in the energy level and behavior, particularly when faced by stressful events. Cognitive impairment, characterized especially by altered reaction time, verbal and visual memory and executive functions, is highly prevalent in BD patients and leads to disability (Vieta et al. 2018). It is currently one of the most disabling psychiatric disorders, especially among young people, because of its long and unpredictable course that often leads to a reduction in the quality of life of patients, in particular for its consequences on working and social functioning and for increased mortality compared to the general population (Grande et al. 2016).

This kind of affective disorders can be classified on the basis of the magnitude and severity of mood elevation along a *continuum*, from unipolar to bipolar II or bipolar I (Phillips & Kupfer 2013).

The quality of life of BD patients is also severely limited by cognitive impairment; in particular altered reaction time, verbal and visual memory and the executive functions are highly prevalent and contribute to disability (Cullen et al. 2016). In a worldwide mental health survey, the prevalence of bipolar disorders, irespective of nationality, ethnic origin, or socioeconomic status, was consistent with a lifetime prevalence of 0,6% for BD I, 0,4% for BD II, 1-4% for subthreshold BD, and 2-4% for the BD spectrum (Alonso et al. 2011). Therefore, BD represents one of the leading causes of disability among young people (Merikangas et al. 2011).

BD is highly comorbid both with medical diseases (Liu et al. 2013, Sharma et al. 2014, Smith et al. 2013), condition characterized by late onset of mania (McDonald & Nemeroff 1996), and psychiatric disorders (Spoorthy et al. 2019). Among the last, the comorbidity between BD and obsessive-compulsive disorder (OCD) is widely known (Amerio et al. 2014).

OCD is a relatively common neuropsychiatric disorder impacting occupational, academic and social functioning that affects 1 to 3% of the worldwide general population (Moreira et al. 2017, Pauls et al. 2014a). It is marked by intrusive, recurrent and persistent unwanted thoughts, urges or images (obsessions) and repetitive behaviors or mental acts (compulsions) that the individual performs in response to the obsessions (Bokor & Anderson 2014, Goodman et al. 2014).

The overlap of OCD with other neuropsychiatric disorders is extremely common and has a negative impact on outcome (Pallanti & Grassi 2014). Several authors agree that comorbid psychiatric disorders predict a short- and long-term worse treatment outcome

and a worse quality of life (Jakubovski et al. 2013). Comorbidity rates between OCD and any other psychiatric disorder range from 78 to 91%; specifically, the association with an anxiety disorder or a mood disorder ranges from 46 to 52% and from 64 to 74%, respectively (Klein Hofmeijer-Sevink et al. 2013, Pinto et al. 2006). In any case, other common psychiatric conditions in OCD patients are tic disorders, impulse control disorders, substance abuse and/or addiction, attention deficit hyperactivity disorder (ADHD) and eating disorders (Klein Hofmeijer-Sevink et al. 2013, Pinto et al. 2006).

The overall rate of association between BD and OCD is very high and varies, depending on the authors, from 11% (Nabavi et al. 2015) to 18% (Amerio et al. 2016), with peaks of 21% in primarily bipolar patients (Amerio et al. 2014). *Vice versa*, about 60% of patients with OCD have a second psychiatric diagnosis, which in 23% of cases turns out to be BD (Saraf et al. 2016). Therefore, is it more correct to speak of comorbidities or rather of a distinct disorder that shares common psychopathological aspects with classic disorders?

The aim of this narrative mini-review is to evaluate the current knowledge on the impact of comorbidity between BD and OCD on the neurocognitive profile. Furthermore, in the light of any differences between patients in comorbidity compared to patients with a single disorder, we will discuss whether it is more correct to speak about comorbidity rather than a distinct disorder that shares common psychopathological aspects with both single diseases.

METHODS

We searched PubMed, Embase, MEDLINE, PsychINFO and the Cochrane Library through December 2019 using generic terms for neurocognition evaluation in the comorbidity between bipolar disorder and obsessive-compulsive disorder without language or time restriction. Two authors (RdF and RG) reviewed the search independently. The reference lists were screened to find additional data. Only eligible publications have been included and cited in this review.

RESULTS

Only one study (de Filippis et al. 2018) dealing with neurocognition in comorbidity between BD and OCD was identified incorporating data on a total of 68 patients (22 BD, 26 BD–OCD, 20 OCD). Due to the lack of data and sufficiently numerous evidences on the topic in the literature, it was not possible to perform a systematic review or any type of qualitative or quantitative analysis regarding neurocognition in the comorbidity between BD and OCD. Therefore, all currently available data sources were put together and discussed in this narrative mini-review.

DISCUSSION

Cognitive symptoms in the comorbidity between BD and OCD

Up to date, the impact of the comorbidity and its timing of presentation on the neurocognitive, clinical and psychopathological profile was assessed in only one paper (de Filippis et al. 2018). The results of this research trial have shown that there is no specific difference between patients who first develop BD and then OCD or *vice versa*. To our knowledge, there were no studies comparing neuropsychological domains that focus this comorbidity before. Thus, the aim of this paper was to evaluate and compare BD, OCD and BD-OCD patients in three widely studied domains of cognition (i.e., set-shifting, central coherence, and decision making) through neuropsychological tests (e.g., WCST, IGT, RCFT). We hypothesized that patients with double comorbidity (BD-OCD) may exhibit a more pathological profile than patients with only BD or OCD. Although both BD and OCD are very serious and disabling disorders when taken singularly, their overlap does not further impair the neurocognitive profile. In fact, it is well known that cognitive impairments have a significant and partially independent impact on psychosocial functioning of psychiatric patients (Valdizán 2008) and BD (Cotrena et al. 2015) and OCD (Sternheim et al. 2014) patients presented impaired cognitive performance.

Kraepelin was the first author to describe, in 1920, the progressive and severe cognitive, clinical and functional deterioration of patients with bipolar disorder (Kraepelin 1920). It is currently highly debated at what stage of the disorder patients begin to experience cognitive symptoms (Tiihonen et al. 2005); but both in clinical and neuroimaging studies (Pomarol-Clotet et al. 2015), BD has been associated with mild neurocognitive deficits in all mood states, including periods of remission (Martinez-Aran & Vieta 2015, Martínez-Arán et al. 2004). Although the cognitive impairment is unsaturated very prematurely, the functional recovery occurs only partially and lags behind symptomatic or syndromal recovery (Tohen et al. 2000).

Several neuropsychological and functional imaging studies have shown impaired functioning in different cognitive domains in OCD patients (e.g., executive function tasks that assess response inhibition, reward-based decision making, task switching and planning) (Pauls et al. 2014a).

Numerous tests have been used to evaluate the cognitive functioning of OCD patients: the go-no-go task, the stroke task and the failure signal have demonstrated deficits in the response inhibition (Kertzman et al. 2018, Lei et al. 2015). In fact, some trials have reported that patients with OCD have committed more erroneous commission errors in "go-no-go" activities (Kertzman et al. 2018), while others have not found this difference (Abramovitch et al. 2011).

Instead, the Iowa Gambling Task (IGT) was used in decision-making assessment, to investigate patients' ability to modify responses according to reward or feedback (Starcke et al. 2010). Also in this case these studies revealed that OCD patients show a reduced ability to adapt their behavior based on monetary gains and losses for "correct" answers (Figee et al. 2011).

The OCD also involves a reduced ability to modify responses based on feedback, as evidenced by clinical trials with the Wisconsin Card Sorting Test (WCST) in which patients showed a significantly higher percentage of persistent errors in the test (Cavedini et al. 2010). Set-shifting impairments have also been reported in individuals with OCD, for example, in the Cambridge Neuropsychological Test Automated Battery (CANTAB) object alternation test and the set-shifting task.

Among all, the most convincing results come from the study of non-verbal memory, which in most surveys was evaluated using the Rey-Osterrieth Complex Figure Test (RCFT) (Penadés et al. 2005). A study, later replicated also in different contexts, showed that the impairments related to the executive function in the organizational strategies associated with the coding of visual-spatial information mediated the poor performance of RCFT in patients with OCD (Savage et al. 1999). This impairment significantly improved, more than healthy controls, following cognitive retraining aimed at improving organizational strategies (Buhlmann et al. 2006).

Thus, the results of neuropsychological studies are heterogeneous but generally support the idea that OCD patients show an underperformance in executive functioning tests (specifically tasks of response inhibition, set shifting and verbal fluency, but also on tasks of non-verbal memory) (Abramovitch et al. 2019, de Filippis et al. 2018, Shin et al. 2014).

At present, the results obtained by the trials on neurocognitive performance of OCD patients do not clarify the current debate regarding the "state" or "trait" nature of neuropsychological impairments in OCD (Pauls et al. 2014b).

In fact, although there are also data on improving the performance of neurocognitive tests after successful treatment, just few studies have reported an association between the symptoms severity and neuropsychological impairments in OCD patients (Segalàs et al. 2008).

Challenges of BD-OCD comorbidity

The term 'comorbidity' was used for the first time in medicine by Feinstein to indicate those cases in which a 'distinct additional clinical entity' occurred during the course of a patient having an index disease (Feinstein 1970). Instead, the first to describe the comorbidity between BD and OCD was the French psychiatrist Bénédict Augustin Morel, raising the problem of the nosological and clinical implication of this condition (Amerio et al. 2015, Morel 1860). However, in most cases it is unclear which of two disorders occurs first (Tonna et al. 2016), although it is currently known that the comorbidity of OCD preceded an earlier onset of BD in BD-OCD patients (Masi et al. 2001), as well as it is unclear whether the concomitant diagnoses actually reflect the presence of distinct clinical entities or refer to multiple manifestations of a single clinical entity, because of part of the observed BD-OCD comorbidity could be an artefact of the overlapping diagnostic criteria for many diagnoses (Maj 2005).

Ozdemiroglu et colleagues hypothesized that the differences between the BD patients with and without OCD were so numerous and important (e.g., different onset of mood episodes, history of suicide attempts, seasonality, rapid cycling and impulsivity) that the comorbidity between BD and OCD may represent a distinct form of BD, similar to cyclothymic BD (Ozdemiroglu et al. 2015).

Another important aspect that has been overlooked in the last years' literature is the "phase-specific" comorbidity as well as the timing of the appearance of different overlapping disorders (Pallanti & Grassi 2014). As reported by a pilot study of Yaryura-Tobias et al., there may be a specific temporal order of comorbid conditions in the OCD across the lifespan and the particular periods in which these conditions have started may have a different impact on the clinical and neurocognitive profile and on the future development of each disorder (Yaryura-Tobias et al. 2000).

A recent study of de Mathis et al. investigated the evolution of comorbid disorders according to the first psychiatric diagnosis and its impact on the clinical development of OCD and the resulting psychiatric comorbidities (de Mathis et al. 2013). This paper shows that separation anxiety disorder, ADHD, and tic disorder tend to precede the onset of OCD, while other anxiety disorders, mood disorders, obsessive-compulsive spectrum disorders, impulse-control, eating, substance abuse, and somatoform disorders tend to develop later during the OCD course (de Mathis et al. 2013).

Future directions

To date there are still many unclear traits on the impact of neurocognition in the comorbidity between BD and OCD which will need to be clarified by future research. First, the understanding of the temporal relationship between cognitive symptoms and onset of BD and OCD is not well understood. Studies in prodromal phases of both BD and OCD are required to improve our knowledge. Second, it would be useful to better define a temporal framework when assessing cognition in this comorbidity in a clinical trial with a bigger sample size. Finally, our hypothesis is that the comorbidity between BD and OCD is not only clinically detectable, but it could also constitute a different neurocognitive, and maybe psychopathological, entity compared to single disorders. This could be deepened with trials focused only on the comorbidity group studying potential interplays of the cognitive profiles of the two disorders when co-existing and differentiating patients with BD onset from those with OCD as first diagnosis.

CONCLUSION

It would be appropriate for the future that further studies could investigate why these two serious disorders with such diverse etiopathogenesis, pathophysiological mechanisms and neurobiological circuits showed similar neurocognitive deterioration profiles, both singly and in comorbidity. Furthermore, the detection of the neurocognitive profile of these patients at the time of the first clinical evaluation could have clinical implications also in the therapeutic and rehabilitative management of this type of patient. Indeed, it would be desirable to develop a new model of rehabilitation that is less differentiated for both BD and OCD or for their comorbidity, also to make cognitive rehabilitation faster and less expensive.

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Designed the study: Renato de Filippis & Pasquale De Fazio:

Made the last critical review and participated to write the final manuscript: Cristina Segura-Garcia & Pasquale De Fazio.

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