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Pituitary gland in Bipolar Disorder and Major Depression: Evidence from structural MRI studies

Special Section on "Translational and Neuroscience Studies in Affective Disorders". Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summarise relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders.

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ABSTRACT

Background: The function of the hypothalamo-pituitary-adrenal axis (HPA) has been widely investigated in mood disorders based on its role in regulating stress response. Particularly, Magnetic Resonance Imaging (MRI) reports have explored pituitary gland (PG) in both bipolar disorder (BD) and major depressive disorder (MDD). In this context, the present review summarizes the results from MRI studies with the final aim of commenting on the presence of common or distinct PG structural alterations between these two disabling illnesses.
Methods: A bibliographic search on PUBMED of all MRI studies exploring PG volumes in BD and MDD as well as first-degree relatives (RELs) from 2000 up to October 2016 was performed.
Results: Following the screening process of the available literature it can be said that a) PG enlargement has been found in both BD and MDD, therefore potentially representing a common neurobiological marker characterizing mood disorders, and b) PG volumes are moderated by age and sex in both illnesses, although the direction and the extent of this moderation are still not fully clear.
Limitations: Few MRI studies with heterogeneous results.
Conclusions: These hypotheses must be taken with caution especially because the heterogeneity of the results of the studies reviewed does not allow for a definite answer about the role of PG in affective disorders. Therefore, larger longitudinal studies investigating PG volumes in BD and MDD patients at the early phases of the illness, by considering females and males separately, are needed to further corroborate these findings.

1. Main text

Although bipolar disorder (BD) and major depressive disorder (MDD) are categorized as two distinct diagnostic entities, they share similar severe depressive symptoms and neurobiological dysfunctions (Delvecchio et al., 2012). Particularly, there is evidence that they may share common dysregulations in the hypothalamo-pituitary-adrenal (HPA) axis (Daban et al., 2005; Belvederi Murri et al., 2014), with particular regards to the pituitary gland (PG), which plays a key role in regulating stress response. Specifically, the HPA axis function has been studied by measuring different parameters within the three endocrine glands, including glucocorticoids, primarily cortisol, and glucocorticoids receptors (GR). Interestingly, several studies reported that both BD and MDD shared a similar HPA axis dysfunction, with both disorders characterized by hypercortisolemia and by reduced number or function of GR compared to healthy controls (HC) (Watson and Mackin, 2006).

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Table 1
Summary of Magnetic Resonance Imaging studies exploring pituitary gland volumes in both bipolar disorder and major depressive disorder.

Diagnosis	Patients > healthy controls	Patients < healthy controls	No differences
Bipolar Disorder	Takahashi et al., 2009; Takahashi et al., 2010; MacMaster et al., 2008; Pariante et al., 2005; Clark et al., 2014	Sassi et al., 2001	Chen et al., 2004; Cousins et al., 2010; Mondelli et al., 2008; Hajek et al., 2008
Major Depressive Disorder	MacMaster and Kusumakar, 2004 MacMaster et al., 2008 Pariante et al., 2005		Eker et al., 2008; Lorenzetti et al., 2009; MacMaster et al., 2006; Sassi et al., 2001

However, only few Magnetic Resonance Imaging (MRI) studies explored the anatomy of PG in BD and MDD. Therefore, a clear picture of the putative role of structural abnormalities within this region as an indirect measure of HPA axis dysfunction in both BD and MDD is still not clear.

In this context, this review aimed at summarizing the MRI results of studies investigating PG in BD and MDD to provide an overview of the presence of common or distinct neurobiological deficits in this structure between BD and MDD. A bibliographic search on PUBMED of all MRI studies exploring PG volumes in BD and MDD as well as first-degree relatives (RELs) from 2000 up to October 2016 was performed. The search terms used to identify the articles of interest were “pituitary gland” in combination with “bipolar disorder”, “major depressive disorder”, “Magnetic Resonance Imaging” and “depression”. We excluded articles that investigated endocrine glands other than the PG and studies exploring PG volumes in other medical or psychiatric illnesses.

We retrieved 14 MRI studies that met the inclusion criteria, six only in BD, four only in MDD, three in both MDD and BD, and one only in RELs of BD patients (Summary and details of the characteristics of the individual studies are shown in Tables 1, 2 respectively). Overall, these MRI studies explored PG volumes in BD, MDD or RELs compared to healthy controls (HC) and investigated age- or sex-related differences between these groups in this structure.

Among the evaluated studies, only six studies found a significant PG volume difference between patients and HC (Takahashi et al., 2009, 2010; MacMaster et al., 2008; Macmaster and Kusumakar, 2004; Sassi et al., 2001; Pariante et al., 2005). The majority showed larger PG volumes in both BD (Takahashi et al., 2009, 2010; MacMaster et al., 2008; Pariante et al., 2005) and MDD (MacMaster and Kusumakar, 2004, 2008; Pariante et al., 2005) patients compared to HC, with the exception of Sassi et al. (2001) which found smaller PG volumes in BD compared to both HC and MDD. Additionally, the presence of larger PG volumes observed in BD patients was further confirmed by a recent meta-analysis by Clark et al. (2014) including seven MRI reports with a total sample of 244 BD patients and 308 HC. In contrast, eight MRI studies showed no differences in PG volumes, four in BD (Chen et al., 2004; Cousins et al., 2010; Mondelli et al., 2008; Clark et al., 2014) and four in MDD patients compared to HC (Eker et al., 2008; Lorenzetti et al., 2009; MacMaster et al., 2006; Sassi et al., 2001). Also, three MRI studies showed preserved PG in RELs with (Hajek et al., 2008) or without (Takahashi et al., 2010; Mondelli et al., 2008) BD in respect to HC. Nonetheless, one reported a significant PG volume reduction in RELs compared to BD patients (Takahashi et al., 2010), while the other showed that PG volumes of the RELs correlated with PG volumes of BD patients (Mondelli et al., 2008). Finally, Takahashi et al. (2010) was the only MRI study reporting that BD patients on Lithium tended to have smaller PG volumes compared to BD not on Lithium, suggesting that PG volume changes may be influence by medication status. Interestingly, PG deficits seem to be a shared neurobiological characteristic across several psychiatric illnesses, including schizophrenia (SCZ) (Pariante et al., 2004) and first episode psychosis (FEP) (Nordholm et al., 2013). Although a divergent pattern of PG volume increases or decreases was also observed in these disorders, the majority of the evidence reported that FEP patients showed larger PG volumes while patients with SCZ reported smaller PG volumes compared to HC, probably due to chronic activation of the HPA axis (Pariante et al., 2004). Nonetheless, overall these evidences suggest that PG volumes alterations are a common biological substrate characterizing both mood disorders and illnesses within the psychosis spectrum, ultimately proposing that the investigation of PG size may be useful for identifying abnormalities in stress response, and consequently in HPA axis function, in these severe mental illnesses. Additionally, this common biological substrate observed between these disorders is not surprising especially because it has been reported that HPA axis abnormalities are much more common and severe in certain subgroups of depressed patients experiencing psychotic symptoms (Porter and Gallagher, 2006). Therefore, all together these findings suggest that individuals with psychosis might be expose to higher psychosocial stressors, which in turn contribute to HPA axis dysfunction in respect to HC. However, the impact of psychosis on PG morphology in mood disorders is still not possible to uncertain, especially because all the MRI studies reported above did not specify or include, except Clark et al. (2014), a group of BD or MDD with psychotic features.

Based on this evidence, it seems that a clear picture of the presence or the direction of PG abnormalities in both BD and MDD is still not well elucidated. However, possible reasons for these divergent results might be related to different methodologies and to the clinical characteristics of the samples employed by the original studies, as also suggested by Takahashi et al. (2009). Specifically, it might be plausible that the inclusion of BD or MDD patients at different stages/phases of the illnesses between or within studies and/or to the different medication regimes might have affected HPA axis pathology in a specific and unique way, as also reported by previous investigations (Daban et al., 2005), ultimately determining the impossibility to consider PG volumes dysfunctions as trait or state marker of mood disorders. Moreover, all the studies except for MacMaster et al. (2006) explored PG volumes in a sample of BD or MDD patients undertaking different psychotropic medications which might have influenced the pituitary function and consequently PG volumes, as also suggested by previous investigations (Porter and Gallagher, 2006). Surprisingly, none of the MRI studies found a significant correlation between duration of illness and PG volumes in BD or MDD. This result is in contrast with previous findings reporting a significant association between illness severity and HPA axis alterations in mood disorders, especially in BD (Daban et al., 2005). Additionally, although all these studies have manually traced the PG, we identified some methodological differences that are worth to be highlighted. Specifically, the majority of the MRI studies on BD included patients with BD type I but some of them also included in their sample patients with BD type II (Chen et al., 2004; Cousins et al., 2010; Sassi et al., 2001) or with affective first-episode psychosis (Pariante et al., 2005). Also, four MRI studies, two for BD (Chen et al., 2004; MacMaster et al., 2008) and two for MDD (MacMaster and Kusumakar, 2004; MacMaster et al., 2006), explored PG volumes in pediatric samples and their results cannot be comparable to the ones observed in adults. However, the available evidence in pediatric BD and MDD patients seem to confirm the PG enlargement observed in adults, therefore suggesting that PG deficits have a neurodevelopmental origin as they do not appear later during the illnesses course but already at the early stages of the illnesses.

Furthermore, it has been consistently shown that overall female individuals showed larger PG volumes compared to male subjects (Takahashi et al., 2009, 2010; Chen et al., 2004; Cousins et al., 2010; Sassi et al., 2001; Lorenzetti et al., 2009; Eker et al., 2008). Interest-