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UPDATE ARTICLE

The involvement of the orbitofrontal cortex in psychiatric disorders: an update of neuroimaging findings

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Abstract
Objective: To report structural and functional neuroimaging studies exploring the potential role of the orbitofrontal cortex (OFC) in the pathophysiology of the most prevalent psychiatric disorders (PD). *Method:* A non-systematic literature review was conducted by means of MEDLINE using the following terms as parameters: "orbitofrontal cortex", "schizophrenia", "bipolar disorder", "major depression", "anxiety disorders", "personality disorders" and "drug addiction". The electronic search was done up to July 2011. *Discussion:* Structural and functional OFC abnormalities have been reported in many PD, namely schizophrenia, mood disorders, anxiety disorders, personality disorders and drug addiction. Structural magnetic resonance imaging studies have reported reduced OFC volume in patients with schizophrenia, mood disorders, PTSD, panic disorder, cluster B personality disorders and drug addiction. Furthermore, functional magnetic resonance imaging studies using cognitive paradigms have shown impaired OFC activity in all PD listed above. *Conclusion:* Neuroimaging studies have observed an important OFC involvement in a number of PD. However, future studies are clearly needed to characterize the specific role of OFC on each PD as well as understanding its role in both normal and pathological behavior, mood regulation and cognitive functioning.

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DESCRITORES:
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O envolvimento do cortex orbitofrontal em transtornos psiquiátricos: uma atualização dos achados de neuroimagens

RESUMO
Objetivo: Relatar estudos de neuroimagens estruturais e funcionais explorando o papel potencial do córtex orbitofrontal (COF) na fisiopatologia dos transtornos psiquiátricos (TP) mais prevalentes. *Método:* Foi realizada uma revisão não sistemática da literatura no MEDLINE, usando como parâmetros os seguintes termos: "córtex orbitofrontal", "esquizofrenia", "transtorno bipolar", "depressão maior", "transtornos ansiosos", "transtornos de personalidade" e "dependência a drogas". A pesquisa eletrônica foi feita até julho de 2011. *Discussão:* Foram relatadas anormalidades estruturais e funcionais do COF em muitos TP, particularmente esquizofrenia, transtornos afetivos, transtornos ansiosos, transtornos de personalidade e dependência a drogas. Estudos de aquisição de imagens estruturais por ressonância magnética relataram a redução do volume do COF em pacientes portadores de esquizofrenia, transtornos afetivos, TEPT, transtorno do pânico, transtornos de personalidade do grupo B e dependência a drogas. Além disso, estudos de aquisição de imagens funcionais por ressonância magnética empregando paradigmas cognitivos demonstraram alterações na atividade do COF em todos os TP anteriormente relacionados. *Conclusão:* Estudos de neuroimagens observaram um envolvimento importante do COF em vários TP. Entretanto, estudos futuros são claramente necessários para caracterizar o papel específico do COF em cada TP, assim como para a compreensão de seu papel tanto no comportamento normal como no patológico, na regulação do humor e no funcionamento cognitivo.

Introduction

The frontal lobe has been implicated in a number of psychiatric disorders (PD) including depression, anxiety and psychotic disorders.[1,2] The orbitofrontal cortex (OFC) - a subdivision of the prefrontal cortex (PFC) - is connected to neuroanatomical structures directly involved in the emotional and executive processing, such as the hippocampal formation, amygdala, ventral striatum, anterior cingulated, hypothalamus and medial temporal areas.[3,4] The OFC has been associated with adaptive behavior in the face of changing contingencies and unexpected outcomes, reward-guided behavior and decision making.[1,2] In addition, neuropsychological studies have also observed an association between OFC lesions with socioemotional disinhibition and executive dysfunctions.[5,6]

Converging findings from structural and functional neuroimaging, neuropsychology and neurophysiology studies indicate that the human OFC plays an important role in the development of psychiatric disorders (PD) such as schizophrenia, mood and anxiety disorders, personality disorders and drug addiction.[3] In this article, the available structural and functional neuroimaging studies that investigated OFC involvement in the most prevalent PD in clinical practice, such as schizophrenia, mood disorders (major depression and bipolar disorder), anxiety disorders (post-traumatic stress disorder, phobias, and obsessive-compulsive disorder), personality disorders, and substance abuse were reviewed in order to provide an update to clinicians of the translational research involving the possible role of OFC in such PD.

Methods

The authors searched the database of PubMed from January 1980 to July 2011 for the published English-language studies on investigation of OFC involvement in most common PD through structural and/or functional neuroimaging methods. The search terms used as parameters were: "orbitofrontal cortex", "schizophrenia", "bipolar disorder", "major depression", "anxiety disorders", "personality disorders" and "drug addiction". The inclusion criteria were: 1) structural and/or functional neuroimaging studies investigating the role of OFC in those referred PD; 2) presence of a control group (healthy or with other PD); 3) absence of comorbid PD. Although studies with drug-naïve patients were more present in literature, aiming to exclude the effect of psychotropic drugs in neuroimaging, studies which involved patients under the influence of psychotropic drugs were not excluded.

Results

A brief summary of findings of all neuroimaging studies included is shown in Table 1.

Psychiatric Disorders

Schizophrenia

Schizophrenia is one of the most severe and debilitating psychiatric disorders, affecting 0.5%-1.5% of the adult population worldwide. Although the pathophysiology of such disorder remains unclear, studies have consistently suggested an involvement of biological and environmental factors.[7,8] Frontal lobe changes have been considered one of the main characteristics of schizophrenia. The deficits observed in attention, working memory, reasoning and problem solving have been recognized as a fundamental component of the disorder.[8]

Table 1 Involvement of orbitofrontal cortex in psychiatric disorders: summary of findings of neuroimaging studies.

Psychiatric disorder	Author, year	Imaging method and postprocessing technique	N# of patients	Control group	Results in patients
Schizophrenia	Lacerda et al.[10]	Structural – ROI	43	53 healthy	↑OFC volume
Schizophrenia	Waltz et al.[12]	Functional – fMRI	36	24 healthy	↓OFC activation
Schizophrenia	Venkatasubramanian et al.[9]	Structural – MRI ROI	51	47 healthy	↓OFC volume & thickness
Schizophrenia	Bass et al.[11]	Functional – fMRI	12	21 healthy	↓OFC, amygdale and insula activation
MDD	Lacerda et al.[13]	Structural – ROI	31	34 healthy	↓OFC volume
Bipolar Disorder	Altshuler et al.[17]	Functional – fMRI	11	17 healthy	↓OFC activation
PTSD	Hakamata et al.[18]	Structural – VBM	9	67 without PTSD	↓OFC volume
PTSD	Shin et al.[19]	Functional – PET	16	8 healthy	↑CBF in OFC
PTSD	Shin et al.[20]	Functional – PET	17	19 healthy	↑CBF in OFC
Panic Disorder	Roppongi et al.[21]	Structural – VBM	28	28 healthy	↓OFC volume
Panic Disorder	Kent et al.[22]	Functional – PET	5	5 healthy	↓CBF in OFC
OCD	Rauch et al.[23]	Functional – fMRI	12	12 healthy	↑OFC activation
OCD *versus* MDD	Remijnse et al.[24]	Functional – fMRI	20	20 MDD / 27 healthy	↑OFC activation in OCD
BPD	Chanen et al.[25]	Structural – ROI	20	20 healthy	↓OFC volume
BPD	Silbersweig et al.[27]	Functional – fMRI	16	14 healthy	↓OFC activation
SUD	Tanabe et al.[28]	Structural – VBM	19	20	↓OFC volume
SUD	Alia-Klein et al.[29]	Structural – ROI	40	42	↓OFC volume

BPD: borderline personality disorder; CBF: cerebral blood flow; fMRI: functional magnetic resonance imaging; MDD: major depressive disorder; MRI: magnetic resonance imaging; OCD: obsessive-compulsive disorder; OFC: orbitofrontal cortex; PET: positron emission tomography; PTSD: post-traumatic stress disorder; SUD: substance use disorders; ROI: region of interest; VBM: voxel-based morphometry.

Structural and functional MRI studies have been performed in patients with schizophrenia. Venkatasubramanian et al.[9] reported significant volume reductions in left medial and in right and left lateral OFC among antipsychotic-naïve patients with schizophrenia. However, another study showed an increase of the left total and lateral OFC volumes in drug-naïve patients with schizophrenia in comparison to healthy controls, correlating those findings with negative symptoms.[10] Functional magnetic resonance imaging (fMRI) studies have demonstrated altered medial OFC, the amygdala and insula activation during social decision-making in schizophrenia patients.[11,12] In addition, increased left OFC and medial frontal gyrus activation in adolescent-onset schizophrenia compared with controls subjects have also been reported. [12]

Mood Disorders

Major depression

Most recent studies have highlighted that a combination of genetic, psychological, and environmental factors contribute to the onset of Major Depression.[13-15] Structural neuroimaging studies have observed reductions of OFC volumes among MDD individuals. In a MRI study performed in 31 unmedicated MDD and in gender-matched healthy subjects age 34, smaller gray matter volumes in right medial and left lateral OFC were observed among MDD individuals. Left lateral OFC volume was negatively correlated with age in patients but not in control subjects.[13] However, other studies failed to find differences of OFC volume in depressed individuals.[14]

Regarding functional studies, Drevets[15] synthesized the main evidences observed in OFC of MDD individuals: increased glucose metabolism/cerebral blood flow (CBF) in medial and lateral OFC in depressed versus remitted phase and decreased CBF in medial OFC in remitted phase. In addition, a reduction of 5-HT 1A receptor binding in OFC was observed.[15]

Bipolar disorder

The essential feature of Bipolar Disorder (BD) is a clinical course with the occurrence of major depressive episodes and manic or hippomanic episodes.[7] There is evidence that OFC volume may be reduced in adolescents and adults with bipolar disorder, and that the rostral and lateral OFC subregions have reduced activation during manic episodes.[16] Furthermore, it has been shown that OFC activation is attenuated in depressed bipolar subjects.[16] However, other studies examined volumetric measures of the whole brain and prefrontal cortices where no consistent differences were found between BD and controls.[16,17]

Anxiety Disorders

Posttraumatic Stress Disorder (PTSD)

PTSD is characterized by the development of anxiety symptoms and avoidance behavior after exposure to a traumatic external stressor.[7] Hakamata et al.[18] observed reductions of

OFC volumes in survivors of cancer with PTSD when they were compared to cancer survivors without PTSD and to a healthy group control. These results suggest that these alterations might result in a failure of the OFC in inhibiting an exaggerated fear response of the amygdala which could explain some of the intrusive symptoms observed in PTSD subjects.[18]

Functional neuroimaging studies have been conducted to elucidate the neurocircuitry involved in the complex symptomatology of PTSD. Shin et al. [19], in a Positron Emission Tomography (PET) study, compared two women groups with history of childhood sexual abuse, but only one group with PTSD. There was an increase in OFC rCBF during traumatic imagery exposure in both groups, but such increase was greater in the PTSD group.[19] Shin et al. [20] compared a PTSD and a non-PTSD group of Vietnam veterans. Both groups were exposed to neutral and traumatic events (scripts tape-recorded with autobiographic events of the participants) during PET scan. Significant rCBF reductions in OFC and middle frontal gyrus were observed in the PTSD group during traumatic exposure; those reductions were negatively correlated to rCBF in the left amygdala and right periamygdaloid cortex.[20]

Panic Disorder

Although there are few studies that evaluated OFC volume and morphology in PanD, a recent study evaluated the anatomical pattern of the posterior orbital sulcus and the OFC volume using the MRI of 28 patients with PanD and gender-matched healthy controls age 28, observing right posterior-medial OFC reductions among PanD individuals.[21] In a PET study with a panic provocation protocol, reduced rCBF in the OFC was observed in the right OFC in a single case during an unexpected panic attack.[22]

Obsessive Compulsive Disorder

Neuroimaging studies have suggested cortico-striatum-thalamo-cortical circuitry involvement in the pathophysiology of OCD. In fact, OFC hyperactivity in OCD seems to be due to an impairment of thalamic regions.[23] Studies involving fMRI have demonstrated a deviant activation in the OFC in OCD patients during a serial reaction time task and in symptom provocation paradigm studies.[23,24] A recent fMRI study showed blunted responsiveness in the OFC of patients with OCD during a self-paced reversal learning task which corroborates with previous findings.[24]

Personality Disorders

Based on the main personality characteristics, the DSM-IV classifies the personality into three clusters: A – excentric (paranoid, schizoid and schizotypical); B – with marked impulsivity and difficulty to accept social rules (antisocial, borderline, narcisistic and hystrionic); and C – anxious and risk-avoidant.[7] Literature data have suggested a critical role of OFC particularly in cluster B personality disorders, clinically characterized by a marked impulsivity, unsteadiness, mood reactivity, emotional instability and difficulty to accept social rules.[7,25] Structural MRI studies have demonstrated decreased OFC volumes in patients with borderline and antisocial personality disorders, suggesting a possible role of this region, added to other frontolimbic structures such as the anterior cingulate, amygdala and hippocampus in the development of cluster B symptoms.[25]

Studies involving fMRI observed an impaired inhibitory function of OFC in borderline personality disorders when patients were exposed to negative emotions.[26,27] Therefore, neuroimaging findings of structural and functional alterations in OFC observed mainly in patients with cluster B personality disorders are in agreement with the critical role of such structure, which is involved in the regulation of mood reactivity and impulsivity.[25-27]

Drug Addiction

Substance use disorders (SUDs) are characterized by a compulsion to seek and take the drug and a loss of control in limiting intake.[7] It is postulated that the OFC is involved in drug addiction due to indirect and direct connections to brain areas known to be involved with: (a) reinforcing effects of drug abuse; (b) motivation and compulsive behaviors; and (c) other brain areas related to reward processing (striatum-thalamus-orbitofrontal circuitry).[28,29]

Most of imaging studies in addiction have used PET and SPECT with multiple radiotracers to detect and measure changes in Dopamine (DA), the most important neurotransmitter involved in addiction in the human brain. In a PET radiotracer [F^{18}] fluoro-deoxyglucose (FDG) study, a significant decrease in OFC activity was found in alcohol, cocaine, crack and marihuana users.[30] The reduced activity was associated with decreased availability of D_2 DA receptors in striatum.[30,31] A ^{99m}Tc-hexametazine (HMPAO) SPECT study involving chronic use of opiates has demonstrated decrease in global brain perfusion abnormalities more significant in OFC.[30,31]

Conclusion

The OFC plays a central role in human behavior. It is connected to association areas of all sensory modalities, limbic structures, and prefrontal cortical regions that mediate executive function, including control and inhibition of inappropriate behavioral and emotional responses, decision making, maintaining behavioral flexibility to switch between different problem solving strategies, and evaluation of contingencies between different stimuli.[1-6] The main aim of such non-systematic revision was to provide an update to clinicians of the translational research involving the participation of OFC in most common PD. These observations have a clinical relevance since they could help in the comprehension of the pathophysiology of psychiatric symptoms and disorders, as well as in the development of treatment strategies. Although functional and structural neuroimaging studies have provided evidence of OFC impairment in PD, characterizing the role of OFC in each PD is complicated by multiple factors. These include differences in underlying pathophysiology of PD and heterogeneity in function across different OFC sub-territories. Therefore, additional neuroimaging studies are necessary to understand and discriminate such aspects.

Disclosures

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