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THE RELATIONSHIP BETWEEN DEPRESSION AND COGNITIVE DEFICITS

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SUMMARY

In the last years cognitive impairment in depression has been widely reported. It is clear that cognitive symptoms persist after remission of psychopathological symptoms but little is known about the pathophysiological events linking depression and cognitive impairment. Novel biological, structural and functional neuroimaging techniques have allowed a better definition of this relation. Depression and cognitive dysfunction share a common neuropathological platform in cortical and sub-cortical brain areas implicated in emotional and cognitive processing which may be under the control of genetic and environmental factors.

Key words: *depression - cognitive impairment - magnetic resonance imaging*

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INTRODUCTION

The public health implications of depression and cognitive impairment are enormous. The World Health Organization Global Burden of Disease Study ranked depression as the most burdensome disease in the world in terms of total disability-adjusted years among people in the middle years of life (Murray & Lopez 1996). Cognitive symptoms appear to represent one of the core features of depressive disorders with an impact on many functional outcomes (Atre-Vaidya et al. 1998, Martinez-Aran et al. 2004).

COGNITIVE DYSFUNCTION IN DEPRESSION

Several evidences have suggested that depression increases the risk of cognitive impairment and functional disability (Lebowitz et al. 1997, Charney et al. 2003). On the other hand, cognitive dysfunction during remission may also play a critical role in increasing the individual's vulnerability for the first onset, maintenance and future recurrence of depressive episodes (Gotlib et al. 2010, Kessing et al. 2001). Cognitive symptoms, such as difficulty making decisions and poor concentration, are included in the DSM-IV diagnostic criteria for major depression. However, in the recent literature regarding depressive cognition we also find consistently implicated working memory, attention and executive dysfunction and processing speed (Doumas et al. 2012, Elderkin-Thomson et al. 2010, Rosenberg et al. 2010, Marazziti et al. 2010, Nakano et al. 2008, Weiland-Fiedler et al. 2004).

During the past years, there has been an increased interest in cognitive impairment in depression, as testimonied by numerous studies. Initially, cognitive impairment has been attributed to depressive symptoms and studies have involved patients during the acute phase of depression. However, in the last decade it has been widely reported that cognitive dysfunction remains unresolved even after remission of depressive symptoms (Reppermund et al. 2009, Smith et al. 2006, Biringer et al. 2005, Paelecke-Habermann et al. 2005, Weiland-Fiedler et al. 2004). Moreover, some authors have suggested that impairment of cognitive measures is not correlated to depression severity and psychiatric co-morbidity (Majer et al. 2004, Bearden et al. 2006, Wang et al. 2006, Reppermund et al. 2009, Castaneda et al. 2010). In addition, cognitive deficits have been reported in healthy first degree relatives of patients with unipolar depression (Christensen et al. 2006). Taken together these data provide evidences for a dissociation between cognitive function and psychopathological symptoms in depression.

Although it is clear that the presence of cognitive deficits in depression is independent of the clinical remission of psychopathological symptoms the reasons for poor cognitive performance in depression remains unclear and little is known about the pathophysiolocal events linking cognitive impairment and depression. In this article we tried to identify and briefly analyze some of these events with the contribution of data obtained with novel biological, structural and functional neuroimaging techniques.

STRUCTURAL NEUROIMAGING EVIDENCE

In vivo structural and functional imaging studies, as well as postmortem investigations suggest that frontal–striatal–thalamic and limbic–thalamic–frontal networks have an important role in the pathogenesis of depression by regulating mood, cognition and behaviour (Mayberg, 2003, Price & Drevets, 2010). White matter hyperintensities and abnormal gray matter in dorsolateral prefrontal cortex, cingulate cortex, orbito-frontal cortex and hippocampus are commonly reported in depression

(Hickie et al. 2005, Heiden et al. 2005, Li et al. 2007, Ballmaier et al. 2008, Ries et al. 2009, Koolschijn et al. 2009, Kempton et al. 2011). Interestingly, alterations of these morphometric measures have been correlated with psychopathological symptoms and cognitive dysfunctions in depression (Huang et al. 2011, Heiden et al. 2005, Dubin et al. 2012). Moreover, some authors have found white matter lesions in frontal and parietal brain areas correlated with current severity of depression and cognitive deficits in subjects at high risk for developing depression by virtue of parental depression (Dubin et al. 2012). These findings support a model of pathogenesis in which hypoplasia within the neural network for cognition and emotional processing predisposes to depression.

FUNCTIONAL NEUROIMAGING EVIDENCE

Functional neuroimaging evidences suggest abnormal (either hyper- or hypo-) activity in neural regions underlying cognitive control and poor behavioral performance during demanding cognitive tasks relative to healthy controls (Holmes & Pizzagalli, 2008, Pizzagalli et al. 2006). One hypothesis is that, given that depression is associated with elevated negative cognitions and rumination (Riso et al. 2003, Siegle et al. 2004), an intrinsic processing, like focusing on negative automatic thoughts, may engage neuronal resources that would otherwise be allocated to processing of cognitive information resulting in poor performance (Christopher & MacDonald 2005, Holmes & Pizzagalli 2008). In fact, depression has been associated with difficulties removing irrelevant negative stimuli from working memory (Joormann & Gotlib 2008). In line with this hypothesis, in a recent study, depressed patients relative to controls have presented a hyperactivation in neuronal regions implicated in affective processing after an initial error on a demanding cognitive task, which is subsequently associated with a failure to recruit dorsolateral prefrontal cortex and poorer performance on the task (Holmes & Pizzagalli 2008). Moreover, in a recent study using different frequencies of pupillary motility as an index of resource allocation to both task-relevant and intrinsic processing, poorer performances in depressed subjects were associated with more pupillary motility in frequencies correlated to intrinsic processes (Jones et al. 2010). Limbic areas engagement during intrinsic processing of emotional information may be the cause of cortical inefficiency and cognitive impairment through inhibitory connections from amygdala to prefrontal cortex (Liao et al. 2012, Siegle et al. 2007, Moses-Kolko et al. 2012). According to a recent study, this abnormal emotional interference processing in the fronto-limbic brain circuitry might be the cause of negative cognitive bias that finally leads to depression (Liao et al. 2012).

However, other evidences support the hypothesis that cognitive impairment in depression is more related to a lack of cognitive resources for goal-directed behavior independently of engaging any intrinsic processing. Some authors have demonstrated a decreased neural activation in brain regions critical for cognitive control in the absence of activity in neural regions implicated in emotional processing, which coincides with deficits in cognitive performance (Audenaert et al. 2002, Okada et al. 2003, Pu et al. 2011). However, other evidences suggest that depressed patients present hyper- or hypo-activity in prefrontal cortex during cognitive tasks relative to controls with intact cognitive performances (Schoning et al. 2009, Fitzgerald et al. 2008, Siegle et al. 2007). These contradictory findings may be clarified by controlling for task performance. Depressed subjects at lower levels of task difficulty may display increased DLPFC (hyperactivity) in order to maintain the same degree of performance as controls when at higher demands of cognitive control depressed individuals cannot compensate because all cognitive resources are being used (hypo-activity) (Walter et al. 2007).

CONCLUSION

In our brief review we have tried to identify the main pathophysiological events relating depression and cognitive deficits. We suggest that cognitive impairment and depression are linked by structural and functional alterations in cortical and sub-cortical brain areas regulating processing of emotional and cognitive information. Genetic polymorphisms (BDNF, GSK3B, 5HTT-LPR) and negative life events have been correlated with emotional and cognitive control and some of the above mentioned brain alterations (Inkster et al. 2009, Gatt et al. 2009, Yang et al. 2010, Juhasz et al. 2011, Molendijk et al. 2012). However, little is known about gene-enviroment interaction and the complex functional architecture underlying the integration of depression and cognition. Future research in this field may add knowledge with potential clinical and therapeutic implications.

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