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Invited review

Cognitive impairment in major depression and the mGlu2 receptor as a therapeutic target

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ABSTRACT

Cognitive impairment, in particular of attention and memory, is often reported by patients suffering from major depressive disorder (MDD) and deficits in attention are part of the current diagnostic criteria of MDD. Objectively measured cognitive deficits associated with MDD have been described in many studies. They have been conceptualized as an integral facet and epiphenomenon of MDD. However, evidence accumulated in recent years has challenged this notion and demonstrated that in a subset of patients the degree of cognitive deficits cannot be accounted for by the severity of depression. In addition, in some patients cognitive deficits persist despite resolution of depressive symptomatology. It is plausible to assume that cognitive deficits contribute to functional impairment even though supportive data for such a relationship are lacking. However, the exact association between cognitive deficits and major depression and the clinical and neurobiological characteristics of patients with MDD in whom cognitive deficits seem partially or fully independent of the clinical manifestation of depressive symptoms remain poorly understood.

This review focuses on objective measures of non-emotional cognitive deficits in MDD and discusses the presence of a subgroup of patients in whom these symptoms can be defined independently and in dissociation from the rest of the depressive symptomatology. The current understanding of brain circuits and molecular events implicated in cognitive impairment in MDD are discussed with an emphasis on the missing elements that could further define the specificity of cognitive impairment in MDD and lead to new therapeutics. Furthermore, this article presents in detail observations made in behavioral studies in rodents with potential novel therapeutic agents, such as negative allosteric modulators at the metabotropic glutamate receptor type 2/3 (mGlu2/3 NAM) which exhibit both cognitive enhancing and antidepressant properties. Such a compound, RO4432717, was tested in tests of short term memory (delayed match to position), cognitive flexibility (Morris water maze, reversal protocol), impulsivity and compulsivity (5-choice serial reaction time) and spontaneous object recognition in rodents, providing first evidence of a profile potentially relevant to address cognitive impairment in MDD.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Subjectively perceived impairment in cognitive function has always been recognized as a symptom in patients with Major Depressive Disorder (MDD) (Rohling et al., 2002; Naismith et al., 2007; Mowla et al., 2008). Consequently the diagnostic criteria of both DSM-IV and ICD-10 include items of 'Diminished ability to think or concentrate" and "reduced concentration and attention", respectively. However, subjective complaints of cognitive impairment do not correlate with objectively measured cognitive deficits (Rohling et al., 2002; Naismith et al., 2007; Mowla et al., 2008). Research over the last two decades has convincingly demonstrated the presence of objectively measurable deficits in key cognitive functions in a large proportion of patients in the midst of a major depressive episode (for reviews and meta-analysis studies see: Austin et al., 2001; Biringer, 2007; Castaneda et al., 2008; Clark et al., 2009; McDermott and Ebmeier, 2009; McClintock et al., 2010; Hasselbalch et al., 2011; Lee et al., 2012; Wagner et al.,

Abbreviations: MDD, Major depressive disorder; mGluR, metabotropic glutamate receptor; 5-CSRT, 5-choice- serial reaction time; TRD, treatment resistant depression; BDD, bipolar depressive disorder; DL, dorso-lateral; VM, ventro-medial; PFC, Prefrontal cortex; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; CMS, Chronic mild unpredictable stress.

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2012). The cognitive functions most impaired in MDD included attention, working and episodic memory and executive functions (Clark et al., 2009; McClintock et al., 2010).

To a large extent cognitive deficits[1] have been conceptualized as clinical phenomena that are driven by depressive symptomatology – or the pathophysiology driving depressive symptoms – and hence their resolution has been expected as a function of amelioration of the depressive symptomatology. However, there is emerging evidence that in some patients the cognitive deficits go beyond a degree that can be accounted for by the severity of depressive symptoms (Harvey et al., 2004; Airaksinen et al., 2007; McDermott and Ebmeier, 2009; Reppermund et al., 2009; McClintock et al., 2010; Douglas et al., 2011; Lee et al., 2012). In addition, persistence of cognitive impairment in patients with partial or full resolution of depressive symptoms has been demonstrated (Weiland-Fiedler et al., 2004; Airaksinen et al., 2007; Reppermund et al., 2009; Behnken et al., 2010). Thus, evidence is accumulating that supports the view that in subgroups of patients cognitive deficits constitute a dimension of MDD that is independent of and dissociable from depressive symptomatology (Naismith et al., 2003; Iverson et al., 2011).

Many questions remain to be answered as to the characteristics of these patients and their deficits (Dunkin et al., 2000; Gudayol-Ferre et al., 2010), the exact relationship between subjective complaints of impaired cognitive processes and objective measures of cognitive deficits in this subgroup, and finally how the well demonstrated negative 'cognitive' bias relates to cognitive impairment (Barry and Livingstone, 2006; Everaert et al., 2012). The most important point to clarify is the role that cognitive dysfunctions play in the relationship between functional outcome and remission of depression (Baune et al., 2010). Current antidepressant therapies have limited capacity to alleviate the cognitive deficits in MDD (Biringer, 2005; Herrera-Guzman et al., 2009; Behnken et al., 2010; Spronk et al., 2011). There is some evidence that cognitive deficits in MDD patients are predictive of a failure to respond to SSRI/SNRI, suggesting that some cognitive aspects of MDD may define a subtype of patients who require additional therapeutic interventions (Dunkin et al., 2000; Gorlyn et al., 2008; Herrera-Guzman et al., 2008). Novel antidepressants that also enhance cognition, independently of their antidepressant activity, might offer a clear therapeutic advantage in these patients (Clark et al., 2009).

2. Definition of cognitive impairment in MDD versus hot cognition, negative cognitive set

It is important to note that cognitive impairment in patients with MDD are defined as deficits in cognitive functions that are *objectively* measurable by validated neuropsychological tests. Often these impairments are confused with *subjective* complaints of patients about their inability to think and concentrate and their memory problems. Although such complaints do not directly correlate with cognitive deficits (Rohling et al., 2002; Naismith et al., 2007; Mowla et al., 2008) and represent another aspect of MDD they may still be related in some fashion to specific characteristics of cognitive impairment. However, such relations have not been characterized in larger studies. Likewise, care must be taken to differentiate cognitive impairment from the well demonstrated bias in processing of emotional stimuli in favor of negatively valenced information and the resulting negative 'cognitive' set or bias often referred to as cognitive dysfunction (Clark et al., 2009; Roiser et al., 2011). This negative cognitive bias is more aptly defined as an abnormal over-efficiency in processing negative emotional information at the cost of positive emotional information rather than as a general deficit and has been referred to as abnormalities in 'hot cognition'. (Roiser et al., 2009a,b) Deficits in cognition that are associated with depression have typically been studied separately from this negative cognitive bias with no unifying hypothesis linking the two aspects, except the "resource allocation" theory which proposes that reduced psychomotor function and preferential negative processing and rumination limits available resources for cognitive processing. The current review focuses only on impairments in objectively assessed cognitive domains in MDD and the specific domains affected are discussed below.

2.1. Cross-sectional findings

Recent comprehensive reviews have tried to define the extent and characteristics of cognitive impairment in MDD (McDermott and Ebmeier, 2009; McClintock et al., 2010). There is good evidence that many patients with MDD demonstrate clinically significant deficits particularly in executive, attention and memory functions when assessed during a depressive episode although there are also studies that did not find such deficits suggesting that cognitive impairment may only affect a subset of patients (Iverson et al., 2011). Likewise, the relationship of cognitive impairment to the severity of the current depressive episode and to the number of previous episodes is inconsistent, suggesting that at least in some patients, cognitive impairments are not related to severity of current depression. In some patients, the number and severity of previous episodes may contribute to the development of cognitive impairment in the sense of increasing 'scarring' of key brain circuits (McClintock et al., 2010). McDermott and Ebmeier (2009) conducted a systematic review and meta-analysis in order to quantify the association of severity of depression with the level of impairment across cognitive domains. Out of 69 studies that met the initial inclusion criteria of their literature search only 14 studies were included in the final meta-analysis highlighting the diverse nature of studies on cognition and major depression. The number of patients in the studies that provided the basis for the meta-analysis ranged from 41 up to 1150 again highlighting the challenge when trying to uniformly assess the relationship of depression to cognitive impairment. The authors found significant correlations between impairment in episodic memory, executive function and processing speed with severity of depression. The mean correlation ranged from 0.16 for processing speed to, 0.31 for episodic memory and 0.32 for executive function. No significant correlations were evident for semantic and visuo-spatial memory. Importantly, the relationship to severity of depression was observed both for tests in which an element of speed was important and those where speed did not count. This indicates that the association of specific function with severity of depression cannot be explained by increased psychomotor retardation in more severely depressed patients. However, as the authors point out, even in the case of significant correlations the variance explained by severity of depression is small and does not exceed 10%. It may be conceded that the most widely used tools to assess the severity of depression (HAMD and MADRS scales) may not be optimal to measure the "true" severity of depression in a linear fashion similar to cognitive tests that measure the severity of cognitive deficits objectively. Thus, a relatively small correlation between a pseudo-linear, monotonic measure and a truly linear assessment may to some extent be due to this problem. Nonetheless, it does seem to be a fair conclusion that a large proportion of cognitive deficits observed during a depressive episode cannot be solely accounted for as a pure epiphenomenon of the

[1] We use the terms 'cognitive deficit' and 'cognitive impairment' interchangeably in this article.