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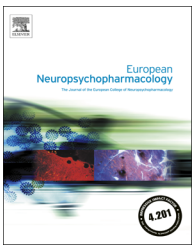

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Psychomotor retardation is a scar of past depressive episodes, revealed by simple cognitive tests

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Abstract
The cumulative duration of depressive episodes, and their repetition, has a detrimental effect on depression recurrence rates and the chances of antidepressant response, and even increases the risk of dementia, raising the possibility that depressive episodes could be neurotoxic. Psychomotor retardation could constitute a marker of this negative burden of past depressive episodes, with conflicting findings according to the use of clinical versus cognitive assessments. We assessed the role of the Retardation Depressive Scale (filled in by the clinician) and the time required to perform the neurocognitive d2 attention test and the Trail Making Test (performed by patients) in a sample of 2048 depressed outpatients, before and after 6 to 8 weeks of treatment with agomelatine. From this sample, 1140 patients performed the TMT-A and -B, and 508 performed the d2 test, at baseline and after treatment. At baseline, we found that with more past depressive episodes patients had more severe clinical level of psychomotor retardation, and that they needed more time to perform both d2 and TMT. When the analyses were performed again after treatment, and especially when the analyses were restricted to patients with clinical remission, the cognitive tests were the only ones correlated with past depressive episodes. Psychomotor retardation tested at a cognitive level was therefore systematically revealing the burden of past depressive episodes, with an increased weight for patients with less remaining symptoms. If prospectively confirmed, interventions such as cognitive remediation therapy could benefit from a more specific focus on neurocognitive retardation.

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1. Introduction

The cumulative duration of depressive episodes, as well as their repetition, has a detrimental effect on depression recurrence rates (Solomon et al., 1997), the chances of antidepressant response (Keller et al., 1992), time to obtain remission (Kanai et al., 2003), and the presence of social recovery (Sarapas et al., 2013). Memory impairment (Burt et al., 1995), atrophy of the hippocampus (Sheline et al., 1999), and higher risk for dementia (Kessing, 2012) have also been observed, raising the possibility that depressive episodes could be neurotoxic (Gorwood et al., 2008).

Some neurocognitive deficits may constitute a core feature of major depressive disorder (MDD), as they have also been observed during clinical remission (Austin et al., 2001; Bhardwaj et al., 2010; Weiland-Fiedler et al., 2004) and predict a higher degree of follow-up symptoms over and above the initial symptoms (Sumner et al., 2010). The cognitive functions involved concern reduced memory capacity (Gorwood et al., 2008), decreased flexibility and psychomotor speed (Beats et al., 1996; Austin et al., 2001), attention and set-shifting deficits (Purcell et al., 1997; Austin et al., 2001), reduced vigilance, and psychomotor slowness (Den Hartog et al., 2003; Egeland et al., 2003; Arnett et al., 1994; Kertzman et al., 2010). The fact that Attention Deficit-Hyperactivity Disorder symptom severity was significantly correlated with the occurrence of lifetime depressive episodes, even after controlling for current comorbidity (Simon et al., 2013), might also plead in favor of a tight relationship between attention processes and major depressive disorder.

Psychomotor retardation could be involved more specifically. Not only is this considered a core clinical feature of depression by many clinicians (Widlocher, 1983), but it is also a neurocognitive trait frequently assessed in mood disorders. For example, the presence of 'marked psychomotor retardation' is included among the symptom criteria required for a diagnosis of a depressive episode in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and has proven to have both diagnostic and prognostic value in major depression (Calugi et al., 2011). Psychomotor retardation can also be easily assessed as a cognitive trait through the use of simple drawing tasks (Sabbe et al., 1999; Buyukdura et al., 2011), which have the advantage of being independent from clinical assessments, the latter being frequently contaminated by the severity of depressive symptoms. High levels of psychomotor retardation have indeed been observed in depressed patients using a variety of paradigms, even in patients who are in remission (Beats et al., 1996; Austin et al., 2001; Den Hartog et al., 2003; Egeland et al., 2003; Arnett et al., 1994; Kertzman et al., 2010; Hasselbalch et al., 2013).

The link between psychomotor retardation in depressive disorder and cognitive impairment remaining after depressive disorder needs to be highlighted because of the therapeutic strategies that could be involved. Actually, clinical psychomotor retardation, unlike the intensity of a depressive episode, appears to correlate with a decrease in performance level on attentive tasks, which attests to the specific value of clinical psychomotor retardation as a predictor of cognitive deficits in depressed patients (Lemelin and Baruch, 1998). Furthermore, in a study in patients with remitted MDD, the deficit in psychomotor speed remained significant, suggesting that it constitutes a vulnerability marker for, or stigma of, MDD (Weiland-Fiedler et al., 2004).

Two tests are of significant interest when assessing psychomotor retardation as well as attentive and set-shifting processes. One of these is a Trail Making Test (TMT A & B), a frequently-used neurocognitive drawing test that can measure psychomotor retardation (Buyukdura et al., 2011; Partington, 1949), especially when the interest is in speed rather than number of mistakes. The other is the d2 test of attention, a graphic-motor test of cancellation aimed at assessing basic attention level (Brickenkamp, 1981) through the number of correct items quoted by the patient within a limited amount of time. As the three tests (d2 test, TMT-A, and TMT-B) all rely on speed, they are good indicators of psychomotor retardation. However, these tests vary in terms of their level of demand and thus have variable sensitivity for psychomotor retardation: the d2 test (theoretically) is limited to the attention process, while TMT-A also involves a motor task (drawing adequate lines) and TMT-B, besides these aspects, also requires set-shifting skills.

The majority of studies, but not all, report beneficial effects of antidepressants in improving different neurocognitive functions (i.e., executive function, memory, and/or attention skills) in depressed patients (for example Herrera-Guzman et al., 2009), including psychomotor retardation. We focused on agomelatine because of its activity in relation to circadian rhythms, which are an important aspect of psychomotor retardation (Moffoot et al., 1994; Sabbe et al., 1999). The other reason for our focus on agomelatine was its activity in relation to dopamine neurotransmission (Chenu et al., 2013), a key player in psychomotor retardation (Rampello et al., 1991).

In order to more precisely define which stigmas characterize patients with past depressive episodes, we analyzed the level of psychomotor retardation in depressed patients and tested the hypothesis that it would reflect the number of past depressive episodes, even when patients are in clinical remission. Furthermore, we also tested whether a simple cognitive drawing test (TMT and/or d2 tests) could be more informative in determining past depressive episodes than a specific scale assessing clinical psychomotor retardation (the retardation depressive scale [RDS]). To test this hypothesis, we analyzed different aspects of psychomotor retardation using data from an original, large, prospective and non-interventional study of agomelatine in the treatment of depressed outpatients, which included neurocognitive tests in a subsample of patients assessed before and after treatment.

2. Experimental procedures

The present multicentre, non-interventional study was conducted in a naturalistic treatment setting in 388 community psychiatry centres in France between October 2011 and October 2012. A total of 2048 outpatients (Table 1) were initially recruited, all of whom fulfilled the DSM-IV criteria for major depressive disorder and required (according to the clinician) the prescription of one (and only one) antidepressant treatment. Exclusion criteria were being aged under 18 years, having a psychotic manifestation, an