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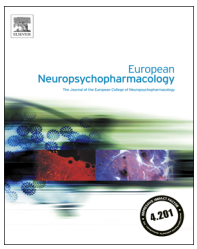

Limbic versus cognitive target for deep brain stimulation in treatment-resistant depression: Accumbens more promising than caudate ☆

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Abstract
High-frequency deep brain stimulation (DBS) represents a major stake for treatment for treatment-resistant depression (TRD). We describe a preliminary trial of DBS of two potential brain targets in chronic TRD: the nucleus accumbens (Acb) and, in the event of failure, the caudate nucleus. Patients were followed for 6 months before surgery (M0). From M1 to M5, they underwent stimulation of the Acb target. PET scans allowed us to track metabolic modifications resulting from this stimulation. The caudate target of nonresponders was stimulated between M5 and M9. Patients then entered an extension phase, in which it was possible to adapt stimulation parameters and treatments. Six patients were included and four were operated on. At M5, none of the patients were either responders or remitters, but we did observe a decrease in Hamilton Depression Rating Scale (HDRS) scores. Three patients were switched to caudate stimulation, but no improvement was observed. During the extension phase, the Acb target was stimulated for all patients, three of whom exhibited a significant response. A decrease in glucose metabolism was observed after Acb stimulation, in the posterior cingulate gyrus, left frontal lobe, superior and medial gyrus, and bilateral cerebellum. An increase in metabolism was observed in the bilateral frontal lobe (superior gyrus), left frontal lobe (medial gyrus), and right limbic lobe (anterior cingulate gyrus). The results of this trial suggest that Acb is a more promising target than the caudate. NCT01569711.

1. Introduction

Major depressive disorder (MDD) is one of the leading causes of handicap worldwide (Lopez et al., 2006). It contributes to an increase in mortality (Murphy et al., 1987), through suicide and cardiovascular disease (Musselman et al., 1998). Its consequences include recurrences, with a five-year rate of 80%, and chronicity for 20% of patients (Eaton et al., 2008; Keller, 2003). 30% of depression cases prove resistant to antidepressant drugs (Fava, 2003). The medical histories of these patients are marked by multiple hospitalizations, and by multiple trials of ultimately ineffectual and therefore discouraging treatments. This so-called chronic, treatment-resistant depression (TRD) is a major public-health issue, as well as a pathophysiological conundrum. Several data suggest that dysfunctional brain circuits are implicated, and that high-frequency deep brain stimulation (DBS) could represent an adjustable and reversible method of modulating these brain areas, just as it does for neurological disorders (Houeto et al., 2005; Houeto et al., 2007) and obsessive-compulsive disorder (OCD) (Mallet et al., 2008).

In TRD, a number of case reports have been published, describing a range of different targets, including the lateral habenula (Sartorius et al., 2010), inferior thalamic pedoncle (Jimenez et al., 2005), and the medial forebrain bundle (Coenen et al., 2011). Using larger samples, Mayberg and Lozano reported striking results over the short (Lozano et al., 2012,2008) and longer-term (Holtzheimer et al., 2012) effects of DBS targeting the subgenual cingulate cortex. Their results have been confirmed by Puigdemont et al. (2012). Other teams (Bewernick et al., 2010; Bewernick et al., 2012; Malone et al., 2009; Schlaepfer et al., 2008) have also obtained promising results with brain targets corresponding to the ventral part of the striatum, including the ventral caudate and nucleus accumbens (Acb).

There are currently many arguments in favor of using Acb as the main target. This structure lies at the center of a circuit involved in depression that is connected to the ventral tegmental area, amygdala, hippocampus,

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