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Cognitive functioning after deep brain stimulation in subcallosal cingulate gyrus for treatment-resistant depression: An exploratory study

Maria Serra-Blasco [a], Sol de Vita [a], Mar Rivas Rodríguez [b], Javier de Diego-Adeliño [a], Dolors Puigdemont [a], Ana Martín-Blanco [a], Rosario Pérez-Egea [a], Joan Molet [c], Enric Álvarez [a], Victor Pérez [a], Maria J. Portella [a,*]

[a] Department of Psychiatry – Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona (UAB), Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Catalonia, Spain
[b] Department of Psychiatry – Universidad Autónoma de Madrid, Hospital Universitario de la Princesa, Madrid, CIBERSAM, Madrid, Spain
[c] Department of Neurosurgery – Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Catalonia, Spain

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ABSTRACT

Deep brain stimulation (DBS) is being investigated as a therapeutic alternative for patients with treatment-resistant depression (TRD), but its cognitive safety has been scarcely explored. The aim of this exploratory study is to evaluate cognitive function of patients before and after deep brain stimulation of the subgenual cingulate gyrus (SCG). Eight treatment-resistant depressed patients were implanted in subgenual cingulate gyrus. A neuropsychological battery was used to evaluate patients before surgery and 1-year after. A matched group of eight first-episode patients was also assessed. A MANOVA was performed for each cognitive domain and those tests showing main time effects were then correlated with depressive symptoms and with medication load. There were significant group and time effects for memory and a group effect for language. No significant interactions between groups or cognitive domains were observed. Medication load was negatively correlated with memory at *time* 1, and clinical change negatively correlated with memory improvement. These findings support the cognitive safety of DBS of subgenual cingulate gyrus, as cognitive function did not worsen after chronic stimulation and memory performance even improved. The results, though, should be interpreted cautiously given the small sample size and the fact that some treatment-resistant patients received electroconvulsive therapy (ECT) before implantation.

1. Introduction

There is a wide variety of pharmacological and psychotherapeutic interventions that have proven efficacious in the treatment of major depressive disorder (MDD). However, as many as 30% of patients treated with antidepressants fail to respond, and around 50% do not achieve a complete and sustained recovery, suffering further relapses (Fava, 2003; Holtzheimer and Mayberg, 2011). Individuals who fail to respond to more than two psychopharmacological treatments are suffering from treatment-resistant depression (TRD). Electroconvulsive therapy (ECT) has demonstrated efficacy for TRD patients (Sienaert, 2011), but it is often accompanied by memory disturbances and relatively high relapse rates (Rasmussen, 2002). Other treatments such as transcranial magnetic stimulation (rTMS) or vagal nerve stimulation (VNS) appear to have limited efficacy (Kennedy and Giacobbe, 2007). Ablative techniques like anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy and limbic leucotomy are more invasive and their efficacy is far from being established (Nuttin et al., 2014). As reviewed by Dougherty and Rauch (2007) only few studies have explored their cognitive effects, raising the conclusion that cognitive deficits are among the more serious adverse events although relatively infrequent and usually transient. In any case, impairment of cognitive functions has to be taken into consideration when facing these latter treatment strategies, as it may contribute to worse long-term functional outcomes and may be cumulative over the course of the illness (Beblo et al., 2011).

Deep brain stimulation (DBS) has become a potential therapeutic alternative to treat TRD patients. Different promising brain targets are being investigated. One of them is the subgenual cingulate gyrus (SCG), which has yielded an average of 68% of response and 44% of remission rates in five different studies (Anderson et al., 2012). To

* Corresponding author. Tel.: +34 935537840x7836; fax: +34 935537842.
E-mail address: MPortella@santpau.cat (M.J. Portella).

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date, some of these previous studies have also investigated the cognitive effects of DBS for TRD, reporting cognitive safety of the nucleus accumbens (Grubert et al., 2011) and SCG stimulation (McNeely et al., 2008; Holtzheimer et al., 2012; Bogod et al., 2014; Moreines et al., 2014). However, these previously cited studies did not have a control group, and, if they did (Moreines et al., 2014), it was not followed over time. As concluded in a recent review (Bergfeld et al., 2013), DBS seems to be cognitively safe in most of the psychiatric diseases and, particularly, in TRD. However, the authors also point out the necessity of more studies adding further evidence to give support to these findings that in turn overcome some of the limitations of previous works. In the present study, a comprehensive battery of neuropsychological tests was used to evaluate the main cognitive domains affected in depression, and a control group of patients with a first episode (FE) of depression, instead of a group of healthy controls, was included. The rationale for using such a group of patients was the intention to control for practice effects and at the same time, the effects of acute symptomatology during evaluations.

We previously reported (Puigdemont et al., 2011) clinical outcomes during the first year of DBS in eight TRD patients, in which half of the sample showed full remission and most of them had responded after 1 year of chronic stimulation, supporting its validity as a new therapeutic strategy for TRD. Electrodes were implanted bilaterally in the subgenual cingulate gyrus (SCG; Broadman areas 24–25). The objective of the present exploratory study is to investigate cognitive effects of chronic stimulation of SCG in this sample. We hypothesized that cognitive performance would improve after DBS of Cg25 in TRD patients.

2. Methods

2.1. Participants

Eight individuals diagnosed of MDD according to DSM-IV-TR criteria were selected to be intervened for DBS in SCG. Participants had to be resistant to pharmacological treatment, at least in stage IV of the Thase–Rush scale (Thase and Rush, 1997), (i.e. on average, 9.8 different drug tryouts), and with lack of efficacy of ECT or partial response to its maintenance. Admission score on the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) had to be ≥ 18. Before being implanted, they were assessed with a comprehensive neuropsychological battery to determine their cognitive status. Four out of eight received maintenance ECT, (but it was stopped 2 weeks before study entry). A group of eight patients with a first episode (FE) of MDD matched on age, gender and level of education, was also assessed in order to control for possible practice effects and interference of acute symptoms on cognitive performance. To be eligible as a FE, patients had to be newly diagnosed from an episode of MDD, following DSM-IV-TR criteria, with a HDRS score above 14. Exclusion criteria for both groups included: Axis I comorbidity according to DSM-IV-TR criteria; acute, serious or unstable comorbid neurological or medical illness; current or past non-affective psychotic disorder; severe personality disorder and current or unstable remitted substance abuse or dependence (except nicotine). Pharmacological treatment could not have been changed during the previous month of study commencement. Deficits on neuropsychological performance of all patients were characterized using normative databases for Spanish samples (CIBERSAM, Banco de Instrumentos y metodologías en salud Mental). Current depressive symptoms were measured with HDRS.

All participating individuals were of a similar age [mean: 46.4 years (S.D. 9.1)] to avoid age-related variations in cognitive functioning. All patients were recruited from the Psychiatry Department of *Hospital de la Santa Creu i Sant Pau* from Barcelona.

2.1.1. Informed consent

The study was approved by the Research Ethics Committee of Hospital Sant Pau in Barcelona and the *Agencia Española de Medicamentos y Productos Sanitarios* (Spanish regulatory drug agency) and was carried out in accordance with the latest version of the Declaration of Helsinki. All subjects gave informed and written consent after a full explanation of the study protocol.

2.2. Neuropsychological assessment

Neuropsychological tests covered four cognitive domains: *Memory* which was assessed by means of the Rey Auditory Verbal Learning Test (RAVLT), using the number of words recalled in the first trial, total number of words after all trials and delayed recall; *Executive Functioning*, through the Trail Making Test B (TMT-B), Verbal fluency (FAS), the Digit Span backwards subtest of WAIS-III and the Tower of London (TOL); *Language* was assessed by means of the Vocabulary subtest of Wechsler Adult Intelligence Scale III version (WAIS-III) and the Category test (total number of animals named); and finally, *Processing Speed* and *attention* were evaluated via the Digit Span forward subtest (WAIS-III), Digit Symbol Coding subtest (WAIS-III) and TMT-A.

Standardized neuropsychological tests are described in detail by Strauss (2006) neuropsychological manual and validated Spanish versions of test involving verbal material have been used (RAVLT, FAS, Vocabulary and Digit Span). The Tower of London is a non-standard test widely used to evaluate planning functions (Van den Heuvel et al., 2003; Unterrainer et al., 2004; Wagner et al., 2006), and the version used in this study overcomes the ceiling effects of other versions (Portella et al., 2003). In order to control for practice effects, parallel forms were used when available (i.e., RAVLT).

2.3. Pharmacotherapy

TRD patients had been on medication for more than 2 years previous to the study inclusion, while FE patients were treated for the very first time with an SSRI (and benzodiazepines when required). Table 1 displays detailed information of medications for each group of patients at *time* 1 and *time* 2. A composite measure of medication load was estimated for each patient in the two assessments (Hassel et al., 2008; De Diego-Adeliño et al., 2013), which is based on Antidepressant Treatment History Form (Sackeim, 2001). This index was then used to examine associations of medication load and cognition.

2.4. Statistical analyses

Demographics and clinical variables were analyzed with the statistical package SPSS v.18 using *t*-test and analyses of variance (ANOVAs) for quantitative variables and χ^2 for categorical variables. Level of statistical significance was set at $p < 0.05$. Neuropsychological scores were transformed to *T* scores (mean = 50, S.D. = 10) based on normative data for Spanish samples with the exception of the Tower of London test. The longitudinal analysis was performed with repeated measures multivariate ANOVAs which were carried out for each cognitive domain to analyze group and time effects. Before carrying out the MANOVAs, normal distribution and homocedasticity were checked by means of Shapiro–Wilk's test (for small samples) and Levene's test. Most of the requirements to apply MANOVA were assumed, as only few variables did not show normal distribution or equality of variances. Further post-hoc analyses were performed to determine univariate effects of time and group. Subsequently, paired *t*-test of those tests showing time effects was carried out for each group separately. Level of statistical significance was set at $p < 0.05$. To explore whether neuropsychological domains (those showing time effects in the MANOVAs) were associated with clinical and pharmacological variables, Spearman correlations analyses of the whole sample were carried out. In order to reduce the number of correlations, a single index of each cognitive domain was obtained by averaging standardized scores and criterion for significance was set at $p < 0.05$.

3. Results

As can be observed in Table 1, groups were equally distributed regarding gender, age, marital status and years of schooling. HDRS score did not differ between groups at time 1 although TRD patients had a higher score. Medication load was statistically different, as TRD patients received further medication at *time* 1 and at *time* 2 than first episode patients, but there were no significant changes in medication over time within groups nor in type of medication (McNemar's $p > 0.8$) neither in medication load index (FE $t(7) = 0.15$, $p = 0.9$; TRD $t(7) = -0.31$, $p = 0.8$).

Table 2 displays *t*-standardized scores of all neuropsychological tests at *time* 1 and *time* 2 for TRD and FE patients. Repeated measures MANOVAs showed different patterns for each cognitive domain. Memory did not show a significant interaction of time × group ($F(12,2) = 0.60$, $p = 0.626$) but showed significant main effects of group ($F(3,12) = 4.47$, $p = 0.025$) and time ($F(3,12) = 9.95$, $p = 0.001$), where FE patients rated higher than TRD patients and the two groups improved over time in all tests (see Fig. 1): First trial ($F(1,14) = 5.62$, $p = 0.033$), Total Recall ($F(1,14) = 4.64$, $p = 0.049$) and Delayed Recall ($F(1,14) = 11$, $p = 0.005$). Paired *t*-tests between first and second assessments, carried out separately for each group, showed that TRD patients significantly