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Visuospatial Memory Improvement after Gamma Ventral Capsulotomy in Treatment Refractory Obsessive–Compulsive Disorder Patients

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Gamma ventral capsulotomy (GVC) radiosurgery is intended to minimize side effects while maintaining the efficacy of traditional thermocoagulation techniques for the treatment of refractory obsessive–compulsive disorder (OCD). Neuropsychological outcomes are not clear based on previous studies and, therefore, we investigated the effects of GVC on cognitive and motor performance. A double-blind, randomized controlled trial (RCT) was conducted with 16 refractory OCD patients allocated to active treatment ($n=8$) and sham ($n=8$) groups. A comprehensive neuropsychological evaluation including intellectual functioning, attention, verbal and visuospatial learning and memory, visuospatial perception, inhibitory control, cognitive flexibility, and motor functioning was applied at baseline and one year after the procedure. Secondary analysis included all operated patients: eight from the active group, four from the sham group who were submitted to surgery after blind was broken, and five patients from a previous open pilot study ($n=5$), totaling 17 patients. In the RCT, visuospatial memory (VSM) performance significantly improved in the active group after GVC ($p=0.008$), and remained stable in the sham group. Considering all patients operated, there was no decline in cognitive or motor functioning after one year of follow-up. Our initial results after 1 year of follow-up suggests that GVC not only is a safe procedure in terms of neuropsychological functioning but in fact may actually improve certain neuropsychological domains, particularly VSM performance, in treatment refractory OCD patients.
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INTRODUCTION

Obsessive–compulsive disorder (OCD) is a debilitating condition with a lifetime prevalence between 2 and 3% (Andrade *et al*, 2012; Ruscio *et al*, 2010). Clinical trials have established the use of selective serotonin reuptake inhibitors and/or cognitive behavioral therapy as first-line treatment options (Belotto-Silva *et al*, 2012). Unfortunately, up to 10% of patients remain refractory to all conventional treatments, including augmentation strategies (Bloch *et al*, 2006). Anterior capsulotomy (AC), a neurosurgical intervention that acts by disrupting white matter tracts of the cortico–striatal–pallido–thalamic–cortical circuitry (hypothesized to be dysfunctional in OCD), has been successfully employed in carefully selected cases (Lopes *et al*, 2004; Rauch *et al*, 1994; Rück *et al*, 2008). Specifically, AC by thermocoagulation and gamma-knife radiosurgery (Gamma ventral capsulotomy, GVC) have demonstrated comparable efficacy in reducing obsessive–compulsive symptoms (OCS), although there are no studies directly comparing these techniques (Fodstad *et al*, 1982; Kondziolka *et al*, 2011; Lopes *et al*, 2004, 2009; Miguel *et al*, 2004; Rück *et al*, 2008). However, the safety profile of both surgical methods remain less clear, in particular regarding post-operative cognitive performance, with only a few studies investigating neuropsychological outcomes (Csigó *et al*, 2010; Fodstad *et al*, 1982; Nyman and Andreewitch, 2001; Nyman and Mindus, 1995; Rück *et al*, 2008; Taub *et al*, 2009).

The available literature reports stability of intellectual functioning (Csigó *et al*, 2010; Nyman and Andreewitch, 2001; Taub *et al*, 2009), but also development of verbal memory deficits (Binder and Iskandar, 2000) and executive dysfunctions (Nyman and Mindus, 1995) after AC. Long-term follow-up results are also inconsistent: Rück *et al* (2008) reported persistent mild deficits in executive functions eleven years after AC using both surgical techniques, whereas

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Nyman and Andreewitch, 2001; reported improvement in neuropsychological performance 7 years after GVC and Csigó *et al* (2010) reported similar results two years after thermocapsulotomy. These improvements were found in neuropsychological domains such as intellectual functioning (IQ), planning, verbal fluency, inhibitory control, and decision making.

It is difficult to establish the neuropsychological consequences of AC given that most studies comprised small groups of patients in open-label, uncontrolled designs (Csigó *et al*, 2010; Nyman and Andreewitch, 2001; Nyman and Mindus, 1995; Rück *et al*, 2008; Taub *et al*, 2009). Moreover, it is unclear whether changes on neuropsychological measures can be attributed to the neurosurgical procedures *per se*, are secondary to OCS improvement, or are practice-related improvements following repeated neuropsychological testing. In order to better address these limitations, we conducted a longitudinal neuropsychological investigation in refractory OCD patients during a double-blind, placebo-controlled, randomized GVC trial (RCT). The efficacy and general safety of this study has been previously published by our group (Lopes *et al*, 2014).

Our main objective was to investigate the effects of GVC on cognitive and motor performance in both trial groups. Also based on previous reports that neurosurgical ablative procedures can be associated with cognitive adverse events (Binder and Iskandar, 2000; Nyman and Mindus, 1995; Rück *et al*, 2008), our secondary objective was to evaluate the neuropsychological safety of GVC by analyzing the outcome of all patients operated during the pilot study (Taub *et al*, 2009) and both blind and open trial phases. We hypothesized that cognitive and motor performance would improve 1 year after GVC while remaining stable in the control group. Finally, we expected that GVC would not cause severe impairments on cognitive or motor performance when considering all operated patients.

MATERIALS AND METHODS

Ethical Aspects

This study was approved by the institutional review board of the General Hospital of the University of São Paulo Medical School (USPMS) and by the Brazilian National Commission of Research Ethics. All patients signed informed consent forms and all procedures were in accordance with rigorous psychiatric surgery guidelines previously published by our group (Miguel *et al*, 2004).

Subjects and Study Design

The eligibility of 87 OCD patients was assessed at the USPMS OCD Spectrum Clinic, a tertiary referral center for nationwide highly refractory cases. Sixty-six subjects did not meet our selection criteria, mostly due to other comorbid diagnoses, intellectual deficiency, or insufficient refractoriness status (Lopes *et al*, 2014). Twenty-one patients were considered eligible: the first five were enrolled in an open pilot study (Lopes *et al*, 2009; Taub *et al*, 2009) and the remaining 16 participated in the RCT (refer to Lopes *et al* (2014) for a detailed description of study subjects, study design, randomization procedures, consort diagram, and methods of sham surgery. Trial registration: www.clinicaltrials.gov identifier NCT01004302).

Patients participating in the RCT were randomized into two groups: active treatment (ATa, patients who received true GVC, $n=8$), and sham (ST, $n=8$; Figure 1a). Patients and examiners remained blinded for the first year of follow-up. This intended to evaluate the long-term clinical efficacy of the procedure, as well as to measure the neuropsychological effects, minimizing test–retest related issues. When the blind phase was completed after 1 year, patients from the ST group were offered a true GVC procedure, and four of these eight patients were then operated (ATb, $n=4$; Figure 1b).

GVC Procedure

A detailed description of the gamma-knife-based GVC technique has been previously published (Lopes *et al*, 2009, 2014). In short, GVC procedures consisted of bilateral double lesions at the ventral border of the anterior limb of the internal capsule (7–10 mm rostral to the posterior edge of the anterior commissure—Supplementary Figure S1). Targets received the intended volume of necrosis defined by the 50% isodose line, with a maximum dose of 180 Gy at the 100% point, with 4-mm collimators. Calculations for each procedure were performed by an on-site neurosurgeon (MMC) and two psychiatrists (ACL and ECM) and further reviewed remotely by a neurosurgeon (GN) and a psychiatrist (BDG), from Brown University, all authors of the present study.

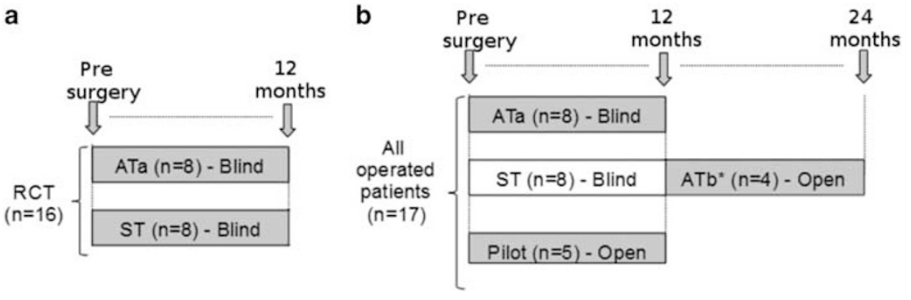

Figure 1 Groups, neuropsychological assessment time points and study design. Groups and neuropsychological assessments time points, showing the two comparisons: (a) RCT within and between-groups comparisons: blue boxes represent ATa and ST groups, evaluated before and 12 months after the procedure; (b) Within-group comparisons for all operated patients: blue boxes represent ATa, ATb and pilot study groups; ATa, randomized active treatment group; ATb, open active treatment group (four patients initially from the ST group, operated after blind was broken); BVMT-R, Brief Visuospatial Memory Test-Revised; NS, nonsignificant; RCT, randomized clinical trial; ST, randomized sham treatment group. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

Psychiatric Evaluation

Psychiatric diagnosis were made by two psychiatrists (ACL and ECM) using the Structured Clinical Interview for DSM-IV Diagnoses. OCD severity was accessed longitudinally by Y-BOCS scores, whereas depression and anxiety symptoms were measured by Beck Depression and Beck Anxiety Inventories (BDI and BAI, respectively; Beck *et al*, 1961, 1988). Patients were considered responders if 35% or more reduction of baseline Y-BOCS scores was achieved after GVC, with Clinical Global Impression improvement scores of 1 ('much improved') or 2 ('improved'; Guy, 1976).

Neuropsychological Assessment

All patients underwent a comprehensive neuropsychological evaluation with emphasis in memory and executive functions, known to be deficient in OCD. The following domains were assessed: intellectual functioning, cognitive screening, attention, language, verbal and VSM, spatial perception (visuospatial abilities), executive functions (cognitive flexibility), and motor functioning. Tests and their respective function domains are presented in Table 1 and in the online Supplement.

Neuropsychological assessments were performed by trained evaluators (MCB and CCD) in a single interview lasting up to 3 h, depending on the patient's performance and symptom severity. Short break intervals were allowed as long as they did not disturb the evaluation (mostly delayed recall). Patients were assessed 1 week before GVC (true or sham) and re-evaluated after 1 year, before the blind was broken. Patients from the ATb group (originally from the sham group but later submitted to a true GVC) also received a third evaluation, 1 year after the final procedure (Figure 1b).

Statistical Analysis

Statistical analyses were conducted with the PASW Statistics, version 18 (2009) and the software R, version 2.14.1 (2012). The Kruskal–Wallis nonparametric test was used for between-group comparisons of demographic and clinical variables. Neuropsychological comparisons in the RCT (ATa *vs* ST) were conducted with the nonparametric Mann–Whitney *U*-test, and the Wilcoxon signed-rank test was used for within group comparisons (pre *vs* post surgery). Delta scores (ie, pre minus post surgery) were used in nonparametric multivariate analysis of variance (NP-MANOVA) to test the interaction effect group *vs* time for neuropsychological variables (Anderson, 2001). This technique provides a measure of effect size (F* value) similar to the parametric MANOVA's (F value), and it was intended to control for type I errors. Dependent variables were clustered for each NP-MANOVA, according to neuropsychological domains: intellectual functioning, attention, verbal memory, VSM, executive function (cognitive flexibility), spatial perception, and motor functioning (Table 2). *Post hoc* nonparametric repeated measures analysis of variance (NP-RM-ANOVA), corrected for Bonferroni's multiple comparisons, were also conducted (Singer *et al*, 2004).

Secondary analysis merged data from all operated patients (pilot study ($n=5$), ATa ($n=8$), and ATb groups ($n=4$) Figure 1) and within-group comparisons (pre *vs* post) were conducted with the nonparametric Wilcoxon signed-rank test for two related samples.

Finally, the effect of clinical symptomatology changes on neuropsychological performance was analyzed using Spearman's correlations to compare delta scores from Y-BOCS, BDI, and BAI with neuropsychological variables. This was conducted separately for each RCT group and for all operated patients.

Analyses were based on raw scores, with the exception of IQ values. We adopted a two-tailed alpha level of significance of 0.05 and all statistical tests were based on exact significance (more conservative and appropriate to use in small samples).

RESULTS

Baseline Measures

Patients from the pilot group did not differ from the RCT groups regarding demographic and clinical data before surgery (Table 3). Patients from the ATa and ST groups were also similar in terms of age, gender, handedness, years of education, OCS severity, years of illness, IQ, depression, and anxiety symptoms (Table 3) and there were no differences in neuropsychological variables (Supplementary Table S1).

Treatment Outcomes

Randomized clinical trial. Three patients from the ATa group (37.5%) and none from the ST group were responders after the blind phase (Table 2). Consistent reductions on Y-BOCS scores were observed only in the ATa group (38.4%, p-value = 0.008, $Z=2.5$, Wilcoxon/Exact). There were no significant changes in depression and anxiety symptoms for ATa patients along the blind phase, whereas ST patients improved from their depressive symptoms after sham treatment (46%, p-value = 0.008, $Z=2.5$, Wilcoxon/Exact, Table 3).

All patients treated with GVC. One patient from the ATb group (25%) and two patients from the pilot study (40%) were classified as responders after 1 year of follow-up. Considering all operated patients (ATa, Atb, and pilot groups), six out of 17 patients (35%) were responders after 1 year, with significant reductions in Y-BOCS (35.8%, p-value = 0.001, $Z=3.1$) and BAI (37.4%, p-value = 0.007, $Z=2.6$), but not in BDI scores (24.4%, p-value = 0.123; Table 3).

Neuropsychological Outcomes in the RCT

ATa patients showed improved performance on measures of VSM when compared with ST patients after 1 year of follow-up, with significant group *vs* time interactions in the VSM NP-MANOVA (p-value = 0.008; F* value = 6.1). Raw scores from four dependent variables were used in this analyses: (1) Brief Visuospatial Memory Test-Revised (BVMT-R) immediate total recall; (2) BVMT-R delayed recall; (3) BVMT-R discrimination index (a recognition score); and (4) Rey–Osterrieth Complex Figure Test (ROCF) delayed recall (Table 2). NP-RM-ANOVA *post hoc* analysis found group

Table 1 Neuropsychological Domains, Functions and Tests Employed in the Study

Domain/function	Test
Intellectual functioning	
Verbal and non-verbal Intelligence	Wechsler abbreviated scale of intelligence (WASI; Wechsler, 1999)
Cognitive screening	
Screen for cognitive impairment	Mini mental state examination (MMSE; Folstein *et al*, 1975)
Verbal skills	
Language	Boston naming test (BNT; Kaplan *et al*, 2001; Miotto *et al*, 2010)
Verbal learning and memory	
Episodic memory for word-lists	Hopkins verbal learning test-revised (HVLT-R; Benedict *et al*, 1998)
Short- (immediate) and long-term (30 min) contextualized verbal memory	Logical memory (LM) Wechsler memory scale-revised (WMS-R; Wechsler, 1987)
Visuospatial learning and memory	
Episodic visuospatial memory—delayed recall (30 min)	Rey–Osterrieth complex figure test (ROCF; Osterrieth, 1944)
Visuospatial learning and memory; immediate and delayed recall (20 min)	Brief Visual Memory Test-Revised (BVMT-R; Benedict *et al*, 1998)
Attention	
Attention, speed and mental flexibility	Trail making test (TMT; Strauss *et al*, 2006)
Executive functioning	
Inhibitory control	Victoria stroop test (VST; Strauss *et al*, 2006)
Cognitive flexibility	Wisconsin card sorting test (WCST)—64 cards (Heaton *et al*, 1993; Heaton *et al*, 2005)
Planning	Rey–Osterrieth complex figure test (ROCF; Osterrieth, 1944)
Visuospatial abilities	
Spatial perception and visual judgment	Benton judgment of line orientation test (BLJT; Benton *et al*, 1978)
Visual constructional ability	Rey–Osterrieth complex figure test (ROCF; Osterrieth, 1944)
Motor functioning	
Visual–motor coordination	Grooved pegboard test (GPT; Strauss *et al*, 2006)
Tapping speed and fine motor skills	Halstead finger tapping test (FTT; Strauss *et al*, 2006)
Hand grip strength	Hand dynamometer (HD; Strauss *et al*, 2006)

vs time interaction effects for the BVMT-R immediate total recall and ROCF delayed recall (Figure 2 and Table 2). Significant effects were not found in other cognitive domains (Table 2).

Neuropsychological Outcomes for all Patients Treated with GVC

Considering the 17 patients treated with GVC, within-group comparisons revealed improvement in several neuropsychological domains 1 year after the procedure: vocabulary (p-value = 0.027), performance IQ (p-value = 0.036), total IQ (p-value = 0.022), ROCF delayed recall (p-value = 0.017), Grooved Pegboard Test dominant-hand time (p-value = 0.042), Hand Dynamometer nondominant-hand (p-value = 0.040), Wisconsin Card Sorting Test (WCST) correct responses (p-value = 0.049), and Trail A (p-value = 0.034; Supplementary Figure S2 and Supplementary Table S2). Although there were individual variations during the course of the follow-up, there was not a pattern of decreased neuropsychological performance for any patient, and ultimately there were no adverse changes in any neuropsychological domain 1 year after surgery.

Neuropsychological Changes and Symptom Improvement

Measures of clinical symptomatology based on Y-BOCS, BDI, and BAI scores did not significantly correlate with neuropsychological changes in the analyses of RCT groups, and the same was found for the secondary analysis (considering all operated patients).

Table 2 Clusters of Functions and the Respective Tests Enrolled in Each NP-MANOVA for Difference Within Performances

Cognitive ability	*p*-value NP-MANOVA	F[a] value	*p*-value NP-RM-ANOVA	QW[b] value
Intellectual functioning	0.671	0.6	—	—
Vocabulary + similarities + block design + matrix reasoning				
Attention	0.516	0.5	—	—
Stroop (time part 1) + trail (time part A)				
Verbal memory	0.807	0.2	—	—
HVLT-R total immediate recall + LM immediate recall + HVLT-R delayed recall + LM delayed recall				
Visuospatial memory	**0.008**	**6.1**	—	—
BVMT-R total immediate recall +	—	—	**0.0025**[a]	**9.2**
BVMT-R delayed recall +	—	—	0.0445[a]	4.0
BVMT discrimination index +	—	—	0.0394[a]	4.2
ROCF delayed recall	—	—	**0.0006**[a]	**11.7**
Cognitive flexibility	0.435	0.7	—	—
WCST total corrects responses + WCST categories				
Spatial perception	0.911	0.1	—	—
BLJT + ROCF copy + ROCF planning				
Motor functioning	0.936	0.1	—	—
GPT total time + FTT mean of 10 trails + HD mean of three trails.				
Dominant hand:	0.969	0.1	—	—
Non-dominant hand:	0.733	0.3	—	—

Abbreviations: NP-MANOVA, nonparametric multivariate analysis of variance; NP-RM-ANOVA, nonparametric repeated measures analysis of variance.
Post hoc analyses are indicated by NP-RM-ANOVA.
[a]Patients submitted to ATa improved after the procedure in comparison with ST, in bold the statistically significant comparisons considering a Bonferroni's correction *p*-value of 0.0125.
[b]QW is a measure of effect size similar to the F values of parametric ANOVA.

DISCUSSION

To our knowledge, this is the first RCT of an ablative surgical intervention for refractory OCD to have assessed neuropsychological functions, providing an opportunity to observe how patients fared without true surgery, controlling for time and practice effects. Results from the RCT suggests that GVC significantly improved VSM in patients actively treated (ATa group) when compared with the sham group (ST). Considering all patients who underwent the procedure (ATa, ATb, and pilot), improvements were observed on the following neuropsychological functions: vocabulary, intelligence, VSM delayed recall, motor performance, attention, and executive functioning. Therefore, in our sample, GVC not only showed efficacy in reducing OCS in treatment refractory OCD patients, but was also safe from a neuropsychological perspective.

Several studies have identified VSM as a specific and central neuropsychological deficit in OCD (Bloch *et al*, 2011; Grisham *et al*, 2009; Kuelz *et al*, 2004, 2006; Kim *et al*, 2002; Penadés *et al*, 2005; Purcell *et al*, 1998; Rao *et al*, 2008; Segalàs *et al*, 2008; Shin *et al*, 2013). Cross-sectional studies have shown that OCD patients present difficulties in VSM when compared with healthy controls (Kuelz *et al*, 2004; Purcell *et al*, 1998; Rao *et al*, 2008; Savage *et al*, 1999), and longitudinal studies indicate the presence of visuospatial deficits even before the onset of symptoms (Bloch *et al*, 2011; Grisham *et al*, 2009). Moreover, the improvement of VSM has been described after successful treatment for OCD (Kim *et al*, 2002). Kuelz *et al* (2008) found that major responders to treatment improved significantly more than minor responders on the ROCF immediate and delayed recall. Indeed, a recent meta-analysis on neuropsychological data and OCD has indicated that VSM is the most consistently cognitive improvement in OCD (ie, VSM presented the largest effect size among all neuropsychological domains; Shin *et al*, 2013).

Neuropsychological functioning has been previously assessed in patients with OCD following AC using thermocoagulation. Nyman and Mindus (1995) found that three out of five patients presented more perseverative responses in the WCST (a mental flexibility task), 1 year after surgery. Rück *et al* (2008) included two additional patients in this sample and reported mental flexibility deficits in six out of seven patients after 11 years of follow-up. Contrary to these findings, within-group comparisons in our study demonstrated improved WCST performance in the ATa group (Supplementary Table S1). One possible explanation could be that the smaller radiosurgical lesions employed in our study (Lopes *et al*, 2004, 2009) in comparison with the previous literature (Nyman and Mindus, 1995; Rück *et al*, 2003, 2008) could cause less disruption in the neural circuitry responsible for these measures of neuropsychological functioning.

It has been previously postulated that neurosurgery for psychiatric disorders can modulate neuropsychological

Table 3 Demographic Characteristics, Clinical Scores and Treatment Outcomes for Each Study Group

	Pilot ($N=5$) mean (SD) [range]	Sham group ST ($N=8$) mean (SD) [range]	Active treatment ATa ($N=8$) mean (SD) [range]	Exact *p*-value[a]	Open treatment ATb ($N=4$) mean (SD) [range]	Pilot+ATa+ATb ($N=17$) mean (SD) [range]
Gender, female:male	3:2	3:5	3:5	—	1:3	7:10
Handedness, right:left	5:0	7:1	7:1	—	4:0	16:1
Age	35 (11.1) [23–49]	34.1 (10.1) [24–53]	32.1 (10.6) [21–55]	0.796	38.0 (11.8) [26–54]	34.4 (10.6) [21–55]
Years of education	12.0 (5.1) [4–16]	12.5 (2.8) [8–16]	13.2 (1.8) [12–16]	0.893	13.0 (2.0) [12–16]	12.8 (3.0) [4–16]
Age of symptom onset	8.4 (1.7) [6–10]	14.8 (4.5) [9–22]	11.9 (5.7) [5–21]	0.054	14.0 (5.6) [9–22]	11.3 (5.0) [5–22]
Illness duration after first onset of OCS (years)	25.0 (12.9) [9–39]	19.4 (11.0) [10–40]	20.3 (13.8) [6–48]	0.700	23.5 (13.5) [12–40]	22.4 (12.8) [6–48]
Responders	2:5	0:8	3:8	—	1:4	6:17
Y-BOCS pre scores	32.2 (1.48) [30–34]	34.8 (4.0) [29–40]	33.3 (2.8) [30–36]	0.365	34.3 (4.4) [30–40]	32.9 (2.6) [23–40]
Y-BOCS post scores	20.6 (12.3) [10–40]	31.9 (4.1) [27–40][b]	20.9 (11.0) [1–34][b]	0.067	23.8 (17.3) [0–40]	21.4 (11.7) [1–40]
Y-BOCS percentage decrease	36.4%	7.4%	38.4%	—	30.8%	35.8%
BDI pre scores	25.2 (9.9) [16–37]	29.1 (18.5) [4–56]	23.9 (12.1) [12–46]	0.740	23.5 (15.0) [11–45]	24.2 (11.5) [11–46]
BDI post scores	16.6 (13.2) [1–32]	14.8 (13.7) [3–45]	18.6 (11.9) [3–35]	0.774	21.5 (11.6) [7–35]	17.7 (13.9) [1–35]
BDI percentage decrease	45.1%	46.0%	21.5%	—	4.4%	24.4%
BAI pre scores	27.6 (11.5) [17–45]	19.3 (15.3) [0–45]	22.9 (17.1) [3–60]	0.542	13.0 (4.9) [7–19]	21.9 (13.9) [3–60]
BAI post scores	12.6 (8.11) [2–24]	11.0 (5.8) [3–19]	13.4 (10.5) [4–37]	0.933	9.8 (6.1) [3–17]	10.8 (8.2) [2–37]
BAI percentage decrease	71.3%	30.8%	22.4%	—	25.0%	37.4%
Estimated IQ (WASI)	93.0 (13.5) [77–108]	87.1 (10.8) [71–103]	90 (15.4) [76–122]	0.692	89.3 (14.8) [77–109]	90.7 (13.8) [76–122]

Abbreviations: ATa, randomized active treatment group; ATb, open active treatment group (four patients initially from the ST group, operated after blind was broken); OBS, obsessive–compulsive symptoms; ST, randomized sham treatment group.
[a]Kruskal–Wallis test.
[b]Statistically significant difference (Mann–Whitney *U*-test) between ATa and ST groups (*p*-value 0.019).

performance in different ways (Nyman and Andreewitch, 2001): (1) negatively impact performance by disrupting neural pathways; (2) positively impact cognitive functioning due to amelioration of symptoms; or (3) positively impact cognitive performance by interrupting abnormal circuits. The following discussion is based on these three assumptions: (1) the lack of long term neuropsychological deficits in our sample supports the view that the interruption of frontal-striatal neural pathways does not have a negative impact on neuropsychological performance; (2) we did not find correlations between measures of clinical symptoms and cognitive function (although both improved) in the RCT analysis or when considering all operated patients, indicating that the improvement on VSM occurred independently from psychopathological symptom reductions, although we could have been limited of statistical power for correlation analysis due to small sample sizes. Another explanation is that current clinical rating scales did not reliably characterize symptom changes in refractory OCD samples. Future measures based on the research domain criteria initiative may overcome this issue, focusing in biological markers rather than clinical symptomatology (Insel *et al*, 2010). Alternatively, it is also possible that symptom improvements, together with other aspects that interfere with patients' motivation or concentration, had a role in the post-operative neuropsychological evaluation; and (3) since the amelioration of neuropsychological functions in our patients submitted to surgery probably did not occur by chance, the third assumption possible interpretation seems to better explain our results. The interruption of hyperfunctional frontal–striatal circuits involved in the pathophysiology of OCD (Fodstad *et al*, 1982; Kondziolka *et al*, 2011; Lopes *et al*, 2009; Rück *et al*, 2008) could directly or indirectly lead to restorative changes in prefrontal cortex and therefore VSM pathways, restoring previous dysfunctional VSM circuits (Curtis, 2006; Figee *et al*, 2013).

Distinct cognitive domains assessed by VSM tests, including visual attention, spatial perception, visuomotor skills, and visuospatial organization, could have contributed to our overall findings. However, results from tests that specifically evaluated these functions (respectively the Trail Making Test, Benton Judgment of Line Orientation, Block Design test, and planning score of ROCF) did not show group *vs* time interactions (ATa *vs* ST, pre *vs* post surgery), suggesting that our findings represent a primary improvement in VSM. Moreover, improvements in VSM were consistently obtained by two distinct and well-recognized VSM neuropsychological tests: BVMT-R and ROCF. Also, although we have searched for variables that could be responsible for the improvement of VSM in the ATa group, none of the following variables have influenced our results: gender, symptom severity, number of comorbidities, and number of previous complete treatments.

Group and individual analysis of results from our study showed no impairments in neuropsychological function for all the operated patients after 1 year of follow-up. In fact, neuropsychological improvements were observed in different domains like intelligence, attention, memory, motor

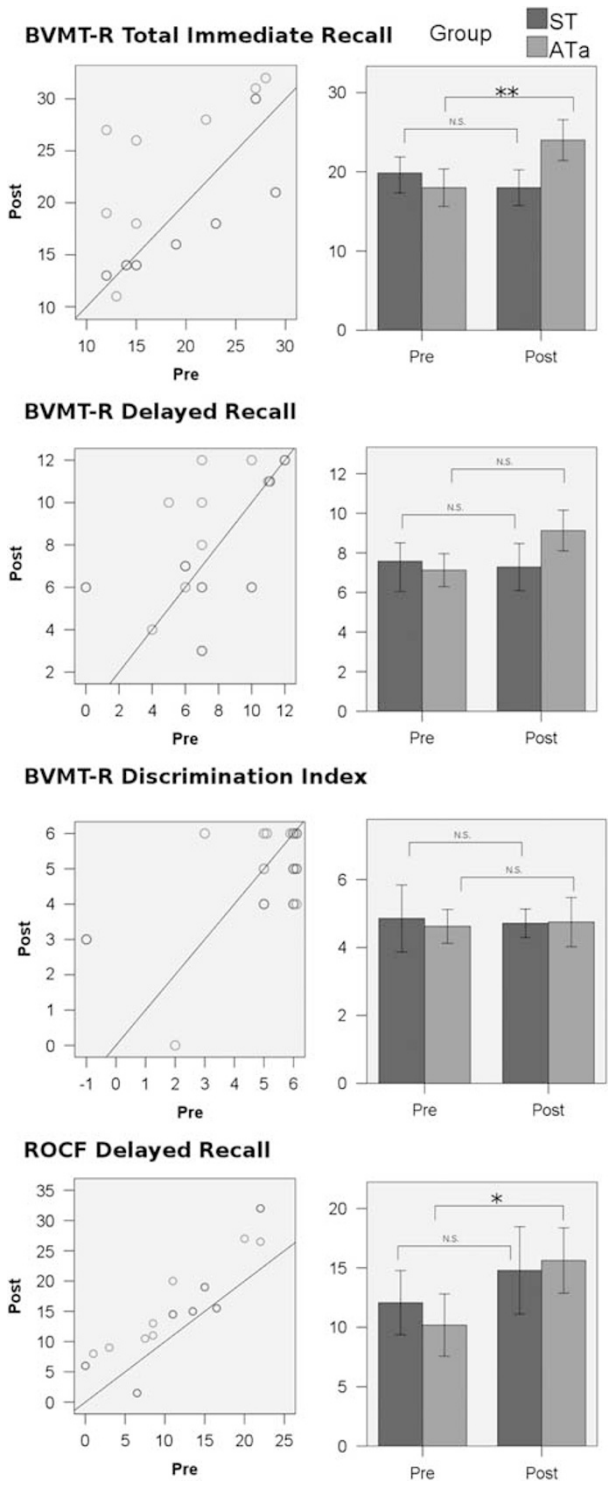

Figure 2 Interaction effects of four visuospatial memory tests (NP-MANOVA). Statistically significant differences of within-group comparisons for the ATa group (green): *p-value = 0.016/**p-value = 0.008. The error bars represent the 95% confidence interval; ATa, randomized Active Treatment group (green); BVMT-R, Brief Visuospatial Memory Test-Revised; ROCF, Rey–Osterrieth complex figure; ST, sham treatment group (blue). A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

functions, and executive functions. Although this analysis had its limitations (eg, learning effects and different evaluations time points), it is still in accordance with a recent study by Csigó *et al* (2010) reporting improvement in five of ten neuropsychological domains in five refractory OCD patients submitted to traditional AC followed for 24 months.

Despite our results, caution should still be warranted for GVC. Given our very strict inclusion and exclusion criteria, our results may not be generalized. Also, 1 year of follow-up may be considered a relatively short period considering the risks of long-term complications of radiosurgery, and in fact one of our patients developed an asymptomatic radionecrotic cyst later in the follow-up, as previously reported (Lopes *et al*, 2014). Thus, other complications may develop over longer follow-up periods. Learning effects may also have occurred, although a 12-month interval between neuropsychological assessments seems reasonable. This could have been especially relevant for the analysis that combined all operated patients, as patients from the ATb group were evaluated three times (in the RCT learning effects were controlled by the study design). Finally, it was not possible to conclude if the observed improvement of VSM in the ATa group resulted directly from the surgical intervention, or was due to other factors such as improvement of motivational drive or represented just an epiphenomenon. In fact, it is unknown if VSM deficits are trait or state dependent in OCD, and a healthy control group could have helped to investigate if even with the observed improvement of neuropsychological functioning after surgery, patients would still have deficits when compared with healthy controls.

Despite these and other limitations, our study provides new evidence regarding the possible effects of GVC on cognitive and motor performance—there was a significant VSM improvement in the RCT treated group. Also, our analysis revealed that intellectual functioning, attention, memory, motor skills, and executive functioning improved in the group of patients that received GVC. Even if taken with caution (especially in the case of secondary analysis), these findings and the absence of significant cognitive deficits 1 year after surgery corroborates to previous reports by our group (Taub *et al*, 2009) and others (Csigó *et al*, 2010), regarding the potential benefit and neuropsychological safety of GVC for patients with refractory OCD.

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The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)