

Dalgleish, T., Yiend, J., Bramham, J., Teasdale, J., Ogilvie, A., Malhi, G. & Howard, R. (2004). **Neuropsychological processing associated with recovery from depression following stereotactic subcaudate tractotomy (SST)**. *American Journal of Psychiatry*, 161, 1913-1916.

Neuropsychological processing associated with recovery from depression following
stereotactic subcaudate tractotomy (SST)

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This research was supported by the Medical Research Council of the United Kingdom

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This research was previously presented at the 8th Annual meeting of the Cognitive
Neuroscience Society in New York City, March 25th-27th, 2001.

Keywords: MOOD DISORDER; COGNITIVE NEUROSCIENCE;
PSYCHOSURGERY; NEUROPSYCHOLOGY; COGNITIVE PROCESSING

Abstract

Objective: We compared still-depressed and recovered-depressed psychosurgery (Stereotactic Subcaudate Tractotomy [SST]) patients in an effort to identify therapeutic mechanisms. Method: Ten still-depressed and 8 recovered-depressed SST patients, along with 9 never-depressed and 9 medication-recovered-depressed controls, completed the Iowa Gambling Task (IGT) - a measure of on-line decision making in the face of feedback information. SST patients also completed a battery of neuropsychological tests. Results: SST-recovered patients exhibited a relative insensitivity to negative feedback on the IGT compared to the SST-depressed, never-depressed control, and medication-recovered control groups. The difference between the SST groups remained when general neuropsychological performance was covaried out. Conclusions: These findings suggest acquired relative insensitivity to negative information as a specific mechanism mediating the anti-depressant effect of SST. Such insensitivity is not secondary to deficits in general neuropsychological functioning and is not a function of recovery from depression *per se*.

We compared still-depressed and recovered-depressed psychosurgery (Stereotactic Subcaudate Tractotomy [SST])(1) patients in an effort to identify therapeutic mechanisms. We hypothesized that SST leads to depression recovery by reducing sensitivity to negative information. According to this hypothesis, brain regions involved in negative information processing are less affected by SST in patients who remain depressed than in patients who recover.

To test this hypothesis we used the Iowa Gambling Task (IGT)(2). The IGT requires participants, on each trial, to choose a card from one of 4 decks. Every card offers an immediate financial reward. Occasionally a card also results in financial penalty. There are two 'good' decks where immediate rewards are modest but occasional penalties are small and two 'bad' decks where, although immediate rewards are high, occasional penalties are severe. Consequently, persevering with good decks leads to a net profit and with bad decks to a net loss. The goal is to make a net profit; something healthy participants achieve, but patients with ventro-medial orbitofrontal cortex (OFC) damage fail(2). As SST targets posterior, ventral OFC white matter(1), these data suggest that IGT performance is associated with the brain regions compromised by SST.

On the IGT, any over-sensitivity to negative information (and/or reduced reward-related behaviour), as typically shown by depressed patients(3), would render the bad decks aversive and the less punitive good decks appealing. This would lead to unimpaired performance, as is indeed the case in Major Depressive Disorder (MDD)(4). In contrast, insensitivity to negative information would reduce the deterrent effect of

occasional severe punishments, making the bad decks (with their high immediate rewards) more appealing, resulting in impaired IGT performance.

The present hypothesis therefore predicts that, on the IGT, SST-recovered-depressed patients will show greater insensitivity to negative information (in the form of financial punishments) and will be impaired overall, relative to SST-still-depressed patients.

SST patients completed a neuropsychological test battery to provide a context for interpreting any IGT differences. None of these tasks involved negative feedback information.

Method

Participants

Ten SST-depressed participants (3 men; 32-60 years [$M=50.3$; $SD= 8.6$]; MDD, $n=8$; Bipolar Disorder [BPD], $n=2$, according to the SCAN(5)), who had remained depressed since their operation, were compared with 8 SST-recovered patients (2 men; 39-75 years [$M=58.0$; $SD=11.3$]; prior MDD, $n=7$; BPD, $n=1$), who had been largely free of mood episodes since surgery. All SST-depressed and 3 SST-recovered patients were medicated. For all patients, post-operative lesions were appropriate as verified by brain scans.

Nine further participants (4 men; 24-51 years [mean = 39.44; $SD= 7.65$]; BPD, $n=2$; MDD, $n=7$) had recovered from depression with medication alone and nine (2 men; 43-76 years [$M = 55.67$; $SD = 11.08$]) had no history of depression.

After complete description of the study, written, informed consent was obtained.

The Iowa Gambling Task (IGT)

The IGT was as described above. The (standard) score is the number of choices from good decks minus the number from bad decks. Chance responding yields a score of zero. A positive score represents a net profit and successful performance(2). Insensitivity to negative feedback (INF) on the IGT was the proportion of occasions that participants persevered with one of the bad decks (deck A) immediately following a financial penalty trial on that deck (INF-A). There were two reasons for focusing on deck A. First, this computation only makes sense for the bad decks where INF is disadvantageous in terms of overall task performance. Secondly, of the two bad decks, it is only in deck A that financial loss (negative feedback) trials are sufficiently frequent (out of 20) to perform valid statistical analyses.

_Neuropsychological tests measured: IQ; memory; language ; attention; and executive function.

Results

SST groups were comparable on age, IQ and sex ratio. SST-recovered patients were post-operative for longer (87.3 ± 66.3 months) than SST-depressed patients (28.1 ± 23.9 months), $t(8.5) = 2.4$, $p < .05$, but this did not relate to any of the variables of interest and so is not discussed further. Never-depressed controls were comparable on age and IQ with SST groups, and on BDI with the SST-recovered group. Medication-recovered participants were comparable on IQ and BDI with SST-recovered patients, but were younger, $t(15) = 4.00$, $p < .01$.

On the IGT, both SST-recovered ($M=18.88$; $SD=37.08$) and SST-depressed patients ($M=31.20$; $SD=29.65$) selected more cards from good decks than bad, making a net profit. Only SST-depressed patients performed significantly better than chance, $t(9)$

= 3.33, $p < .01$ (SST-recovered: $t(7) = 1.44$, $p > .1$). However, these groups did not differ significantly from each other. Similar results were obtained by analyzing blocks of 20 trials separately.

SST-recovered subjects evidenced greater insensitivity to negative feedback (INF-A) than SST-depressed subjects (Figure 1), $t(16) = 3.62$, $p < .002$; Cohen's $d = 1.65$, and there was a negative correlation between INF-A and BDI scores across all SST subjects, $r = -.53$, $p < .04$. These data indicate that, on both categorical and continuous measures, greater INF-A was associated with lower depression.

ANOVA of INF-A scores for SST-recovered, SST-depressed, and healthy controls revealed a significant difference between groups, $F(2, 24) = 7.00$, $p < .005$ (Fig. 1), with SST-recovered patients being more insensitive to negative feedback than healthy controls, $p < .01$, and SST-depressed participants, $p < .005$, who did not differ from each other. That is, it was the SST-recovered patients who were abnormally insensitive to negative feedback.

It was possible that the INF of SST-recovered patients concerned depression recovery *per se*, and was not specific to SST. However, ANOVA comparing SST-recovered, medication-recovered, and healthy controls revealed a significant difference across groups on INF-A, $F(2,23) = 4.65$, $p = .02$ (Fig. 1), that was due to the SST-recovered subjects being more insensitive than both the medication-recovered subjects and the never-depressed controls, $ps < .01$, who did not differ from each other. This effect remained with age covaried out, $F(2,14) = 3.27$, $p < .05$.

Finally, the difference in INF-A scores between the 2 SST groups remained significant even with the six neuropsychological test scores as covariates, $F(1, 9) = 8.74$,

$p < .02$, indicating that it was not secondary to any differences in more general cognitive functions.

Conclusions

Analysis of the Iowa Gambling Task (IGT)(16) showed that recovery from depression following SST, on both categorical and continuous measures of depression, was associated with a relative insensitivity to negative information. This insensitivity was not a function of recovery from depression *per se* as it was not present in patients successfully treated with medication alone. It was also not secondary to general deficits in neuropsychological functioning. Present results therefore suggest that an acquired relative insensitivity to negative information represents a plausible mechanism for the anti-depressant effect of SST.

We should note possible limitations of the findings: a) We cannot be certain that post-operative differences between SST groups were not present pre-operatively. However, depressed patients generally show increased sensitivity to negative information(3), making it unlikely that the relative insensitivity in SST-recovered patients was present pre-operatively when they were in episode. b) Sample sizes were relatively small.

However, the IGT was developed for small-sample studies and present sample sizes are comparable to other studies(2). Nevertheless, there were two areas where power was a potential problem: the comparison between SST groups on the IGT standard score, and the comparison of this score against zero (representing chance responding) for the SST-recovered participants. c) The SST-depressed group were more medicated than the SST-

recovered group. However, it is not clear how this could account for the key findings of the study which are a function of abnormal performance in SST-recovered participants.

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Figure 1

Insensitivity to negative feedback (% of trials) on deck A of the Iowa Gambling Task

(INF – A; mean + s.d.).

