Abulia: The Pathology of “Will” and Dopaminergic Dysfunction in Brain-Injured Patients

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ABSTRACT: Objective - The present paper describes a series of single-case evaluations of the effects of bromocriptine, a dopamine D2 post-synaptic receptor agonist, in 13 patients with clinical features of abulia. Method - An open trial in seven males and six females who had either traumatic brain injury or subarachnoid haemorrhage between two months and five years previously. After repeated baseline assessments, bromocriptine was administered in gradually increasing doses. Assessments were repeated at increasing doses, during maintenance, and after withdrawal. Some newly developed structured instruments for quantifying motivation were used, measures of anxiety and depression, and cognitive tests sensitive to motivation were also administered. Results - Following bromocriptine treatment improved on all scores measured other than mood. Improvement was maintained after bromocriptine withdrawal in nine of the patients. Conclusion - Abulia in patients with brain injury may result from dysfunction in the mesocorticolimbic dopaminergic circuitry, giving rise to associated deficiencies in reward responsiveness and cognitive function. New rating scales are proposed of motivation in brain injured patients.

Keywords: abulia, motivation, rewards, dopamine, bromocriptine, functional recovery, traumatic brain injury, subarachnoids haemorrhages, drug therapy, cognitive-processes

The basic function of the central nervous system is to translate sensory impulses into adaptive behaviour. According to William James (1890), a prerequisite for this translation is "selection of stimuli and choice of response." Such 'translation' is manifest in motivated behaviour that may be construed as a response to incentive; that is, as the potential reward for a given behaviour increase, so response output should normally increase and 'drive', 'effort' or 'motivation' will be inferred. Motivation may be apparent both at the level of perceiving the incentive properties of potentially rewarding stimuli and/or at the level of planning, monitoring and executing goal-directed behaviours. An individual will be perceived as low in motivation if she or he fails, or is unable, to respond to normal incentives with enhanced responses. It is therefore hypothesized here that if poor motivation manifests clinically after brain injury there would be an association with low incentive motivation (or 'reward responsiveness').

Relevant to impaired motivated behaviour is the
concept of abulia, a term derived from the Greek “boul” (will), and usually defined as a lack of will or motivation. According to Druybach et al. (1995), abulia refers to a specific neurologic syndrome manifested by lack of spontaneity of action and speech, deficiency in initiation, apathy, inertia, mental and motor slowness, reduction in an excursion of motion, poor attention and easy distractibility. Caplan (1990) has suggested three criteria for the diagnosis of abulia: decreased spontaneity in activity and speech; prolonged latency in responding to queries, directions and other stimuli; and reduced ability to persist with a task. Other terms that are akin to abulia or construed as behavioural markers of abulia, include apathy (Marin, 1990), loss of psychic self-activation (Laplane, 1990), bradyphrenia (Naville, 1922), psychic akinnesia (Starkstein, Berthier and Leiguarda, 1989), catatonia (Arieti, 1959), anhedonia (Ribot, 1886), annihilation of will (Cutting, 1992), akinnesia (Bermanzohn and Siri, 1992), and Pierre Janet's concept of psychasthenia (Pitman, 1987).

Animal studies assisted the development of a technique for tracing circuits in the central nervous system, i.e. retrograde transneuronal transport of herpes simplex virus type 1. Therefore, from an anatomical perspective it is suggested that frontal-subcortical circuits are linking specific regions in the frontal lobe with thalamus and basal ganglia (Alexander, DeLong and Strick, 1986; Middleton and Strick, 1996). The focal lesion of frontal-subcortical circuitry induced by encephalitis, tumours, haemorrhages, or other vascular lesions and trauma have been associated with abulic like impairment (Baddley and Wilson, 1988; Barrett, 1991; Damasio, 1996; Starkstein et al., 1993; Galynker et al., 1995; Kaelin, Cifu and Matthies, 1996).

From neurochemical and pharmacological studies, comes evidence implying that abulia is strongly associated with abnormal dopaminergic (DA-ergic), manufactured in nerve cells within the ventral tegmental areas and released in the nucleus accumbens and the frontal cortex (for review, Al-Adawi and Al-Azri, 1996). In animals, mesocorticolimbic dopamine (DA) system mediates reward processes, motivational mechanism and frontal functions. DA-ergic neurons are the preferred sites for self-stimulation, therefore suggesting that the DA system plays an important role in reward and reinforcement, contributing to initiation of action (Robbins and Everitt, 1996; Watanabe, 1996). Saint-Cyr et al. (1992) have emphasized the important role of forebrain DA-ergic systems in the behavioural functions of expectancy and anticipation. These systems play key roles in both motivation and the incentive act; dysfunction would result in diminished desire to perform activities. Fibiger and Phillips (1987) hypothesized that the abnormalities in these systems would diminish the effectiveness of reward mechanisms and contribute to anhedonia, loss of motivation, and apathy dysfunction of reward-oriented systems could explanation for abulia.

In clinical reports, as well as studies of normal subjects, DA neurotransmitter is associated with goal-directed behaviour an processes construed as manifestation of behaviour (Cummings, 1993). In support of th deficiency has been shown to play a role in pathogenesis of Parkinson Disease, depressive schizophrenia (van Praag, 1975), disorders w motor and psychological dysfunction, but may override poverty of willed action or abulia. Abulia is a major clinical problem rehabilitation of brain-injured patients (Pow 1996). It may present a serious barrier to rehabilitation, and vocational adjustment, poss so than other deficits. A long-term outcome is limited as much by abulia as by physical impairments (Wrobleski and Glenn, 1994). To Alderman (1996), “…patients with traumatic injury (TBI) are not popular among the professionals because of their general motivation” (p.162).

It is plausible that injury to the brain, be it tearing and shearing, may compromise the integrity of the neuronal projections involved in motivation and indications that some of those functions may constitute an abulia (Al-Adawi and Al-Azri, 1996; Ackermann and Ziegler, 1995). Of relevance to our discussion are some studies that have shown that DA function is dramatically affected by brain injury; for example, Bareggi et al. (1975) reported diminished levels of dopamine and its metabolites in cerebral spinal fluid following traumatic brain injury in animals. In humans, Kaelin et al. (1975) reported changes of homovanillic acid (HVA) in the ventricular cerebrospinal fluid after brain injury. The decline of DA metabolite was notable in patients with long duration of unconsciousness while HVA showed no correlation with the state of consciousness. More recently, Yang et al. (1995) measured catecholamine changes in 48 adult patients in the acute stage (the first seven days) after a severe head injury. They found significant changes in the levels of DA in serum.

Bhatia and Marsden (1994) have conducted a study of patients with Parkinson's disease and their clinical manifest of dysfunction of DA activity.
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and apathy,
administration, dosage, or therapeutic level. Thus, the rigorous design of a double-blind trial with predetermined dose levels was not feasible at this point.

Drug Regime

Bromocriptine, or 2-bromo-alpha-ergocryptine, is a post-synaptic, DA agonist with particular direct affinity for D2 receptors and mild D1 receptor antagonism (Corrodi et al., 1973). Traditionally, bromocriptine's biological effect has been thought to parallel that of amphetamine and Levodopa (Wroblewski and Glenn, 1994). More recently, however, it is becoming increasingly clear that bromocriptine acts differently. For example, it has been reported that during the early phase of treatment, bromocriptine tends to decrease locomotor activity, rather than to increase it as with other stimulants. According to Muller and Von Cramon (1994), "... this unusual biphasic effect has not been observed with other stimulant drugs..." It has been suggested that the initial depression is mediated via presynaptic D2 autoreceptors with a consequent reduction in DA synthesis or release" (p. 1108). In neurological disorders, it is widely used in the treatment of Parkinson's disease, either alone or in combination with levodopa (Portin and Rinnie, 1980; Lee et al, 1978). It has been efficacious in various endocrine disorders (Thorner and Vance, 1989). Bromocriptine can trigger gastrointestinal irritation, i.e. nausea and vomiting. This can safely be prevented by concurrent prescription of domperidone, a selective D2 receptor blocker with antiemetic properties, which does not cross the blood-brain barrier. Medical contraindications to its use include mental disturbances such as agitation, confusion, hallucinations and nightmares (Wroblewski and Glenn, 1994), and poor cardiovascular regulation (Schobel et al., 1995). Therefore, no patient with documented ischaemic heart disease or a history of a psychosis was offered treatment.

Other adverse side-effects include hypoxemic seizures, and respiratory arrest has been reported after abrupt withdrawal from higher doses than those used in the present study (Riley, Grossman and Martin, 1992). Although these effects are rare, inpatients in the present study were monitored carefully throughout by medical staff on the ward. Thus, patients' blood pressure was monitored over the first week, and any adverse gastric effects were noted. The starting dose was 2.5 mg/day, and this increased by 2.5 mg/day per week to a maximum of 10 mg/day. In some cases it took slightly longer to increase the dose, for instance when the unit closed over Christmas or there were changes in medical clinical staff.

None of the 13 patients described below in fact showed any adverse side-effects resulting either in premature discontinuation of bromocriptine or additional medication. However, there was one additional patient who was administered bromocriptine but with becoming nauseated on the first day. He re-ecption of restarting with concurrent domperido

Subjects

Of the 13 patients receiving bromocriptine, seven were males and six females with an age range 21 to 55 (mean 39.75 ± 10.43). Table 1 presents demographic and clinical details.

Thirteen patients from the present study were significantly disabled at admission, as reflected by average scores on the Functional Independence Measure (FIM; Granger et al., 1993) and on the Barthel Index (Wade and Collin, 1988). The average score was 90.5 ± 29.7; and for BI; 14.1 ± 6.4. The severity score indexed by the Glasgow Coma Scale (Jennett Teasdale et al., 1974) was 6.33 ± 3.2 (<equated with disturbed consciousness and amn

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Cause of injury</th>
<th>Weeks since injury</th>
<th>MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>34/M</td>
<td>RTA</td>
<td>20.57</td>
<td>5</td>
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<tr>
<td>#2</td>
<td>21/M</td>
<td>RTA</td>
<td>22</td>
<td>1</td>
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<tr>
<td>#3</td>
<td>55/F</td>
<td>SAH</td>
<td>28.86</td>
<td>1</td>
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<tr>
<td>#4</td>
<td>38/F</td>
<td>RTA</td>
<td>26.28</td>
<td>5</td>
</tr>
<tr>
<td>#5</td>
<td>37/M</td>
<td>Unknown</td>
<td>28.42</td>
<td>1</td>
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<tr>
<td>#6</td>
<td>45/M</td>
<td>RTA</td>
<td>204.4</td>
<td>1</td>
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<tr>
<td>#7</td>
<td>46/M</td>
<td>Fall</td>
<td>116.1</td>
<td>7</td>
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<tr>
<td>#8</td>
<td>26/F</td>
<td>RTA</td>
<td>94.71</td>
<td>7</td>
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<tr>
<td>#9</td>
<td>25/F</td>
<td>SAH</td>
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<td>#10</td>
<td>55/F</td>
<td>RTA</td>
<td>101.2</td>
<td>10</td>
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<tr>
<td>#11</td>
<td>52/F</td>
<td>SAH</td>
<td>17.14</td>
<td>10</td>
</tr>
<tr>
<td>#12</td>
<td>52/M</td>
<td>Fall</td>
<td>94.3</td>
<td>10</td>
</tr>
<tr>
<td>#13</td>
<td>38/M</td>
<td>RTA</td>
<td>56.71</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations:

M: Male
F: Female
RTA: Road Traffic Accident
SAH: Subarachnoid Haemorrhage
GAS: Glasgow Coma Scale
MAXBROMO: Maximum Dose of Bromocript
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E but withdrawal. He refused
compliance treatment on an age
without signs of delirium or
 exhibent substantial
improvement in functional
dependence (Barthel Index score
was 94 out of 100). The patient
econtrolled pain. The patient
	TABLE 2

<table>
<thead>
<tr>
<th>Neuroimaging and Neuropathology information for each patient.</th>
<th>Neuroimaging and Neuropathology information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Contusions of both temporal lobes and of the left cerebral peduncle</td>
</tr>
<tr>
<td></td>
<td>Cerebral oedema and chronic frontal subdural haematoma</td>
</tr>
<tr>
<td></td>
<td>Subarachnoid haemorrhage resulting from a right middle cerebral artery aneurysm</td>
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<td></td>
<td>Right frontal lobectomy and right tarsorrhaphy</td>
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<tr>
<td></td>
<td>Atrophic ventricular dilation and area of ischaemic change in the right hemisphere</td>
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<tr>
<td></td>
<td>Diffused intracranial haemorrhages more on the right than on the left</td>
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<td></td>
<td>A large boggy swelling and bruising over the occipital regions</td>
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<tr>
<td></td>
<td>Hypoxic brain damage</td>
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<tr>
<td></td>
<td>Right middle cerebral artery infarct</td>
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<tr>
<td></td>
<td>Diffused cortical injury, without major haematoma</td>
</tr>
<tr>
<td></td>
<td>Subarachnoid haemorrhage resulting from a right middle cerebral artery aneurysm rupture</td>
</tr>
<tr>
<td></td>
<td>Multiple fractures and diffused cerebral oedema</td>
</tr>
<tr>
<td></td>
<td>Diffuse injury with a right temporal contusion.</td>
</tr>
</tbody>
</table>

The time elapsed since brain injury ranged from two months to five years, this duration being less than six months for three patients, between six and 15 months for five patients, and more than two years for five patients.

Eight patients, seven of whom were in the RNRU, the other patient at Northwick Park Hospital, started bromocriptine treatment whilst in the hospital. One patient transferred to another hospital from the RNRU whilst on bromocriptine; treatment and assessments were continued there. Two were discharged home shortly after bromocriptine withdrawal but prior to the two post-withdrawal assessments, and these were conducted in their own homes. The remaining five patients were being treated in the community throughout and their general practitioners were responsible for prescribing.

Where possible, all of the measures described below were administered to all patients on each assessment occasion. Occasionally, some assessments could not be administered. For example, one patient did not speak English, and two had severe deficits in both expressive and receptive language; consequently, the language-based tests were not administered to these patients.

**Measures**

1. **LEVEL OF PARTICIPATION IN THERAPY:** The rationale and quantification of participation in therapy chart have been described in detail by Powell et al. (1996; see Appendix 1), and only briefly summarised here. All of the therapists (Physiotherapist, Occupational Therapist and Speech Therapist) recorded the length of time the patient was actively working on/concentrating on the required activities and this was computed into an “Percent Participation Index” (PPI). In addition, therapists rated patient’s perceived level of “Spontaneity” and “Motivation” during each session on a 5-point scale ranging from 0 (extremely low) to 4 (extremely high). Other factors; in particular, these commonly include distractibility and actively obstructive behaviour are not reported here.

These three measures (PPI, Spontaneity and Motivation) were obtained for all those patients in a hospital setting on each occasion. Additionally, for one community-treated patient, the community therapist was able to give ratings of spontaneity and level of motivation.

In total, complete assessment data were available for nine patients at assessments one to three (AAB) and for seven patients for the post-withdrawal assessments. Each assessment occasion averaged the records from all sessions conducted by all therapists in that week.

2. **RESPONSIVENESS TO EXPERIMENTAL INCENTIVE:** The CARROT: The Card Arranging Reward Responsivity Objective Test (CARROT) was used to assess patient’s responsiveness to ‘reward’ as described in details elsewhere (Al-Adawi and Powell, 1998). In brief, CARROT measures the extent to which patients increase their speed of performance on a simple psychomotor task when offered a small financial incentive. In this paper, “reward responsivity” (REWRESP), was computed as the differences between non-rewards and rewarded trials (for detail, see Powell et al, 1996).

3. **TESTS OF COGNITIVE FUNCTION:** Cognitive tests sensitive to attentional span, working memory and frontal lobe functions were included. These cognitive domains are sensitive to improvement in motivation as described
in Al-Adawi and Powell (1998): (i) Digit Span (as in Wechsler, 1986): Different number strings were used on each assessment occasion. (ii) Buschke Selective Reminding Test (BSRT; Buschke and Fuld, 1974). Six different word lists were developed (fruit, occupations, animals, flowers, birds, and towns respectively). The word lists were given in fixed order; if any patient was assessed on more than six occasions, the order of the lists was repeated in exactly the same order. (iii) Verbal Fluency (Benton et al., 1983): Four alternate versions of approximately equivalent difficulty were employed (CFL, PRW, DOT and FAS). These versions were administered in a fixed order in consecutive assessments, and the sequence was repeated in the same order in assessments after the fourth. Patients with severe language deficits and the non-English speaking patient were not assessed on this measure.

4. Mood state: The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) was administered on each assessment occasion, to ascertain whether or not changes in the other indices were paralleled by alteration in anxiety and depression.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS/Windows) was used for statistical analyses. In the presentation of data below, scores are presented for the following occasions: two baseline assessments (BL1 and BL2); the assessment when stabilized at maximum bromocriptine doses (MAXBROMO), i.e. the second measure, which varied for individual patients between 5 and 10 mg (see Table 1 for each patient’s dosage); and the two post-withdrawal assessments (POST1 and POST2).

Repeated measures analyses of variance (ANOVAs) were conducted for each variable, with five levels of assessment OCCASION:

(i) BASELINE 1
(ii) BASELINE 2
(iii) MAXBROMO
(iv) POST-WITHDRAWAL 1
(v) POST-WITHDRAWAL 2

Each reported ANOVA is based on the subset of subjects with complete data for that variable. As there were more than two assessment occasions, Huynh-Feldt's correction was applied when appropriate (Huynh and Feldt, 1976). In the event that there was a significant main effect of OCCASION, posts hoc contrasts were used to compare BL1 with BL2; BL2 with MAXBROMO; MAXBROMO with POST1; and MAXBROMO with POST2. Given the number of comparisons involved here, a conservative probability level of 0.01 was adopted.

Results

First, it is necessary to comment on the second phase of bromocriptine treatment. All patients showed improvements after the first bromocriptine in accordance with the protocol. When assessed for the second time post (POST2), nine patients were continuing to feel very close to the level at which they were first MAXBROMO, on most measures. However, did show some decline after bromocriptine withdrawal. Two were outpatients whose weight bromocriptine were the most modest of all studied. Their scores on most tests fell, after a point midway between their baseline and second MAXBROMO levels, and it was not considered appropriate to reinitiate bromocriptine. The fourth patient, who showed large gains while on bromocriptine, clear reversal after withdrawal, had by then transferred to a different and more distant clinical staff at that site expressed the desire to restart bromocriptine, continuing with a different dose. Assessments was logistically impossible. The fourth patient, after making striking gains on bromocriptine, became manifestly depressed after BRM withdrawal. A clinical decision was made to treat her with a traditional antidepressant rather than recommencing bromocriptine.

Therapy Participation

Figure 1 presents the mean percent of the index (PPI) and the motivation and spontaneous Complete data was available for six, seven patients respectively.

ANOVA disclosed significant main effects for PPI [F (4, 20) = 13.15, P < 0.001] and Motivation [F (4,24) = 11.52, P < 0.001], and [F (4,24) = 12.97, P < 0.001]. For all three variables, post hoc contrasts confirmed that there were no changes across the baseline period, MAXBROMO to POST1 or POST2. There were highly significant increases from MAXBROMO for all three variables (PPI: t = 0.01; motivation: t = -4.15, P < 0.003; spontaneous rating: t = 11.31, P < 0.001). Case-by-case inspection revealed that all patients on whom treatment records were available showed improvement in at least one index, and only one patient showed a significant change in any measure.
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2; MAXBROMO = maximum dose of bromocriptine; POST1 = post-withdrawal 1; POST2 = post-withdrawal 2.

Figure 2. Responsiveness to experimental incentive: the CARROT across assessment occasions. BL1 = baseling 1; BL2 = baseling 2; MAXBROMO = maximum dose of bromocriptine; POST1 = post-withdrawal 1; POST2 = post-withdrawal 2.

Reward Responsivity: The Carrot

Figure 2 shows REWRESP assessed for the 11 patients who had complete data across all assessment occasions. The main effect of OCCASION was significant (F (4, 40)= 10.82, p < 0.001). Post hoc contrasts confirmed there to be no significant changes across the baseline period, but highlighted a significant increase after bromocriptine was introduced (BL2 to MAXBROMO; t = -5.98, P < 0.001); indeed all 11 patients showed an increase in REWRESP from BL2 to MAXBROMO. After bromocriptine withdrawal, the increment was maintained (MAXBROMO to POST2: t=- 0.85, ns).
Figure 3. Cognitive test scores across assessment occasions. BL2 = baseline 2; MAXBROMO = maximum dose of bromocriptine; POST1 = postwithdrawal 1; POST2 = postwithdrawal 2.

Figure 4. Mood scores across assessment occasions. BL1 = baseline 1; BL2 = baseline 2; MAXBROMO = maximum dose of bromocriptine; POST1 = postwithdrawal 1; POST2 = postwithdrawal 2.

Cognitive Measures

Figure 3 presents Digit Span, BSRT, and Verbal Fluency scores. Complete data were available for eleven, eleven and ten patients respectively. There were significant main effects of OCCASION for all three: Digit Span (F(4, 40) = 6.75, P < 0.001), BSRT (F(4, 40) = 6.14, P < 0.001) and Verbal fluency (4, 36) = 15.93, P< 0.001). Post hoc contrasts showed significant improvements from BL2 to MAXBROMO.
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Span: \( t = -5.75, p < 0.001 \); BSRT: \( t = -4.13, p < \);
Verbal Fluency: \( t = -5.38, p < 0.001 \). There were
non-significant reductions in scores on all three
immediately after withdrawal (MAXBROMO vs
T1), and non-significant recovery close to
BROMO levels by POST2. All patients assessed on
Span, BSRT and Verbal Fluency showed increased
at MAXBROMO compared with BL2. Five
ents continued to show increased scores from
BROMO to POST2 in Digit Span, BSRT and Verbal
ancy.

Mood State

Figure 4 shows HADS anxiety and depression scores;
were complete for 10 patients. There was no
significant main effect of OCCASION for either anxiety
depression \( [F(4,36) = 2.46 \) and 2.11 respectively].

Discussion

The results of the present open trial of bromocriptine
suggested that treatment with the DA agonist,
bromocriptine, affected these abulic patients’ performance
in various measures thought to be related to motivation:
level of participation in therapy, reward responsivity in an
experimental task (CARROT) and cognitive functions
require effortful processing. Improvements on these
measures were found in 13 consecutive patients of both
sexes, differing atiology, loci of brain injury, and time
elapsed since injury (which varied between two months
and five years). These results thus corrobate and
lengthen the anecdotal reports of positive effects of DA
agonists with similar patients reported elsewhere (i.e.
Barrett, 1991; Al-Adawi, Powell and Greenwood, 1994).
Assessment techniques developed here for assessing
abulia, clinical motivation (PP1) and reward responsivity
(CARROT), have potential, pending replication, as
evaluation tools for use in future motivational research.

Averaging across all subjects, bromocriptine
treatment did not produce any significant changes in
mood scores as the HADS, suggesting that the
pharmacological intervention affected directly on abulia,
rather than via an effect on affective state; it is worth
noting however that mood was not in the clinical range
before treatment and therefore enhancement was unlikely.
However, it is interesting that this dissociation was found,
since there is a significant overlap between the behaviours
one would expect to be related to poor motivation and low
mood, and in the neurochemical systems that modulate
them. This dissociation suggests that production of abulia
and the subjective symptoms of depression may involve
different mechanisms. Because of the obvious disability
that frequently results from neurological illness,
depression has been considered an appropriate reaction to
the functional impairment (Robinson et al., 1984).
Depression clearly can and does occur in some brain-
injured patients. It has been argued that this can be a
result either of injury to specific brain areas (e.g. parietal
cortex) or as emotional reactions to the injury and the
disability involved (Silver, Hales and Yudofsky, 1990).
There is some evidence that specific biochemical and
neuropathological abnormalities may trigger the
development of apparent depression in patients with brain
injury (Silver, Yudofsky and Hales, 1991). Although
damage to the frontal lobe and basal ganglia tends to
produce “depression,” the mood changes in these patients
appear not to follow “classical” symptoms of depression,
i.e. worsening of moods in the morning, marked
psychomotor agitation or retardation. The absence of
these symptoms makes it unclear whether these patients
were classically depressed. It may be those negative
features, like abulia, that occur as aspects of the frontal
lobe syndrome are mistaken for depression (Flint and
Eastwood, 1988). The present findings appear to lend
credence to the model advanced here, that abulia is
closely related both to a loss of responsiveness to normal
reward and to an impairment of cognitive functioning and
that the mechanism underlying these associations is DA-
ergic functioning in the mesolimbic cortical-subcortical
circuit.

An unpredicted finding in the present study was that
the improvements did not reverse following drug
withdrawal in over half (all but four) of the patients. This
raises the possibility that initial improvement may have
been the result of spontaneous recovery. There are in fact
a number of behavioural and neurochemical studies with
animals that suggest that catecholamine
neurotransmission, i.e. in the striatum, may be depressed
in the early post-surgical period, but may eventually
return to normal (e.g. Robinson and Coyle, 1979).
However, this explanation seems unlikely to explain the
present data, since functional improvements occurred
following a stable baseline period in all patients.
Furthermore, time lapsed since injury was highly variable
(between two months and five years), so that spontaneous
recovery was most unlikely to have coincided with the
introduction of bromocriptine in all of these patients.

A second possibility arises from the fact that the trial
was not conducted “blind”. Thus, demand characteristics
of the treatment may directly have motivated patients to
use more effort, either because they had their own
expectancies of the treatment or they responded to the
changed attitudes of the therapist. However, it is
important to note that assessment measures were diverse,
including both ratings by therapy staff and objective
cognitive tests. The assessments were made across several
session by different therapists; although such
indices may be susceptible to the “eye of faith,” the
striking consensus between therapists does indicate some

P < 0.001

P < 0.05

P < 0.01
underlying "real" improvement. Also, a criterion for the selection of these patients for treatment consisted of extreme under-responsiveness to other forms of encouragement and explicit rewards. The fact that there were nine responses to treatment in these patients makes the placebo effect implausible. It is clearly important that bromocriptine treatment should be more rigorously evaluated via a double blind, randomized controlled trial to exclude the effect of such factors.

While recognizing the possible limitations of the present design, it is nevertheless relevant to consider the theoretical implications of the present findings. If the maintained gains were genuinely triggered by bromocriptine treatment, how might the persistence of the effects be explained? On one hand, it may be that the effects of bromocriptine outlast the half life of the drug, with readaptation taking place over a longer period than assessed here. Such an effect is not uncommon with neuroleptic treatment for psychoses, in which relapse may occur after several months free of medication (Marder, 1992). Following up patients over a longer period would be important for future research.

It is possible that the short, low dose treatment may effectively have "kick-started" the system back into more normal self-sustaining function. Theoretically, this could happen either via structural adaptations, e.g. changes in receptor densities, sensitivities, DA synthesis etc., or via neurobehavioural interactions in which increased behavioural output leads to increased experience of rewarding outcomes which in turn stimulate DA-ergic function, and therefore lead to more goal-directed (motivated) behaviour. It would be interesting, in future studies, to explore temporal relations between changes in behaviour, cognition and physiological indices of central DA activity.

Evidence is growing indicating that catecholamine neurons may modulate recovery after brain injury (for review; Feeney, 1997). In animals, previous work has shown, for example, that DA activating agents, e.g. d-amphetamine and methylphenidate, can improve beam-walking impairment following unilateral sensorimotor or frontal cortex ablation in rats (Hurwitz et al., 1991; Kline et al., 1994). Similarly, Hovda, Sutton and Feeney (1989) injected d-amphetamine following bilateral frontal cortex ablation in cats; as in rats, the drug treatment resulted in improvement in beam-walking ability relative to saline-treated controls. Carey (1983) assessed self-stimulation response rates in rats first in a baseline condition and later after lesioning DA-ergic circuitry using 6-hydroxydopamine. The latter resulted in decreased responding. It was further unequivocally shown that bromocriptine, a DA agonist, was effective in reversing the self-stimulation deficit induced by DA deficiency. Conversely, haloperidol, a DA-ergic antagonist, impedes recovery of locomotion in rats

(Feeney, Gonzales and Law, 1982). In humans with DA activating drugs resulted in outcome. Crisostomo et al. (1988) treated following cerebral infarction: four patic amphetamine whilst the other four were gi: Amphetamine treated patients made greater; placebo group. More recently, Walker et al., ten hemiplegic patients who had suffered ac infarction. The administration of dextrostes paired with physical therapy increased the ra of motor recovery. Conversely, in a retrospec of clinical treatments reported by Gold suggested that DA receptor antagonists appe behavioural recovery after focal brain injur (1993) found that when patients who ha strokes were administered DA antagonists poorer sensorimotor function and lowe involvement in activities of daily living the patients who did not receive those drugs reached a similar conclusion (Pulaski and En Kaelin, Cifu and Matthies, 1996; Her Naritoku, 1997).

Further support for this conjecture c animal research implying that experimental can activate "auto-destructive" neurochem including chemical messengers that intena systems (McIntosh, Yu and Gennarelli, morphological changes (Basavappa and Ello is interesting that glutaminergic systems proj of the same regions innervated by DA neuro glutamate systems of the brain may modula target cells, or even regulate each other. As y been no research examining this question i population but it is an area where resear overdue, for the implications are enormous. It insight into therapeutic and preventive measur neurological and psychiatric conditions (Kornhuber, 1997).

If bromocriptine has restored function injured patients, can we extrapolate this conjeuropsychiatric disorder like PD? Although ti DA pharmacotherapy in PD patients and its efficacy is a contentious issue (for review, 1996), there are reports indicating bromocriptin has a therapeutic effect on PD but also progression (Tashiro et al. 1996). In animal ex bromocriptine has been shown to 'retard' e cascade generated by glutamate-calcium follow to the brain (Ogawa et al., 1994). However, the excitotoxic causes PD has never been demor humans, although there are speculative si (Iversen, 1995). It is worth noting here the neurodegenerative condition undermined by mechanism, whereas if there is a neurode process in brain-injury, it is likely to be underli
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In humans, the neglect of trauma. In spite of this caveat, if the cellular glutamate concentration below neurotoxic greater gains by enhancing uptake activity, as has been shown in goldstein / Goldstein / Goldstein et al. (1995). The open question to be offered acute and is what is the most productive approach to dextroamphetamine, management and ameliorations of deficits in the rate and mechanism of injury. Is it early pharmacological protection and, or simply the avoidance of accumulation of destructive enzymes? This obviously is a difficult question to answer for it will require a long term study of injury. Goldstein, carefully documented from the beginning of their who had ischemia, and assessed for outcomes in meaningful ways.

The present findings, considered in the context of the cited literature, suggest that treatment with the DA 4/4/4/4, and the concept of bromocriptine, affected these abulic patients' performance on various measures thought to be related to}

Henderson: (i) level of participation in therapy; (ii) reward responsivity in an experimental task (ARROT); and (iii) cognitive functions that require ure comes formful processing. Averaging across all subjects, entral brain bromocriptine treatment did not produce any significant changes in mood scores, suggesting that the interact with pharmacological intervention impacted directly on abulia, elli, 1994) other than via an effect on affective state. Improvements Ellory, 1995; these measures were found in 13 consecutive patients project to two sexes, differing aetiology, loci of brain injury, eurons, and time elapsed since injury. An unpredicted finding in dulate the see present study, and yet compatible with emerging y, this evidences on neuroplasticity, was that the improvements on in a clinical not reverse following drug withdrawal in over half (all search is out four) of the patients.

Acknowledgements

Our thanks to the therapists and the staffs of the Homsororh Hospital, Northwick Park Hospital and the Royal Hospital and Home, London, U.K., whose active cooperation with data collection made this research possible. We are grateful to Stephanie Hamer for helpful comments on the manuscript. Also, the first author (All- dine notes) warmly acknowledges, in the midst of all the delays and detouring social predicaments, the support and encouragement, from His Excellency Yahya bin Mahfoof Al-Mantheri, Minister of Higher Education. This research was conducted as part of the first author’s doctoral dissertation and funded by the government of Oman.

References


LAYNE, C., GROSS, R.S. and BUCKLEY, M.F. (1) of the reward values and punisher aversive undergraduates. *Journal of Clinical Psychol.


MINABE, Y., KADONO, Y. and KURACHI, schizophrenic syndrome associated with a mis *Biological Psychiatry*, 27, 661-663.

MULLER, U. and YVES VAN CRAHAMON, D. therapeutical potential of bromocriptine in re rehabilitation of patients with acquired brain *in Neuro-Psychopharmacology and Biology*, 1103-1120.


POWELL, J., AL-ADAWI, S., MORGAN, J. and GR Motivational deficit after brain ii bromocriptine in 11 patients. *Journal
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Appendix 1

Aspects of motivation

Clinical Motivation: The Percent Participation Index (PPI)

The original observation of poor motivation in therapy lies at the heart of this research programme, and considerable time has therefore been spent designing and piloting an instrument to be completed by therapists which is high in face validity as well as operationally defined and easy to complete accurately and reliably.

All therapists working with each patient were asked to keep a structured diary recording various features of each session they conducted with the patient during one complete week. They were asked to record (i) duration of direct contact with the patient (X minutes), excluding any time spent accompanying him or her to or from the session, and (ii) total number of minutes within the session for which they judged the patient to have been actively participating (Y minutes). This was operationally defined as "the length of time for which you feel the patient was actively co-operating with treatment, i.e. putting in at least the minimum amount of effort needed, even if not working as hard as s/he could be." X was computed as a percentage of Y to give the Percent Participation Index (PPI).

The PPI is likely to be determined not only by passivity but also by other factors; in particular, these
commonly include distractibility and actively obstructive behavior. To explore the relative contributions of these different factors, therapists were asked to make estimates of the number of minutes 'lost' from each session for separately defined reason of passivity ("when the patient is aloof, detached, or non-involved, thus failing to participate actively"), distractibility ("when the patient's attention is diverted to something other than the assigned task; e.g., watching other patients or chatting about something irrelevant"), and disruptive behavior ("when the patient behaves in a way which actively disrupts, interferes with, or prevents treatment, e.g., shouting, being aggressive"). In addition, they were requested to give global ratings of the amount of spontaneity/prompting they had given ("any verbal or physical gesture that encourages the patient to cooperate with the treatment") and also of their subjective impression of the patient's motivation during each session, using 5 point scales with responses ranging from 0 (none at all), 1 (once or twice only), 2 (occasionally), 3 (frequently), to 4 (continuously) for motivation.

These operational definitions were devised as a pilot phase in which therapists kept an independent record of the number of minutes lost from each session due to these behaviors. To maximize the independence of these observations, each therapist kept separate records, and they did not have access to the records of other therapists. Each therapist recorded his observations and they were averaged together, thereby reducing the variability of spuriously high scores.