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

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اعتلال الإرادة والإضطراب في نشاط الدوبامين عند المرضى المصابين بشدة على الدماغ

سمير العدوي ، وج . هـ . باول ، وس . باسافابا ، ور . ج . جركرين وود

خلاصة : يصف هذا البحث تقييم أُحادي الحالة لفعالية بروموكربتين إشادة (لمستقبلات ما بعد المشبك) في ١٣مريضاً مشخصين بمرض أبوليا . استخدمت الطريقة المفتوحة لسبعة مرضى وست مريضات ممن أصيبوا إما بشدة في المخ أو بنزف تحت العنكبوتية لمدة تتروح ما بين شهرين وخمس سنوات سابقة . وبعد عدة فحوصات أساسية ، أُعطي عقار بروموكربتين بجرعات متزايدة تدريجياً ، وأُعيد التقييم بعد زيادة كل جرعة وعند الجرعة المستمرة وبعد التوقف عن العلاج استخدمت وسائل مهيكلة جديدة لتكميم الواعز ، كذلك مقاييس للقلق والاكتئاب ، واستخدمت فحوصات للمعرفة ذات حساسية للواعز ، وبعد استخدام بروموكربتين علاجياً ، تحسنت كل القياسات السابقة ما عدا الاكتئاب ، واستمر هذا التحسن بعد سحب علاج البروموكربتين في تسعة مرضى . خلُص البحث إلى أن أبوليا في المرضى المصابين بشدة في الدماغ قد تصيب دائرة الدوبامين مما يؤدي إلى نقص مصاحب في استجابات التعزيز وفعاليات المعرفة . لذا نقترح إجراء قياسات جديدة للواعز في المرضى المصابين بشدة في الرأس .

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 Drubach 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 akinesia (Starkstein, Berthier and Leiguarda, 1989), catatonia (Arieti, 1959), anhedonia (Ribot, 1886), annihilation of will (Cutting, 1992), akinesia (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 (Baddeley 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 apat dysfunction of reward-oriented systems coul explanation for abulia.

In clinical reports, as well as studies d 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 r pathogenesis of Parkinson Disease, depressive schizophrenia (van Praag, 1975), disorders w motor and psychological dysfunction, bu override poverty of willed action or abulia.

Abulia is a major clinical probler rehabilitation of brain-injured patients (Pow 1996). It may present a serious barrier to ma rehabilitation, and vocational adjustment, poss so than other deficits. A long-term outcome i limited as much by abulia as by physical or impairments (Wroblewski and Glenn, 1994). A to Alderman (1996), "... patients with traum injury (TBI) are not popular among reha professionals because of ... their general motivation" (p. 162).

It is plausible that injury to the brain, be tearing and shearing, may compromise the integr neuronal projections involved in motivation and indications that some of those functions may constitute an abulia (Al-Adawi and Al-Azr Ackermann and Ziegler, 1995). Of relevance to t are some studies that have shown that DA functio dramatically affected by brain injury; for e Bareggi et al.(1975) reported diminished level metabolites in cerebral spinal fluid following traumatic brain injury in animals. In humans, V al. (1975) reported changed homovanillic acid (H ventricular cerebral spinal fluid after brain inju decline of DA metabolite was notable in patients v longest duration of unconsciousness while HVA showed no correlation with the state of consciou More recently, Yang et al.(1995) measured catecho changes in 48 adult patients in the acute stage (tha first seven days) after a severe head injury. They significant changes in the levels of DA in serum.

Bhatia and Marsden (1994) have conducted a analysis of studies describing behavioural and dysfunction in 240 patients with basal ganglia le The commonest behavioural disturbance foll lesions affecting the caudate nucleus, putamen and g pallidus was abulia. Clinical information rega damage restricted to the mesolimbic/mesocorticoli tract is limited. However, there is evidence that a lesion in the midbrain can result in abulia. Mi Kadono and Kurachi (1990) described a patient clinical manifest of dysfunction of DA activit

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netic Resonance Imaging (MRI) scan revealed a
n in the ventral midbrain. Significantly, this patient
ormed poorly on neuropsychological tests sensitive to
-directed behaviour. More recently, Adair et al.
6) described a patient who was marked with apathy
frontal-executive dysfunction following a stroke in
subcortical structure. His MRI revealed an
ormality restricted to a small region of ventral
brain. These authors speculated that patients impaired
ivated behaviour and 'frontal' deficit is a result of
on in his mesolimbic DA system.

It may be hypothesised from these findings that when
uired brain injury disrupts DA functioning, there are
sequences for goal-directed behaviour, with patients
wing abulia in a range of situations. Dysfunction in
relevant circuitry, arising either from focal structural
nage to relevant neuronal pathways or from disruption
the synthesis, release, or metabolism of DA itself,
uld affect the functioning of the whole system and thus
e observable effects at the three levels of 'real'
uation motivation, reward responsivity and specific
gnitive functions.

There are some indications (primarily anecdotal
ngle case studies) that abulia can be prevented,
proved, or even reversed by treatment with compounds
at by different means will increase DA
urotransmission, i.e. bupropion (Lauterback et al.,
90); amantadine (Van-Reekum et al., 1995 Kraus and
aki, 1997); methylphenidate (Kaelin et al., 1996);
esipramine (Reinhard, Whyte and Sandel, 1996);
arbidopa/levadopa (Drubach et al., 1995); bromocriptine
Watanabe et al., 1995; Barrett, 1991; Powell et al., 1996).

The present study was designed to test, using
uantitative measures in a consecutive series of patients
ith abulia following organic brain injury, whether
reatment with the DA agonist, bromocriptine, would
mprove abulia and those cognitive functions gauging
ffortful functioning. If so, this would substantiate the
argely anecdotal reports available so far.

Design

The study treated inpatients and outpatients with single-incident brain injury receiving rehabilitation at the Regional Neurological Rehabilitation Unit (RNRU) of Homerton Hospital in London, U.K. Patients identified clinically as manifesting poor motivation, which was not obviously secondary to low mood and which presented as pervasive passivity both in therapy and in their daily lives, were routinely considered for treatment with bromocriptine.

A series of 13 consecutive patients from the RNRU, and one additional patient treated at another hospital, were assessed using identical single-case methodology.

Baseline assessments were conducted twice before commencement of treatment across a period of 14-21 days to establish that the patient's performance was stable and to evaluate the impact of possible practice effects on some tests. Bromocriptine was then introduced, using the regime described below, and the assessments were repeated as far as possible after every increase of 2.5 mg (i.e. at 2.5 mg, 5 mg, 7.5 mg, 10 mg). If and when improvements were observed and maintained across two successive weeks, bromocriptine was then withdrawn. Patients were reassessed on two further occasions, after a minimum of two weeks. The basic single-case methodology adopted was a repeated measure, a multiple baseline, shown schematically below:

A - BASELINE 1 (BL1)
A - BASELINE 2 (BL2)
B* - MAXIMUM DOSE OF BROMOCRIPTINE (MAXBROMO)
A - POST-WITHDRAWAL 1 (POST1)
A - POST-WITHDRAWAL 2 (POST2)
B - MAXIMUM DOSE OF BROMOCRIPTINE (MAXBROMO)

**Patients were assessed repeatedly at incremental doses*

The timing of the second post-withdrawal assessment depended on the outcome of the first post-withdrawal assessment, that is, whether drug withdrawal had affected the target behaviour, but also on other clinical factors. The time between POST1 and POST2 was variable, the mean delay in between ranging from a month to a half year. Since this assessment was introduced as part of the methodology part-way through study, some patients had longer delays than others.

The planned experimental design included a reversal component. Any patient who showed a reversal of gains made while on bromocriptine was to have the drug reintroduced, with further assessments when the patient was taking the drug again to determine whether the improvements were reinstated. However, no patients received a second phase of bromocriptine treatment, for reasons that will become evident.

Given the experimental nature of this drug treatment, it was not clinically and ethically appropriate to keep either patients or staff blind to the treatment condition. The use of bromocriptine to address poor motivation in patients with brain injuries has not previously been studied adequately to take full account of possible adverse effects. Silver and Yodofsky (1994) have stated that a person with a brain injury of any type is far more likely to be sensitive to the side effects of medications than patients without brain injury. Also, as mentioned above, the existing literature is mostly anecdotal; as far as DA-ergic pharmacotherapy in brain injured patients is concerned, there is no standard protocol for

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 anti-emetic 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 case 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 withd becoming nauseated on the first day. He re option of restarting with concurrent domperido

Subjects

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

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

TABLE 1

Clinical information for each patient.

Patient	Age/Sex	Cause of injury	Weeks since injury	MAX
#1	34/M	RTA	20.57	5
#2	21/M	RTA	22	1
#3	55/F	SAH	28.86	1
#4	38/F	RTA	26.28	5
#5	37/M	Unknown	28.42	1
#6	45/M	RTA	204.4	1
#7	46/M	Fall	116.1	7.
#8	26/F	RTA	94.71	7.
#9	25/F	SAH	24.71	7.
#10	55/F	RTA	101.2	1
#11	52/F	SAH	17.14	1
#12	52/M	Fall	94.3	1
#13	38/M	RTA	56.71	1

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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Ten had sustained their brain injuries as a result of natic head injury (seven in a road traffic accident, from falls, and one patient with unknown cause of y). The remaining three patients had suffered rachnoid haemorrhage. Neuroimaging data, usually scans, (see Table 2) disclosed four patients with ns involving predominantly frontal cortex; three with use cortical lesions; one with a brainstem lesion (left bellar penduncle) and contusion to the bilateral poral lobes; one with a right temporal lesion; one n occipital lobe injury; two with right cerebral infarct; one with middle cerebral artery infarct.

TABLE 2

uroimaging and neuropathology information for each patient.

atient	*Neuroimaging and Neuropathology information*
1	Contusions of both temporal lobes and of the left cerebral peduncle
2	Cerebral oedema and chronic frontal subdural haematoma
3	Subarachnoid haemorrhage resulting from a right middle cerebral artery aneurysm
4	Right frontal lobectomy and right tarsorhaphy
5	Atrophic ventricular dilation and area of ischaemic change in the right hemisphere
6	Diffused intracranial haemorrhages more on the right than on the left
7	A large boggy swelling and bruising over the occipital regions
8	Hypoxic brain damage
9	Right middle cerebral artery infarct
10	Diffused cortical injury, without major haematoma
11	Subarachnoid haemorrhage resulting from a right middle cerebral artery aneurysm rupture
12	Multiple fractures and diffused cerebral oedema
13	Diffuse injury with a right temporal contusion.

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-rewarded 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, Huyhn-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 t
second phase of bromocriptine treatment ir
All patients showed improvements after the
of bromocriptine in accordance with the moc
here. When assessed for the second time pos
(POST2), nine patients were continuing to f
very close to the level at which they were fi
MAXBROMO, on-most measures. Fo
however, did show some decline after bi
withdrawal. Two were outpatients whose ga
bromocriptine were the most modest of all
studied. Their scores on most tests fell, after
to a point midway between their ba
MAXBROMO levels, and it was not consider
appropriate to reinitiate bromocriptine. The t
who showed large gains while on bromocr
clear reversal after withdrawal, had by tha
transferred to a different and more dista
although clinical staff at that site expressed
to restart bromocriptine, continuing w
assessments was logistically impossible.
fourth patient, after making striking gair
bromocriptine, became manifestly depressed
its withdrawal. A clinical decision was made
to treat her with a traditional antidepressant
rather than recommencing bromocriptine.
reasons, the intended re-initiation of bromo
not occur and so the experimental design
AABAA.

Therapy Participation

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

ANOVA disclosed significant main
OCCASION for PPI [F (4, 20) = 13.15, I
Motivation [F (4,24) = 11.52, P < 0.001], and
[F (4,24) = 12.97, P < 0.001]. For all three va
hoc contrasts confirmed that there were no
changes across the baseline period,
MAXBROMO to POST1 or POST1 to POST2
there were highly significant increases fro
MAXBROMO for all three variables (PP1: t =
0.001; motivation: t = -4.15, P < 0.003; spon
11.31, P < 0.001). Case-by-case inspection re
all patients on whom treatment records were a
the relevant sessions (more than 7 patients fo
and MAXBROMO) showed improvement in
three indices, and only one patient showed a
any measure.

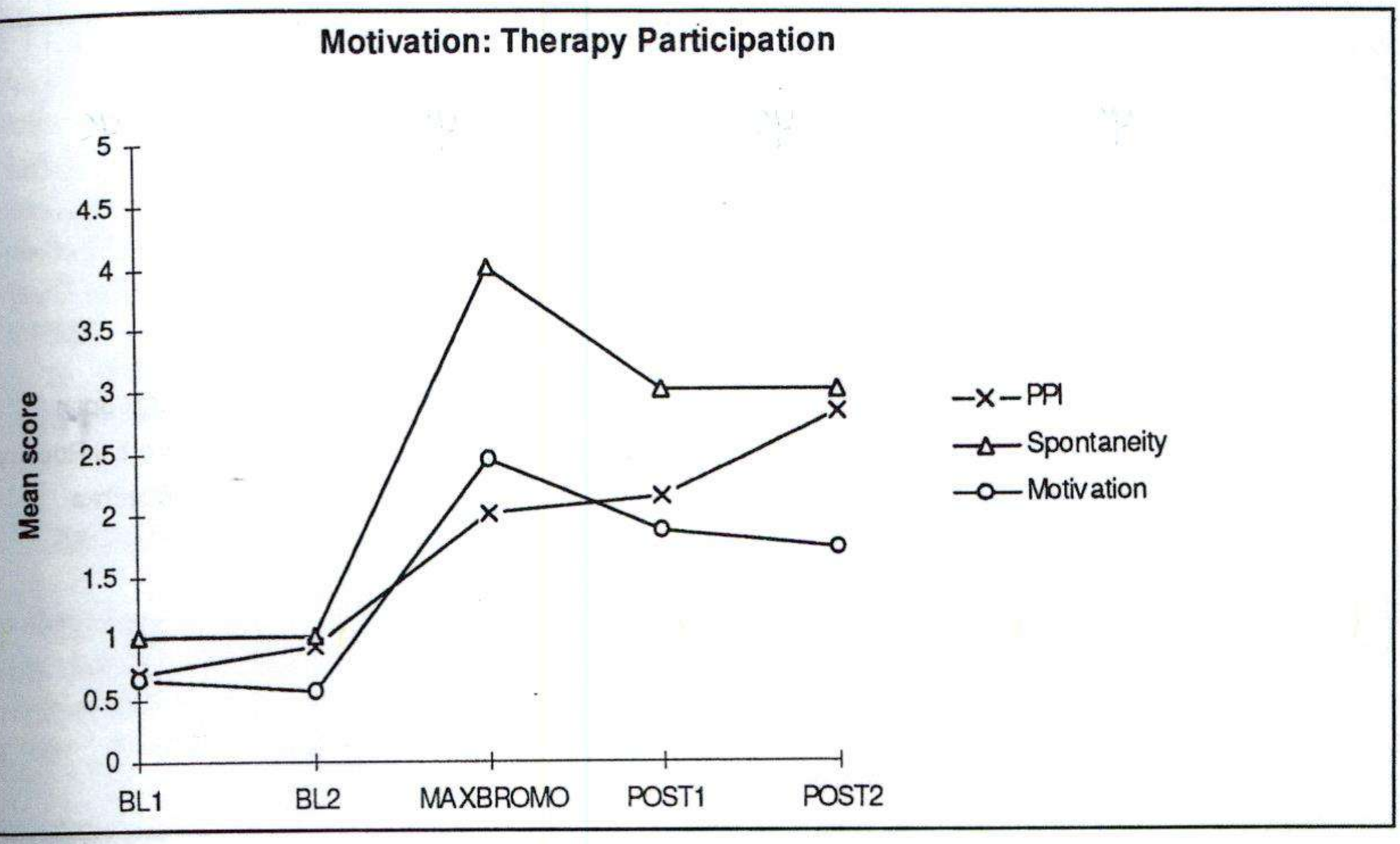

Figure 1. Clinical motivation across assessment occasions. BL1 = baseline 1; BL2 = baseling 2; MAXBROMO = maximum dose bromocriptine; POST1 = postwithdrawal 1; POST2 = postwithdrawal 2.

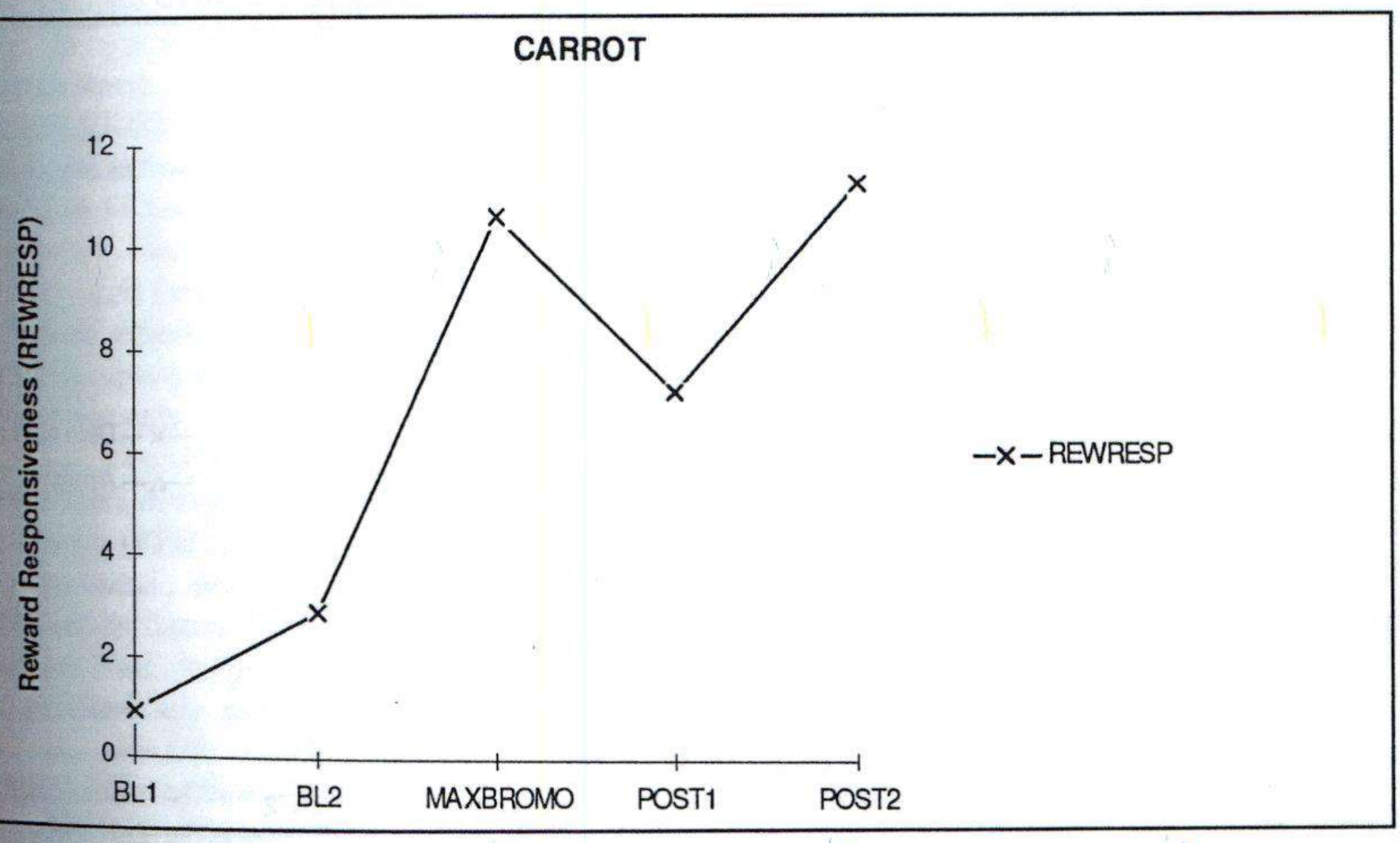

Figure 2. Responsiveness to experimental incentive: the CARROT across assessment occasions. BL1 = baseling 1; BL2 = baseling 2; MAXBROMO = maximum dose of bromocriptine; POST1 = postwithdrawal 1; POST2 = postwithdrawal 2.

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).

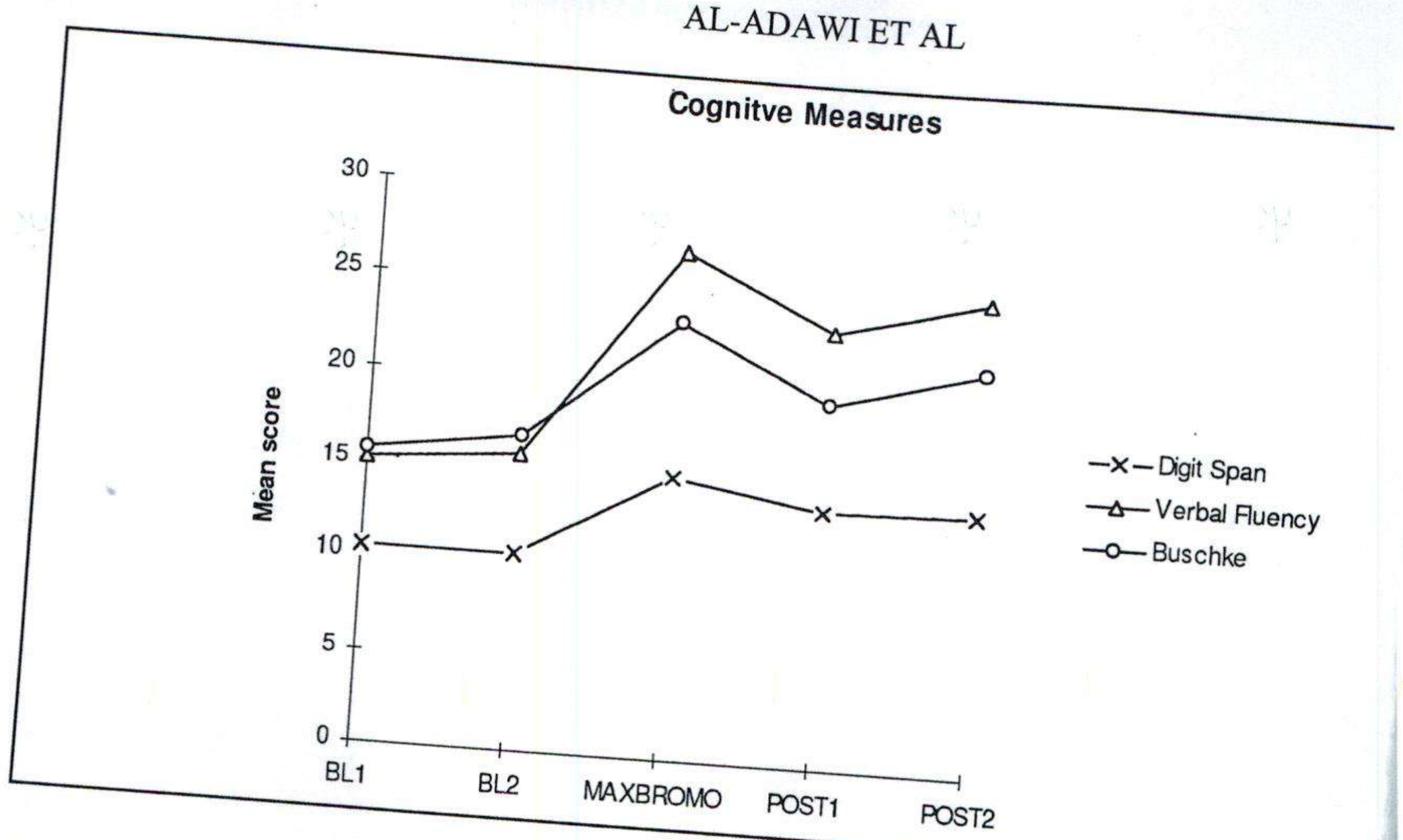

Figure 3. Cognitive test scores across assessment occasions. BL2 = baseline 2; MAXBROMO = maximum dose of brom
POST1 = postwithdrawal 1; POST2 = postwithdrawal 2.

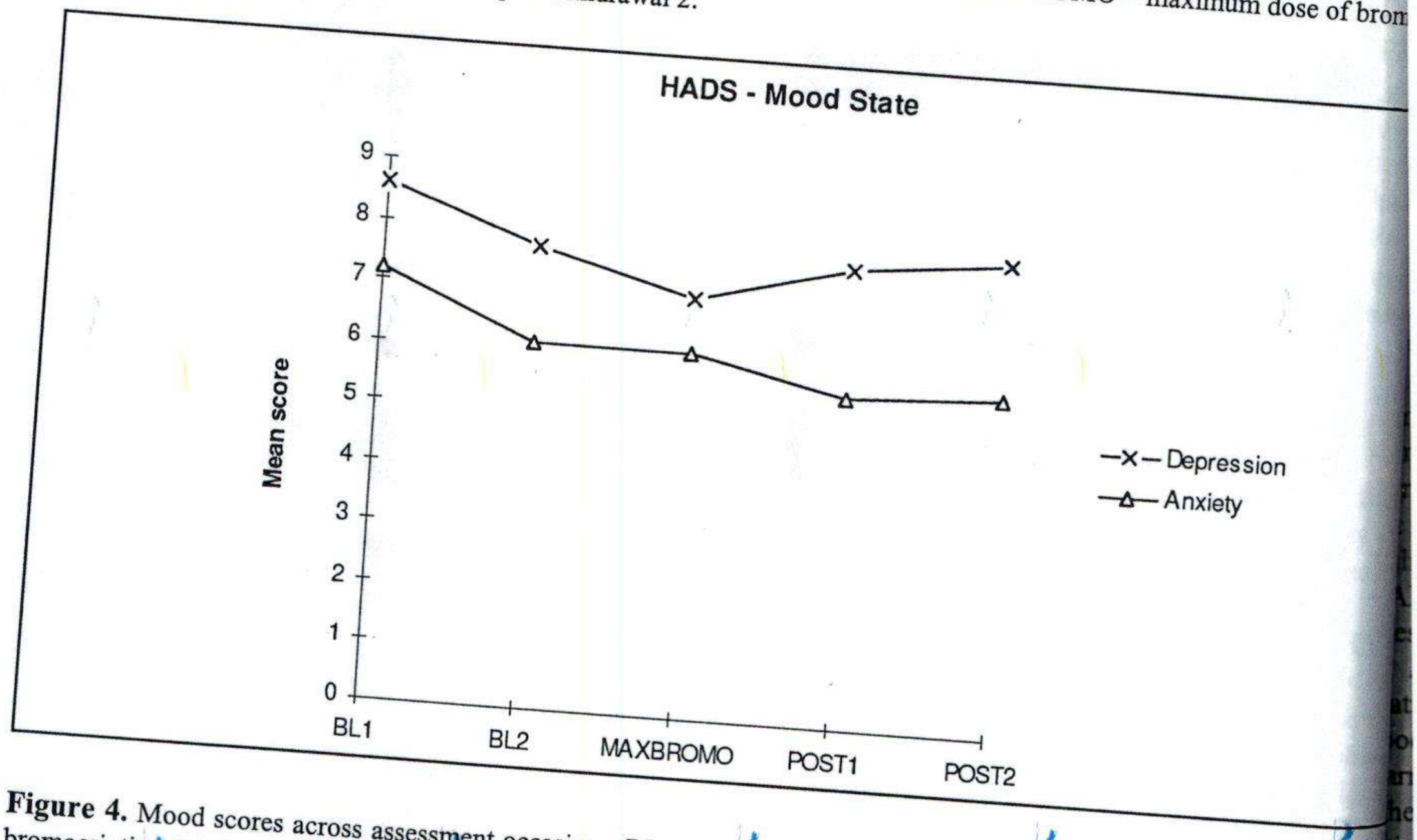

Figure 4. Mood scores across assessment occasions. BL1 = baseline 1; BL2 = baseline 2; MAXBROMO = maximum d
bromocriptine; POST1 = postwithdrawal 1; POST2 = postwithdrawal 2.

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 ($F(4, 40) = 6.75$, $P < 0.0$ BSRT ($F(4, 40) = 6.14$, $P < 0.001$) and Verbal fluen ($4, 36) = 15.93$, $P < 0.001$). *Post hoc* contrasts showed over the baseline period all cognitive scores rema stable. For all three variables, there were hi significant improvements from BL2 to MAXBRO

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 1), and non-significant recovery close to BROMO levels by POST2. All patients assessed on Span, BSRT and Verbal Fluency showed increased s at MAXBROMO compared with BL2. Five nts continued to show increased scores from BROMO to POST2 in Digit Span, BSRT and Verbal ncy.

Mood State

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

Discussion

The results of the present open trial of bromocriptine gested that treatment with the DA agonist, mocriptine, affected these abulic patients' performance various measures thought to be related to motivation: el of participation in therapy, reward responsivity in an perimental task (CARROT) and cognitive functions t require effortful processing. Improvements on these asures were found in 13 consecutive patients of both es, differing aetiology, loci of brain injury, and time psed since injury (which varied between two months d five years). These results thus corroborate and engthen the anecdotal reports of positive effects of DA onists with similar patients reported elsewhere (i.e. rrett, 1991; Al-Adawi, Powell and Greenwood, 1994). e assessment techniques developed here for assessing ulia, clinical motivation (PPI) and reward responsivity ARROT), have potential, pending replication, as ssessment tools for use in future motivational research.

Averaging across all subjects, bromocriptine eatment did not produce any significant changes in oods scores as the HADS, suggesting that the harmacological intervention affected directly on abulia, ther than via an effect on affective state; it is worth oting however that mood was not in the clinical range efore 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 moods, 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 neuroanatomical 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 treatment sessions by different therapists; although such indices may be susceptible to the "eye of faith," the striking consensus between therapists does indicate some

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 huma
with DA activating drugs resulted in
outcome. Crisostomo et al.(1988) treated
following cerebral infarction: four patie
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 dextro
paired with physical therapy increased the ra
of motor recovery. Conversely, in a retrospe
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 tha
patients who did not receive those drugs.
reached a similar conclusion (Pulaski and En
Kaelin, Cifu and Matthies, 1996; Herr
Naritoku, 1997).

Further support for this conjecture
animal research implying that experimental
can activate "auto-destructive" neurochemi
including chemical messengers that intera
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 ye
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 (Y
Kornhuber, 1997).

If bromocriptine has restored function
injured patients, can we extrapolate this conje
neuropsychiatric disorder like PD? Although t
DA pharmacotherapy in PD patients and its
efficacy is a contentious issue (for review,
1996), there are reports indicating bromocriptir
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 glutomate-calcium follow
to the brain (Ogawa et al., 1994). However, the
excitotoxic causes PD has never been demor
humans, although there are speculative st
(Iversen, 1995). It is worth noting here tha
neurodegenerative condition undermined by
mechanism, whereas if there is a neurodeg
process in brain-injury, it is likely to be underlir

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lae of trauma. In spite of this caveat, if the nption that the release of cytodestructive enzyme s in neuronal death, then it is possible that ocriptine via an unknown mechanism reduces cellular glutamate concentration below neurotoxic by enhancing uptake activity, as has been shown in als (Yamashita et al., 1995). The open question to be d is what is the most productive approach to ment, management and ameliorations of deficits in n injury. Is it early pharmacological protection and ncement, or simply the avoidance of accumulation of destructive enzymes? This obviously is a difficult stion to answer for it will require a long term study of ents, carefully documented from the beginning of their ry, and assessed for outcomes in meaningful ways.

The present findings, considered in the context of ted literature, suggest that treatment with the DA nist, bromocriptine, affected these abulic patients' formance on various measures thought to be related to l-directed behaviour: (1) level of participation in rapy; (ii) reward responsivity in an experimental task ARROT); and (iii) cognitive functions that require ortful processing. Averaging across all subjects, mocriptine treatment did not produce any significant anges in moods scores, suggesting that the armacological intervention impacted directly on abulia, her than via an effect on affective state. Improvements these measures were found in 13 consecutive patients both sexes, differing aetiology, loci of brain injury, d time elapsed since injury. An unpredicted finding in present study, and yet compatible with emerging idences on neuroplasticity, was that the improvements d not reverse following drug withdrawal in over half (all t four) of the patients.

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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, ie putting in at least the minimum amount of effort needed, even if not working as hard as s/he could be."* Y was computed as a percentage of X 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 behaviour. To explore the relative con-tributions 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 behaviour** ("*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 co-operate 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 (*c* 3 (*frequently*), to 4 (*contin* spontaneity/prompting and from 0 (*not* (*extremely*) for motivation.

These operational definitions were deve a pilot phase in which therapists kept discussed any difficulties with the researche study itself, written definitions were give therapists involved; the researcher intr therapists to the protocol before they be records. To maximize the independence of t observations, each therapist kept separate r and they did not have access to the records colleagues. Each therapist recorded this inf up to three consecutive sessions per patient. patient could be seen by up to three therap records were averaged together, thereby redu of spuriously high scores.