Neuropsychological profile linked to low dopamine: in Alzheimer’s disease, major depression, and Parkinson’s disease

Nicola Wolfe, Douglas I Katz, Martin L Albert, Abraham Almozlimo, Raymond Durso, Marcia C Smith, Ladislav Volcic

Abstract
A distinct pattern of neuropsychological deficits was associated with low homovanillic acid (HVA) in the cerebrospinal fluid of 21 patients with Alzheimer’s disease (9), Parkinson’s disease (8) and major depressive disorders (4). Regardless of clinical diagnosis, patients with low HVA were slower on a test of efficiency of processing timed information, and showed greater benefit from semantic structure on a verbal fluency task than patients with high HVA. However, low HVA subjects were not significantly impaired on confrontation naming (Boston Naming Test). Across three diagnostic groups, patients with lower HVA also tended to have more extrapyramidal motor signs and were significantly more depressed. These results demonstrate a significant relationship between specific neurobehavioural deficits and dopaminergic activity which cuts across traditional diagnostic categories.

Based on a description of the role of dopamine in dementia by Buchman and Albert, we suspected that patients with dopamine deficiency might exhibit a characteristic neurobehavioural profile that cuts across the traditional diagnostic categories of Alzheimer’s disease, Parkinson’s disease, and major depressive disorders. Low dopamine has been associated with extrapyramidal motor signs, cognitive impairment and depression within each of these disorders. We suspected that low dopamine could be a common neurochemical pathology which accounts for similarities observed across these diagnostic groups. In this pilot study, we tested the hypothesis that regardless of diagnosis, subjects with low cerebrospinal fluid (CSF) homovanillic acid (HVA) would exhibit a syndrome consisting of the following: Parkinsonian motor signs, slowed cognition (bradyphrenia), and depression.

Patients and methods
We evaluated twenty one male inpatients with diagnoses of dementia of the Alzheimer type (9) (ADRDA-NINCDS criteria), Parkinson’s disease (8) (clinical consensus by two neuropsychologists on (a) the presence of at least three of the four cardinal features: resting tremor, rigidity, bradykinesia, postural instability, and (b) absence of other known aetiologies of extrapyramidal symptoms), or major depressive disorder (4) (DSMIII). Exclusion criteria for all patients were: evidence of structural lesion on CT scan, Hachinski Ischaemia Score greater than 4, or history of seizure. Neuropsychological testing included the following range of tests: the Mini-Mental State Test (MMS), a standard index of overall cognitive ability, and the Confrontation Naming Test (Katz, unpublished data) showed it to be sensitive to efficiency of processing speeded information and to attentional deficits.

The Controlled Oral Word Association Test (FAS) of verbal fluency was used to assess benefit from semantic structure in word list generation. Benefit from structure was calculated as: number of correct responses in Semantic Categories (animals, fruits and vegetables, first names); number of correct responses in Phonemic Categories (starting with first letter F, A, and S successively) (Total correct responses). The Boston Naming Test (BNT) (30 item version) was included as an index of language function predicted to be uncorrelated with dopamine deficiency. Extrapyramidal motor signs were assessed with the Parkinson’s Disease Motor Performance Scale (PDS), based on the scale by Duvoisin; and affect was measured with the Hamilton Depression Rating Scale (HDRS).

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Lumbar puncture was performed using standard clinical procedure with the patient in the lateral recumbent position at 9 am after the patient had fasted and remained in bed from midnight of the previous day. CSF was quickly frozen at the bedside and stored at −70°C until the day of assay. HVA in the 7th was measured by high pressure liquid chromatography based on the method described by Matson et al.\(^7\) using absolute coulometric detection with high selectivity and resolution. HVA levels obtained were comparable with other studies.\(^8\)

Most patients were not taking drugs, but 14% (3/21) had received major tranquilizers (minimum washout period 10 days) and 19% (4/21) had previously received levodopa therapy (Sinemet for Parkinson's disease minimum washout period two days). The length of the washout period was not significantly correlated with CSF HVA in these patients, however, the number of these patients is too small to rule out the possibility of residual drug effects. Age and education were not significantly different across the diagnostic groups.

**Results**

The mean (SD) cerebrospinal fluid HVA levels were: 40.5 (17.1) ng/ml for Alzheimer's disease, 34.6 (16) ng/ml for Parkinson's disease, and 29.9 (17.2) ng/ml for major depression. To define the pattern of cognitive deficits associated with dopamine deficiency, we compared patients with "low HVA" (9) to those with "high HVA" (12). Raw scores were residualised to correct for baseline differences in group means.\(^9\) (Group effect = grand mean–group mean). The "low HVA" subset of patients, defined as those with HVA level below the mean of residualised scores included four with Alzheimer's disease, three with Parkinson's disease and two with major depressive disorder. The "low HVA" patients, regardless of clinical diagnosis, exhibited a distinctive pattern of performance on the neuropsychological tests selected to assess bradyphrenia, ability to benefit from structured tasks, and anoma (Fig. table).

On the efficiency of processing speeded information (VIST), patients with low HVA performed significantly worse compared with high HVA patients (t(16) = −2.31, p < 0.025) (one-tailed t-tests were used to test this directional hypothesis). On the Verbal Fluency Task, subjects with low HVA displayed significantly greater benefit from the structured condition compared with the unstructured condition (t(16) = 2.86, p < 0.01, one-tailed). Patients in the low HVA group had slightly lower overall Mini Mental State Scores (t(16) = −2.19, p < 0.025, one-tailed). However, cognitive impairment in patients with low CSF HVA was not present in all domains. For example, scores on confrontation naming (Boston Naming Test) were not significantly impaired in patients with lower HVA compared with the high HVA group. Subjects in the low HVA group also had a significantly greater number of Parkinsonian motor features (t(16) = 2.31, p < 0.025, one-tailed) and more depression (t(16) = 2.08, p < 0.05, one-tailed).

**Discussion**

In this study, patients with low CSF HVA, regardless of clinical diagnostic category, exhibited a characteristic profile of cognitive deficits, depressive symptoms, and extrapyramidal motor signs. Other investigators have described aspects of this neuropsychological profile in subgroups of patients in each clinical category.\(^10\) This analysis draws together these aspects.

Research on cognitive deficits in Parkinson's disease provides the best comparison to the neuropsychological pattern described in the current study. Bachman and Albert\(^1\) emphasised the pattern of slowed thinking, impaired

**Table**

Cognitive profiles of patients with low versus high CSF HVA

<table>
<thead>
<tr>
<th>Test</th>
<th>High HVA (n = 12)</th>
<th>Low HVA (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State (MMS)</td>
<td>23.7 (12.4)</td>
<td>18.9 (14.0)</td>
</tr>
<tr>
<td>Varied Interval Summation Task (VIST)*</td>
<td>7.8 (3.1)</td>
<td>4.6 (2.2)</td>
</tr>
<tr>
<td>Verbal Fluency (FAS)**(Benefit from Structure)</td>
<td>0.169 (19.9)</td>
<td>0.049 (25.4)</td>
</tr>
<tr>
<td>Boston Naming Test (BNT)**(item version)</td>
<td>22.4 (7.4)</td>
<td>18.6 (6.0)</td>
</tr>
<tr>
<td>Hamilton Depression Rating (HDRS)</td>
<td>3.9 (4.9)</td>
<td>14.1 (6.7)</td>
</tr>
<tr>
<td>Parkinson Disease Motor Performance Scale (PDS)</td>
<td>4.7 (3.5)</td>
<td>9.8 (5.5)</td>
</tr>
</tbody>
</table>

Values are given as mean, standard deviation (scores corrected for diagnostic group effects) and in brackets (percent of total possible score).

*VIST score is the number of correct trials (presented with successively decreasing interstimulus interval) (Maximum possible score equals 14).

**FAS score from semantic structure was computed as (number correct using semantic categories minus number correct using phonemic categories) (total correct responses). (Maximum possible score = 100).

†Student t test for significance of difference between low and high CSF HVA; †p (one-tailed) < 0.05, ††p (one-tailed) < 0.025, †††p (one-tailed) < 0.01.
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manipulation of acquired knowledge, and impaired memory, without aphasia. Studies measuring cognitive speed in Parkinson's disease and multiple sclerosis, and Huntington's disease often use the common term bradyphrenia, but methods to measure cognitive speed vary considerably. For example, cognitive speed has been measured using: speed of scanning elements in short term memory, time to prepare a manual movement, difference in time to perform two digit symbol tasks which differed in cognitive complexity, attention and vigilance using a continuous performance task, reaction time on tasks differing in cognitive complexity and the Paced Auditory Serial Addition 'Test'. In this pilot study, we used a simpler serial addition task (VIST) to disentangle motor speed and the efficiency of processing speed information. Because the motor response from the patient was not timed, the score represents an individual's success at processing auditory stimuli at increasingly rapid intervals. However, this efficiency of processing speed information cannot be equated with cognitive speed. Performance on this task is also depend-ent on motivation, auditory acuity, short term memory, distractibility, difficulty with calculation, and other factors.

Many investigators have reported decreased verbal fluency in Parkinson's disease (using the FAS test), but have not specifically examined the benefit provided by semantic categories compared with phonemic categories. In this study, we observe a need for structure from semantic categories on a verbal fluency test. Comparable observations in the literature on Parkinson's disease include the description by Lees and Smith of "mental inflexibility" and observations by Taylor et al of impairment in the ability to generate efficient strategies on spontaneously self-directed tasks.

Most reviews of dementia in Parkinson's disease agree that naming is relatively spared and not affected by levodopa treatment. Our findings that naming is relatively spared supports the hypothesis that only a specific set of cognitive functions is impaired and that we are not simply reporting a global cognitive decline.

The results of our study, as well as those from other laboratories, seem to support the earlier theory on the association between dopaminergic and cognitive impairment. Although there may be a role for mesolimbocortical dopaminergic neurons to account for this behaviour, other neurotransmitters have also been implicated, for example, in cognitive impairment in Parkinsonism. We have described a potential neurobehavioural "signature" associated with relatively low dopamine, but only the HVA level in CSF has been examined to date. It is likely that other neurotransmitter systems contribute to the neurobehavioural profile we have identified.