The effect of levodopa on cognitive function in Parkinson’s disease with and without dementia and dementia with Lewy bodies

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ABSTRACT:

Background: Levodopa (L-dopa) is the gold standard treatment of Parkinson’s disease (PD) but a lack of clear efficacy combined with a perceived liability to neuropsychiatric side effects has limited L-dopa use in patients with parkinsonism and dementia. Therefore, the effect of L-dopa on the cognitive profile of dementia with Lewy bodies (DLB) and Parkinson’s disease with dementia (PDD) is unclear.

Aim: To ascertain the acute and long-term effects of L-dopa on aspects of attention and cognition in patients with DLB and PDD and compare it to that in PD.

Method: Baseline cognitive and motor function was assessed off L-dopa in patients with PD (n=22), PDD (n=27) and DLB (n=11) using standard “bedside” measures and a computerised programme detecting reaction times and accuracy. All patients then underwent an acute L-dopa challenge with subsequent subjective and objective analysis of alertness, verbal recall, reaction times and accuracy. The same parameters were measured after three months on L-dopa to assess the prolonged effect.

Results: Acute L-dopa challenge significantly improved motor function and subjective alertness in all patients without compromising either reaction times or accuracy but increased fluctuations were noted in both groups with dementia. Neuropsychiatric scores improved in PD patients both with and without dementia on L-dopa at three months. However whilst PD patients also had better mean global cognitive function at this time, mean verbal attention and memory deteriorated and PDD patients had slower reaction times in some tests. No individual had a significant deterioration over this time. DLB patients did not experience any adverse cognitive or neuropsychiatric effects after three months of L-dopa therapy.

Conclusion: The use of L-dopa in patients with parkinsonism with dementia does not adversely affect cognitive function.

INTRODUCTION

Dementia occurs six times more frequently in PD than in age-matched controls whilst DLB is recognised as the second commonest form of degenerative dementia in an ageing population. Early cognitive deficits are found in many patients with PD and are typically disorders of verbal memory, dysexecutive syndromes and visuospatial impairment. Dementia in PD characteristically features prominent fluctuating attention and an overall clinical cognitive and neuropsychiatric profile similar to that seen in DLB. Visual hallucinations are common to both conditions and may reflect drug usage. PDD and DLB are currently differentiated by the temporal evolution of motor and cognitive impairment with an arbitrary cut off of 12 months used to differentiate the two dementias. Distinguishing therapeutic features include neuroleptic sensitivity in DLB whilst early diminished verbal fluency and L-dopa induced confusion may be predictive of incident dementia in PD. L-dopa improves extrapyramidal signs in PD, PDD and to a variable extent in DLB but may have both beneficial and deleterious effects on cognitive performance and attention in PD. The influence of this drug on cognition in PDD and DLB has not, to our knowledge, been previously compared but notably, the apparent adverse influence of L-dopa on cognitive and behavioural features has lead to drug withdrawal in DLB. Therefore, the treatment of...
parkinsonism in dementia may be sub-optimal due to concerns of worsening cognitive and 
behavioural function. 
Many neurobehavioural features of both DLB and PDD reflect underlying cholinergic 
dysfunction and are responsive to therapy with cholinesterase inhibitors (ChEI). Attention, 
apathy, excessive somnolence and hallucinations are most likely to benefit in DLB 10 whilst in 
PDD, both cognitive and neuropsychiatric function may also improve with this treatment. 11 
Dopaminergic therapy can potentially exacerbate psychosis and pharmacokinetic studies have 
reported an increased risk of adverse events with the concomitant use of L-dopa and ChEIs in 
PD patients. 12 
We aimed to clarify the acute and prolonged effects of L-dopa on the cognitive, attentional 
and neurobehavioural profiles in patients with PD and in PDD and DLB patients on ChEI 
therapy.

PATIENTS AND METHODS
All patients were recruited from hospital and community populations under the care of 
neurologists, psychiatrists and geriatricians. The Newcastle and North Tynesside ethics 
committee approved the study and all participants either gave informed consent to be included 
or assent was obtained from the main carer in the case of patients with significant dementia. 
Diagnosis was made by agreement between experienced clinicians using the consensus 
criteria for DLB 6 and the UK Parkinson’s Disease Society Brain Bank criteria for PD. 13 
Patients with PDD conformed to the criteria for PD but also fulfilled DSM IV criteria for 
dementia 14 and clinical diagnostic criteria for probable DLB, namely fluctuating cognition 
and visual hallucinations, developing more than 12 months after the onset of motor 
symptoms. 6 In total 31 patients with PD, 33 with PDD and 27 with DLB were screened for 
this study. Of these, 22 patients with PD, 27 with PDD and 11 with DLB completed the acute 
L-dopa challenge and three month follow-up period. Patients did not participate in this study 
due to lack of regular Ldopa therapy (DLB, n=2), side effects of L-dopa (DLB, n=4; 2 
gastrointestinal, 2 neuropsychiatric), inability to complete the assessment programme due to 
cognitive frailties (DLB, n= 7), co-morbidities and/or mortality (DLB, n= 3). Only L-dopa 
(co-careldopa/co-beneldopa) therapy was permitted to manage parkinsonism and 100% of 
PDD patients were on regular treatment for at least three years compared to 91% of DLB and 
36% of PD patients who were L-dopa naive at study entry. Most patients with dementia had 
received a trial of ChEI treatment at one stage and during this study 91% of DLB and 85% 
PDD patients were on a stable dose of one of these agents (Donepezil or Rivastigmine). 
Patients with L-dopa induced dyskinesias were included (n=10, 9 with PDD, 1 with PD) and 
all patients were encouraged to use their preferred hand for tasks. 
Concomitant depression was diagnosed in two patients with PDD, using DSM IV criteria.14 
Whilst premorbid level of education was not recorded a mini mental state examination 
(MMSE) at study entry provided a global measure of cognition. 15 Information regarding 
neuropsychiatric and neurobehavioural clinical features was obtained using the 
Neuropsychiatric Inventory (NPI), 16 which was completed by the same carer at each visit. 
Subjective change in alertness was calculated using a derivative of the Bond & Lader Visual 
Analogue Scale (VAS; range 0 to 100, with higher scores implying greater alertness). 17 
Verbal working memory and attention were tested using a Reverse Digit Span (RDS) 
sequence assessment (derived from the Weschler Adult Intelligence Scale). 18 
Cognitive function was further assessed using tests from the CDR computerised assessment
system that has previously proved sensitive to deficits in patients with parkinsonism and dementia. The battery included examination of simple (SRT) and choice (CRT) reaction times, CRT response accuracy (CRT ACC), digit vigilance reaction time (DVIG RT), numeric working memory reaction time (NWM RT) and episodic memory, using delayed picture recognition reaction time (DPIC RT). Fluctuating cognition was assessed using CRT standard deviation (CRTSD), representing within-trial variability as previously described. 

This information was supported by measuring the coefficient of variation in choice reaction time (CVARCRT), calculated by dividing CRTSD by CRT, controlling for differences in mean performance in that task. Cognitive RT (COGRT) was calculated by subtracting SRT from CRT and provided a measure of cognitive processing time.

In PD, there are two recognised therapeutic motor responses to L-dopa. The short duration response is primarily seen in drug naïve patients but also in advanced disease, on long-term therapy after each dose. The main recommendation in assessing the short duration response in treated patients is that a positive response should be defined in advance. For this study, the goal was set in motor terms whereby an improvement of greater than 20% in UPDRS III indicated a positive therapeutic response. Patients on L-dopa at study entry underwent a baseline cognitive assessment in the morning, after an overnight fast and prior to their first daily dose of L-dopa, in a practically defined “off” state. This method has been used in previous motor studies but has limitations particularly due to an inability to fully exclude the effects of the long duration response to L-dopa, which can last days to months after discontinuation of treatment. Patients then received dispersible co-beneldopa in a dose equivalent to their regular morning L-dopa dose. Motor and cognitive changes were monitored over two hours before they recommenced their regular daily Ldopa therapy. Patients who were not already on L-dopa at study entry had an identical baseline assessment before commencing regular L-dopa at a dose of co-careldopa 12.5/50 three times daily which was gradually titrated to the maximum tolerated according to dose response and/or systemic side effects encountered over three months. No patient had dose escalation limited due to neuropsychiatric side effects. A fasting assessment with acute L-dopa challenge was performed after three months regular therapy. Therefore no patient underwent a de novo acute L-dopa challenge.

The assessment schedule included baseline MMSE, NPI, RDS, VAS and CDR testing and concluded with assessment of motor function, using the UPDRS III in all patients whilst off L-dopa. An acute L-dopa challenge involved repeated SRT, CRT, RDS, VAS and UPDRS III measures at 60, 90 and 120 minutes post therapy. The effects of treatment were calculated by comparing baseline measures off L-dopa to sequential measures post therapy over two hours. Long-term influence was determined using a full assessment to detect change in MMSE, NPI, RDS, VAS and CDR at three months whilst on L-dopa compared to the off treatment measures.

**Statistical Analysis**

SPSS for Windows (version 11) was used for data analysis. Distributions of baseline data were examined using histograms and Kolmogorov-Smirnov testing. For continuous normally distributed baseline variables, differences across groups were assessed using analysis of variance (ANOVA) with post-hoc Games-Howell tests to determine pair-wise group differences. For non-parametric baseline data, Kruskal-Wallis testing measured differences across groups. Chi squared analysis determined differences in frequency data. In order to
determine any differences in performance between diagnostic groups and any within subject temporal effect of acute treatment response over the two-hour acute test period, sequential acute responses were compared to baseline using a mixed between-within subjects ANOVA (an extension of a repeated measures design). Log transformation of SRT, CRT, COGRT and CRTSD scores was performed prior to analysis because these results were positively skewed whereas CRTACC scores were negatively skewed and were thus subtracted from 101 (i.e. a max score of 100% plus 1) prior to being log transformed. Baseline and three month test scores were compared using paired t-tests or Wilcoxon-Signed Ranks tests as appropriate within each group.

RESULTS
PDD patients were younger (Games-Howell: \( p=0.007 \)) but had a longer disease duration (Mann-Whitney: \( z=-3.281, \ p=0.001 \)) and more severe parkinsonism (Games-Howell: \( p=0.016 \)) than those with PD (Table 1). As expected, all baseline cognitive measures were better in patients with PD than either group with dementia. PD patients also reported feeling more alert than PDD (Games-Howell: \( p<0.0005 \)) but not DLB patients (Games-Howell: \( p=0.386 \)).

Acute L-dopa challenge:
The mean dose of L-dopa administered acutely was higher in PDD patients (137(±55) mg) than either PD (105(±21) mg; \( p=0.007 \)) or DLB (95(±35) mg; \( p=0.041 \)). The mean acute improvement in UPDRS III scores post L-dopa was 22% for both PD and PDD patients whereas for DLB, this was just 14.8%. Following acute L-dopa there was no significant within subject effect of treatment on SRT, CRT, CRTSD, CRTACC or RDS scores over two hours (Table 2). PD patients consistently performed better than either group with dementia in SRT, CRT, CRTSD, and RDS (\( p \leq 0.001 \)) whereas PDD and DLB patients were indistinguishable by these measures. Similarly, whilst there was no change in COGRT in any group post L-dopa, PD patients required less cognitive processing time than PDD (\( p<0.0005 \)). No COGRT differences were detected between either PD and DLB or PDD and DLB (\( p=0.194 \) and 1.0 respectively). By contrast, L-dopa appeared to acutely influence CVARCRT, VAS and UPDRS III scores (\( p=0.009, 0.005 \) and \( <0.0005 \) respectively), representing increased CRT fluctuation, (despite controlling for mean score), increased subjective alertness and improved motor function after treatment. PD patients scored better than PDD in CVARCRT, VAS and UPDRS III (\( p<0.0005, p=0.002, p=0.035 \) respectively) and better than DLB in CVARCRT (\( p=0.001 \)). Again, PDD and DLB patients could not be differentiated by effect of L-dopa on these measures (CVARCRT; \( p=1.0 \) VAS; \( p=0.158, \) UPDRS III; \( p=0.651 \)). An interactive effect between time point and diagnosis was apparent for CRT and CRTSD (\( p=0.006 \) and 0.033 respectively) that could suggest a higher likelihood of fluctuating attention in patients with dementia.

Chronic L-dopa use:
Cognitive parameters off L-dopa were compared to measures on regular L-dopa at three months to determine the effect of prolonged use (Table 1). The mean daily dose of L-dopa was larger in PDD patients (672 ± 451mg) than in PD (407 ± 197mg, \( p=0.02 \)) or DLB patients (286 ± 105 mg, \( p=0.001 \)). No difference between baseline and three month MMSE scores was apparent for either group with dementia but the mean MMSE increased in PD patients by 1.3 points (\( t=-2.339, p=0.029 \)). RDS scores deteriorated in PD (\( t=2.183, p=0.040 \)) and DVIG
RT scores worsened in PDD patients (t=-2.145, p=0.041) over this time. NPI scores improved in patients with PD either with (z=-2.039, p=0.041) or without (z=-2.096, p=0.036) dementia but PDD patients showed deterioration in SRT (z=-2.138, p=0.032). Accuracy of CRT response did not change over three months in any group. DLB patients manifested no significant change in any measure over this time period. A sensitivity analysis identified whether any individual showed cognitive deterioration after three months of L-dopa compared to baseline (data not shown). A decline of greater than two standard deviations below the mean was considered significant and revealed that no individual, in any patient group, declined consistently across more than one cognitive test.

**DISCUSSION**

This study showed that L-dopa does not compromise the cognitive or behavioural profiles of patients with parkinsonism and dementia either acutely or over three months. Following acute L-dopa challenge most cognitive measures did not change significantly. Subjective alertness and UPDRS III scores improved to a greater degree in PD patients than in PDD. Over the course of two hours post L-dopa a significant change in level of fluctuating attention was detected but this was not in any particular direction and most likely reflects fluctuation in CRT performance despite controlling for the mean performance levels in this task. This is a recognised feature of both PDD and DLB and this study has replicated previous work by suggesting that both conditions are indistinguishable in CRT, CRT SD or COG RT, but are significantly different to PD. An interaction between time point and diagnosis for measures of within trial variability (CRT and CRT SD) could simply represent increased fluctuation in attention in patients with dementia compared to PD. The alternative explanation, that L-dopa caused increased fluctuation in patients with dementia is, however, impossible to exclude. As with the acute data, most cognitive measures did not change significantly with L-dopa use over three months although mean simple and digit vigilance reaction times worsened in PDD patients whilst mean reverse digit span scores deteriorated in the PD group (despite an apparent improvement in mean MMSE). However, with sensitivity analysis demonstrating no significant individual patient deterioration in this time, these results are of uncertain significance. Overall neuropsychiatric function improved in both PD and PDD and showed no change in DLB patients as demonstrated by NPI scores. It is, however, conceivable that an improvement in some scores was masked by concomitant deterioration in others on this measure.

Striatal dopaminergic function reduces by 6-10% per decade from early to late adulthood. Cognitive decline in PD may be influenced by the degree of motor impairment and hence the response to L-dopa whilst motor response may decrease with the development of dementia in PD. We did not find any difference in motor response to acute L-dopa challenge between PD and PDD groups although the latter were younger and received a higher mean dose of L-dopa. Alternatively, dementia may impair UPDRS III performance and the ability to perform manually based cognitive tasks and severe cognitive impairment may have an alternative dopamine response. Previous studies have suggested a link between bradyphrenia in PD and simultaneous cognitive task performance, as demonstrated by slower choice reaction time tasks. The level of cognitive slowing may correspond to the level of independently assessed motor slowing, raising the possibility that cognitive impairment may reflect dysfunction in the striatum or premotor cortex.

The most profound short and long-term cognitive deficit in animals with MPTP-induced
parkinsonism is impaired spatial working memory, representing damage in the fronto-striatal system. L-dopa administration to MPTP treated monkeys can significantly ameliorate these impairments. Similarly, dopamine withdrawal in patients with PD can highlight selective frontal lobe dysfunction, particularly spatial working memory, executive function and thinking time and accuracy. L-dopa replacement in PD improves aspects of working memory, particularly visuospatial and object tasks, but by contrast, apomorphine can worsen reaction times without affecting accuracy. These results may represent preferential dopaminergic receptor activation and are supported by animal studies where D1 dopamine receptor agonist infusion enhances attention in rats with similar results reported from L-dopa and D2 receptor antagonists in humans. In the current study, neither visuospatial tasks (represented by picture recognition) nor numeric working memory changed after three months L-dopa treatment.

Executive function includes the inhibition of inappropriate responses to external stimuli. Elevated dopamine levels have been linked to an increased frequency of premature response and thus decreased accuracy of response by diminishing the ability to suppress the wrong response, reflecting impulsivity. Other studies have, however, failed to detect either change in reaction time responses or working memory subsequent to dopamine administration. Furthermore, choice reaction times have been reported by others to deteriorate in PD patients after acute L-dopa challenge, potentially due to a sedative effect of treatment. Therefore the acute effect of L-dopa administration on reaction time and accuracy in dopamine depleted conditions remains unclear. We found no adverse acute effect of L-dopa on any aspect of cognitive function in our PD cohort, including reaction times and accuracy. However, the mean acutely administered dose of L-dopa was less than that recommended in acute motor challenges possibly accounting for the lack of change in reaction times and also the maintenance of CRT accuracy.

Apparently conflicting data concerning the role of dopamine on cognition may be reconciled through animal studies which demonstrate that insufficient as well as excessive dopaminergic stimulation in the prefrontal cortex impairs working memory. Baseline cognitive performance can influence the impact of dopaminergic drugs, hence in PD patients, treatment with L-dopa can have both beneficial and deleterious effects on cognitive function dependent on the task assessed and the underlying basal cortico-striatal dopaminergic function. Whilst no adverse acute effect of L-dopa on cognition was found in the present study the results were limited by sub-maximal acute L-dopa dosing and future studies may replicate this “inverted U” dose related cognitive response curve for patients with parkinsonism and dementia. Although objective measures remained unchanged in our study, subjectively DLB and PDD patients felt more alert, despite increased fluctuating cognition. Reduced SRT or CRT did not accompany this acute improvement in subjective alertness in any group. The beneficial effect of L-dopa on sense of alertness could reflect concomitant motor benefit but against this is the fact that these values did not temporally correlate. A dissociable motor and cognitive effect on withdrawal of dopaminergic medication has previously been suggested with support from functional imaging data which has demonstrated that dopamine modulates cognitive and motor function by separate pathways, with direct dopaminergic input to the prefrontal cortex facilitating working memory via the mesocortical circuits.

Our study has several methodological flaws, including an open-label design, small sample size, use of modest L-dopa dosing in acute challenges, particularly to patients with DLB, and the recognised inadequacies of an overnight fast in excluding the long duration response to L-
dopa. Furthermore, the majority of demented patients were receiving ChEIs and the study was therefore unable to address the effect of L-dopa on cognition in parkinsonism with dementia in ChEI naïve subjects or the potential interactions between ChEIs and L-dopa. We conclude that L-dopa does not have any clinically significant adverse cognitive or behavioural effects in PDD patients. Furthermore the cautious use of L-dopa in DLB is not contraindicated when increasing severity of motor impairment warrants treatment.

REFERENCES

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1992; 55: 1168-76
Table 1: Demographics and baseline and three month cognitive data (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>PDD</th>
<th>DLB</th>
<th>Comparison of baseline characteristics across groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>78.1 (6.4)</td>
<td>72.6 (5.2)</td>
<td>76.4 (6.8)</td>
<td>F (2,57)=5.282, p=0.008*</td>
</tr>
<tr>
<td>Gender M: F</td>
<td>17.5</td>
<td>19.8</td>
<td>7.4</td>
<td>X²=0.712, p=0.700**</td>
</tr>
<tr>
<td>Disease Duration (years)</td>
<td>5.0 (5.1)</td>
<td>9.4 (6.0)</td>
<td>2.8 (1.7)</td>
<td>X²=19.339, p&lt;0.0005**</td>
</tr>
<tr>
<td>Number taking Levodopa at baseline</td>
<td>14</td>
<td>27</td>
<td>1</td>
<td>X²=31.429, p&lt;0.0005**</td>
</tr>
<tr>
<td>Number taking ChEs at baseline</td>
<td>0</td>
<td>23</td>
<td>10</td>
<td>X²=42.600, p&lt;0.0005**</td>
</tr>
<tr>
<td>UPDRS III at baseline</td>
<td>32.6 (9.5)</td>
<td>42.0 (13.2)</td>
<td>34.3 (12.7)</td>
<td>F (2,57)=4.185, p=0.020*</td>
</tr>
<tr>
<td>SRT Baseline</td>
<td>40 (64)</td>
<td>696 (664)</td>
<td>575 (249)</td>
<td>X²=11.709, p=0.003**</td>
</tr>
<tr>
<td>SRT 3 Months</td>
<td>411 (134)</td>
<td>855 (671)</td>
<td>540 (144)</td>
<td>X²=21.890, p&lt;0.0005**</td>
</tr>
<tr>
<td>CRT Baseline</td>
<td>582 (106)</td>
<td>1209 (606)</td>
<td>1055 (600)</td>
<td>X²=13.306, p=0.001**</td>
</tr>
<tr>
<td>CRT 3 Months</td>
<td>579 (128)</td>
<td>1245 (639)</td>
<td>1286 (1009)</td>
<td>X²=15.203, p&lt;0.0005**</td>
</tr>
<tr>
<td>CRT ACC Baseline</td>
<td>96.1 (6.5)</td>
<td>85.8 (14.5)</td>
<td>85.1 (13.2)</td>
<td>X²=12.757, p&lt;0.0005**</td>
</tr>
<tr>
<td>CRT ACC 3 Months</td>
<td>96.1 (4.3)</td>
<td>88.1 (13.2)</td>
<td>81.5 (18.8)</td>
<td>X²=14.579, p&lt;0.0005*</td>
</tr>
<tr>
<td>NWM RT Baseline</td>
<td>1266 (1091)</td>
<td>396 (2009)</td>
<td>4255 (2472)</td>
<td>X²=11.102, p&lt;0.0005*</td>
</tr>
<tr>
<td>NWM RT 3 Months</td>
<td>932 (258)</td>
<td>329 (2437)</td>
<td>4313 (2581)</td>
<td>X²=10.429, p&lt;0.0005*</td>
</tr>
<tr>
<td>DWG RT Baseline</td>
<td>51 (675)</td>
<td>610 (140)</td>
<td>687 (124)</td>
<td>X²=9.025, p=0.001**</td>
</tr>
<tr>
<td>DWG RT 3 Months</td>
<td>526 (62)</td>
<td>751 (206)</td>
<td>647 (91)</td>
<td>X²=9.025, p=0.001**</td>
</tr>
<tr>
<td>DPC RT Baseline</td>
<td>1384 (1022)</td>
<td>2723 (2371)</td>
<td>3560 (3407)</td>
<td>X²=13.641, p&lt;0.0005*</td>
</tr>
<tr>
<td>DPC RT 3 Months</td>
<td>1123 (306)</td>
<td>2658 (1995)</td>
<td>4279 (3584)</td>
<td>X²=10.429, p&lt;0.0005*</td>
</tr>
<tr>
<td>RDS Baseline</td>
<td>6.2 (2.0)</td>
<td>3.9 (1.5)</td>
<td>3.4 (2.3)</td>
<td>X²=11.102, p&lt;0.0005*</td>
</tr>
<tr>
<td>RDS 3 Months</td>
<td>5.4 (1.5)</td>
<td>3.7 (2.1)</td>
<td>3.4 (1.4)</td>
<td>X²=10.429, p&lt;0.0005*</td>
</tr>
<tr>
<td>VAS Baseline</td>
<td>66.6 (12.6)</td>
<td>46.9 (16.0)</td>
<td>58.6 (17.4)</td>
<td>X²=13.641, p&lt;0.0005*</td>
</tr>
<tr>
<td>VAS 3 Months</td>
<td>68.2 (16.5)</td>
<td>48.2 (16.4)</td>
<td>59.8 (14.1)</td>
<td>X²=13.641, p&lt;0.0005*</td>
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<tr>
<td>MMSE Baseline</td>
<td>25.6 (2.2)</td>
<td>20.7 (4.8)</td>
<td>19.5 (3.6)</td>
<td>X²=9.025, p=0.001**</td>
</tr>
<tr>
<td>MMSE 3 Months</td>
<td>26.9 (2.5)</td>
<td>19.7 (5.2)</td>
<td>18.6 (4.6)</td>
<td>X²=9.025, p=0.001**</td>
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<tr>
<td>NPI Baseline</td>
<td>5.6 (11.0)</td>
<td>14.9 (15.1)</td>
<td>11.9 (12.1)</td>
<td>X²=9.025, p=0.001**</td>
</tr>
<tr>
<td>NPI 3 Months</td>
<td>2.5 (5.4)</td>
<td>9.6 (15.4)</td>
<td>8.4 (9.6)</td>
<td>X²=9.025, p=0.001**</td>
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</tbody>
</table>

*ANOVA results. **Kruskal-Wallis results. ***Chi-Squared results. ChEI = cholinesterase Inhibitors. SRT, CRT, NWMRT, DVIGRT, DPICRT measured in milliseconds. CRTACC expressed as a percentage.
Table 2: Acute L-dopa challenge data at each time point (mean ±SD).

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Group</th>
<th>0mins</th>
<th>60 mins</th>
<th>90mins</th>
<th>120mins</th>
<th>Within subjects effects</th>
<th>Between subjects effects</th>
<th>Interaction effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>PDD</td>
<td>701(562)</td>
<td>807(812)</td>
<td>661(390)</td>
<td>580(283)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DLB</td>
<td>946(780)</td>
<td>1109(1126)</td>
<td>905(453)</td>
<td>835(366)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>401(94)</td>
<td>387(76)</td>
<td>390(84)</td>
<td>409(84)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>PDD</td>
<td>1223(902)</td>
<td>1548(1535)</td>
<td>1367(1377)</td>
<td>1230(1260)</td>
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*Within subjects effects examine the effect of treatment with time (expressed as Wilks Lambda (WL), F (df, df error), p, Eta-Squared (ES)).

**Between subjects effects examine the differences between diagnostic groups (expressed as F (df, df error), p, Eta-Squared (ES)).

*** Interaction effects examine the combination of diagnosis with time (expressed as Wilks Lambda (WL), F (df, df error), p, Eta-Squared (ES)).

SRT, CRT, CRTSD, COGRT, measured in milliseconds. CRTACC expressed as a percentage.
The effect of levodopa on cognitive function in Parkinson’s disease with and without dementia and dementia with Lewy bodies
S Molloy, E N Rowan, J T O’Brien, I G McKeith, K Wesnes and D J Burn

J Neurol Neurosurg Psychiatry published online September 4, 2006

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