Articles

Quantifying fluctuation in dementia with Lewy bodies, Alzheimer’s disease, and vascular dementia

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Background: Case reports and clinical observations suggest that fluctuating cognition (FC) is common in the major dementias, particularly dementia with Lewy bodies (DLB), where it is one of three core clinical diagnostic features.

Objectives: To examine the frequency, characteristics, and diagnostic utility of FC in dementia using clinical, attentional, and EEG markers. Method:— A total of 155 subjects (61 with AD, 37 with DLB, 22 with vascular dementia [VaD], 35 elderly controls) received clinical evaluation for FC using a semiquantified measure applied by experienced clinicians and 90-second cognitive choice reaction time (CRT) and vigilance reaction time (VIGRT) trials. Forty subjects also received an evaluation of mean EEG frequency across 90 seconds.

Results: Patients with DLB had a greater prevalence and severity of FC than did patients with AD or VaD rated using clinical, attentional, and EEG measures. The
90-second cognitive and EEG trials demonstrated that FC occurs on a second-to-second basis in patients with DLB. Patients with VaD had a higher prevalence of FC than did those with AD, although the profile of FC was different from that expressed by DLB cases. Optimal cutoff values on the clinical scale achieved good discrimination between the dementia groups (sensitivity 81%, specificity 92%, DLB versus AD; sensitivity 81%, specificity 82%, DLB versus VaD; sensitivity 64%, specificity 77%, VaD versus AD).

**Conclusion:** Standardized assessment methods demonstrate that FC is significantly more common and severe in DLB than in other major dementias. The periodicity of FC is different in DLB and VaD cases, with important implications for the underlying causal mechanisms and for differential diagnosis.

**Key words:** Fluctuating cognition; Variability; Attention; EEG; Dementia with Lewy bodies; AD; Vascular dementia.

**Introduction**

Dementia is a disabling and distressing disorder that affects 5% of the population older than 65 and 20% of those over 80. Dementia imposes significant emotional and financial costs, especially as the elderly population grows. The most common form of degenerative dementia is AD, which constitutes approximately 70% of cases, followed by dementia with Lewy bodies (DLB), accounting for 10 to 15%. Vascular dementia (VaD) comprises a further 10 to 15% of cases.

Fluctuating cognition (FC) is a common and problematic symptom in patients with dementia, particularly those with DLB, in whom it has a frequency of 80 to 90%. FC also occurs in 35 to 50% of people with VaD and 20% of AD cases. Byrne et al. described fluctuations in the level of arousal and cognitive performance in 12 patients with DLB. One patient had day-to-day changes of more than 50% on the Mini-Mental State Examination; another patient experienced confusional episodes that were so catastrophic that she varied from being mute, confused, and unable to stand without assistance to being capable of carrying on a conversation. In another investigation of DLB cases examined by Gibb et al., one patient was observed to have episodes of stupor with closed eyes and was difficult to rouse, but on other occasions the patient appeared alert and responsive to commands.

FC represents one of the three core elements in the operationalized clinical criteria of DLB, two of which must be present for a diagnosis of probable DLB. Moreover, a positive rating on the “fluctuating course” item of the Hachinski index accounts for more than a quarter of the points required to indicate a diagnosis of VaD. Fluctuating confusion therefore not only represents a common symptom in patients with dementia, but is also an important element in differential diagnosis. The issue of accurate and early diagnosis is becoming increasingly important owing to established treatments for
AD and VaD, and complex management issues related to neuroleptic and antiparkinsonian treatment in DLB.

Assessment methods for FC in dementia have relied largely on expert judgement, often with poor inter-rater reliability. Mega et al. reported that agreement between raters was as low as 58% (Kappa = 0.25) for FC, whereas a subsequent study demonstrated even lower levels of agreement (Kappa = 0.06). There is clearly a need for assessment methods that are more detailed and have better standardization. A semiquantified clinical instrument has been used successfully as part of an operationalized procedure for clinical diagnosis. This instrument has achieved good sensitivity and specificity against neuropathologic diagnosis, although the judgment of an experienced clinician is still required.

Neuropsychological and electrophysiologic markers of FC would have the advantage of better objectivity and improved reliability. Several studies focusing on neuropsychological performance have identified pronounced deficits of attention ability in DLB—impairments that are significantly greater in magnitude than those seen in AD. This psychometric profile is also described in the international consensus clinical criteria for the operationalized diagnosis of DLB as part of the typical neuropsychological pattern. Current hypotheses suggest that the severity of attentional impairments may fluctuate in parallel with the fluctuations in cognition, related to a common underlying cholinergic deficit. These models are consistent with the suppositions of the DLB consensus criteria. If correct, a standardized evaluation of fluctuations in attention may be an important component of more objective FC assessments.

FC is commonly associated with episodes of disturbed consciousness. As a measure of cortical arousal, EEG has been used to define and stage levels of human awareness (e.g., delirium, coma, and sleep). It is therefore possible that patients experiencing FC will express equivalent levels of variability in the frequency of cortical EEG rhythms. This is supported by numerous case reports of slow wave flurry activity in patients with DLB, a large proportion of whom were clinically described as experiencing FC or disturbed consciousness.

Episodic reductions in electrocortical arousal and fluctuations in attentional performance have not been quantified in people with dementia, and their relationship with clinically identified FC in dementia has not been empirically studied. The current study aims to provide a detailed characterization of FC using existing clinical scales and measures of variability in attentional performance and EEG activity in patients with dementia. We hypothesized that clinical measures of FC, cognitive–attentional performance, and mean cortical EEG frequencies would fluctuate in DLB patients to a greater extent than in subjects with other dementias. In addition, we hypothesized that these fluctuations in EEG frequency and attentional performance would correlate with the severity of clinically measured FC, and that these measures would aid in the differential diagnosis among DLB, AD, and VaD.
Methods.

Subjects.
The study cohort was recruited from a case register cohort of 329 consecutive referrals with dementia to old age psychiatry services in Tyneside, UK, with spouses of patients recruited as healthy elderly volunteers. All patients with a Mini-Mental State Examination (MMSE) score greater than six and who were able to use the computerized cognitive testing system were asked to participate. A total of 155 people were enrolled in the study (37 with DLB, 61 with AD, 22 with VaD, and 35 healthy elderly volunteers). Subjects were matched for age and sex, with dementia patients also matched for cognitive impairment using the MMSE.

All patients were assessed with a structured psychiatric history (history and etiology schedule), a standardized physical examination that incorporated the Unified Parkinson’s Disease Rating Scale (UPDRS), and a validated instrument to evaluate psychotic symptoms (Columbia University Scale of Psychopathology in Alzheimer’s Disease [CUSPAD]).

Clinical assessment of FC.
The semiquantified clinical measure of FC uses a series of screening questions regarding FC and impaired consciousness during the month before the interview, providing a severity rating of FC (Appendix; FI scale 1). These features are assessed by a specialist clinician, independent of other cognitive and electrophysiologic measures, using a semistructured informant assessment. These assessments were completed before attribution of the operationalized clinical diagnosis. For FC to be rated as present, the informant is required to give a clear-cut example. In the current study, extensive discussions took place among the three clinician raters (I.G.M., C.G.B., J.O.), focusing on illustrations from previously assessed cases, to achieve consistency in the way that these criteria were applied. If present, the frequency and duration of FC episodes were rated on a 0 to 4 scale and multiplied to produce a severity score of 0 to 12 (0 representing no FC, 12 representing severe FC; a score of 16 would signify a continuous clouded state that by definition would denote no fluctuation).

Operationalized clinical diagnoses.
Patients with DLB were clinically diagnosed according to the internationally accepted consensus criteria by three experienced old age psychiatrists (I.M., J.O., C.B.G.) after the baseline assessment had been completed. This approach has achieved a sensitivity of 0.83 and a specificity of 0.91 against neuropathologic diagnosis in our cohort in Newcastle for the first 50 patients from the overall case register series coming to postmortem. Patients with AD were diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA), whereas an operationalized clinical diagnosis of VaD was made using the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria. Neuropathologic confirmation of clinical
diagnosis has not yet been obtained for these patients.

**Experimental assessments of FC.**
All 155 subjects received a psychometric assessment of FC including computerized evaluation of attentional reaction time performance. An independent administrator, blind to dementia diagnosis and clinical FC severity rating, performed all evaluations. Forty participants (15 DLB, 15 AD, 10 elderly control) also received an electrophysiologic examination of FC involving mean EEG frequency analysis. The first 40 participants evaluated in the study were recruited for this purpose in an attempt to prevent selection bias. EEG analysis was also performed by an independent experimenter, blind to both dementia diagnosis and individual clinical FC severity rating.

**Neuropsychological evaluation of FC.**
All subjects were assessed using the Cognitive Drug Research Assessment System, dementia version (COGDRAS-D) neuropsychological test battery, a validated, well-tolerated computerized assessment. These tests were administered using a portable laptop computer placed at a standard distance in front of the subjects. Participant responses were recorded using an attached response pad containing two nonlatching buttons, one marked “no” and the other marked “yes,” connected to the serial port of the computer. All participants received training on the use of the response module. If participants were unable to place their fingers (or thumbs) on the buttons owing to physical disability, testing was discontinued and participants excluded. This action was taken to limit the potential for mobility difficulties influencing reaction time data. Participants were trained in the use of the response module by completing the choice reaction time (CRT) task (see below). All data from this practice CRT were disregarded. Appropriate use of the response buttons was monitored by the experimenter throughout the assessment session. If after initial training the participant was not able to use the response box correctly, the practice CRT task was repeated. If participants failed the second practice owing to poor test comprehension, poor visual acuity, or unwillingness, they were omitted from the study. Attentional reaction time from a version of the COGDRAS-D test battery specially designed for use in an elderly or demented population were employed.

**Choice reaction time.**
Each time “yes” or “no” was presented in the center of the screen, the participant was required to press the corresponding “yes” or “no” button as quickly as possible.

**Digit vigilance (VIG).**
A digit was displayed constantly on the right hand side of the screen and 90 digits were serially presented (80 min⁻¹) in the middle of the screen. Participants were required to press “yes” every time that digit matched the digit constantly displayed on the right side of the screen.

Within trial variability (standard deviation [SD]) in the attentive measures of CRT and
VIG reaction time (VIGRT) were assessed in single trials, all lasting approximately 90 seconds. Thus, cognitive–attentional functioning could be profiled across a 90-second period. The coefficient of variation (CV) was also applied to investigate the potential effect of mean reaction time length.

Electrophysiologic evaluations of FC.
Fluctuations in electrocortical activity were also assessed in the first 40 subjects (15 DLB, 15 AD, 10 elderly control) across 90 seconds using EEG. Seventeen primary channel electrodes, placed according to the international 10-20 system, recorded EEG from Fp1, Fp2, Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, T3, T4, T5, T6, O1, and O2 linked to mastoid electrodes. Eye movement compensation was derived from nasion-linked mastoid electrodes. Signals were amplified using a SynAmps and Neuroscan (Neuroscan Inc.; Sterling, VA) acquisition system. The mean spectral frequency was obtained from all electrodes across this 90-second period in a state of either resting eyes open (REO) or resting eyes closed (REC). The variability (SD) in frequency from this mean was used as a generalized measure of fluctuating electrocortical activity. These measures provide an overall estimate of variability in the dominant EEG frequency and has been used as a general measure of cortical arousal (for full methodology, see reference [38]).

The Joint Ethics Committee of Newcastle and North Tyneside Health Authority University of Newcastle upon Tyne granted ethical approval. Following full explanation and discussion of the study, patients and healthy volunteers gave their consent to the assessment, with additional assent from the next of kin for all cognitively impaired patients.

Analysis of data.
The characteristics of clinical FC, variation in attention, and variation in mean EEG frequency are described in dementia patients and controls. The relationship between the clinical severity scores of FC (rated using the Fluctuation Inventory) and variability in both attentional performance and mean EEG activity were calculated using Spearman’s rank method. The presence or absence of FC was compared between dementias using the $\chi^2$ test. Two sample t-tests were used to compare the clinical FC score as well as the 90-second measures of variability, attention performance, and fluctuations in mean EEG activity between individual patient groups and elderly controls. Sensitivity and specificity values were calculated for the measures when there were statistically significant differences between the different dementias, using optimal cutoff values determined by receiver operator curve (ROC) analysis in the first 40 cases (15 DLB, 15 AD, 10 control). Linear regression analysis was used for key experimental variables to identify confounding factors of dementia severity and degree. A similar regression analysis was performed within the DLB cohort across the 90-second CRT trial (as it requires the greatest motor involvement) to investigate any possible effects that parkinsonian severity may impose upon reaction time pressing. All statistics were undertaken with the SPSS package.
Results.

Subject data.
A total of 155 subjects (37 DLB, 61 AD, 22 VaD, and 35 healthy elderly volunteers) were assessed. Sixty-five percent of DLB patients, 71% of AD cases, 59% of VaD cases, and 72% of elderly controls were women. The mean ages for study groups were; DLB 77.3 (±7.8), AD 80.0 (±7.3), VaD 76.6 (±6.8), healthy elderly volunteers 74.46 (±7.7). The mean MMSE score was 17.6 (±5.1) for the DLB cohort, 17.8 (±4.4) for AD cohort, 17.8 (±4.3) for the VaD group, and 27.74 (±1.2) for elderly volunteers.

Clinical characterization of fluctuating cognition in DLB.
Using the semiquantified clinical FC scale, FC was identified in 34 (89%) patients with DLB, 14 (23%) patients with AD, and 14 (64%) patients with VaD (VaD versus AD \( z^2 \) 12.0, \( df \) 1, \( p = 0.0005 \)). Scores on the clinical FC score (1 month) discriminated significantly between DLB and AD patients (table 1), as well as being significantly higher in DLB patients than those with VaD (table 2), and significantly greater in VaD patients than those with AD (table 3). Clinical FC scores were also significantly greater in the dementia patients than elderly controls (table 4).

Table 1. Comparative analyses using clinical and cognitive fluctuating cognition assessments: dementia with Lewy bodies (DLB) versus AD

<table>
<thead>
<tr>
<th>Variable</th>
<th>DLB, n = 37</th>
<th>AD, n = 61</th>
<th>Statistical evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluctuation Inventory, scale 1, mean ± SD</td>
<td>7.1 ± 3.4</td>
<td>1.1 ± 2.6</td>
<td>( t = 10.5, p &lt; 0.0001 ) *</td>
</tr>
<tr>
<td>Choice reaction time (CRT) variability (SD)</td>
<td>818.9 ± 900.0</td>
<td>218.4 ± 146.2</td>
<td>( t = 5.1, p &lt; 0.0001 ) *</td>
</tr>
<tr>
<td>(CV = 53.2)</td>
<td>(CV = 28.4)</td>
<td></td>
<td>( t = 2.2, p &lt; 0.03 ) *</td>
</tr>
<tr>
<td>Vigilance variability (SD)</td>
<td>130.3 ± 71.0</td>
<td>113.1 ± 45.2</td>
<td>( t = 1.45, p = 0.15 )</td>
</tr>
<tr>
<td>(CV = 20.9)</td>
<td>(CV = 18.7)</td>
<td></td>
<td>( t = 0.96, p = 0.33 )</td>
</tr>
<tr>
<td>Overall attentional performance (CRT SD × vigilance SD)</td>
<td>134,250 ± 173,871</td>
<td>25,259 ± 20,882</td>
<td>( t = 4.85, p &lt; 0.0001 ) *</td>
</tr>
</tbody>
</table>

CV = coefficient of variation.
* Statistically significant.
Table 2. Comparative analyses using clinical and cognitive fluctuating cognition assessments: dementia with Lewy bodies (DLB) versus vascular dementia (VaD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>DLB, n = 37</th>
<th>VaD, n = 22</th>
<th>Statistical evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluctuation Inventory, scale 1, mean ± SD</td>
<td>7.1 ± 3.4</td>
<td>3.1 ± 3.3</td>
<td><em>t = 4.4, p &lt; 0.0001</em> *</td>
</tr>
<tr>
<td>Choice reaction time (CRT) variability (SD)</td>
<td>818.9 ± 900.0</td>
<td>551.9 ± 1001.6</td>
<td>*t = 1.1, p = 0.29</td>
</tr>
<tr>
<td></td>
<td>(CV = 53.2)</td>
<td>(CV = 34.52)</td>
<td><em>(t = 1.4, p = 0.14)</em></td>
</tr>
<tr>
<td>Vigilance variability (SD)</td>
<td>130.3 ± 71.0</td>
<td>98.4 ± 33.3</td>
<td><em>(t = 2.3, p = 0.02)</em></td>
</tr>
<tr>
<td></td>
<td>(CV = 20.9)</td>
<td>(CV = 14.7)</td>
<td><em>(t = 2.6, p &lt; 0.01)</em></td>
</tr>
<tr>
<td>Overall attentional performance (CRT SD × vigilance SD)</td>
<td>134,250 ± 173,871</td>
<td>67,267 ± 118,393</td>
<td><em>(t = 1.7, p = 0.09)</em></td>
</tr>
</tbody>
</table>

CV = coefficient of variation.
* Statistically significant.

Table 3. Comparative analyses using clinical and cognitive fluctuating cognition assessments: vascular dementia (VaD) versus AD

<table>
<thead>
<tr>
<th>Variable</th>
<th>VaD, n = 22</th>
<th>AD, n = 61</th>
<th>Statistical evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluctuation Inventory, scale 1, mean ± SD</td>
<td>3.1 ± 3.3</td>
<td>1.1 ± 2.6</td>
<td><em>t = 3.10, p = 0.002</em> *</td>
</tr>
<tr>
<td>Choice reaction time (CRT) variability (SD)</td>
<td>551.9 ± 1001.6</td>
<td>218.4 ± 146.2</td>
<td><em>t = 2.53, p = 0.01</em> *</td>
</tr>
<tr>
<td></td>
<td>(CV = 34.52)</td>
<td>(CV = 28.4)</td>
<td>* (t = - 1.27, p = 0.20)*</td>
</tr>
<tr>
<td>Vigilance variability (SD)</td>
<td>98.4 ± 33.3</td>
<td>113.1 ± 45.2</td>
<td>* t = - 1.39, p = 0.17</td>
</tr>
<tr>
<td></td>
<td>(CV = 14.7)</td>
<td>(CV = 18.7)</td>
<td><em>(t = - 1.59, p = 0.11)</em></td>
</tr>
</tbody>
</table>
Table 4. Comparative analyses using clinical and cognitive fluctuating cognition assessments: dementia cohorts versus controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dementia, n = 120</th>
<th>Controls, n = 35</th>
<th>Statistical evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluctuation Inventory, scale 1, mean ± SD</td>
<td>3.3 ± 3.8</td>
<td>0 ± 0</td>
<td>$t = 5.07, p &lt; 0.0001$</td>
</tr>
<tr>
<td>Choice reaction time (CRT) variability (SD)</td>
<td>466.8 ± 712.9</td>
<td>99.4 ± 32.9</td>
<td>$t = 3.04, p = 0.003$</td>
</tr>
<tr>
<td>(CV = 37.1)</td>
<td>(CV = 18.3)</td>
<td></td>
<td>($t = 2.66, p = 0.008$)</td>
</tr>
<tr>
<td>Vigilance variability (SD)</td>
<td>115.7 ± 53.7</td>
<td>64.7 ± 21.3</td>
<td>$t = 5.5, p &lt; 0.0001$</td>
</tr>
<tr>
<td>(CV = 18.6)</td>
<td>(CV = 12.8)</td>
<td></td>
<td>($t = 3.34, p = 0.001$)</td>
</tr>
<tr>
<td>Overall attentional performance (CRT SD × vigilance SD)</td>
<td>65,644 ± 118,916</td>
<td>7861 ± 8312</td>
<td>$t = 2.9, p = 0.005$</td>
</tr>
</tbody>
</table>

CV = coefficient of variation.
* Statistically significant.

The optimal cutoff value of greater than 5 (determined using ROC analysis in the first 40 subjects; see figure 1) was used to determine the presence of clinically significant FC. Clinically significant FC was rated as present over the month before the assessment in 30 (81%) DLB patients, 4 (18%) VaD patients, and 5 (8%) AD patients, but none of the controls (DLB versus AD, $\chi^2 51.7, df 1, p < 0.00001$; DLB versus VaD, $\chi^2 22.4, df 1, p <$
0.00001). The optimal cutoff value of greater than 5 achieved a sensitivity 81%, specificity 92% for discriminating DLB and AD, and a sensitivity 81%, specificity 82% in differentiating DLB and VaD patients. For discriminating between VaD and AD, the optimal threshold was 0 to 1, which equated with presence or absence of FC. This value accomplished a sensitivity of 64% (14/22) and a specificity of 77% (47/61) for distinguishing the VaD and AD groups.

Figure 1. Receiver operator curve analysis to determine the optimal cutoff value for FI scale 1 in the first 40 subjects (15 dementia with Lewy bodies, 15 AD, 10 elderly controls) assessed.

Cognitive–attentional assessment of fluctuating confusion.
Fluctuation in cognitive–attentional performance (both SD and CV) were consistently greater in the DLB cohort compared with the AD, VaD, and elderly control groups (see Table 1, Table 2, Table 3). The pattern of attentional variability in patients with clinically significant FC are shown in Figure 2, Figure 3, Figure 4. The optimal cognitive–attentional (CRT × VIGRT) variability cutoff score of >75,000 achieved a sensitivity of 46% and a specificity of 98% for discriminating DLB and AD cases. The same cutoff value also produced a sensitivity of 46% and a specificity of 86% for discriminating DLB and VaD patients.
Figure 2. Quantity of variability (SD) in cognitive–attentional performance choice reaction time and vigilance reaction time (CRT × VIGRT) across 90 seconds in subjects with dementia with Lewy bodies (DLB), AD, and vascular demetia (VaD), and control subjects.
Figure 3. Quantity of cognitive–attentional variability (performance choice reaction time [CRT] × vigilance reaction time [VIGRT] SD) for subjects with clinically significant fluctuating consciousness (Fluctuation Inventory scale 1 scores [5]) in individual study groups. DLB = dementia with Lewy bodies; VaD = vascular dementia; dark gray bars = FI-1 < 5; light gray bars = FI-1 = 5.
Fluctuating profiles in choice reaction time (CRT) responses across a single 90-second trial for two individual subjects with different clinical fluctuating cognition (FC) severities. Subject A does not have FC (clinical FC score = 0), demonstrating a relatively fast and consistent CRT attentional performance; Subject B has severe FC (clinical FC score = 12), demonstrating a slower, continuously variable pattern of CRT attentional performance.

Electrophysiologic characterization of fluctuating confusion.
DLB patients expressed greater fluctuation (SD) in mean EEG frequency across 90-second periods than the AD and control groups in both paradigms (REO: 2.91 > 2.42 > 2.06; REC: 2.25 > 1.93 > 1.44). Comparative brain map examples of 90-second EEG fluctuations for DLB and AD subjects with differing clinical FC scores are shown in Figure 5, Figure 6.
Figure 5. Continuous mean EEG frequency brain map plot (2-second epochs) across 90 seconds (resting eyes open) in an elderly control who does not have fluctuating cognition (clinical FC score = 0). Although there are different amounts of activity in different cortical regions, this pattern of cortical activation remains stable and consistent across 90 seconds.
Figure 6. Continuous mean EEG frequency brain map plot (2-second epochs) across 90 seconds (resting eyes open) in a patient with dementia with Lewy bodies (DLB) with severe fluctuating cognition (clinical FC score = 12). The pattern of electrocortical arousal demonstrates an unstable, continually fluctuating rhythm of activation across the 90-second period.

**Independent correlations.**

The clinical severity of FC significantly correlated with all measures of cognitive–attentional variability within the DLB cohort, although it demonstrated much weaker association in the AD cohort (table 5). Patients with VaD did not demonstrate a significant correlation between clinical severity ratings of FC and any attentional variability measures across 90 seconds (see table 5).
Table 5. Spearman correlation analyses between clinical severity ratings of fluctuating confusion (FI scale 1) and variability in cognitive attentional measures for the entire study cohort and for individual study groups

<table>
<thead>
<tr>
<th>Assessment measure</th>
<th>FI scale 1 correlation: total cohort (n = 155)</th>
<th>FI scale 1 correlation: AD (n = 61)</th>
<th>FI scale 1 correlation: DLB (n = 37)</th>
<th>FI scale 1 correlation: VaD (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT variability (SD)</td>
<td>( r = 0.52; p &lt; 0.0001 )</td>
<td>( r = 0.14; p = NS )</td>
<td>( r = 0.56; p &lt; 0.0001 )</td>
<td>( r = 0.26; p = NS )</td>
</tr>
<tr>
<td></td>
<td>( (CV \ r = 0.46; p &lt; 0.0001) )</td>
<td>( (CV \ r = 0.18; p = NS) )</td>
<td>( (CV \ r = 0.54; p = 0.001) )</td>
<td>( (CV \ r = 0.33; p = NS) )</td>
</tr>
<tr>
<td>VIGRT variability (SD)</td>
<td>( r = 0.38; p &lt; 0.0001 )</td>
<td>( r = 0.09; p = NS )</td>
<td>( r = 0.52; p &lt; 0.0001 )</td>
<td>( r = 0.11; p = NS )</td>
</tr>
<tr>
<td></td>
<td>( (CV \ r = 0.26; p = 0.001) )</td>
<td>( (CV \ r = 0.09; p = NS) )</td>
<td>( (CV \ r = 0.49; p &lt; 0.002) )</td>
<td>( (CV \ r = 0.18; p = NS) )</td>
</tr>
<tr>
<td>CRT × VIGRT variability (SD)</td>
<td>( r = 0.53; p &lt; 0.0001 )</td>
<td>( r = 0.16; p = NS )</td>
<td>( r = 0.61; p &lt; 0.0001 )</td>
<td>( r = 0.19 p = NS )</td>
</tr>
</tbody>
</table>

DLB = dementia with Lewy bodies; VaD = vascular dementia; CRT = choice reaction time; CV = coefficient of variation; VIGRT = digit vigilance reaction time; NS = not significant.

Similar associations were evident between clinical FC severity ratings (FI scale 1) and the variability (SD) in the mean EEG frequency across 90 seconds (n = 40: REO, \( r = 0.45, p < 0.003 \); REC, \( r = 0.42, p < 0.007 \)). Correlation analyses were also performed between independent experimental measures of FC to establish the levels of internal consistency. CRT variability (SD) within a single 90-second trial demonstrated strong positive associations with the variability in mean spectral frequency across 90 seconds in both experimental paradigms (REO, \( r = 0.56, p < 0.0001 \); REC, \( r = 0.41, p < 0.01 \)).

**Examination of potential confounders.**

In a linear regression analysis, CRT variability (SD) across 90 seconds demonstrated a strong correlation with clinical FC ratings (\( t = 3.32 p < 0.001 \), but no association was evident with the degree of cognitive impairment on MMSE (\( t = - 0.93, p = NS \). A separate regression analysis was performed in the DLB cohort alone to identify any potential effect of parkinsonian features in reaction time performance (using UPDRS scores). Once again, CRT variability (SD) across 90 seconds remained strongly associated with clinical ratings of FC (\( t = 3.83, p < 0.001 \), whereas there was no relationship with the UPDRS score (\( t = - 1.42, p = NS \).)

In addition, no differences in the severity of clinical FC were evident when the dementia
cohort was stratified using the MMSE group median of =18 ($t = -1.56, p = 0.12$). Objective attentional measures also did not differ between dementia patients above and below this cutoff (CRT SD: $t = -1.64, p = 0.10$; CRT × VIGRT SD: $t = -1.53, p = 0.13$), indicating similar levels of cognitive fluctuation in patients with more marked dementia than those with less severe dementia.

Discussion.

FC has been recognized and observed consistently in all the major degenerative dementias, although the highest prevalence rates are reported in patients with DLB. No prior investigation has attempted to characterize or empirically quantify FC or investigate its use in differentiating among the major degenerative subtypes. The detailed assessment of FC adds to previous work in the area, but it is important that the limitations are acknowledged. This study, for example, used operationalized clinical diagnoses, which have not been verified at postmortem examination. Although our group has demonstrated high levels of specificity for the clinical diagnosis of DLB, there is the possibility that some cases may have been misdiagnosed. In addition, as FC is one of the core diagnostic features for DLB, it is not surprising that the FC score is higher in clinically diagnosed DLB cases. However, a second independent assessment of FC, undertaken by a separate rater, blind to diagnosis, based upon a caregiver diary, showed a very high level of correlation with the FC score, and the neuropsychological and electrophysiologic investigations were undertaken by a separate investigator, blind to diagnosis. As patients with MMSE scores under 7 and those who were unable to complete a computerized assessment were excluded, there may have been a bias toward excluding some of the more physically impaired patients with VaD, and the results cannot be generalized to patients with lower MMSE scores.

Using the FC scale, an optimal cutoff score of 5 or greater, FC not only was more common in DLB patients (89%) than in those with AD (23%) and VaD (64%), but also was more severe (DLB 81% > AD 8% > VaD 18%). Indeed, the 81% versus 8% difference in FC severity between DLB and AD is currently the largest single reported symptom frequency difference between these two conditions, greater in magnitude than is seen for any of the other core features. This is particularly useful for clinical practice, where the major difficulty is often deciding whether very mild levels of FC are significant. However, using a severity threshold, this question becomes redundant as an issue for differential diagnosis. Whereas the severity of FC may help to distinguish between DLB and AD, the presence or absence of FC also helps to discriminate between VaD and AD.

Although significant differences in FC were evident among the dementia subtypes, this investigation did not directly examine the validity of these new assessment methods within the diagnostic framework of the consensus clinical criteria. This needs to be addressed in larger clinicopathologic studies including the evaluation of other distinguishing features such as psychosis and parkinsonism and precisely determining
the additional value of FC assessment in the accurate diagnosis of different dementia syndromes.

Moreover, patients with DLB consistently demonstrated greater variability in attentional performance across 90 seconds, independently of dementia severity, reaction time length, and degree of parkinsonism. A similar fluctuating profile was observed in the mean electrocortical rhythm across 90 seconds. The variability in these psychophysiologic measures was strongly associated with independent semistandardized clinical ratings of FC, as well as each other. This level of internal consistency provides additional evidence to support the hypothesis that measures of attentional and EEG variability represent accurate, standardized, and reliable tools with which to quantify and characterize FC in dementia. Furthermore, the relationship among clinical, attentional, and electrocortical ratings provides clear empirical support to the original supposition in the DLB consensus diagnostic criteria that FC can manifest as fluctuations in attention and alertness. It therefore appears that quantified, objective measure of FC can be attained in a time efficient manner. These types of neuropsychological and electrophysiologic investigations can hence make an important contribution to the detailed clinical work-up for these patients.

The current work adds to previous studies indicating that quantified measures of attentional variability and fluctuating EEG activity are not only consistently greater in DLB than other dementias, but that these marked fluctuations occur continuously on a second-to-second basis in these patients. It would therefore appear that past clinical observations have only highlighted extremes of the spectrum, seriously underestimating the impact of FC in dementia patients. This characteristic periodicity of FC has important implications regarding the underlying pathophysiologic causality of FC in DLB, a profile that is consonant with a neurochemical rather than structural etiology. If correct, this would indicate the specific potential for pharmacologic interventions for FC in DLB, supported by recent case reports using cholinesterase inhibitors.

Even though a proportion of patients with VaD were clinically rated as having FC, the majority of VaD cases did not express fluctuations in 90-second attentional reaction time performance. This would suggest that much of the FC reported in VaD is the result of a different pathophysiologic mechanism than the proposed neurochemical causality of FC in DLB. A logical explanation for these more protracted FC episodes in VaD would be an intermittent compromise of cerebral blood flow due to vascular pathology, necessitating a different treatment approach.

The availability of detailed and standardized assessment procedures will enable further studies to explore underlying mechanisms, using neuroimaging techniques as well as a clinicopathologic paradigm. Approaches that use SPECT and PET techniques to examine the ascending cholinergic pathways may be particularly valuable. More sensitive measures of change will also facilitate the treatment response of FC to a variety of cholinergic therapies, such as cholinesterase inhibitors, muscarinic agonists, and nicotinic agonists, to be evaluated.
References


Abstract


Abstract


Citation


Citation


Full Text


Abstract


Full Text


Abstract


Abstract


Abstract


Abstract


Abstract


Abstract


Citation

33. Dewey ME, Copeland JRM, Lobo A, Saz P, Dia J-L. Computerized diagnosis from a standardized history schedule: a preliminary communication about the organic section of the HASAGECAT system. Int


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Appendix

The semiquantified clinical FC rating scale (FI scale 1) from the DLB clinical consensus diagnostic criteria.
Fluctuation Inventory–Scale 1: FC is rated as present if either impaired consciousness or fluctuating confusion are identified by a positive answer to either one or both of these questions:

A. Does the patient ever have spontaneous impaired alertness and concentration—i.e., appears drowsy but awake, looks dazed, is not aware of what’s going on? (Clear examples demonstrating impaired consciousness with variations in performance/cognition are required to receive a positive rating.) Have these episodes occurred within the last month?

0 = No
1 = Yes
9 = Not known

B. Has the level of confusion experienced by the patient tended to vary recently from day to day or week to week? For example, becoming worse, then perhaps improving for a while (i.e., up and down)? (Significant fluctuation is regarded as present if distinct examples of differences in performance/cognition can be given on at least two occasions over the last month.)

0 = No
1 = Yes
9 = Not known

If a positive rating of FC is present, a severity rating should be made:

Frequency of FC:

1 = =1 per month
2 = Monthly–weekly
3 = Weekly–daily
4 = Daily

Duration of FC:
0 = Seconds
1 = 5 minutes
2 = 5 minutes–1 hour
3 = 1 hour
4 = 1 day