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Cognitive fluctuations in Lewy body dementia: towards a pathophysiological framework

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Fluctuating cognition is a complex and disabling symptom that is seen most frequently in the context of Lewy body dementias encompassing dementia with Lewy bodies and Parkinson's disease dementia. In fact, since their description over three decades ago, cognitive fluctuations have remained a core diagnostic feature of dementia with Lewy bodies, the second most common dementia in the elderly. In the absence of reliable biomarkers for Lewy body pathology, the inclusion of such patients in therapeutic trials depends on the accurate identification of such core clinical features. Yet despite their diagnostic relevance, cognitive fluctuations remain poorly understood, in part due to the lack of a cohesive clinical and scientific explanation of the phenomenon itself. Motivated by this challenge, the present review examines the history, clinical phenomenology and assessment of cognitive fluctuations in the Lewy body dementias. Based on these data, the key neuropsychological, neurophysiological and neuroimaging correlates of cognitive fluctuations are described and integrated into a novel testable heuristic framework from which new insights may be gained.

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Abbreviations: CAF = Clinician Assessment of Fluctuation Scale; DLB = dementia with Lewy bodies; MFCS = Mayo Fluctuations Composite Scale; OFS = One Day Fluctuation Scale; PDD = Parkinson's disease dementia; RBD = REM sleep behaviour disorder

Introduction

Cognitive fluctuations refer to a recognizable yet variably defined set of symptoms that describe a spontaneous and time-varying alteration of cognitive abilities, often accompanied by disturbances in alertness or arousal. Whilst such fluctuations have been reported across several dementia syndromes, including Alzheimer's disease (20%) (Robertsson *et al.*, 1998), and vascular dementia (30–50%) (Roman *et al.*, 1993), they are considered to be the most characteristic and frequent symptom of Lewy body dementias—dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)—where they are seen in up to 90% of patients (Walker *et al.*, 2000*b*).

Collectively, Lewy body dementias represent the second most common neurodegenerative cause of dementia in the elderly (Walker *et al.*, 2015) with fluctuating cognition a core clinical feature in the diagnostic criteria for DLB since first being introduced in 1992 (McKeith *et al.*, 1992, 2017). Cognitive fluctuations sit alongside the other core features of

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DLB, namely visual hallucinations, parkinsonism and the more recently introduced feature of REM sleep behaviour disorder (RBD; McKeith *et al.*, 1992, 2017). Traditionally, the diagnosis of PDD represents a dementia syndrome that shares the same clinical profile, being distinguished from DLB if the motor symptoms precede the dementia by an artificially defined period of 12 months or more (McKeith *et al.*, 2017; but see Postuma *et al.*, 2015; Boeve *et al.*, 2016). Although the clinical entities of DLB and PDD follow differing clinical trajectories, both converge on a common neuropathological endpoint characterized by neuronal inclusions of α-synuclein aggregates distributed extensively throughout cortical and subcortical structures (Walker *et al.*, 2015) coupled with a varying degree of concomitant Alzheimer pathology, which is typically greater in DLB (Tsuboi *et al.*, 2007; Jellinger and Korczyn, 2018). That cognitive fluctuations occur in high rates in both disorders has suggested a fundamental association between their clinical expression and the pathology of Lewy body dementias. Accordingly, fluctuations have and continue to be most studied in the context of PDD and DLB.

Despite the early recognition and consensus regarding its diagnostic significance, 'fluctuating cognition' remains arguably one of the most evasive and least understood symptoms of the Lewy body dementias. This is reflected both in the paucity of reproducible objective biomarkers and the relative absence of new insights over the last decade that have moved forward our understanding of the underlying pathophysiology. We argue that this in part relates to the need for an integrative theoretical framework for understanding this phenomenon to inform and test hypotheses, constrain predictions and help contextualize the significance of new findings (see Muthukrishna and Henrich, 2019). To develop such a framework, we review and integrate relevant studies from citation lists from landmark studies and from a systematic search of all articles generated in PubMed and Embase, using the search terms 'Dementia' and/or 'Lewy bod*', 'fluctuation*'.

Semiology of cognitive fluctuations

The most current diagnostic criteria for DLB define fluctuations as deficits in cognitive performance or daily functioning that alternate with periods of normal or close-to normal functioning (McKeith *et al.*, 2017). Fluctuating symptoms are permitted to occur anywhere along a spectrum of reduced responsiveness, through to global and dramatic changes in function affecting speech, memory or behaviour.

Variations in attention and alertness are emphasized and have been proposed to underlie fluctuations in the other cognitive domains (McKeith *et al.*, 1996; Walker *et al.*, 2000*a*). Along this spectrum are caregiver reports of 'staring spells'—episodes where the patient appears 'blank', 'vague' and momentarily 'unresponsive', whilst still seeming to be awake (McKeith *et al.*, 1992, 1996). These self-limiting episodes, which bear some semblance to absence seizures, commonly last in the order of seconds to minutes but can be more prolonged. Unlike seizures, carers can often interrupt these episodes, for instance by calling out to the patient. Likewise, the temporary functional loss seen in fluctuations occasionally triggers investigation for and misdiagnosis with transient ischaemic attacks. As a differentiator, it is worth noting that acute motor or sensory changes and visual loss have not been reported to occur with cognitive fluctuations.

Disturbances in arousal have also more recently been emphasized as an integral component to fluctuations and have been shown by several studies to be the most differentiating characteristic of fluctuations in DLB (Ferman *et al.*, 2004; Lee *et al.*, 2014). Impaired arousal can take the form of intermittent or pervasive drowsiness and lethargy (despite getting enough sleep the night before) and frank hypersomnolence with periods of daytime sleep (Ferman *et al.*, 2004). Transient confusion on waking may be part of this symptom complex (McKeith *et al.*, 1996), often exacerbated by unstimulating environments or poor sleep. Notably, 'periods of lucidity' may coincide with novel or stimulating environments (e.g. a medical clinic), which can confound formal cognitive testing. Fluctuations do not tend to have a strict diurnal rhythm, and clinicians should be mindful of differentiating regular nocturnal variations from the 'sun-downing' typically seen in many forms of dementia (Bachman and Rabins, 2006).

The periodicity of fluctuations is highly variable ranging from short episodes (seconds, minutes and hours) through to longer periods (over days or weeks). Indeed, in the earlier descriptions, even monthly variations were allowed (McKeith *et al.*, 1996). Thus, the examining physician should be mindful of potential fluctuations in performance both within a single interview and between interviews. Whether variations in periodicity and/or severity occur within or between individuals has not been rigorously studied though it is presently accepted that multiple forms may exist within the same individual and indeed evolve with duration and severity of the disease.

Fluctuations are diagnosed either by direct observation or more commonly in interview with a reliable informant. Several semi-structured questionnaires have been developed to extract the features of fluctuations discussed above during the interview or examination (Walker *et al.*, 2000*a*; Ferman *et al.*, 2004; Lee *et al.*, 2014). Capturing variations in attentional performance objectively through repeated neuropsychometric measurement with standard or computer-based tasks is also an accepted method of diagnosing fluctuations (discussed below). The present diagnostic criteria require the documented use of at least one of these assessment methods to justify the presence of fluctuations. However, either due to impracticalities of testing, or more often, unfamiliarity with these instruments, formal assessment of fluctuations outside of research settings or dedicated specialist practices, remains limited.

Measurement of fluctuations in the clinic

With increasing acceptance and application of the DLB consensus criteria, questionnaires were developed to operationalize the rich descriptions of cognitive fluctuations for use in diagnostic and research settings (Lee *et al.*, 2012). So far four separate scales have been introduced for this purpose and remain the most common method of detecting and quantifying fluctuations. These include the Clinician Assessment of Fluctuation (CAF) scale and the One Day Fluctuation Scale (OFS) (Walker *et al.*, 2000*a*); the Mayo Fluctuations Composite Scale (MFCS; Ferman *et al.*, 2004); and the Dementia Cognitive Fluctuation Scale (DCFS) (Lee *et al.*, 2014). Although the scales differ slightly in their emphasis on aspects of the phenomenology, all have shown to have good utility in detecting fluctuations and discriminating Lewy body dementia from other forms of dementia. Table 1 summarizes the main features of these questionnaires.

Several important insights have been gained about fluctuations through the development of the scales above. The parametrization of this symptom by the CAF and OFS permitted, for the first time, the ability to explore associations between fluctuations and other clinical, neuropsychological and neuroimaging measures discussed below. The scales also furthered our understanding of the clinical phenomenology associated with fluctuations in Lewy body dementias as compared to other disorders. Using the CAF and OFS, Bradshaw *et al.* (2004) concluded that fluctuations in DLB, which often took the form of spontaneous internally driven interruptions of awareness and attention, differed qualitatively from the more 'situational' fluctuations described in Alzheimer's disease that tended to represent more the unmasking of pre-existing impairments by the cognitive demands of the immediate environment (Bradshaw *et al.*, 2004). Additionally, the MFCS and DCFS, which were designed specifically to identify differentiating features, emphasized the relevance of disturbances in arousal as a defining and likely biologically relevant feature of fluctuations in Lewy body dementias. Finally, common to all questionnaires was their ability to reinforce, either by way of severity, frequency or associated symptoms, a prominence of cognitive fluctuations in Lewy body disorders.

Challenges in quantifying fluctuations using questionnaires

Although useful, limitations within the existing scales have arguably affected the translation of the above insights into an understanding of the neural and biological correlates of fluctuations. Some of these relate to the intrinsic problems associated with use of questionnaire and caregiver reporting, which are vulnerable to many potential sources of bias including the informant's ability to observe and recall such episodes and subjective judgements about what constitutes a change in their baseline (Lee *et al.*, 2012). It is also often practically difficult to delineate non-neurological factors that may account for variability in performance perceived as fluctuations by the caregiver such as concurrent illness, social stressors, time spent in unfamiliar environments, cognitively demanding situations and fatigue (Ferman *et al.*, 2004).

It is relevant to note that all of these scales were designed with practical considerations in mind to assist clinicians in the diagnosis of fluctuations and to help differentiate DLB from other forms of dementia. This process necessarily introduces a degree of artificiality that limits the extent to which the responses on questionnaires can represent the true extent of the phenomenon and consequently its underlying mechanisms. For example, the quantification of fluctuation severity using the CAF relies on the product of duration and frequency. Accordingly, fluctuations of short duration (<5 min) occurring several times throughout the day achieves the same score compared to a daily episode of confusion occurring once a month. Yet it could be argued that these two extremes could be represented by different pathological processes that would require different methods of objective testing. Limiting the resolution of fluctuation frequency on the CAF to 'daily' introduces ceiling effects that fail to capture variance in subjects who fluctuate many times a day. The OFS on the other hand, restricts questioning to symptoms experienced in the last 24 h and thus may under-represent patients who fluctuate less frequently than daily. Furthermore, the OFS includes a number of non-specific symptoms that may overlap with other common elderly syndromes (e.g. falls) and thus may be accounted for by factors unrelated to fluctuations such as visual impairment, infection and polypharmacy. The MFCS and clinician version of the DCFS, while robust in being able to distinguish DLB fluctuations from other dementias, restricts the aspects of fluctuations being assessed to just a few of the discriminating features. This lack of granularity may therefore mask meaningful variance within DLB subjects that may correlate with objective markers.

These limitations demonstrate the challenges of clinically detecting and quantifying fluctuations and reinforces the need for objective markers. It is also clear that to move towards such markers, new research-oriented instruments will be needed. Ideally such instruments will need to be grounded in a sensible theoretical framework that integrates key findings of fluctuations from the clinical descriptions and scales above with emerging evidence from the neuropsychological, physiological and imaging studies evaluated below.

Correlates of fluctuations: insights into mechanisms?

Neuropsychological and electrophysiological signatures of fluctuations have been proposed (Tables 2 and 3) and

Table 1 Measurement of fluctuations through semiquantitative scales

Questionnaire	Description	Utility	Limitations
Clinician Assessment of Fluctuation scale (CAF) Walker *et al.* (2000)	Short four-item scale conducted by experienced clinician in presence of informant. Measures presence of fluctuating confusion and impaired conciouscness. Frequency and duration of events are rated and multiplied to give total score.	Score correlates with neuropsychological and electrophysiological fluctuation measures. Good discrimination between DLB and Alzheimer's disease (sensitivity = 81%, specificity = 92%); and DLB and vascular dementia (sensitivity = 64%, specificity = 77%). Time-efficient and easy to administer in clinical settings.	Need to be scored by an experienced clinician. Responses subjective and therefore heavily dependent on informant interpretation. Assumes severity dependent on frequency and duration, which are limited in resolution—does not distinguish between types of fluctuations.
One Day Fluctuation Scale (OFS) Walker *et al.* (2000)	Seven-item scale conducted with informant assessing confusional behaviour over the last 24 h – falls, fluctuation, drowsiness, attention, disorganized thinking, altered level of consciousness, and communication.	Correlates with neuropsychological and electrophysiological measures of fluctuation. Good internal consistency. Does not require clinician rater. Good agreement (>90%) with CAF. Good discrimination from controls (sensitivity = 93%, specificity = 87%).	Features are not specific to DLB and can be seen in other dementias and geriatric syndromes. Inter-rater reliability uncertain. May fail to capture fluctuations that occur less frequently but may occur over longer time scales.
Mayo Fluctuation Composite Score (MFCS) Ferman *et al.* (2004)	Four-item informant-based composite scale distilled from original 19-item questionnaire to differentiate DLB from Alzheimer's disease. Included (i) drowsiness and lethargy; (ii) daytime sleep ⩾2 h; (iii) staring into space for long periods; (iv) illogical flow of ideas.	Score ⩾3 discriminates between DLB versus Alzheimer's disease (sensitivity = 63%, specificity = 88%), PPV = 83%. Good test-retest reliability. Convergent validity with related scales. Cross-validated in separate cohort. Does not need experienced clinician rater.	Did not correlate with unstandardized clinician diagnosis of fluctuations. Does not directly address phenomenology of fluctuations themselves. Score not necessarily concordant with severity. No information on frequency.
Dementia cognitive fluctuation scale (DCFS) Lee *et al.* (2014)	Informant-based 17-item test across four domains (confusion, sleep, daytime alertness, communication) derived from above scales. Each item scored to a 5-point scale.	Discriminative items between dementia subtypes consistent with MFCS. Reasonable discrimination between dementias of these items (sensitivity = 79–80%, specificity = 74–79%). Good test-retest and inter-rater reliability.	Lengthy to administer. Captures various clinical features of DLB and so similar to MFCS, discriminability may not relate to nature of fluctuations themselves. Fluctuations included in core features of DLB cohort. Convergent validity with objective measures of fluctuations yet to be demonstrated.

PPV = positive predictive value.

various brain regions and networks implicated in the generation of cognitive fluctuations (Table 4). Based on the clinical descriptors above, we find it possible to empirically derive a set of key insights into fluctuations that are supported by these studies of objective correlates (summarized in Fig. 1). Such insights, we argue, should be accounted for in any comprehensive mechanistic model of fluctuations. In this section we present these tenets and the corresponding evidence.

Disrupted attentional processing is an early and sensitive feature of fluctuations

Patients with DLB exhibit pronounced impairments in tasks of attention, visuospatial and executive function relative to Alzheimer's disease, Parkinson's disease and controls (Collerton *et al.*, 2003; Bradshaw *et al.*, 2004). This distinctive profile supported the early notion that fluctuations could be assessed through formal neuropsychological testing of these domains (Table 2).

Successful attempts to characterize fluctuations by neuropsychometric means have primarily involved the use of computerized batteries looking at serial measures of attentional performance (Walker *et al.*, 2000*c*; Ballard *et al.*, 2001*c*). Higher variability, defined as the standard deviation in response time within and between repeated administrations of either a choice reaction time (CRT), simple reaction time (SRT) and digit vigilance (VIG) has been shown to be consistently greater in DLB (and PDD) than other forms of dementia (Walker *et al.*, 2000*b*, *c*). Despite relying on motor output, these measures have been found to be independent of disease duration, parkinsonism and baseline reaction time. Moreover, the specificity of attentional variability for DLB, as opposed to Alzheimer's disease, has been found to be greatest in the early stages of the condition (Ballard *et al.*, 2001*a*).

Across-trial variability in all three of these attentional tasks (CRT, SRT and VIG) has shown significant associations with performance on the CAF, thus demonstrating a degree of convergent validity between clinical and neuropsychological measures of attention (Walker *et al.*, 2000*b*; Ballard *et al.*, 2001*b*). Although variability in other cognitive domains, such as verbal or visuospatial function, have also been demonstrated in DLB, these measures were not as strongly or significantly correlated with the CAF, hence favouring attention as the most sensitive domain to be affected by fluctuations (Ballard *et al.*, 2001*c*).

The validity of attentional disruption as a physiologically relevant feature of fluctuations is also supported by convergent neurophysiological changes demonstrated using EEG. In the initial studies of formal attentional testing to characterize fluctuations, CRT variability was found to strongly correlate with mean spectral frequency variability on EEG (Walker *et al.*, 2000*a*). This, and other electrophysiological markers of fluctuations discussed in more detail below, support a relationship between fluctuations, attentional variability and electrocortical instability.

Fluctuations occur over multiple time scales

Apart from clinical observations, several objective measures of fluctuations have been proposed that emphasize the range of timescales over which cognitive fluctuations occur. Studies of electrocortical activity in DLB provide the most convincing evidence of physiological changes occurring over short (millisecond–second) intervals as potential correlates of fluctuations (for a summary of electrophysiological correlates of fluctuations, see Table 3).

Consistent electrophysiological changes had already been demonstrated to have predictive and diagnostic value in separating DLB from other dementias (Briel *et al.*, 1999; Bonanni *et al.*, 2008). Widespread delta (<4 Hz) and theta (4–7 Hz) power coherence across the scalp and the presence of temporal lobe slow-waves and sharp transients has been repeatedly shown to be higher in DLB (and PDD) compared to Alzheimer's disease patients (Briel *et al.*, 1999; Doran and Larner, 2004; Kai *et al.*, 2005; Andersson *et al.*, 2008; Bonanni *et al.*, 2008). Recent sophisticated approaches, such as network analyses of EEG connectivity, have continued to unveil unique electrophysiological differences in DLB (Dauwan *et al.*, 2016; Babiloni *et al.*, 2018; Peraza *et al.*, 2018).

EEG studies focusing on fluctuations specifically have found that variability in the dominant frequency band may underlie or serve as a surrogate marker of current cognitive fluctuations in individuals, findings that correlate with the CAF scale as well as with neuropsychometric measures of attentional variability (Walker *et al.*, 2000*b*, *c*; Onofrj *et al.*, 2003; Bonanni *et al.*, 2008; Stylianou *et al.*, 2018). Differences in methodology aside, these EEG studies have all been able to link variations in cortical rhythms over timescales of seconds to the reporting of fluctuations, resulting in the incorporation of EEG as a potential biomarker into the most recent consensus criteria (McKeith *et al.*, 2017). However, whether this state of electrocortical activity represents a form of fluctuations occurring at the neuronal population level or a predisposing biological state for overt behavioural fluctuations remains unknown. Either way, these studies suggest that a mechanistic account of fluctuations needs to incorporate variations in cortical activity occurring over short timescales.

Objective measures of fluctuations occurring over longer timescales using neuropsychological testing have also been reported. First, studies involving computerized attentional tasks have found that significant variations in DLB patient responses can be observed within a 90-s testing paradigm, but also between testing periods separated by 1 h and even 1 week (Walker *et al.*, 2000*b*; Ballard *et al.*, 2002). This variation in performance discriminated between DLB and other dementias as well as correlating with clinical

Table 2 Neuropsychometric measurement of fluctuations

Neuropsychological task	Description	Correlation with other fluctuation measurements	Reference
Choice reaction time (CRT)	Subjects required to press one of two buttons corresponding to the same cue displayed on-screen.	Within and between (⩾1 week) trial variability (SD) correlates with CAF and OFS.	Walker *et al.* (2000*a*), Ballard *et al.* (2001*c*)
Digit vigilance task (VIG)	Series of numbers displayed sequentially on-screen. Subjects press a button when a specific number is displayed.	Within and between (2–3 days to 1 week) trial variability (SD) correlates with CAF and OFS.	Walker *et al.* (2000), Ballard *et al.* (2001*a*, *b*)
Simple reaction time (SRT)	Subject presses button as soon as a cue is shown on-screen.	Within and between trial (three trials over 1 week) variability (SD and CoV) correlates with CAF.	Ballard (2001*a*, *b*)
Digit span	Series of digits read aloud to patient with progressively increasing difficulty (length). Patient asked to repeat back string of digits in forward or reverse order.	Variability (CoV) in digit span conducted over 48 h correlated with MFCS rating of fluctuations.	Bliwise *et al.* (2014)
Immediate and delayed verbal recognition	Twelve words presented initially. Subject asked subsequently to recognize original words from separate list with distractors.	Between-trial (three trials over 1 week) variability (SD and CoV) correlates with CAF.	Ballard *et al.* (2001*a*)
Numeric working memory	Three digits presented initially. Subject asked subsequently to recognize original digits from separate list with distractors.	Between-trial (three trials over 1 week) variability (SD and CoV) correlates with CAF.	Ballard *et al.* (2001*a*)
Mini-Mental State Examination (MMSE)	Linear trajectory of global cognitive decline based on MMSE over years calculated from linear mixed model for DLB cohort. Fluctuations estimated from standard deviation of subject specific residuals.	Fluctuations in global cognition correlate with neocortical Lewy body pathology after adjusting for age, sex, education, Alzheimer's disease pathology and infarct pathology	Schneider *et al.* (2012)

CoV = coefficient of variance; SD = standard deviation.

Table 3 Neurophysiological biomarkers correlating with measures of cognitive fluctuations in DLB

Modality	Correlates to cognitive fluctuations	Index of fluctuations	References
EEG	Higher variability of mean spectral frequency	CAF score, CRT variability	Walker *et al.* (2000)
	Slower dominant frequency	CAF score	Bonanni *et al.* (2008), Stylianou *et al.* (2018)
	Higher dominant frequency variability in the theta (4–7.75 Hz) range	CAF score	Stylianou *et al.* (2018)
Auditory event-related potentials	Increased P300 latency, reduced P300 amplitude posteriorly, increased anterior to posterior latency gradient	CAF score	Bonanni *et al.* (2010)

CRT = Choice Reaction Time.

fluctuation scales. Significant fluctuations could also be elicited through repeated testing of digit span every few hours over a 48-h period (Walker *et al.*, 2000*c*). At even longer timescales (~7 years), one clinicopathological study investigating the variability in longitudinal cognitive decline in a community-dwelling population found a significant correlation between deviation in a subject's residuals from a predicted trajectory of decline (taken to indicate fluctuations) and regional Lewy bodies (Schneider *et al.*, 2012).

Altogether qualitative and quantitative reports support the concept that fluctuations can occur over variable timescales. This raises several conceptual challenges to the measurement and understanding of fluctuations, particularly over the longer time frames. First, it highlights that fluctuations can be heterogeneous and at the two extremes may potentially represent different phenomena. This leads one to question the extent of concordance between the different tools with the timescales of the fluctuations they are assessing. For instance, EEG may be suitable for measurements of fluctuations occurring over short timescales but may not be sensitive to fluctuations that either last for several hours or are most obvious on a weekly basis. This could be addressed (at least in part) through the use of ambulatory EEG measuring cortical activity over days or weeks. Such a strategy may also help to provide more objective data on whether different timescales of fluctuations are due to different phenomena, and whether they can co-exist within the same individual.

Fluctuations reflect dysfunction in a distributed neural system

While attentional variations may be a sensitive feature of fluctuations, it has long been accepted that fluctuations need not be domain-specific. A corollary of this is that fluctuations cannot be completely explained by discrete cortical lesions underpinning specific sensory-motor, visual, linguistic and mnemonic functions. Rather pathology in one or several components of a distributed neural system (either a network distributed through the brain, or a more focal system that integrates distributed networks in the brain) would be necessary to account for this phenomenon. Support for this can be inferred from the variety and reach of the regions or neuromodulatory systems implicated by neuroimaging studies of fluctuations (Table 4). The studies detailed below are highly variable in the regions identified, potentially due to the distributed nature of the systems responsible and/or to heterogeneous underlying pathologies.

Structural MRI markers

Voxel-based morphometry studies have consistently emphasized relative preservation of cortical grey matter, particularly in the medial temporal lobes in DLB compared to Alzheimer's disease (Beyer *et al.*, 2007; Whitwell *et al.*, 2007; Mak *et al.*, 2017). Meanwhile compared to PDD, which has a comparable incidence of fluctuations, more cortical atrophy in temporal, parietal and occipital areas is seen in DLB (Beyer *et al.*, 2007). This dissociation implies that cortical atrophy alone is unlikely to account for the phenomenon. Of more interest perhaps may be evidence of increased atrophy in DLB relative to Alzheimer's disease in subcortical structures, particularly those that are known to have roles in wakefulness, alertness and cognition, such as the dorsal midbrain, substantia innominata and hypothalamus (Whitwell *et al.*, 2007). Comparisons in white matter tracts between Alzheimer's disease and DLB using diffusion imaging found that DLB was associated with specific involvement of the pons and left thalamus in DLB relative to Alzheimer's disease (Watson *et al.*, 2012). Work in prodromal DLB has also shown the right anterior insula to be an early significantly affected region (Blanc *et al.*, 2015).

Few structural imaging studies offer direct insights into fluctuations apart from a recent study that demonstrated significant bilateral atrophy in the ventral, dorsal and pulvinar regions of the thalamus with relative sparing of the medial thalamus in DLB (Watson *et al.*, 2017). Significantly, this work highlighted that fluctuations in attention measured by variance in choice reaction time were correlated with regional changes in the dorsal-lateral and posterior thalamus. The authors therefore suggested that thalamic involvement may underpin attentional dysfunction and fluctuations in DLB, a finding consistent with functional and radioligand studies discussed further below (Pimlott *et al.*, 2004, 2006).

Table 4 Fluctuations relate to dysfunction in distributed neural systems

Region/network	Modality	Findings	Reference
Thalamus	SPECT	Increased perfusion of left thalamus with higher CAF score.	O'Brien *et al.* (2005)
	MRS	Lower NAA/tCr and higher tCho/tCr values with higher CAF score.	Delli Pizzi *et al.* (2015)
	Diffusion MRI	No relation between mean diffusivity of connectivity defined thalamic subregions with CAF score.	Delli Pizzi *et al.* (2015)
	Volumetric MRI	Atrophy in left pulvinar and ventrolateral nucleus associated with variance on CRT task.	Watson *et al.* (2017)
	rsfMRI	Dynamic connectivity between thalamus and cortical (insular, cerebellar, sensorimotor, occipital) networks varies inversely with EEG microstate duration which correlates with MFCS.	Schumacher *et al.* (2019)
Occipital cortex	SPECT	Decreased bilateral perfusion of left inferior occipital gyrus and right occipital lingual gyrus with increased CAF score.	O'Brien *et al.* (2005)
	FDG-PET	Presence of fluctuations negatively covaried with bilateral occipital metabolism.	Morbelli *et al.* (2019)
Basal ganglia	SPECT	Increased covariant perfusion in network involving basal ganglia, cerebellum and SMA with increased CAF score and variance in CRT.	Taylor *et al.* (2013)
	rsfMRI	Higher mean Z-statistic scores across peak regions (left superior frontal and left anterior cingulate) in basal ganglia-limbic (thalamus, superior frontal and anterior cingulate) network correlate with CAF score.	Lowther *et al.* (2014)
		Dynamic connectivity between basal ganglia and cortical (visual, default mode, sensorimotor, motor) networks varies inversely with EEG microstate duration which correlates with MFCS.	Schumacher *et al.* (2019)
Frontal/parietal cortex	rsfMRI	Reduced functional connectivity in left frontoparietal cluster, especially involving bilateral pallidum and putamen correlated with CAF score.	Peraza *et al.* (2014)
	rsfMRI	Reduced functional connectivity between right middle frontal gyrus and right lateral parietal cortex correlated with higher CAF score.	Franciotti *et al.* (2013)

CRT = Choice Reaction Time task; FDG-PET = ^{18}fluorodeoxyglucose-PET; NAA = N-acetylaspartate; rsfMRI = resting state functional MRI; SMA = supplementary motor area; SPECT = single photon emission computed tomography; tCho = total choline; tCr = total creatine.
Imaging and molecular findings of neural regions and networks relating to fluctuating cognition in Lewy body dementia.

Magnetic resonance spectroscopy and radioligand markers

Given the dynamic nature of cognitive fluctuations, nuclear imaging studies are better suited to investigate fluctuations than more static modalities, such as structural MRI. Perfusion studies using ^{99m}Tc-HMPAO single photon emission computed tomography (SPECT) were among the first imaging studies to demonstrate differences in patients with fluctuations. In an early study, increased CAF scores were significantly correlated with increased left thalamic perfusion and concurrent decreased inferior occipital perfusion bilaterally (O'Brien *et al.*, 2005). Using a combination of diffusion imaging and magnetic resonance spectroscopy (MRS) to identify structural and neurochemical differences in subregions of the thalamus projecting to the prefrontal and parieto-occipital cortices, Delli Pizzi *et al.* (2015) identified changes in thalamocortical connectivity in fluctuating patients. Uniquely, the authors were able to show that alterations in cholinergic metabolites in the right thalamus were not only specific to DLB compared to Alzheimer's disease but could also be associated with the clinical severity of cognitive fluctuations. This is aligned with evidence for thalamic cholinergic denervation in patients with Parkinson's disease, PDD and DLB but not Alzheimer's disease (Kotagal *et al.*, 2012).

Nuclear studies have also been used to draw inferences regarding functional connectivity between brain regions. Spatial covariance analyses of SPECT perfusion imaging identified a single covariant perfusion network in DLB subjects, which was strongly associated with fluctuations measured using the choice reaction time and CAF (Taylor *et al.*, 2013). This network was characterized by changes in perfusion in the cerebellum, basal ganglia, supplementary motor area and bilateral parietal regions. Very recently, 18-fluorodeoxyglucose PET has shown occipital hypometabolism also to correlate with the presence of fluctuations (Morbelli *et al.*, 2019).

Functional MRI markers

Functional MRI offers enhanced spatial resolution over nuclear studies. Unfortunately, task-based functional MRI has lacked utility in the study of cognitive fluctuations due to the lack of a standard neuropsychological paradigm and the technical difficulty with testing dementia patients in the scanner. Consequently, resting state functional MRI (rsfMRI) has

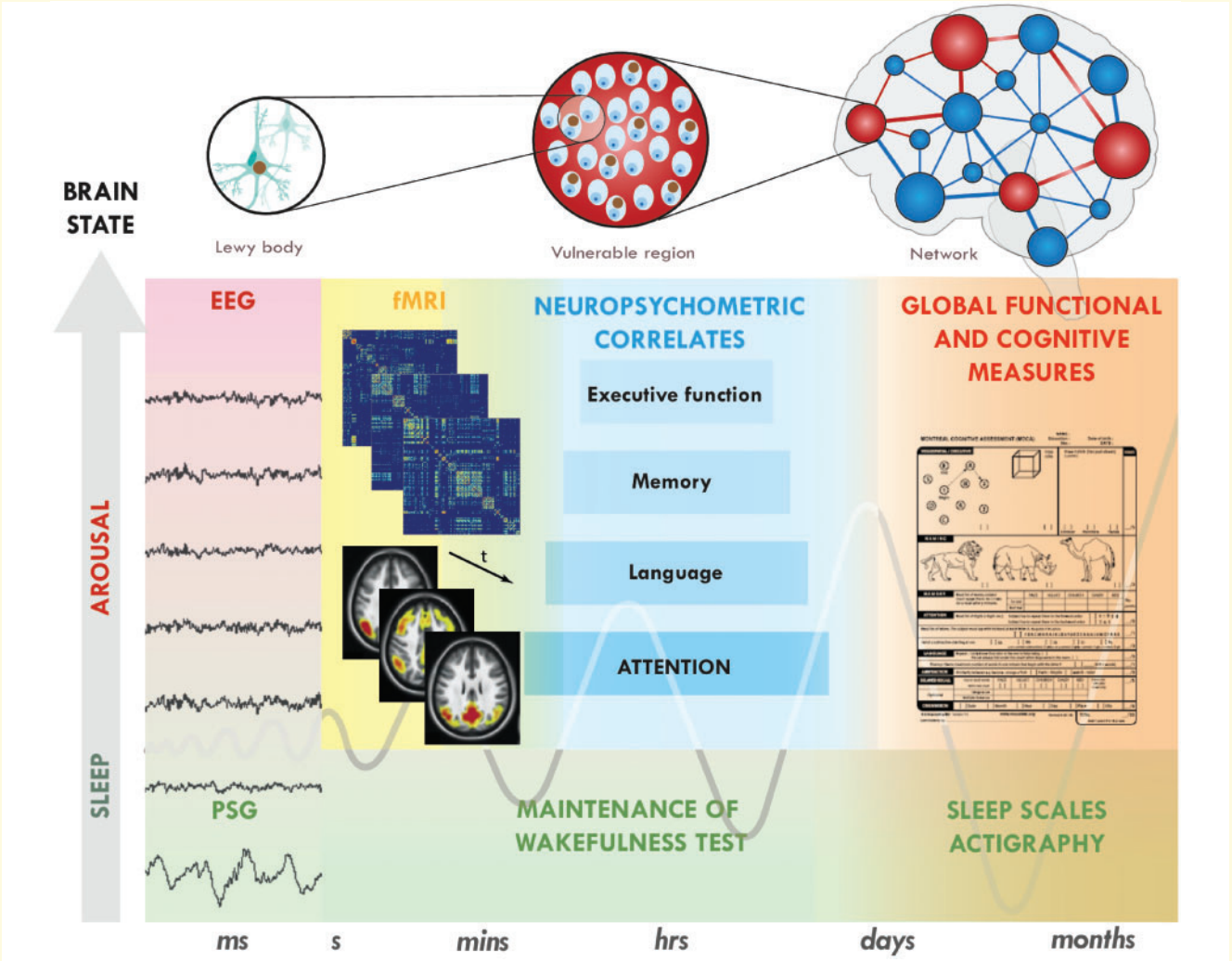

Figure 1 Overview of current methods for assessing and investigating cognitive fluctuations illuminates key heuristics that should be accounted for by pathophysiological models of fluctuations. Disrupted attentional processing is a sensitive neuropsychometric measure of fluctuations and seems to be affected early prior to other, more regionally localized cognitive domains. Fluctuations occur over multiple timescales, having been found to correlate with physiological variations detected in the order of seconds (e.g. EEG, functional MRI), through to changes in global cognitive and functional measures (e.g. Montreal Cognitive Assessment) that can be appreciated at timescales of months to even years. This heterogeneity limits the insights into mechanisms of fluctuations gained by the use any single tool that only reflect variations thin a specific range of time. Different phenotypes of fluctuations suggest dysfunction in a distributed neural system, emphasizing the need to consider the large-scale network-level influences of pathologically affected neural regions. Disrupted sleep and arousal, which are processes subserved by distributed neural systems, characterize fluctuations that are shown in the figure to occur along an axis of unconscious to conscious brain states. Fluctuations occur most frequently in and typify Lewy body dementias, thus the pathological substrate underlying this symptom must be especially influenced by Lewy body pathology.

been the default method for investigating changes in functional brain connectivity in DLB patients.

Many rsfMRI studies highlight the default mode network (DMN)—a collection of brain regions normally active at rest and showing decreased activity during the performance of tasks and orienting of attention to external stimuli (Raichle and Snyder, 2007). Connectivity within the DMN has been shown to be affected in Alzheimer's disease, with particular vulnerability noted in the posterior cingulate and precuneus (Minoshima *et al.*, 1997; Buckner *et al.*, 2005; Binnewijzend *et al.*, 2014). Studies in patients with fluctuations defined by the CAF and concordant EEG abnormalities have failed to identify a significant relationship between the fluctuations and DMN connectivity (Franciotti *et al.*, 2013; Peraza *et al.*, 2014). In DLB generally some studies have shown increased DMN connectivity (Galvin *et al.*, 2011; Kenny *et al.*, 2012), while others have shown reduced connectivity (Lowther *et al.*, 2014) or no change (Franciotti *et al.*, 2013; Peraza *et al.*, 2014; Schumacher *et al.*, 2018). This suggests that Alzheimer's disease-type pathology may influence DMN connectivity more than Lewy pathology.

Lewy pathology is known to concentrate in the anterior cingulate cortex (Braak *et al.*, 2003; Kövari *et al.*, 2003), and greater connectivity in the left superior frontal region and anterior cingulate cortex (forming part of the basal-ganglia-thalamic network) was found to positively correlate with CAF score and overall severity of motor parkinsonism (Lowther *et al.*, 2014). An abnormal increase in connectivity between anterior cingulate cortex and temporal pole networks (despite reduced within-network connectivity in both these networks) has led to the suggestion that the anterior cingulate cortex may be a focal point of disruption to functional connectivity in DLB (Schumacher *et al.*, 2018). By regressing the CAF score to resting state connectivity, fluctuations were significantly associated with desynchronization of regions associated with the left frontoparietal network, elements of which have been implicated in salience detection and orienting of attention (Eckert *et al.*, 2009), consistent with a broader reduction in functional connectivity in DLB (Schumacher *et al.*, 2018).

These imaging findings add weight to the notion that fluctuations arise as a result of one or several regions of pathology within a distributed neural network/s or system/s. Moreover, the functional imaging studies emphasize the importance of considering the dynamics of the system when investigating fluctuations. In a significant effort to address this directly, a recent study has been able to demonstrate a link between altered dynamic connectivity between subcortical (basal ganglia and thalamic) and large-scale rsfMRI networks in DLB with changes in timing of EEG microstates recorded in the same patients (Schumacher *et al.*, 2019). The finding of a correlation between slowing of EEG microstates and cognitive fluctuation severity (MFCS, although not CAF or OFS) offers dynamic functional connectivity as a promising tool for exploring and understanding the neural basis of fluctuations.

Limitations of neuroimaging

In spite of the insights gained, there are a number of challenges to be overcome with respect to the understanding of fluctuations through neuroimaging, such as the inherent limitations of these technologies (e.g. insufficient temporal resolution; and inadequate visualization of skull base structures such as the brainstem where the relevant pathology may be present) as well as the difficulty of reconciling methodological differences between studies. Given the intrinsic relation between fluctuations and Lewy body pathology, one needs to be careful in inferring causality from correlational neuroimaging data that may be affected by unmeasured confounders (e.g. degree of concomitant Alzheimer pathology). Additionally, the transient and intermittent nature of fluctuations may mean that any relevant neural events may be missed in the relatively brief time permitted in the scanner. Multimodal approaches using a combination of neuroimaging, targeted behavioural paradigms and prolonged ambulatory electrophysiological measurement (ideally concurrently) may be required to circumvent such issues in future work.

Disordered sleep and arousal characterize fluctuations in dementia with Lewy bodies

The most consistent finding amongst recent clinical studies is that disturbances of arousal seem to be the most specific feature of the fluctuations observed in Lewy body dementias. Compared to Alzheimer's disease and vascular dementia, the fluctuations in DLB and PDD are more frequently associated with daytime somnolence and drowsiness (Ferman *et al.*, 2004; Bliwise *et al.*, 2011; Lee *et al.*, 2014; Chwiszczuk *et al.*, 2016; Cagnin *et al.*, 2017), implicating circuitry regulating sleep and wakefulness. The complex pathways controlling these processes are distributed in diffusely projecting neural systems that include key regions such as the thalamus, which have already been implicated in fluctuations by imaging (Table 4) and pathological data in DLB (Zhong *et al.*, 2011; Erskine *et al.*, 2017).

Sleep disturbance is recognized as an important symptom affecting the quality of life in patients with DLB (Lee *et al.*, 2018). Efforts over the past decade investigating sleep in DLB have been mostly focused on the role of RBD as a specific and diagnostically important marker of Lewy body pathology (Boeve, 2013). It is now well recognized that RBD is highly prevalent in patients with DLB (seen in up to 80%) and has been shown to be the strongest prodromal marker of the disorder (Ferman *et al.*, 2011). Polysomnography-confirmed RBD predicts a synuclein-based disorder on post-mortem in >90% of cases (Boeve *et al.*, 2013). These features led to the incorporation of RBD as a core feature of DLB in the most recent iteration of the diagnostic criteria (McKeith *et al.*, 2017). The manifestation of RBD is thought to arise from pathology in numerous brainstem nuclei situated in the pons and caudal medulla (Boeve, 2013), which overlap with the structures involved in the regulation of sleep states and wakefulness (Scammell *et al.*, 2017). The relatively high prevalence of both RBD and fluctuations supports a possible underlying pathological relationship, which has been supported by a recent clinical study demonstrating a correlation between the presence of RBD and severity of fluctuations according to the CAF in patients with DLB (Cagnin *et al.*, 2017).

Although commonly reported in the clinic, other areas of sleep disturbance in DLB have not been as extensively investigated. Excessive daytime sleep/hypersomnolence is recognized as a supportive feature of DLB and fluctuations especially, occurring at a higher rate in Lewy body disorders compared to other conditions (Bliwise *et al.*, 2011; Ferman *et al.*, 2014; Videnovic *et al.*, 2014; Cagnin *et al.*, 2017). In addition, DLB patients also commonly suffer from other nocturnal symptoms including urinary dysfunction, periodic leg movements, and frequent unexplained

arousals that can affect sleep quality (Pao *et al.*, 2013; Pillai and Leverenz, 2017). Polysomnographic findings affirm these clinical features, with DLB patients exhibiting more fragmented sleep and significantly reduced sleep efficiency, total sleep time and slow-wave sleep compared to other synucleinopathies (Bugalho *et al.*, 2019).

Unfortunately, attempts to objectively assess the relationship between sleep disturbance and excessive daytime somnolence with attentional fluctuations in DLB have been limited. One study found that fluctuations in alertness, measured using polysomnography-based Maintenance of Wakefulness Test, did not relate to fluctuations on the cognitive performance of a digit span task over that same time period (Bliwise *et al.*, 2014). This led the authors to suggest that fluctuations in cognition might be independent of fluctuations of alertness, thus speaking to the possible existence of different phenotypes of fluctuations. However, this was derived from a small sample of DLB patients whose variations (sleep latency) did not greatly differ from Parkinson's disease patients. It is also uncertain whether this translates to the other subjective and objective measures of fluctuations mentioned above.

The dearth of studies in relation to sleep dysfunction and fluctuations in DLB highlights an important and potentially fruitful avenue of further research. A combination of clinical, polysomnographic, electrophysiological and imaging approaches paired with neuropathological validation may yield further insights into the neuroanatomical and pathophysiological processes that may underlie arousal disturbance and cognitive fluctuations.

A pathophysiological framework for cognitive fluctuations

To date, astute clinical observations have led to an agreement regarding their importance in DLB, yet an understanding of the fundamental neurobiological mechanisms are lacking. Our present review of fluctuations has illuminated key heuristics (Fig. 1) that should be addressed by any mechanistic model of fluctuations.

We suggest that the most parsimonious framework that satisfies these conditions considers fluctuations as arising from the disordered switching of the brain states that subserve the continuum of sleep through to attentive arousal (Harris and Thiele, 2011; Lee and Dan, 2012; McCormick *et al.*, 2015). Transitions in brain states are defined by specific changes in local and global patterns of cortical activity (i.e. 'cortical states'), which accompany corresponding changes in behaviour (Zagha and McCormick, 2014). The most natural and best studied example of this is the transition between wake and sleep, which is characterized by a profound shift in the EEG from desynchronized low amplitude, fast frequency rhythms to more synchronized slower frequencies characterizing non-REM (NREM) sleep (Scammell *et al.*, 2017). Likewise, fluctuations in neuronal activity and behavioural performance also occur within the waking state in normal individuals (McGinley *et al.*, 2015) and there is growing recognition that spontaneous changes in cortical activity denotes variations in performance across a range of cognitive tasks particularly those targeting psychomotor vigilance and selective attention (Weissman *et al.*, 2006; Boly *et al.*, 2007; Fox and Raichle, 2007; Palva and Palva, 2011; Esterman *et al.*, 2013; He, 2013). As with cognitive fluctuations in Lewy body dementia, fluctuations of cortical states have been observed to occur over a variety of timescales from milliseconds/seconds (e.g. the shift from sleep to wake) through to hours/days (e.g. changes in responsiveness with increasing sleep pressure or metabolic influences) (Vyazovskiy *et al.*, 2013; Lewis *et al.*, 2015).

Multiple brain regions and neurotransmitter/neuromodulatory pathways have been shown to play an important role in the transitions and maintenance of cortical states (Lee and Dan, 2012). Specifically, studies have emphasized the importance of ascending projections from monaminergic (e.g. noradrenergic) and cholinergic cell groups in the brainstem and basal forebrain, orexinergic neurons in the lateral hypothalamus, thalamocortical circuits and cortical neurons themselves in the regulation of cortical states (for reviews, see Lee and Dan, 2012; Scammell *et al.*, 2017). Thus, consideration of this framework yields a number of candidate pathological targets that would account for the emergence of cognitive fluctuations and offers testable predictions relating to their clinical detection (Fig. 2).

At short timescales, aberrant switching between normal cortical desynchronization and arousal to inappropriate synchronization and reduced attention/arousal would translate to an intermittent or persistent increase in low frequency activity (delta-theta) on EEG either locally or globally during a fluctuation. Interestingly, altered timing of EEG microstates in this manner has in fact been recently demonstrated in DLB patients (Schumacher *et al.*, 2019). At the level of large-scale network disruption, imbalances between the ascending cholinergic and noradrenergic arousal systems would likely reduce the ability of the brain to dynamically coordinate the network-level reconfigurations that form the basis of cognitive function (Shine, 2019). Consequently, future experimental paradigms that recruit patients for functional MRI scanning during an episode of a fluctuation may find reduced topological flexibility of large-scale networks in patients during fluctuations and DLB. Along these lines, pupil diameter, which has long been used in humans as a marker of cognitive load and alertness (Kahneman and Beatty, 1966; Iriki *et al.*, 1996; Alnaes *et al.*, 2014), has recently been shown in rodents to track rapid fluctuations of cortical state during wakefulness with tight coupling to brainstem noradrenergic and cholinergic activity (Reimer *et al.*, 2014, 2016). Pupillometry may therefore be a useful tool for confirming the role of these systems in cognitive fluctuations and indeed for their clinical detection, which may be

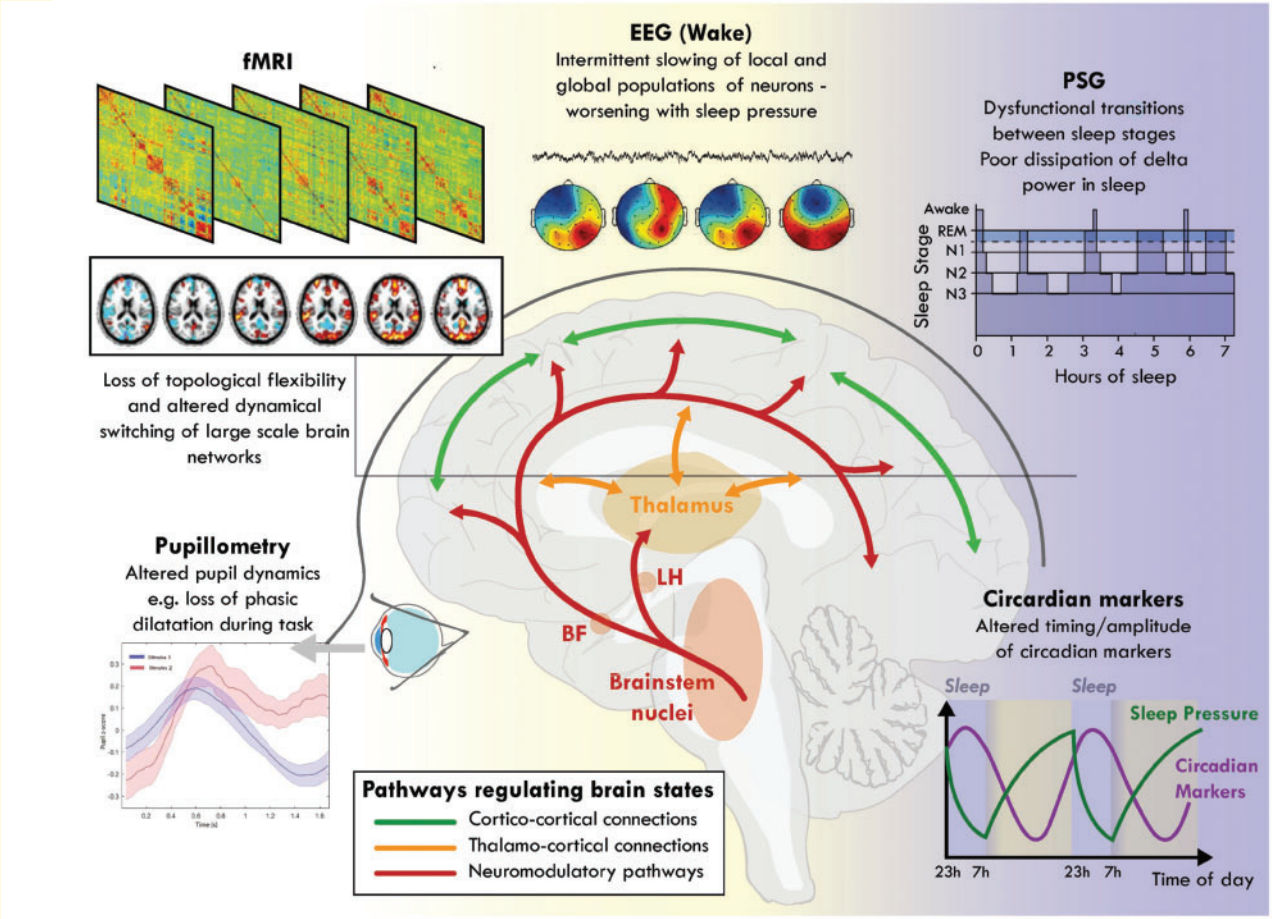

Figure 2 A pathophysiological framework of cognitive fluctuations as dysregulation of cortical states. Cortical state transitions are regulated by multiple neural pathways traversing brainstem nuclei, hypothalamus, basal forebrain, thalamus and cortex. Pathology in various neuromodulatory cell groups in these regions, or disruption of thalamo-cortical or cortico-cortical connections may be candidate mechanisms for cognitive fluctuations. This framework yields several potential methods for the detection and investigation of fluctuations in clinical and research settings, respectively. Disturbed balance in neuromodulatory systems during a fluctuation (in particular acetylcholine and noradrenaline) would manifest as altered pupillary dynamics as measured by pupillometry and changes in the connectivity and topological dynamics of large-scale networks on functional MRI. EEG, and particularly high-density ambulatory EEG, would be useful to detect changes in cortical states with expected slowing and synchronization in both local and global populations of neurons. Based on this framework, the dependence of the above circuits on regulating sleep suggests potential dysregulation of a number of sleep-related measures (*right*) such as altered sleep stage cycling and timing in patients with fluctuations. Vulnerability to increasing sleep pressure, which is reflected in cortical state changes during sleep deprivation, may be associated with altered dissipation of slow wave power during sleep. Disordered phase and amplitude of normal chronobiological rhythms (*far right*) may also vary in time in patients with fluctuations at longer time scales. BF = basal forebrain; LH = lateral hypothalamus.

marked by the loss of phasic dilation during a cognitive task. Lastly, circadian factors and homeostatic sleep mechanisms are known to interact directly with systems controlling cortical states (Morin, 2013; Scammell *et al.*, 2017). Sleep studies therefore provide an important avenue of exploration for cognitive fluctuations that, as we have reviewed, are characterized by excessive daytime somnolence. As suggested above, cognitive fluctuations may reflect dysregulation of these systems and occur in parallel with altered timing or amplitude of circadian gene expression or changes in phase of melatonin secretion. Sleep pressure is reflected by the low-frequency power (<8 Hz) of EEG, which accumulates exponentially in wake and dissipates during the following episode of sleep (Dijk *et al.*, 1987). DLB/PDD patients who experience fluctuations may be especially vulnerable to increasing sleep pressure, and it may be possible to trigger fluctuations for diagnostic or experimental purposes by sleep deprivation.

Overview and future directions

In the past three decades, cognitive fluctuations have remained among the most enigmatic and least understood

core symptoms of Lewy body dementias. Despite early recognition of its importance, translation of key clinical insights into underlying mechanisms and treatments for this symptom have failed to progress. In order to advance the field, we have reviewed the available literature to highlight several key features of fluctuations that should be taken into account by any comprehensive mechanistic model of fluctuations. Based on these, a broad pathophysiological framework is presented that will hopefully motivate future work and lead to better understanding and clinical detection of fluctuations.

In this process, several questions emerge that need to be considered in future studies. For example, does the heterogeneity of phenotype and timescales of cognitive fluctuations imply different categories of fluctuations with separate underlying mechanisms? Present testing paradigms do not distinguish between different forms of fluctuations both in patient selection and in measurement of severity. As a result, certain experimental protocols that may be more relevant to one form of fluctuations (such as EEG for short fluctuations) may be insensitive to others (such as resting state and event-related functional MRI for longer fluctuations). Thus, one suggestion may be to expand the nomenclature surrounding fluctuations and develop new or modify existing research scales that explicitly distinguish between the different phenotypes of fluctuations either based on timescale (short—minutes/seconds to long—hours or more) or their phenotype (e.g. global cognition/arousal versus specific domain) or both. Another key consideration of future experimentation demonstrated by the lack of findings from structural imaging studies are the limitations of studying a transient and unpredictable functional event. It may be that the biological signature of fluctuations may only be present during the ictal period itself and could therefore be missed during the period of testing. Along these lines, timely testing of the phenomenon may require tools where prolonged, ambulatory recording is possible, such as ambulatory EEG or new or yet to be developed wearable technologies. Home testing by the carer using mobile applications may also be useful.

Ultimately, pathophysiological models together with refined and targeted modes of experimentation will lead to more reliable objective markers of fluctuations. Objective markers will be necessary for clinicians who are making determination of a patient's degree of cognitive decline for diagnostic and capacity determining purposes as it is well-known that patients can often present well in clinic as a function of a current fluctuation (Trachsel *et al.*, 2015). An understanding of the underlying mechanisms may shed light on vulnerable circuitry affected by Lewy body pathology that may be targeted by symptomatic treatments. Finally, objective biomarkers will likely improve clinical detection and diagnosis of DLB but may also have utility in prodromal stages for identification of patients at risk and stratification into disease-modifying trials. It is hoped that the present synthesis can be a viable starting platform for the new ideas and additional work required to achieve these goals.

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Competing interests

The authors report no competing interests.

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