DEMENZA A CORPI DI LEWY: AGGIORNAMENTI FISIOPATOGENETICI

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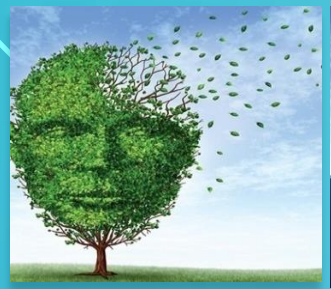
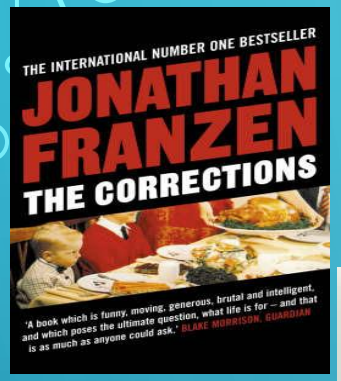
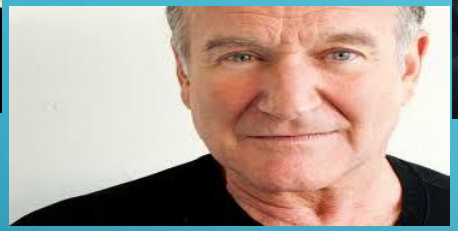
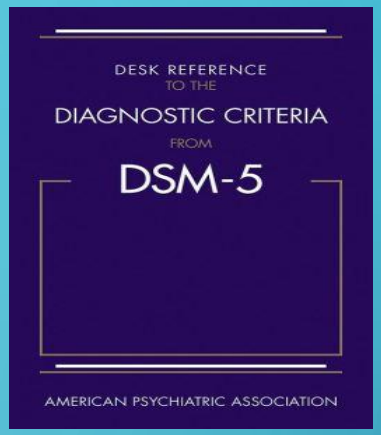






According to a survey by the Lewy Body Dementia Association of 962 caregivers, a typical LBD diagnosis can involve three or more doctors and approximately 6 office visits over the course of 12 to 18 months. These caregivers reported that only 6 percent of LBD diagnoses were made by primary care physicians. Specialists make the vast majority of LBD diagnoses, with 62 percent made by neurologists, but the majority of LBD patients were referred back to primary care. This underscores the importance of more education for primary care physicians about diagnosing and treating non-Alzheimer's dementias.



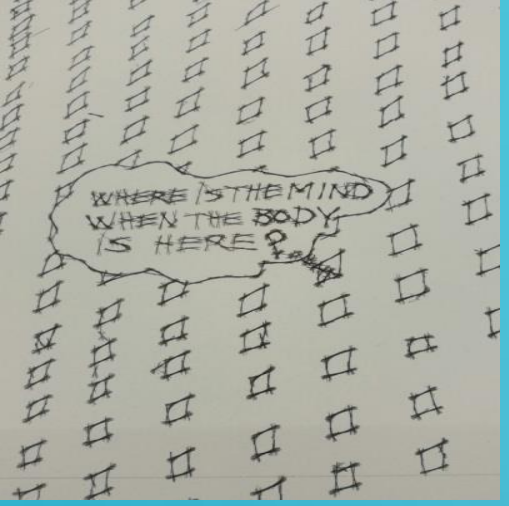
DSM-5 includes DLB for the first time, referring to it as "Major or Mild Neurogocognitive Disorder with Lewy Bodies" and incorporating all of the features and diagnostic criteria by which clinicians across the world diagnose DLB. Separate criteria are also given for "Major or Mild Neurocognitive Disorder due to Parkinson's Disease ".

LBDA
LEWY BODY DEMENTIA ASSOCIATION

NOT POPPY, NOR MANDRAGORA,
NOR ALL THE DROWSY SYRUPS OF THE WORLD,
SHALL EVER MEDICINE THEE TO THAT SWEET SLEEP
WHICH THOU OWED'ST YESTERDAY.

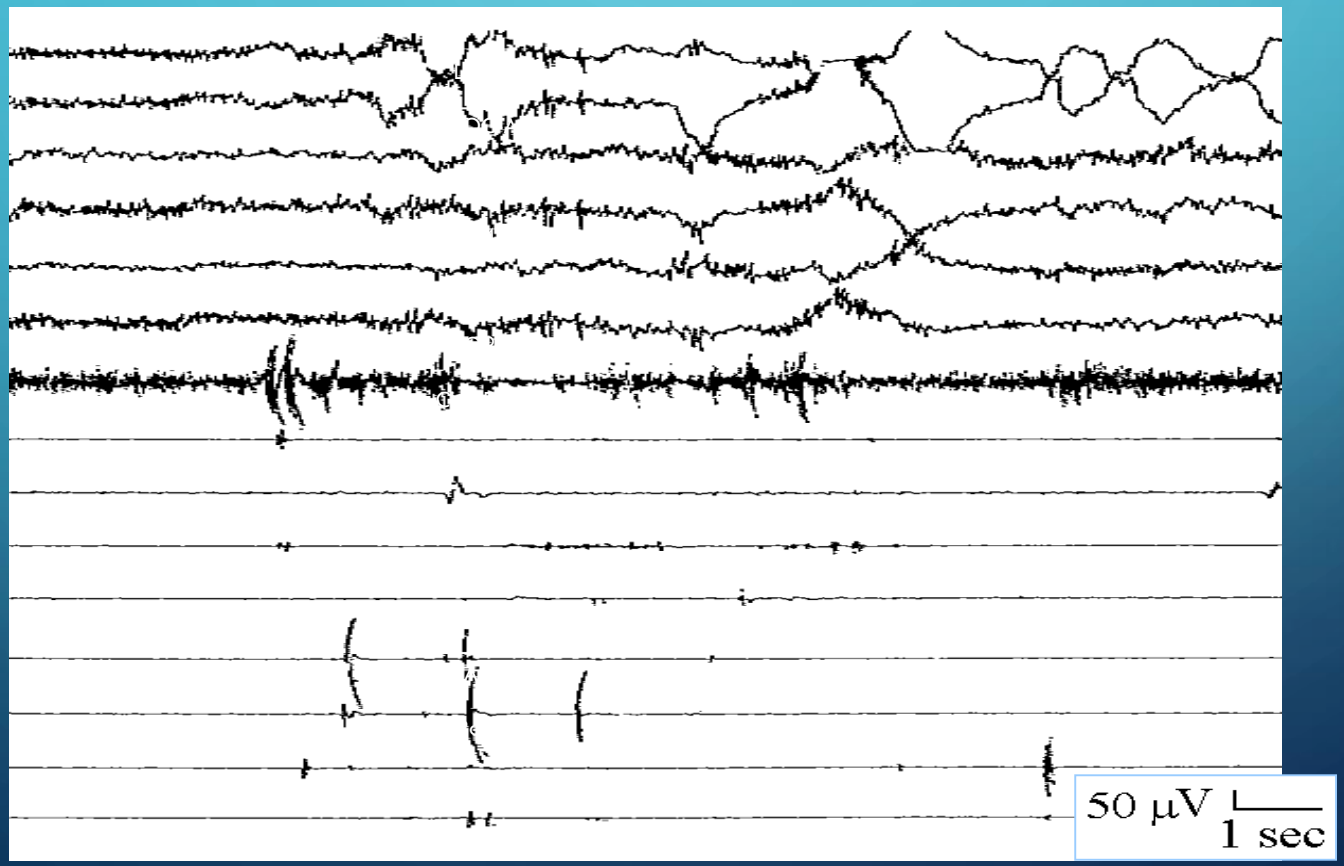
(WILLIAM SHAKESPEARE, OTHELLO, ACT III, SCENE 3)

Patients with DLB have sleep disturbances similar to those with other neurodegenerative dementias, however DLB patients are noted to have greater overall sleep disturbance than patients with AD. Manifestations of their sleep disturbance include some clearly non-circadian phenomena such as a greater incidence of REM sleep behavior disorder, a syndrome characterized by the loss of the ability to maintain muscle atonia during REM sleep. The increased daytime sleepiness and nightime arousals seen in DLB compared to AD could have a source in circadian regulation.



Goshka Macuga: Before the beginning, after the end. Fondazione Prada. Milano

Dissociation from REM sleep, due to intrusion of features of other stages into ongoing REM sleep (mind-body dissociation). In this condition the mind is asleep (REM dream mentation) while the body is awake (spinal motor neurons are still excitable). Mahowald and Schenck 1991



Longitudinal studies of RBD have shown that up to 93% of cases go on to develop a synucleinopathy – PD, PDD, DLB or multiple system atrophy– if followed up for a sufficient number of years.

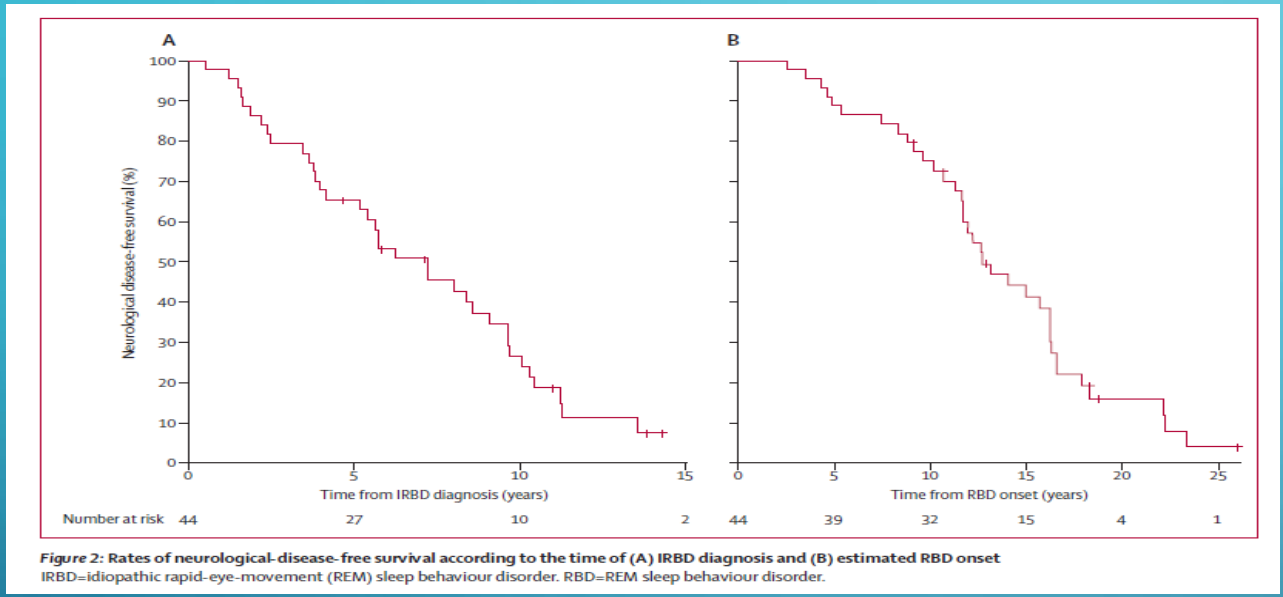
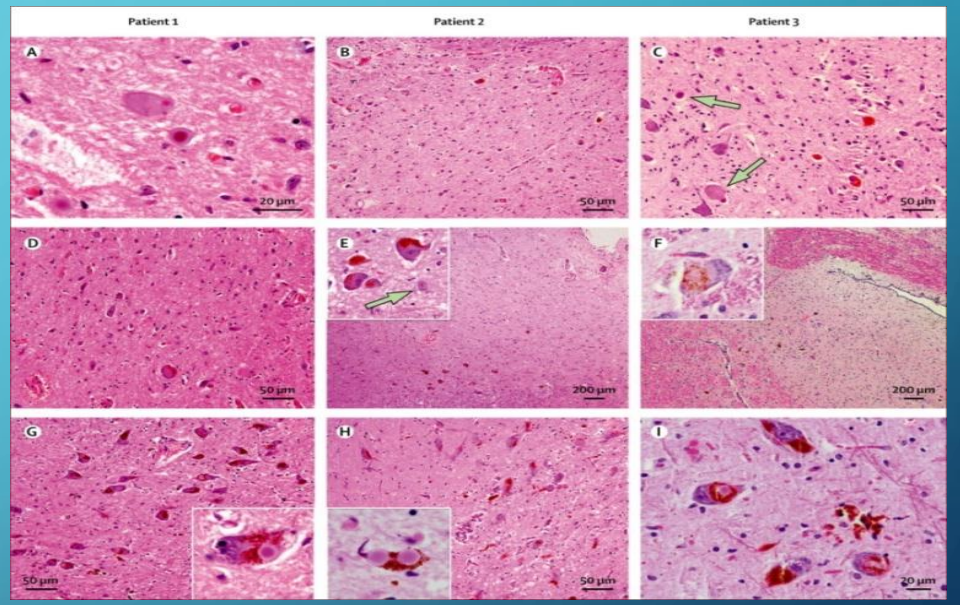


Figure 2: **Rates of neurological-disease-free survival according to the time of (A) IRBD diagnosis and (B) estimated RBD onset**
IRBD=idiopathic rapid-eye-movement (REM) sleep behaviour disorder. RBD=REM sleep behaviour disorder.



Interpretation Most IRBD individuals from our cohort developed a Lewy body disorder with time. Patients who remained disease-free at follow-up showed markers of increased short-term risk for developing PD and DLB in IRBD, such as decreased striatal DAT binding. Our findings indicate that in most patients diagnosed with IRBD this parasomnia represents the prodromal phase of a Lewy body disorder. IRBD is a candidate for the study of early events and progression of this prodromal phase, and to test disease-modifying strategies to slow or stop the neurodegenerative process.

Iranzo A et al, The Lancet Neurology, Volume 12, Issue 5, 2013, 443 - 453

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Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

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ABSTRACT

The Dementia with Lewy Bodies (DLB) Consortium has refined its recommendations about the clinical and pathologic diagnosis of DLB, updating the previous report, which has been in widespread use for the last decade. The revised DLB consensus criteria now distinguish clearly between clinical features and diagnostic biomarkers, and give guidance about optimal methods to establish and interpret these. Substantial new information has been incorporated about previously reported aspects of DLB, with increased diagnostic weighting given to REM sleep behavior disorder and ^{123}iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. The diagnostic role of other neuroimaging, electrophysiologic, and laboratory investigations is also described. Minor modifications to pathologic methods and criteria are recommended to take account of Alzheimer disease neuropathologic change, to add previously omitted Lewy-related pathology categories, and to include assessments for substantia nigra neuronal loss. Recommendations about clinical management are largely based upon expert opinion since randomized controlled trials in DLB are few. Substantial progress has been made since the previous report in the detection and recognition of DLB as a common and important clinical disorder. During that period it has been incorporated into DSM-5, as major neurocognitive disorder with Lewy bodies. There remains a pressing need to understand the underlying neurobiology and pathophysiology of DLB, to develop and deliver clinical trials with both symptomatic and disease-modifying agents, and to help patients and carers worldwide to inform themselves about the disease, its prognosis, best available treatments, ongoing research, and how to get adequate support. *Neurology*® 2017;89:1–13

GLOSSARY

AD = Alzheimer disease; **CHEI** = cholinesterase inhibitor; **DAT** = dopamine transporter; **DLB** = dementia with Lewy bodies; **DSM-5** = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; **LB** = Lewy body; **MCI** = mild cognitive impairment; **MIBG** = metaiodobenzylguanidine; **MMSE** = Mini-Mental State Examination; **MTL** = medial temporal lobe; **PD** = Parkinson disease; **PSG** = polysomnography; **RBD** = REM sleep behavior disorder.

The Dementia with Lewy Bodies (DLB) Consortium last reported on diagnosis and management in December 2005, and its recommendations have been widely cited for both clinical and research use.[1,2] Changes made to the diagnostic criteria at that time increased diagnostic sensitivity for DLB,[e1] but detection rates in clinical practice remain suboptimal,[3] with many cases missed or misdiagnosed, usually as Alzheimer disease (AD). The revised DLB criteria presented here incorporate new developments since then and result from a review process that combined the reports of 4 multidisciplinary, expert working groups with a meeting that included patient and care partner participation (appendix e-1 at Neurology.org). The Consortium recognizes increasing interest in detecting early-stage disease; prodromal DLB criteria are in development and will be reported separately.

SUMMARY OF CHANGES While maintaining their previous structure, the revised DLB clinical diagnostic criteria improve on earlier versions[1,2] by distinguishing clearly between clinical features and diagnostic

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Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies

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ABSTRACT

Objective: To determine whether adding REM sleep behavior disorder (RBD) to the dementia with Lewy bodies (DLB) diagnostic criteria improves classification accuracy of autopsy-confirmed DLB.

Methods: We followed 234 consecutive patients with dementia until autopsy with a mean of 4 annual visits. Clinical diagnoses included DLB, Alzheimer disease (AD), corticobasal syndrome, and frontotemporal dementia. Pathologic diagnoses used the 2005 DLB consensus criteria and included no/low likelihood DLB (non-DLB; n = 136) and intermediate/high likelihood DLB (DLB; n = 98). Regression modeling and sensitivity/specificity analyses were used to evaluate the diagnostic role of RBD.

Results: Each of the 3 core features increased the odds of autopsy-confirmed DLB up to 2-fold, and RBD increased the odds by 6-fold. When clinically probable DLB reflected dementia and 2 or more of the 3 core features, sensitivity was 85%, and specificity was 73%. When RBD was added and clinically probable DLB reflected 2 or more of 4 features, sensitivity improved to 88%. When dementia and RBD were also designated as probable DLB, sensitivity increased to 90% while specificity remained at 73%. The VH, parkinsonism, RBD model lowered sensitivity to 83%, but improved specificity to 85%.

Conclusions: Inclusion of RBD as a core clinical feature improves the diagnostic accuracy of autopsy-confirmed DLB. *Neurology*® 2011;77:875–882

GLOSSARY

“Dreaming” is usually understood as subjective mental experiences during sleep. Although most famously (and strongly) associated with REM sleep (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957), dream-like thought is also reported during other sleep stages

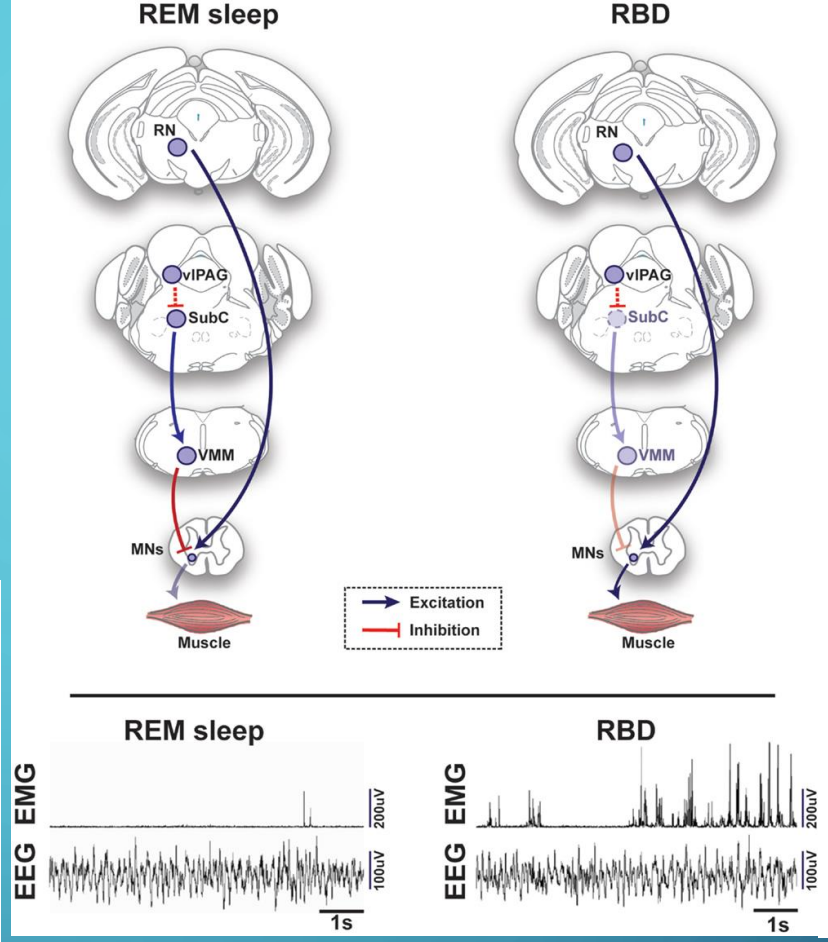
The majority of“dream” reports have been elicited from REM sleep stage laboratory awakenings; only REM sleep shows a particularly strong correlation with dream mentation (~80% of awakenings from REM sleep result in dream reports: Hobson et al.,2000).

REM sleep is initiated by a network of cells in the pons and nearby portions of the midbrain (Siegel,2011), but involves a widespread recruitment of higher cortical brain regions Whereas non-REM(NREM) sleep stages are generally characterized by deactivation of many regions as com- pared to wakefulness (e.g., Kaufmannetal.,2006), REM is unique in that many brain regions are clearly more active than during wakefulness. REM also appears to be the most active state from the subjective point of view, with longer, more emotional, and more frequent dream mentation in REM than any other sleep stage (Hobson et al., 2000). REM therefore appears to be by far the best neural marker of dreaming.

Table 2 | Core cortical components of the neural network underlying REM sleep.

Region	Cluster size (mm^3)	Talairach coordinates (*x*, *y*, *z*) [BA]
ACTIVATIONS (REM > WAKING REST)		
Cortical regions		
Medial prefrontal cortex	368	2, 32, 2 [Area **24**]
Posterior cingulate cortex/lingual gyrus	656	28, −66, 4 [Areas 19, **30**]
Parahippocampal cortex	1088	24, −40, −10 [Areas **36**, 37]
	416	−16, −26, −18 [Area 35]
Parahippocampal/entorhinal cortex	104	18, −30, −6 [Areas **28**, **35**]
Posterior parahippocampus/lingual gyrus	496	−18, −50, −8 [Area 19]
	352	22, −58, −6 [Areas 19, **36**]
Entorhinal cortex/hippocampus	360	22, −18, −14 [Areas **28, 35**]
Subcortical regions		
Pons/midbrain	688	8, −14, −18
Caudate nucleus	472	−6, 16, 10
DEACTIVATIONS (REM < WAKING REST)		
Cortical regions		
Mid/posterior cingulate	752	−8, −34, 28 [Area **23**]
Rostrolateral prefrontal cortex	456	32, 44, 20 [Area 10]
Inferior frontal gyrus	296	−46, 26, −2 [Areas 47, 45]
Orbitofrontal cortex	256	−32, 38, −10 [Area 11]
	224	38, 36, −12 [Area 11]
	120	18, 46, −14 [Area 11]
Superior longitudinal fasciculus	176	28, −42, 20

*Peak cortical foci of likely activation and deactivation from a meta-analysis of all functional neuroimaging (PET) studies of REM sleep compared to a baseline of waking rest. Notably, every cortical cluster of activation overlaps (convergences in bold font) with a core component of the DMN, except for one cluster in left lingual gyrus [Area 19] (compare with **Table 3** and **Figure 2**). Conversely, significant clusters of deactivation overlap with DMN regions in only one case out of seven. The cluster labeled as in superior longitudinal fasciculus is approximate only. BA, Brodmann area; DMN, default mode network; PET, positron emission tomography; REM, rapid eye movement.*



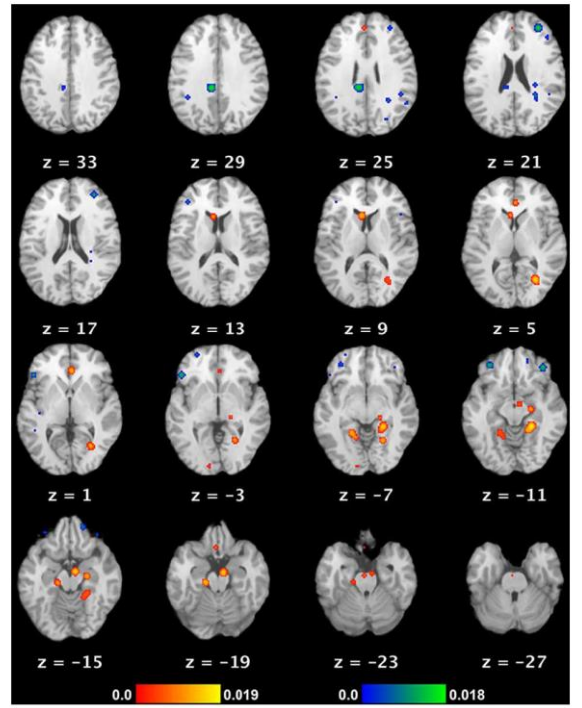


FIGURE 1 | Neural substrate of REM sleep vs. waking rest. Significant meta-analytic clusters contributing to the neural substrate of REM sleep (as a proxy for dream mentation). Axial slices are displayed in Talairach space, with 3 mm skip. Color bars indicate likelihood that peaks represent actual peaks of difference at a given voxel. Activations (REM > waking rest) are in red-yellow, deactivations (REM < waking rest) in blue-green.

Fox et al, 2013

There is an intriguing literature suggesting that sleep may have a role in memory consolidation (Walker andStickgold,2006;BornandWilhelm,2012), including specific roles for REM sleep in consolidation of procedural (Smithetal., 2004) and emotional episodic (Nishidaetal.,2009;Grochetal., 2013) memories.

A dynamic model of sleep-dependent memory consolidation and reconsolidation has recently been proposed, suggesting a complex relationship between sleep stages, memory types and their contribution to cognitive stability, flexibility and brain plasticity (Walker and Stickgold,2006,2010).

It is now well documented that dream content borrows from both temporally proximal and distal memories (Nielsenand Stenstrom,2005). The most proximal memories (those from the previous day) are generally known as "day residue"(Freud, 1908), whereas the recurrence of elements 5–7 days following an experience is referred to as the"dream-lag" effect (Nielsen and Powell,1989).

Personally relevant and emotionally salient events appear to manifest themselves in dream content as day residue and dream lag effects, but can also surface many years after initial encoding (Grenieretal.,2005).

The presence of emotional and personally relevant content in dreams may be related to the fact that emotional and impactful events are preferentially consolidated in memory (McGaughetal.,2002;Nishidaetal., 2009).While dreaming contains clear episodic autobiographical elements, memories only rarely get"replayed"in dream content (~1–2% of reports: Fosse et al.,2003).

Estamos hechos de la misma materia de los cuales están hechos los sueños "El Beso" Pablo Neruda

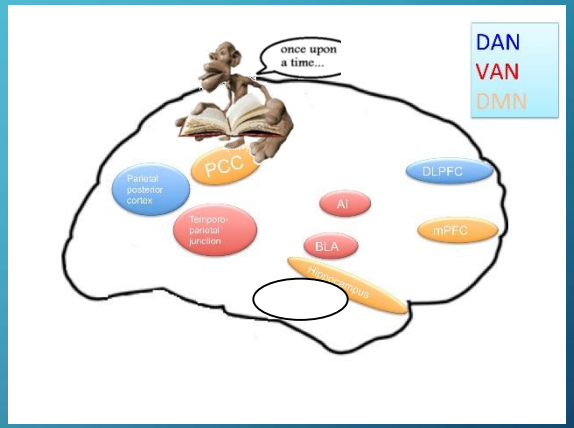
THE DEFAULT MODE NETWORK(DMN) AND REM SLEEP

Though specific neural correlates of dreaming remain somewhat elusive, this mental state, and its associated subjective content, are strongly correlated with the "resting state"and REMsleep, respectively

The DMN was discovered somewhat serendipitously as a pattern of brain *deactivations associated with the difference between brain activity during a quiet, resting state and a goal-oriented, directed task(Raichle et al.,2001).*

It quickly became clear that physical "rest" by no means implied mental inactivity. With no explicit task, subjects almost immediately engaged in spontaneous thought, including daydreaming, planning for the future, and recalling memories, (Gusnardetal.,2001).

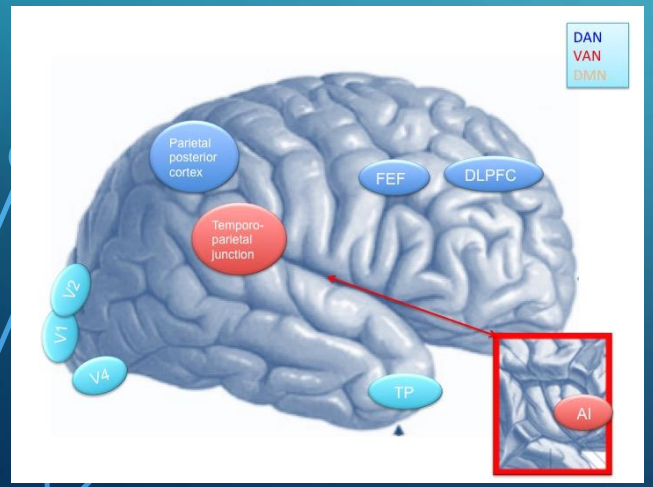
DMN autobiographic narrative



Recent studies suggest that the DMN could be envisioned as the anatomo-functional structure subtending «Id-Es» in the Freudian metapsychology.

Default mode network

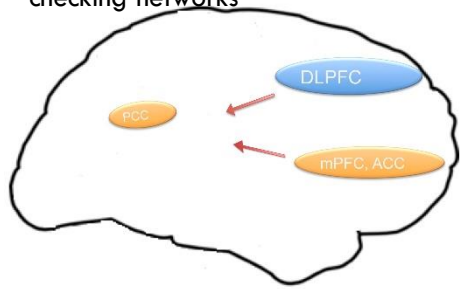
The DMN, which is part of the limbic system, has a key role in the integration of self-referential information into conscious perception and self-centered narrative, and is linked with both DAN and VAN, in a metastable state, varying from:
coupling (corresponding to a stable condition linked to reality checking) to decoupling (corresponding to an entropic state with connectivity motifs which form and fragment across time).
The ventral sensory pathway culminates hierarchically in the hippocampus, which is linked to the cortical hubs of the DMN. Normally, the VAN, including basolateral amygdala, monitors the ventral pathways for salience, leading to inhibition of the DMN and activation of the DAN, which, in feedback, modulates activity within the VAN. The DMN is coupled with VAN and DAN in a complex network interaction with a constrained order, including reality checking and social awareness.



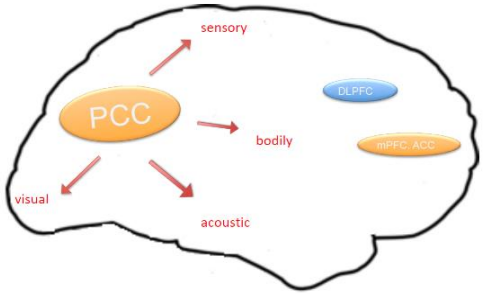
	Regions involved	Role
Default mode network (DMN)	Posterior cingulate, medial prefrontal cortex, and hippocampus	Task-independent thought-mind wandering
Ventral attention network (VAN)	Superior frontal, temporo-parietal junction, anterior insula	Activation of other networks, engages attention to salient stimuli
Dorsal attention network (DAN)	Frontal eye fields, dorsolateral prefrontal cortex, posterior parietal cortex	Voluntary orienting, processing of cognitive information

DMN role in cognitive states

Low entropy: coupled-stable reality checking networks



High entropy: decoupled unstable PCC, randomly connecting motifs



DMN in deep sleep

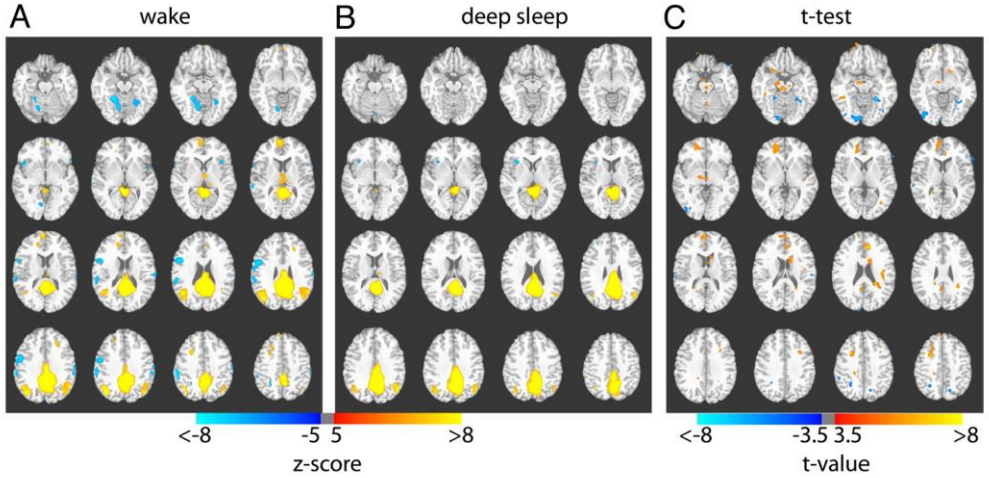


Fig. 1. The default mode network during wake and sleep. Composite maps showing correlations with PCC during (*A*) wake and (*B*) deep sleep, and their significant difference as determined from statistical *t* test (*C*). A significant reduction of involvement of frontal regions is seen during deep sleep, whereas the posterior cingulate–inferior parietal correlations are preserved. The *Z* maps in *A* and *B* are both thresholded at $Z = \pm 5.0$; the *t* map in *C* is thresholded at $t = \pm 3.5$. Both positive (yellow–red) and negative (blue) correlations are shown. *Z* values, *t* values, and Talairach coordinates of all significant clusters are reported in Tables 1 and 2.

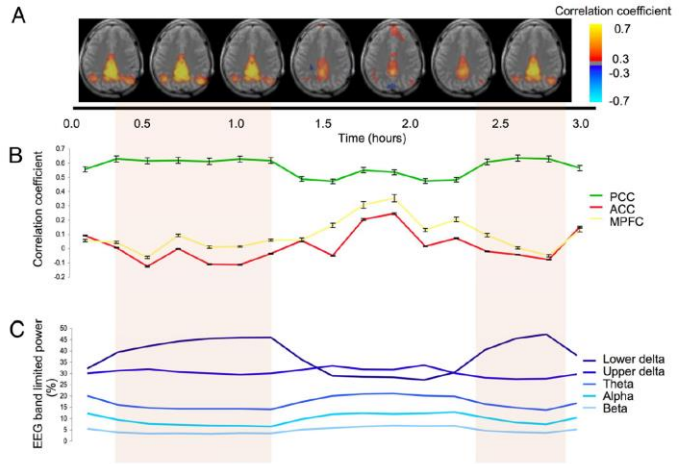


Fig. 3. Temporal evolution of connectivity within DMN at the single-subject level. (*A*) Composite single-slice maps ($Z = 25$) of correlation with seed in PCC. Each image represents the average of 2 10-min correlation maps (for full data see Fig. S3). Periods of deep sleep (indicated by colored background) coincide with a reduced involvement of frontal regions; this is confirmed by the region-based analysis shown in *B*, which shows reduced correlations with ACC and MPFC in the presence of a robust correlation within PCC. Corresponding levels of band-limited EEG activity are given in *C*, with the following definitions: lower delta: <2 Hz; upper delta: 2–4 Hz; theta: 4–8 Hz; alpha: 8–12 Hz; and beta: 12–20 Hz).

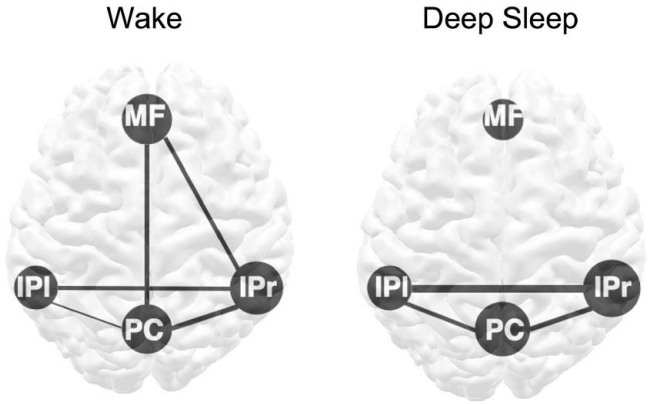


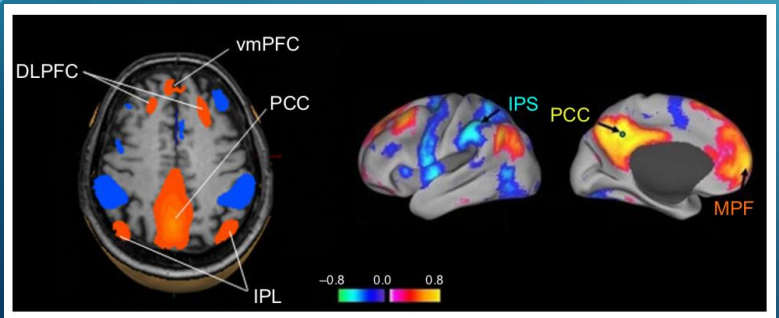
Fig. 2. Connectivity of the main components of the DMN during wake and deep sleep. The connectivity within (disks) and between components (lines) was determined from temporal correlation analysis of average time courses within each ROI. The ROIs were defined as the voxels within each anatomic region that are significantly connected to the PCC seed during wake, using a low threshold ($P = 0.0001$, uncorrected). The size of the disks represents within-region connectivity, whereas thickness of lines represents between-region connectivity. During deep sleep, the posterior areas (bilateral IPC and PCC) strengthen their connectivity, whereas the connections between frontal and posterior regions are lost. See also Tables 3 and 4. MF = medial prefrontal/anterior cingulate cortex; IPl = left inferior parietal/angular gyrus; IPr = right inferior parietal/angular gyrus; PC = posterior cingulate/precuneus.

DMN persist throughout the whole physiologic range of levels of consciousness, from wake to deep sleep; however, the strength of the correlations, and by implication the integrity of the DMN, is dynamically modulated by the level of consciousness.

Horovitz et al, 2009

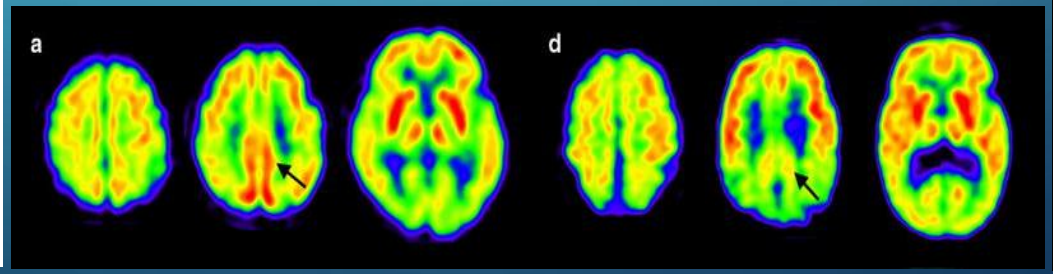
Overactivity of the default mode network

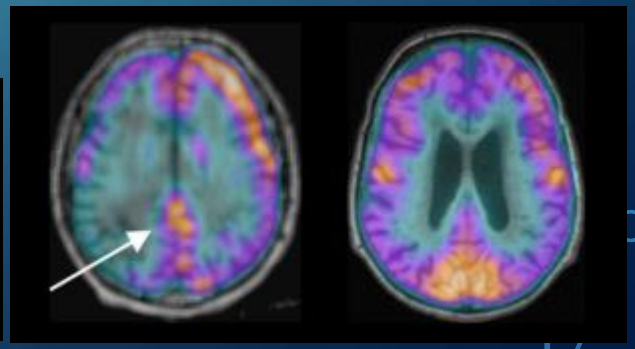
Preserved activity in the PCC clearly distinguishes DLB from AD, where PCC activity is instead severely depressed.
fMRI rest and task-based studies show increased activity and/or connectivity of the DMN in PD and DLB patients. When the DMN is decoupled from attention networks, it is disinhibited into a high entropic state, generated by random connective motifs that form and fragment across time, similar to dreaming states, and fitting with the clinical presentations of PD psychosis. Early psychotic symptoms are intermittent due to transient and random decoupling, quickly suppressed by attention; late psychosis involves more complex narrative including oneiric (paraphrenic) presentations corresponding to persistently high entropy states [Carhart-Harris, 2016]. In this state, self-referential information (identity) is partly preserved, but reality checking is not, in a primitive or infantile state of consciousness. Vivid examples of the entropic DMN state are psychedelic states and normal dreaming (REM sleep), with preserved self-referential information, but with connectivity profiles which form and fragment unpredictably, thus explaining the absence of logic, of physical constraints, the metamorphoses which are part of dreams and confusional delirium.



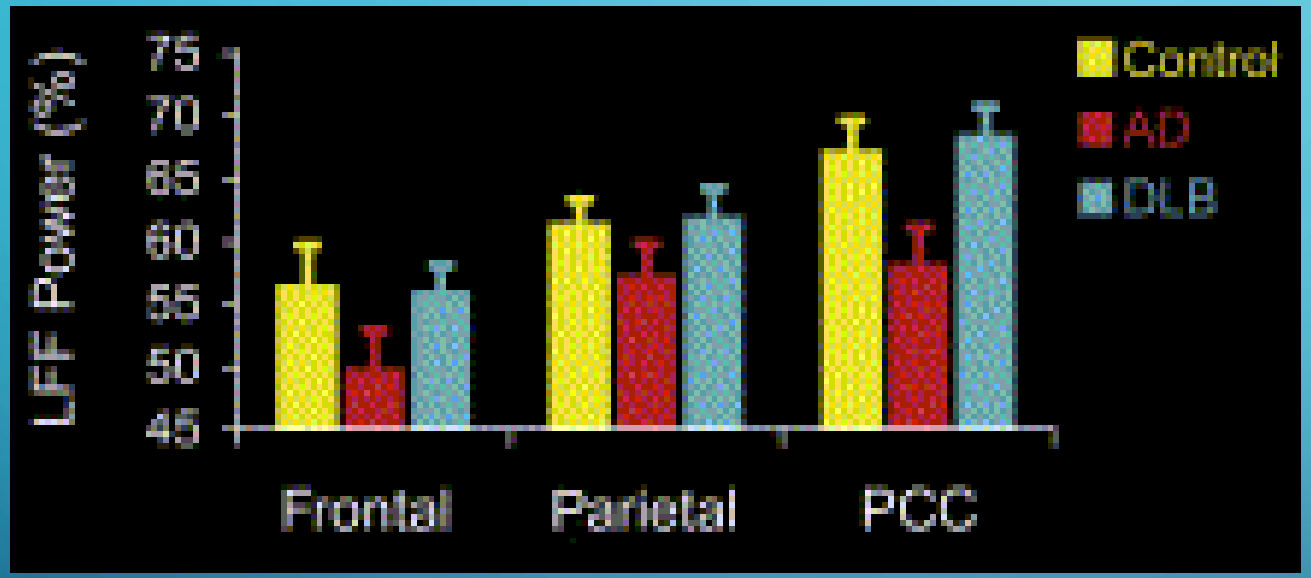
Franciotti et al 2013

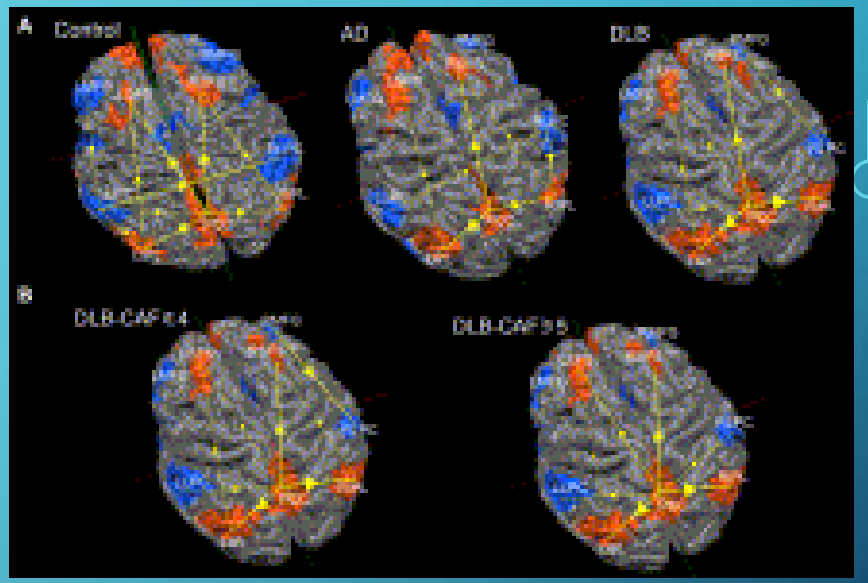
Cingulate Island Sign

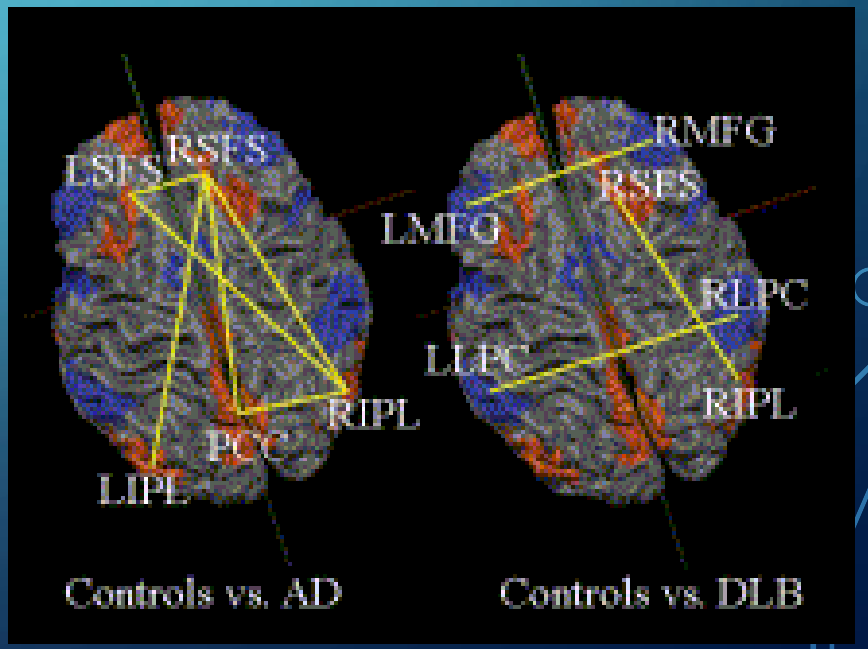




Graff-Radford 2015


LFF Power (%)
75
70
65
60
55
50
45
Frontal
Parietal
PCC
Control
AD
DLB


A
Control
AD
DLB
B


LSFS
RSFS
LMFG
RMFG
RSFS
RLPC
LLPC
RIPL
PCC
LIPL
RIPL
Controls vs. AD
Controls vs. DLB

What controls the DMN?

Synchronization of activity in the component regions of the DMN is effected via coordinated fluctuations in membrane potentials. Such coordination could be orchestrated through central regions, such as the thalamus or hippocampus. Potential involvement of the thalamus is supported by studies that have demonstrated connections between the PCC and the laterodorsal and anteroventral thalamic nuclei in rhesus monkey. In addition, generalized epileptic discharges have been shown to correlate with increase in activation in thalamus and decrease in the DMN areas, suggesting also that thalamocortical circuits regulate activity in the DMN.

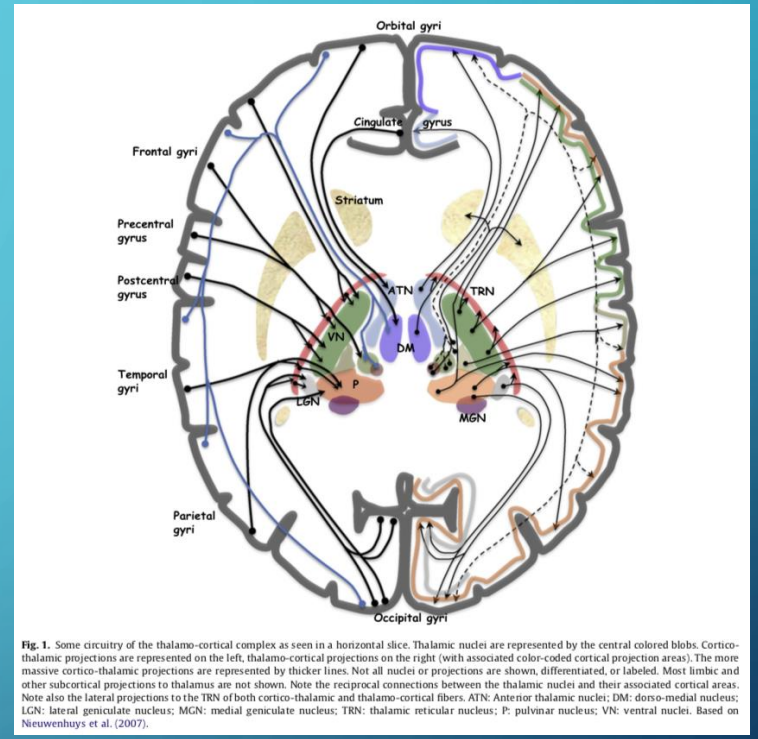
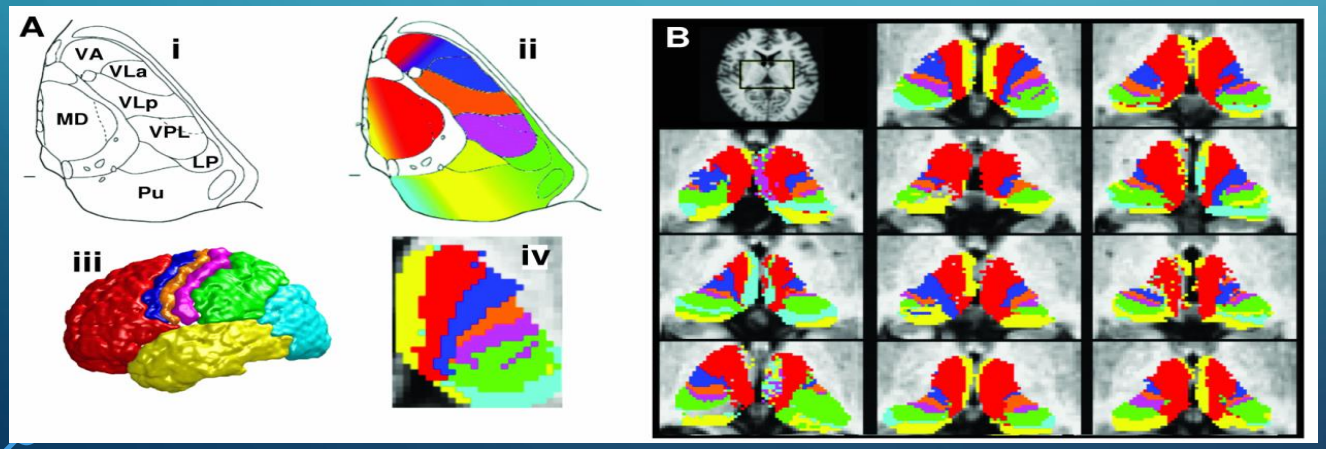


Fig. 1. Some circuitry of the thalamo-cortical complex as seen in a horizontal slice. Thalamic nuclei are represented by the central colored blobs. Cortico-thalamic projections are represented on the left, thalamo-cortical projections on the right (with associated color-coded cortical projection areas). The more massive cortico-thalamic projections are represented by thicker lines. Not all nuclei or projections are shown, differentiated, or labeled. Most limbic and other subcortical projections to thalamus are not shown. Note the reciprocal connections between the thalamic nuclei and their associated cortical areas. Note also the lateral projections to the TRN of both cortico-thalamic and thalamo-cortical fibers. ATN: Anterior thalamic nuclei; DM: dorso-medial nucleus; LGN: lateral geniculate nucleus; MGN: medial geniculate nucleus; TRN: thalamic reticular nucleus; P: pulvinar nucleus; VN: ventral nuclei. Based on Nieuwenhuys et al. (2007).

Ward, 2011



Thalamic somatotopy from Delli Pizzi et al, 2015

Firing properties and ionic conductances of thalamocortical neurons

Thalamocortical neurons respond to input from sensory pathways of the cortex by discharging in 2 modes:

1. Tonic burst
2. Rhythmic burst

These discharge modes affect the pattern of the EEG:

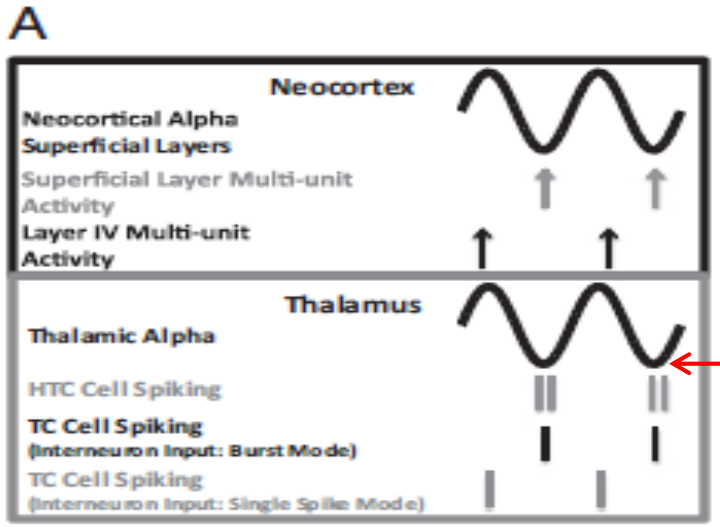
1. Tonic single spike firing occurs during wakefulness or REM sleep.
2. Rhythmic burst firing occurs in non-REM sleep

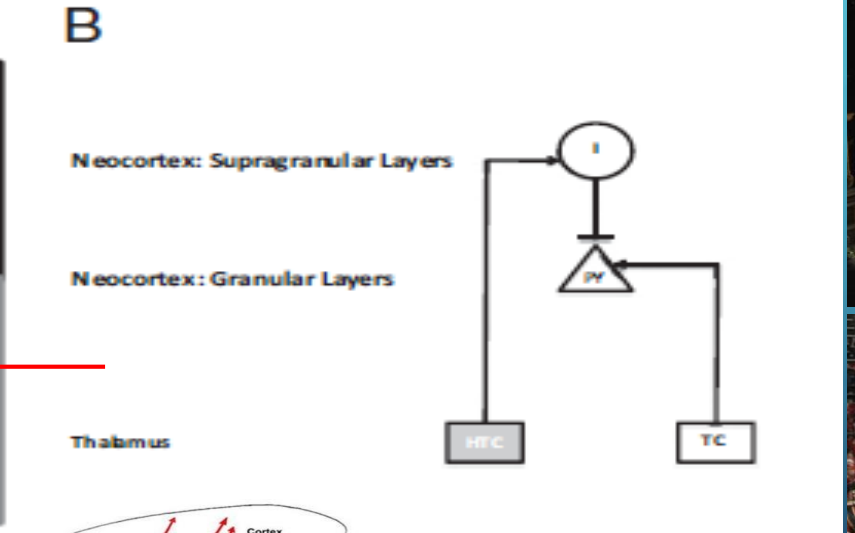
The two patterns of discharge depend on multiple states: the resting membrane potential, activation of calcium channels, and the inputs (excitatory from cortex, inhibitory from reticular nucleus, ascending modulatory input from brainstem cholinergic and monoaminergic nuclei).

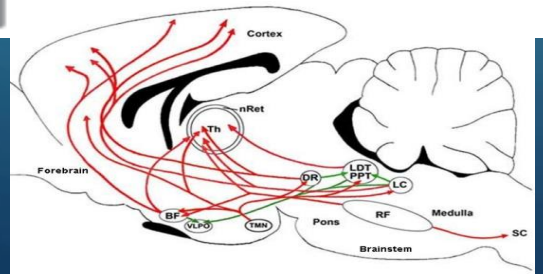
For example, when the resting potential of thalamic cells is relatively hyperpolarized, excitatory inputs activate T-type calcium channels that initiate rhythmic burst activity, leading to synchronization of the EEG (as occurs during non-REM sleep).

The thalamus (Th) drives network oscillations via cortical projections

The thalamus plays a major role in orchestrating the change in the discharge pattern of cortical neurons that underlies the EEG differences between wakefulness and NREM sleep. This is because thalamic neurons, like cortical pyramidal neurons, have intrinsic membrane properties that cause their discharge pattern to change as a function of the level of depolarization of the cell. When depolarized these neurons discharge in a single-spike mode, but when hyperpolarized they display a bursting pattern. Since their level of depolarization is dependent on *ascending activating system* projections to the forebrain, the discharge patterns of thalamic cells will thus be modulated by the varying levels of the *ascending activating system* neurotransmitter levels, as wakefulness alternates with the states of sleep.



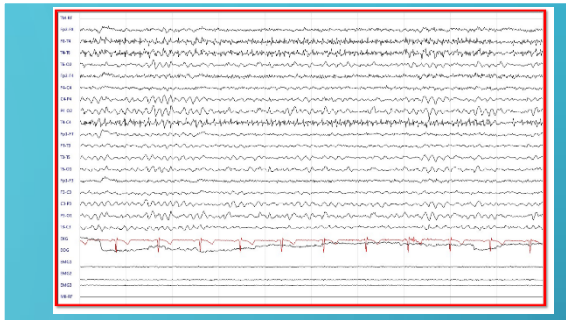




Thalamo-cortical dysrhytmia model

***Thalamo-cortical dysrhythmia*. t**halamic lesions in mediodorsal and anterior nuclei induce confabulatory states with release of self-centered narratives. In PDD and DLB, recent neuroimaging and neuropathological studies have shown microstructural and postsynaptic alterations of thalamic nuclei (Delli Pizzi et al, 2015).

The thalamo-cortical dysrythmia (TCD) theory were based on stereo-EEG recordings performed during stereotactic surgery, showing low threshold bursting activity with a theta rhythmicity in medial thalamic nuclei of PD patients [Steriade]. Cortical EEG recordings showed theta activity coherent with thalamic slow theta rhythms. The seminal papers suggested that, in several disorders including PD, cortico-thalamo-cortical interactions may enter a dysrhythmic state, focal, lobar or widespread, characterized by coherence to slow theta rhythms (4-8 Hz), replacing the tonic gamma band activity, linked to sensorimotor and cognitive functions, and the alpha activity during waking rest. The TCD theory postulated that a portion of the thalamocortical system is trapped in spindle-like theta activity whereas other parts of the brain remain in the waking state, with gamma band activations, at the edge of the dysrhythmia-locked brain portions, in a condition akin to dissociated states of parasomnias.



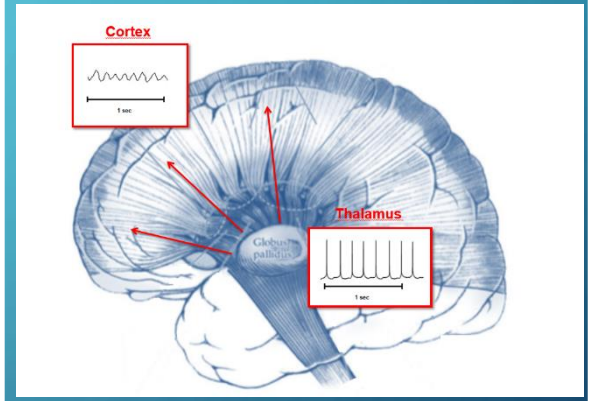


Figure 5 In the top Thalamocortical dysrhythmia (TCD) model in PD-DLB.

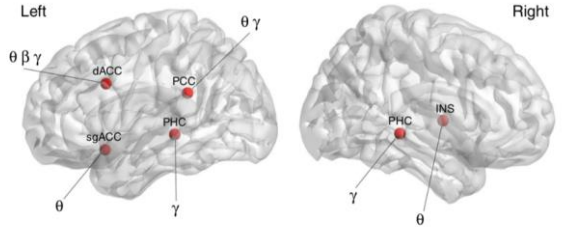


Fig. 4 Support vector machine learning differentiates between thalamocortical dysrhythmia disorder ($N = 277$) including tinnitus, pain, Parkinson, and depression vs. healthy controls subjects ($N = 264$). dACC dorsal anterior cingulate cortex, sgACC subgenual anterior cingulate cortex, INS insula, PHC parahippocampus, AUD auditory cortex, So somatosensory cortex, Mo motor cortex, PCC posterior cingulate cortex, θ theta, β beta, γ gamma

The basic question at hand is:
What happens if a set of neurons in the thalamus displays low rhythmicity in an otherwise awaken brain state?

1. Dissociation from prevailing wakefulness, due to intrusion of features of other stages into ongoing wakefulness (within-mind dissociation); hypnagogic or hypnopompic hallucinations, and complex nocturnal hallucinations appear, in which dream mentation occurs during the transition from sleep to wakefulness and vice versa
2. Dissociation from NREM sleep, due to intrusion of features of other stages into ongoing NREM sleep;
3. Dissociation from REM sleep, due to intrusion of features of other stages into ongoing REM sleep (mind-body dissociation). In this condition the mind is asleep (REM dream mentation) while the body is awake (spinal motor neurons are still excitable).
4. Status dissociatus: motor agitation with enacted dreams, oneirism, continuous or semi-continuous movements. Impaired level of vigilance, with fluctuations in attention and, sometimes, confabulation and mental confusion.

Mahowald and Schenck 1991

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VH

parasomnias

RBD

delirium

Cognitive fluctuations

Mahowald and Schenck 1991

Table 1 **Revised[1,2] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)**

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, *which may precede cognitive decline.*
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

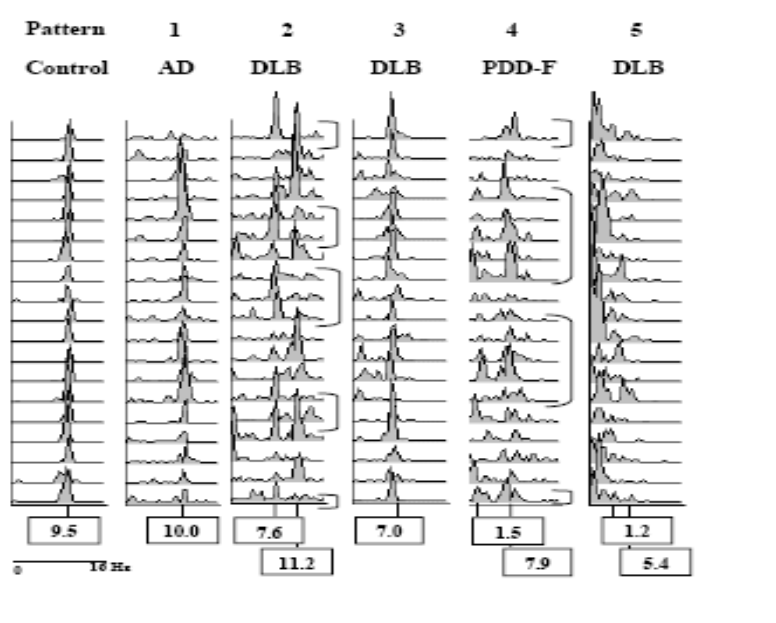
Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

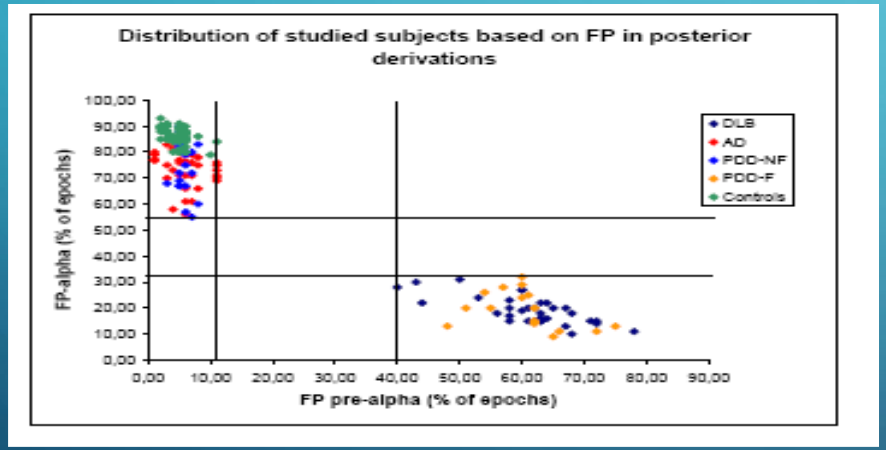
Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

The case of DLB

Electrophysiology





EEG abnormalities highly correlated with FC (only PDDF had the same alterations)

Bonanni et al, Brain 2008

Contents lists available at ScienceDirect
Neurobiology of Aging
journal homepage: www.elsevier.com/locate/neuaging

Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies☆

Laura Bonanni [a,b,*], Bernardo Perfetti [a,b], Stefania Bifolchetti [a,b], John-Paul Taylor [c], Raffaella Franciotti [a,d], Lucilla Parnetti [e], Astrid Thomas [a,b], Marco Onofrj [a,b]

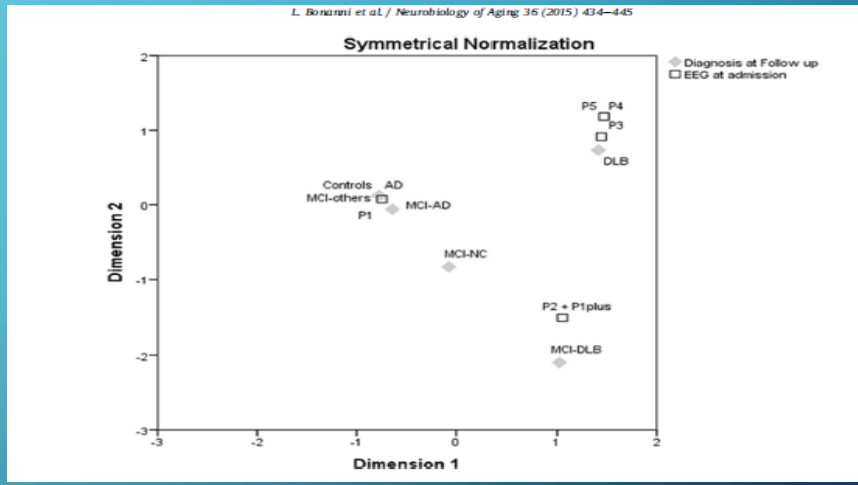


Table 4
Predictive value of EEG CSA salient patterns for the diagnosis of conversion to specific dementia

Observed	Predicted			
	MCI-DLB	MCI-NC	MCI-AD	Correct percentage
MCI-DLB	20	0	0	100.0
MCI-NC	3	0	5	0.0
MCI-AD	1	0	13	92.9
Overall percentage	54.8	0.0	45.2	76.2

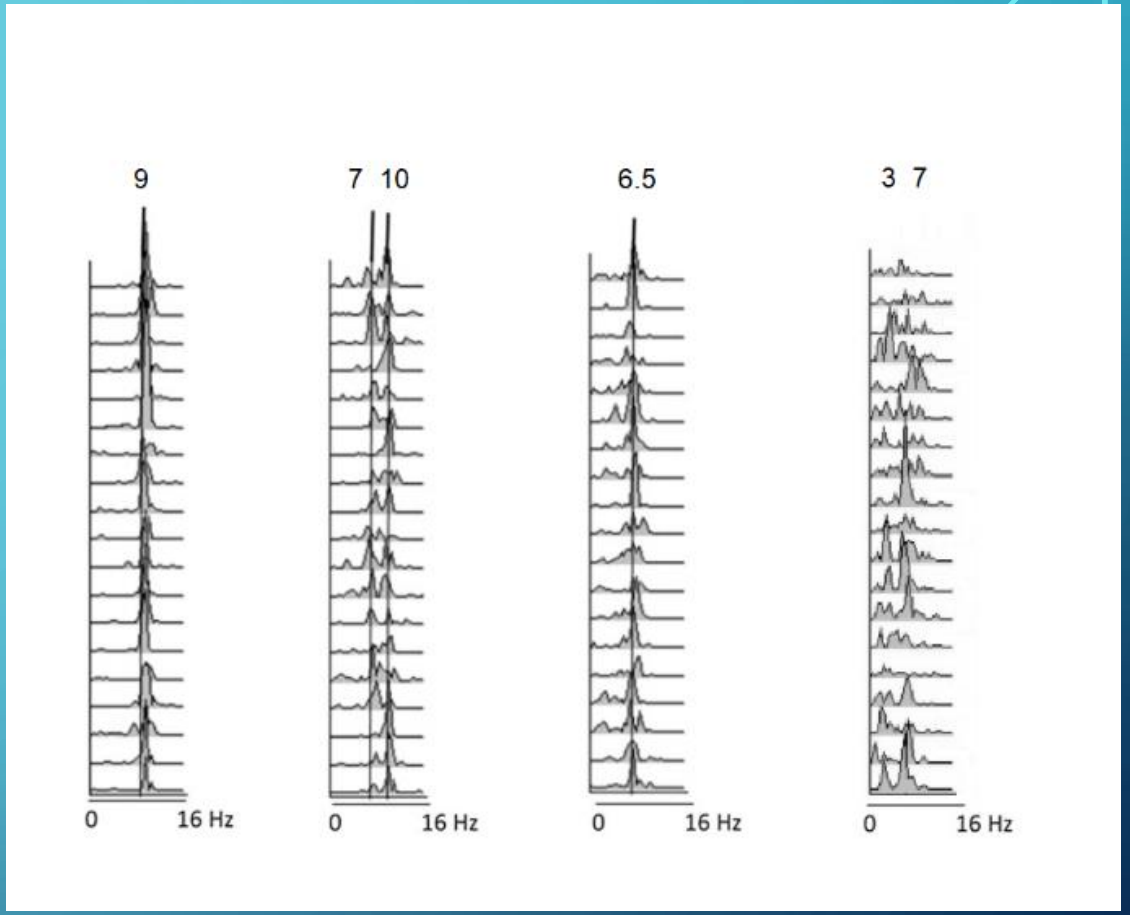
Key: MCI-AD, mild cognitive impairment converted to Alzheimer's disease; MCI-DLB, mild cognitive impairment converted to dementia with Lewy bodies; MCI-NC, mild cognitive impairment non converters.

Bonanni et al, Neurobiol of Aging 2015

EEG alterations in DLB

Evidence for TCD in PD-DLB. The 5-to-8 Hz EEG was only recently confirmed as an uncontroversial feature of DLB, considered a hallmark of cognitive decline rather than of motor symptoms. The abnormal EEG of DLB patients is characterized by the appearance of this fast-theta or pre-alpha activity during wakefulness [Bonanni et al 2008, 2015, 2016]. Its presence predicts occurrence of cognitive decline, tracks the evolution of mild cognitive impairment in PD and is correlated with the severity of cognitive fluctuations in DLB. The pre-alpha activity appears initially as a pseudoperiodic inscription on normal resting state background activity predominantly in the frontal regions, and becomes, with time, diffusely present on all scalp derivations recording cortical activity. Its pattern is rhythmic, as typical of thalamocortical spindling activity. In patients with severe dementia, rhythmic pre-alpha becomes less clearly distinguishable, as it is concealed by slower (theta–delta) arrhythmic activities, which are due to cortical disconnection.

For the first time EEG features were accepted as biomarker of a neurodegenerative condition.

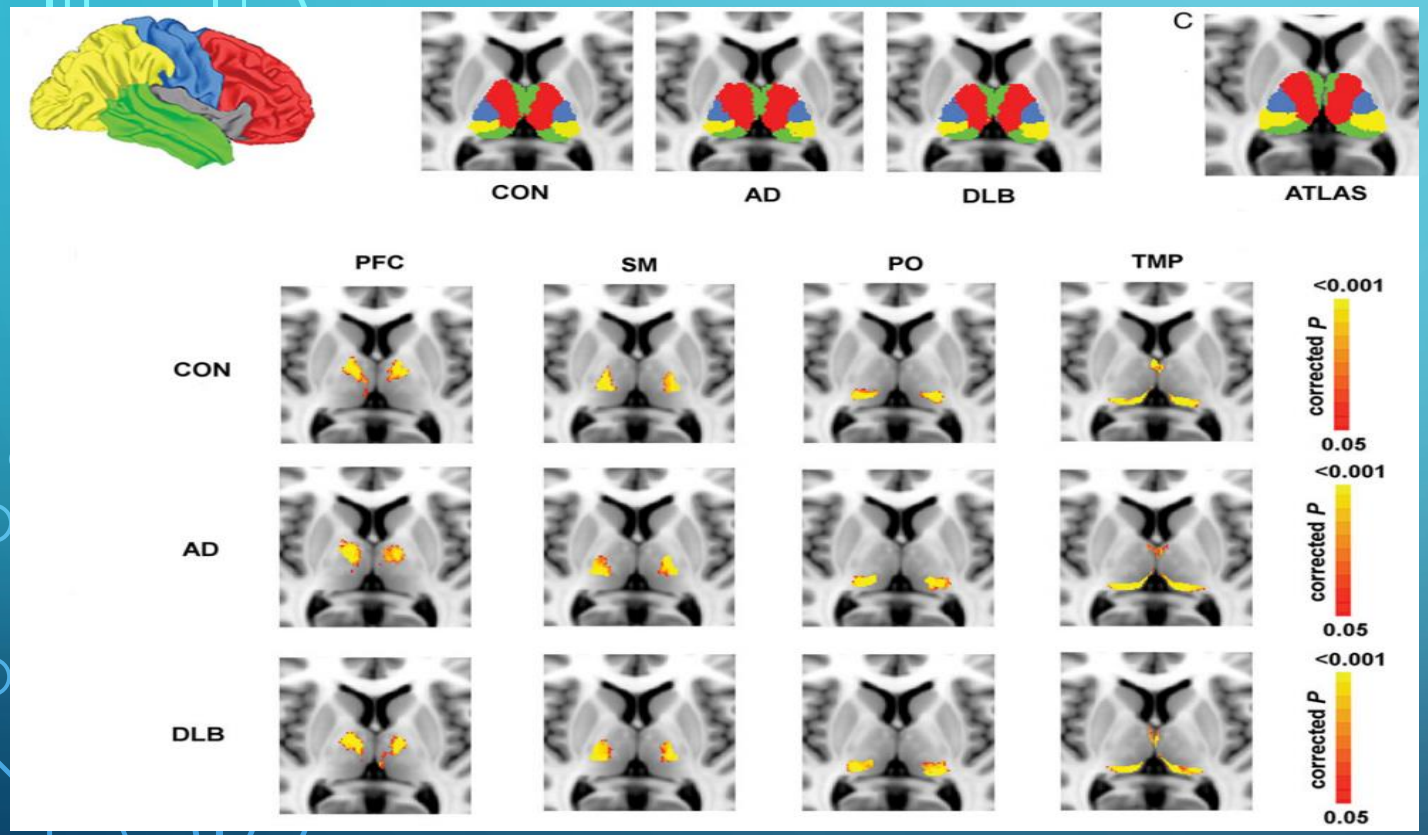


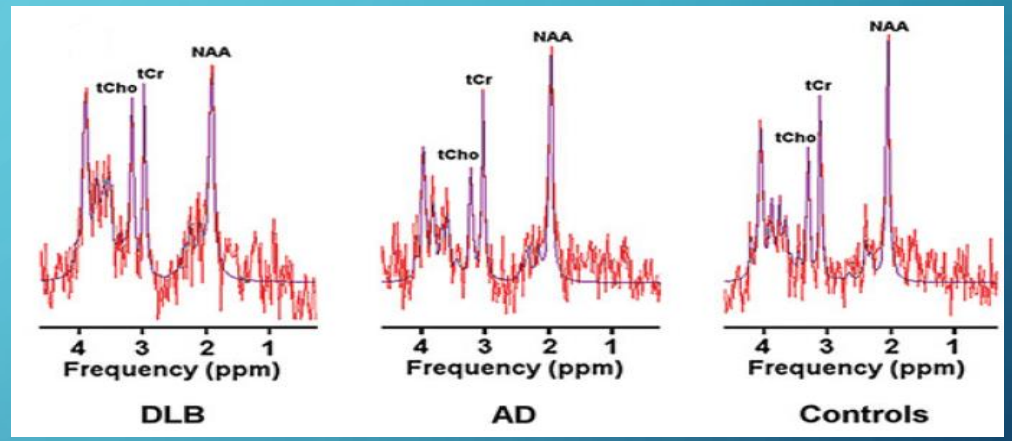
Alfa Alfa + pre-alfa pre-alfa delta + pre-alfa

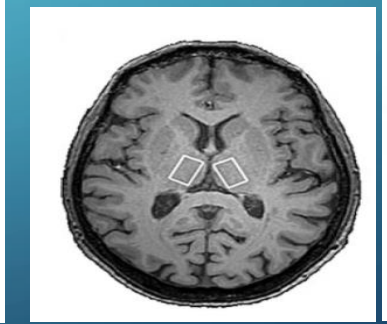
Cerebral Cortex October 2015;25:3682–3689
doi:10.1093/cercor/bhu220
Advance Access publication September 26, 2014

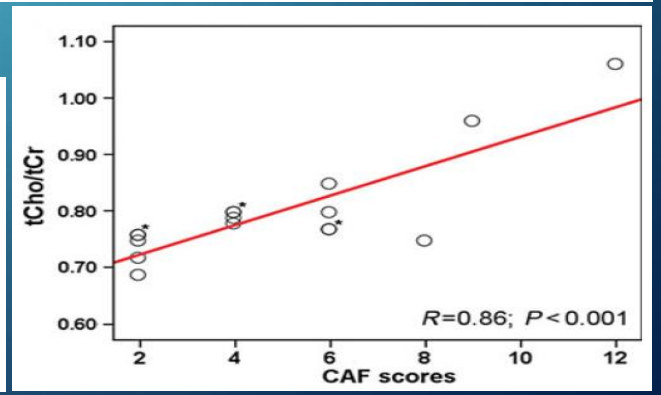
Thalamic Involvement in Fluctuating Cognition in Dementia with Lewy Bodies: Magnetic Resonance Evidences

Stefano Delli Pizzi[1,2,3], Raffaella Franciotti[1,2,3], John-Paul Taylor[4], Astrid Thomas[1,2], Armando Tartaro[1,3], Marco Onofrj[1,2] and Laura Bonanni[1,2]









CORTEX 59 (2014) 133–148

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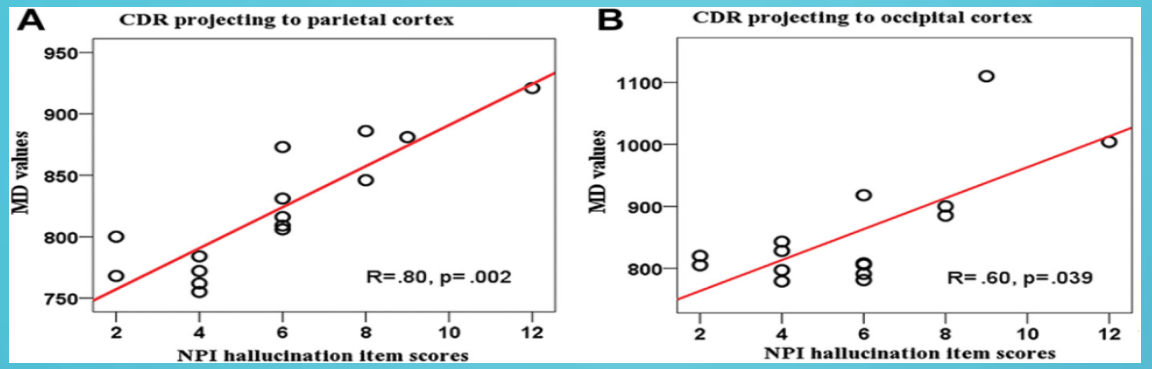
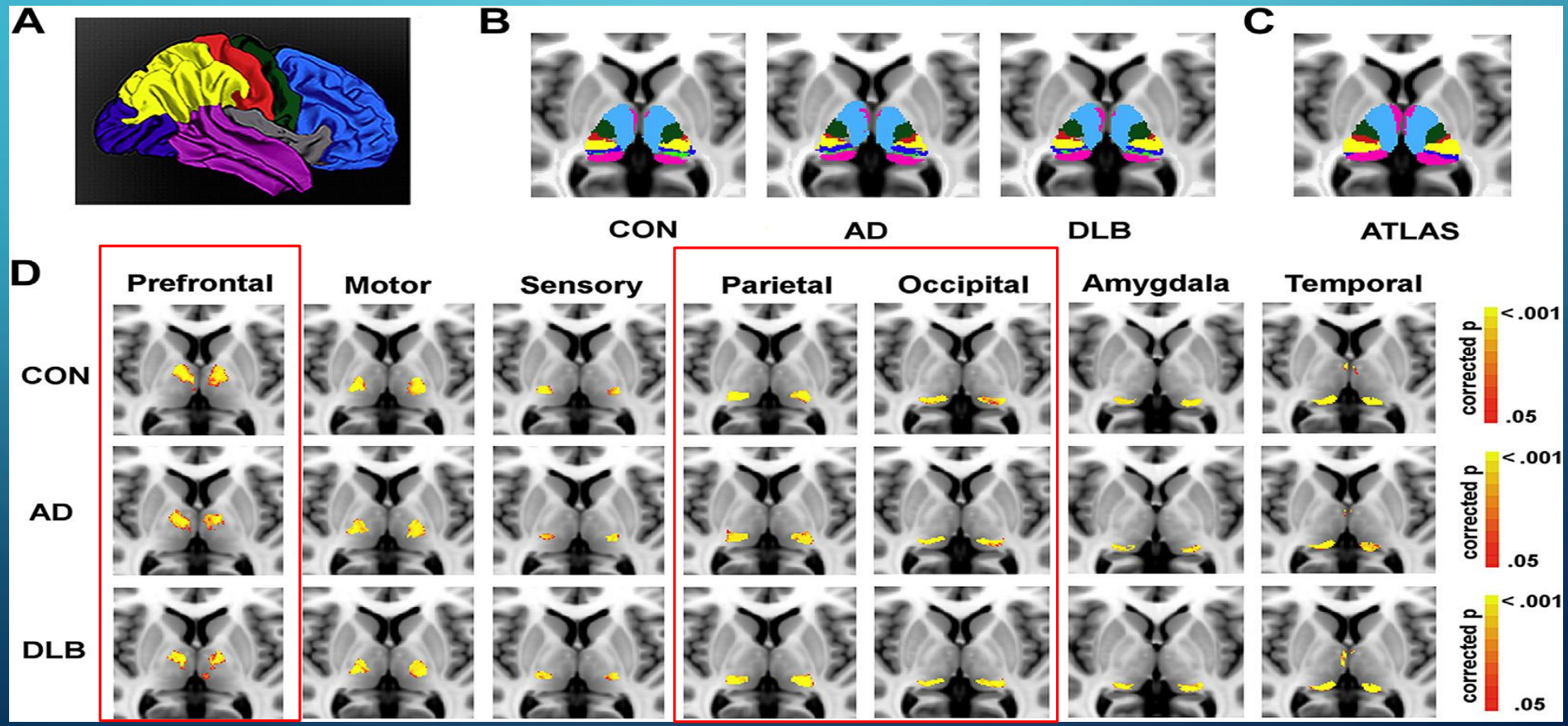
Relevance of subcortical visual pathways disruption to visual symptoms in dementia with Lewy bodies

Stefano Delli Pizzi [a,b,c], Valerio Maruotti [b], John-Paul Taylor [d], Raffaella Franciotti [a,b,c], Massimo Caulo [a,c], Armando Tartaro [a,c], Astrid Thomas [a,b], Marco Onofrj [a,b] and Laura Bonanni [a,b,*]





frontiers in Aging Neuroscience

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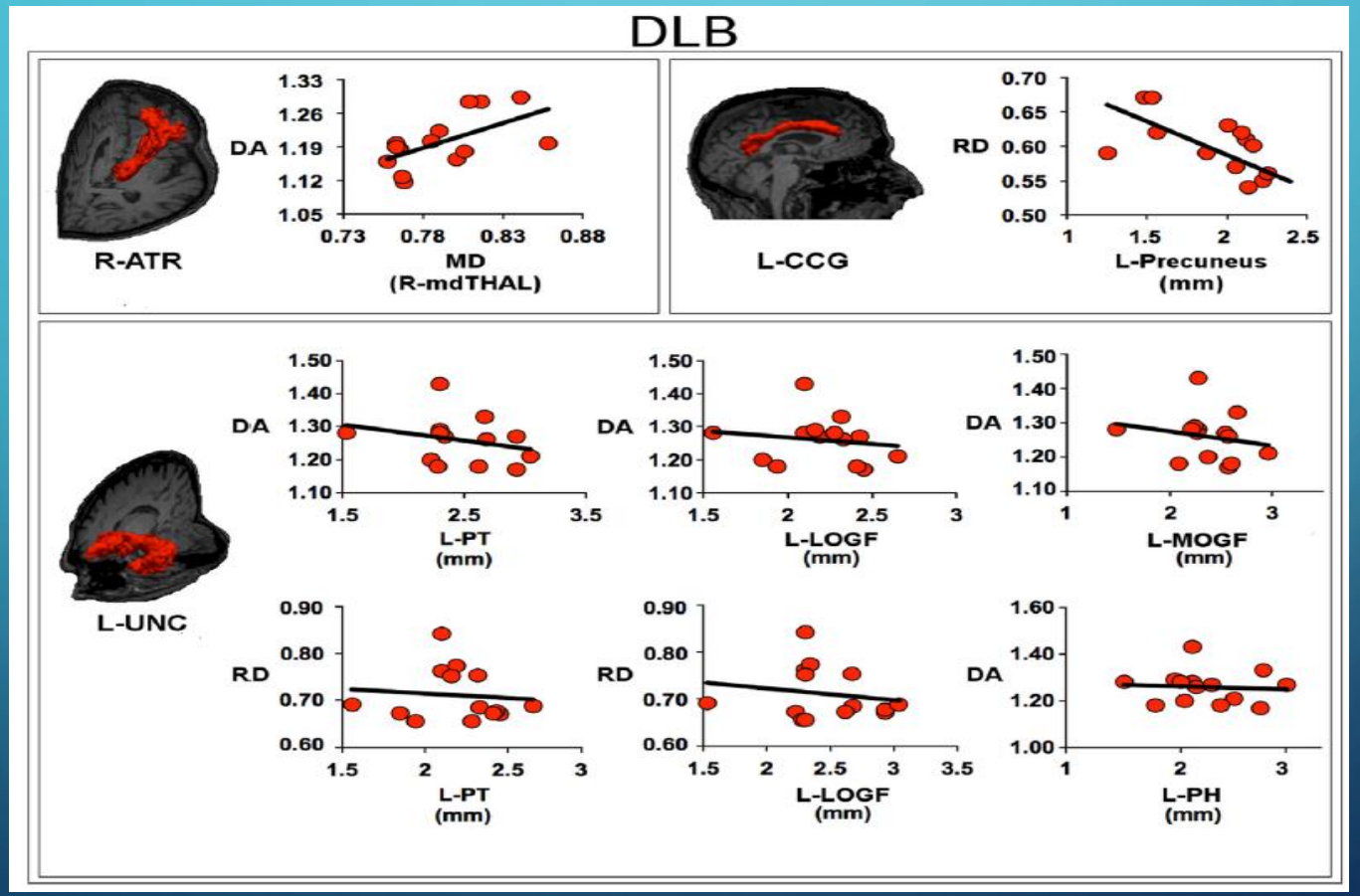
Structural connectivity is differently altered in dementia with Lewy body and Alzheimer's disease

*Stefano Delli Pizzi[1,2], Raffaella Franciotti[1,2], John-Paul Taylor[3], Roberto Esposito[2], Armando Tartaro[2], Astrid Thomas[1,2], Marco Onofrj[1,2] and Laura Bonanni[1,2]**



Specific Patterns of Neuronal Loss in the Pulvinar Nucleus in Dementia With Lewy Bodies

Daniel Erskine, MRes,[1,2] Alan J. Thomas, MD, PhD,[3] Johannes Attems, MD,[1] John-Paul Taylor, MD, PhD,[3] Ian G. McKeith, MD, PhD,[3] Christopher M. Morris, PhD,[1,2] and Ahmad A. Khundakar, PhD[1]*

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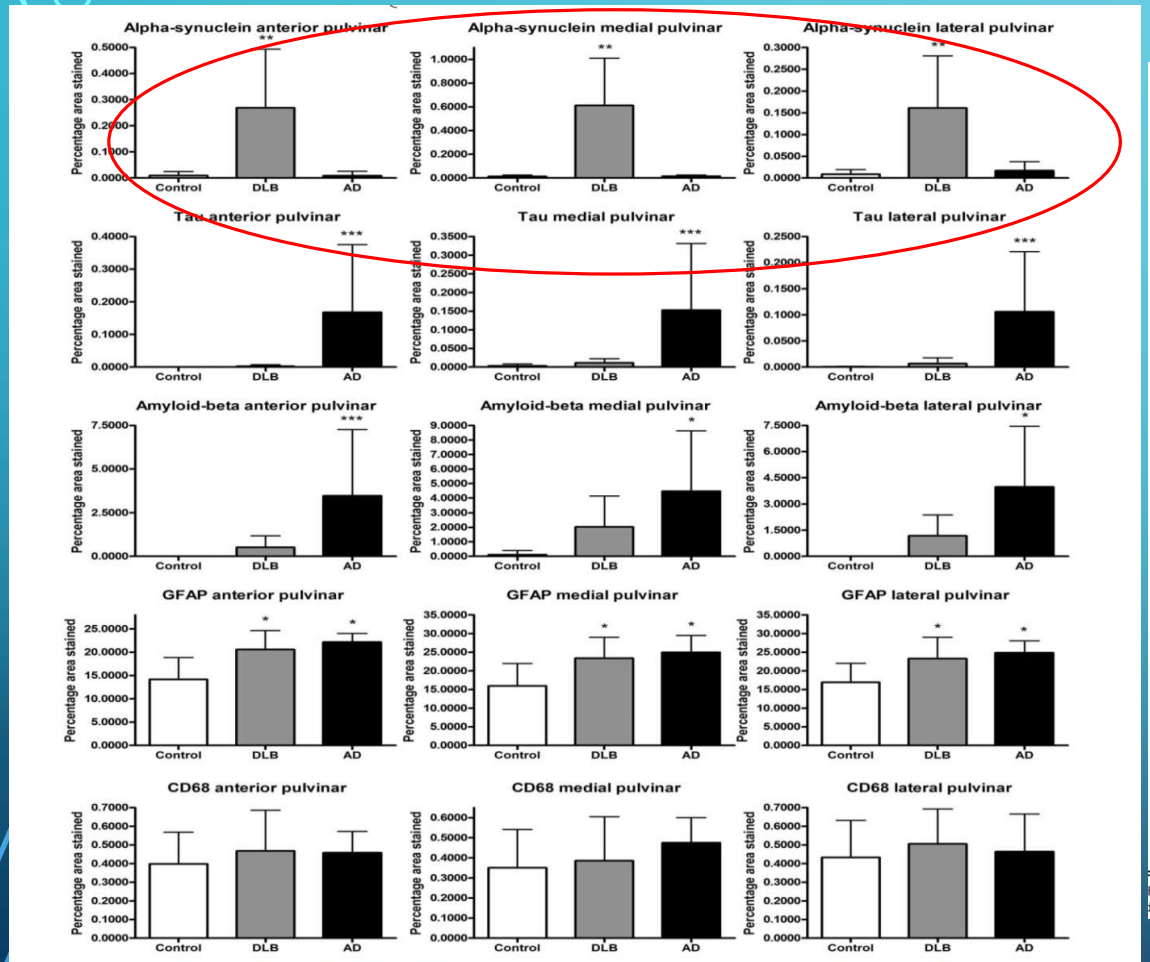

FIG. 2. Quantitative neuropathology in the pulvinar subnuclei. Bars represent means, and error bars represent standard deviation. *$P < 0.05$ compared with control; **$P < 0.05$ compared with control and DLB; ***$P < 0.05$ compared with control and AD.

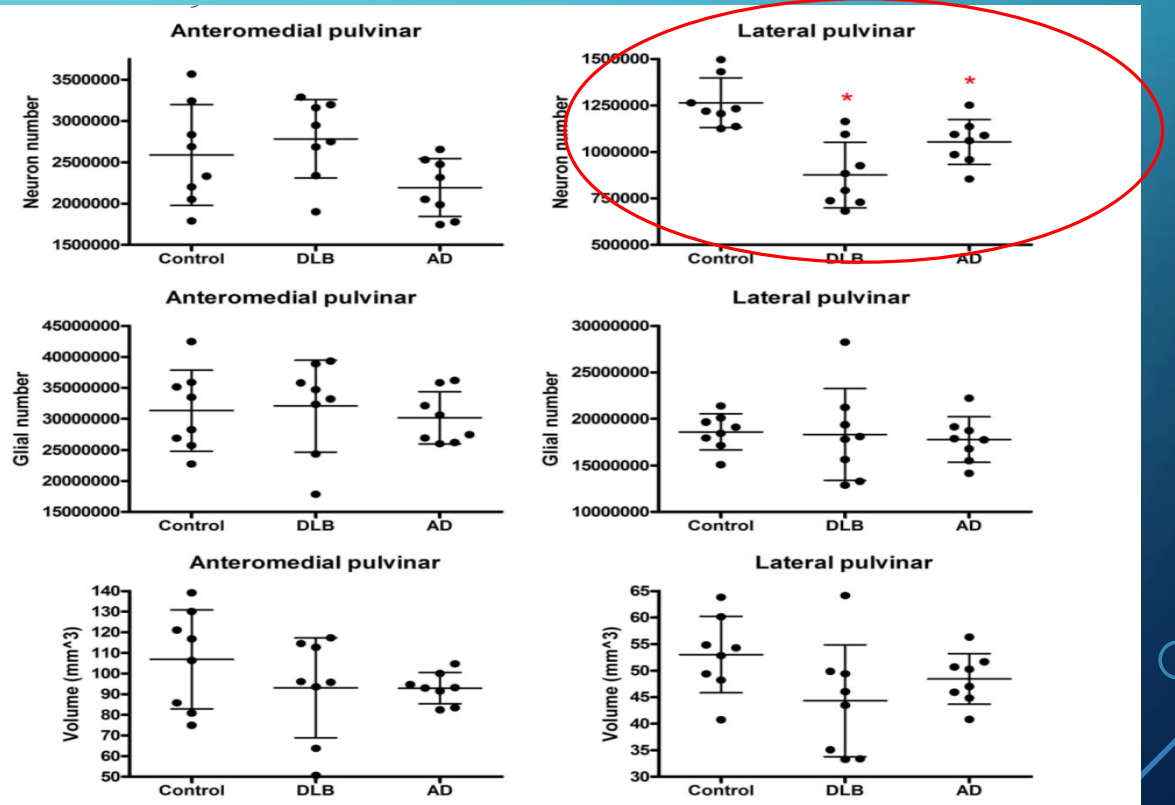

FIG. 3. Stereological estimates of number and volume in the pulvinar nuclei. *$P < 0.05$, **$P < 0.01$. Lines represent the mean, and error bars represent the standard deviation. Levene's test of equality of error variances suggested that homogeneity of variance could be assumed for all stereological data, with the exception of total volume in the anteromedial pulvinar ($P = 0.032$). [Color figure can be viewed at wileyonlinelibrary.com]

TCD and DMN decoupling

We hypothesize therefore that in DLB TCD drives the DMN-PCC decoupling from anterior control and attentional networks, leaving DMN unconstrained, as if during REM sleep. This process is progressive, being initially intermittent and mild and eventually persistent and severe, embedded into cognitive impairment and dementia.