

Disrupted sleep and circadian patterns in frontotemporal dementia

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Background: A study of the pattern of Sleep/Wake disturbance in frontotemporal dementia (FTD). **Methods:** Sleep diaries and prolonged actigraphy were used to record the activity, sleep and wake of 13 patients with a clinical diagnosis of FTD. These were compared with diaries and actigraphy from normal age/sex matched controls and also to a population with probable Alzheimer's disease (AD). **Results:** There was significant sleep/wake disturbance in FTD. This occurred throughout the course of the illness and the nature of the sleep disturbance was different to patients with AD. FTD subjects showed increased nocturnal activity and decreased morning activity compared with controls, suggesting possible phase delay. Sleep diary data confirmed decreased sleep efficiency and decreased total sleep in all FTD patients. **Conclusions:** We describe significant sleep disturbance in non-institutionalized patients with FTD and suggest that early sleep disturbance may help differentiate between FTD and AD.

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Introduction

Frontotemporal dementia (FTD) refers to a group of non-Alzheimer's dementias that are characterized by focal atrophy of frontal and temporal regions. FTD consensus diagnostic criteria have been established [1]. The presence of stereotypic behaviour, reduced empathy, changes in eating preference, disinhibition and features of poor social awareness have been shown to distinguish between FTD and Alzheimer's disease (AD) [2]. Despite this, diagnosis in the early stages is difficult and there is a need for biomarkers which can distinguish AD from FTD. Longitudinal studies have shown that patients with normal or borderline magnetic resonance imaging (MRI) changes at presentation follow a more benign clinical course [3] but neuropathological information about such patients is currently lacking. Their symptomatology is indistinguishable from that seen in those with more rapidly progressive dementia but may reflect functional disruption of frontotemporal systems [4].

Sleep–wake disturbance is frequent in the demented elderly and up to 50% of those with AD will have severe nocturnal restlessness and sleep–wake cycle reversal at some stage [5]. AD patients with sleep disturbance have a more rapid cognitive decline [6] and

sleep disturbance is a major cause of institutionalization [7]. Conversely, those with mild AD often have entirely normal sleep/wake patterns [8].

Circadian timing is controlled by the suprachiasmatic nuclei of the hypothalamus (SCN) [9]. Patients with AD in the latter stages show neuropathology within the SCN [10] implicating degeneration in the core clock mechanism as a cause of sleep disorders, at least in end stage AD.

There is much less available data about sleep or circadian rhythm abnormalities in FTD although a number of the behavioural inventories used in the assessment of FTD highlight prominent sleep disturbance [11,12]. There is a single study of institutionalized patients that suggested that there were differential patterns of circadian rhythm abnormalities in AD patients compared with those patients with FTD (Harper *et al.*, 2001) but there have been no studies of the non-institutionalized or those with early stage disease. It is therefore still unclear whether the circadian rhythm is selectively affected within different neurodegenerative disorders and whether the pattern of sleep–wake disturbance could act as a diagnostic marker for a particular dementia.

A number of carers within our regional memory clinic complain that FTD relatives have significant sleep disturbance prompting us to study the sleep–wake cycles of our non-institutionalized patients in more detail. Sleep diaries and actimetry were used to assess the sleep–wake disturbance in non-institutionalized FTD patients in comparison with normal and AD controls.

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Subjects and methods

Subjects

Ethical approval was granted by the Cambridge Local Research Ethics Committee. Consent was obtained from patients and/or their next of kin. There were two age and sex matched groups selected as controls; the first were healthy subjects, 10 men and 1 female (range 51–71 years, mean 66.8), who were recruited from the MRC Cognition and Brain Science Unit control panel. This comprises healthy, elderly volunteers within the region. The second group of controls were patients recruited from the Addenbrookes Hospital memory clinic who fulfilled the National Institute of Neurological and Communicative disorders and stroke and the Alzheimer's disease and related disorders association (NINCDS ADRDA) criteria for moderately severe, probable AD [13]. Patients with more advanced AD were chosen as previous studies have shown sleep disturbance within this group rather than those with early stage disease. Some controls had been recruited from as part of a previous study [8]. FTD subjects were recruited from the Early Onset Dementia Clinic database. All patients were comprehensively assessed by a neurologist and a neuropsychologist. One female and 12 male subjects (age range 51–72 years, mean 63.9) were recruited. They all fulfilled the Neary Criteria [1] for the diagnosis of FTD with prominent behavioural symptoms, (bvFTD). All subjects were living at home with a carer. Patients had been diagnosed for a mean period of 6.5 years (range 2–17 years).

Extensive assessments were used to determine the severity of disease. The mini-mental state examination (MMSE) [14], Addenbrookes Cognitive Estimate (ACE) [15] and Clinical Dementia Rating (CDR) were used to assess patients. Patients with a CDR of 1.0 were classified as mild and 2.0 as moderate severity. Carers also completed a comprehensive behavioural questionnaire relating to the subjects' behavioural and cognitive symptoms and levels of activities of daily living skills over the last month, the Cambridge Behavioural Inventory (CBI). No subjects met the criteria for depression on the Hamilton depression rating scale [16]. All patients had MRI and a semi-quantitative rating of standardized coronal T2 images [3] was used to further subdivide the bvFTD patients into two groups; a group with normal or borderline MRI changes (MRI-normal) (six patients) and a group (seven patients) who had definite frontotemporal atrophy on MRI (MRI-abnormal). Patients also completed the Epworth Sleepiness Score [17] and a detailed sleep history was taken to exclude any other primary sleep disorders.

Three of the FTD patients took medication with one patient taking a proton pump inhibitor, one taking a low dose of an anticonvulsant (sodium valproate) as well as a tricyclic antidepressant (clomipramine) and one taking a Cox-2 inhibitor for pain relief.

Eight of the healthy normal controls took cardiovascular medication including anti-platelet therapy, antihypertensives and diuretics. One took a proton pump inhibitor and one took allopurinol.

Activity/rest assessment

Subjects wore a wrist mounted activity monitor (Actiwatch; Cambridge Neurotechnology, Cambridge, UK) for 28 days and carers completed a daily sleep diary [18]. Only one subject completed his own sleep diary and this was checked and verified by his wife. In all cases, carers were sleeping in the same room as the subjects. None of the controls or subjects was employed and all were studied within their normal environment. Data were plotted and analysed with CLOCKLAB software (Actmetrix, Evanston, IL, USA) and then subjected to non-parametric circadian rhythm analysis (NPCRA) using the ACTIWATCH software. This is more suitable than cosinor or other parametric analyses for the quantitative analysis of non-sinusoidal data [19]. Inter-daily variability is a measure of stability across days, whilst intra-daily stability reflects the relative consolidation/fractionation within days based on how many transitions occur between activity and rest. The third variable, relative amplitude (RA), reflects the difference in activity level between the 10 most active-(M10) and 5 least-active hours (L5) in the day. It provides a more comprehensive representation of rhythm amplitude than the simple difference between single measures of peak and nadir. The normalized amplitude was also calculated by dividing the RA by the mean hourly activity level for that subject.

In addition the sleep fragmentation index, percentage of sleep and sleep efficiency was derived using the sleep diary data and the ACTIWATCH software. These data are derived from the sleep time recorded by the carer compared with the actigraphically determined sleep time.

The main effects and their interactions were analysed by repeated measures and/or factorial one and two way analysis of variance (ANOVA) using SPSS for PC. Because of the pronounced heterogeneity in the mean activity levels and overall profiles in the FTD population, in order to compare activity/rest profiles between groups, actimetric data were standardized as follows. For each subject, the average profile was expressed relative to the daily mean for that subject. The profiles were then replotted so that all subjects were aligned relative to their individual activity onset (i.e. first increase in

activity level above the daily mean). This method of normalization enabled comparison of the daily profiles to be made independent of differences in the overall activity level of each subject and independently of the very different phasings of activity onsets observed in the traces from different individuals. The normalized profiles were then subjected to repeated measures ANOVA, with group (control or total FTD) and time of cycle as main effects.

One FTD subject found the watch difficult to tolerate and only seven full days of activity were recorded, one subject went into respite care for 2 days and the watch was not worn during this period. The other subjects all wore the watch for 28 days.

Results

Subject profiles

The Epworth Sleepiness Score ranged from 4 to 14 with a mean that was normal at 6.8 (normal < 10) although the carer had to complete the questionnaire in two cases. The mean MMSE, ACE and CBI are shown for all FTD patients ($n = 13$) and for the two sub groups, seven MRI abnormal and six MRI normal, in Table 1. The mean MMSE and ACE scores were lower for the progressive group with higher CBI reflecting greater functional disability, but there was a substantial overlap between the two groups. There was no statistically significant differences between any of the other measures within Table 1.

Actograms

The control subjects all exhibited robust, high amplitude activity bouts, clearly consolidated to the daytime hours (Fig. 1a). The night hours were characterized by low levels of activity. Morning activity onsets and late evening offsets were well defined and consistent from day to day. Within the FTD group there was much

more variation in the activity/rest cycles (Fig. 1b–d). Some patients showed consolidated, well defined patterns similar to the control subjects (Fig. 1b) but there were also patients with disrupted patterns of activity who displayed poorly defined onsets and offsets to activity (Fig. 1c and d). They were variable from day to day and these subjects exhibited fragmented patterns of rest and activity. The range of total activity also varied more within the FTD subjects (M10 activity level range 3680–29612) compared with the control subjects (M10 activity level range 7902–29123).

Activity profiles

The activity of the control group showed a sharp, well-defined transition from rest to activity, with a marked maximal activity in the morning hours after waking and a smaller increase in activity in the afternoon. Activity levels then declined progressively and gradually through the late afternoon and into the evening. In marked contrast, the group profile for FTD showed less definition of the morning transition from rest to activity, both because of a trend for earlier activity onset and because of less pronounced peak activity after waking. Moreover, the secondary post-noon activity peak was less evident and delayed in the FTD subjects.

Consequently, although (following normalization) ANOVA revealed no significant difference between groups in the overall activity level of the normalized data ($P = 0.26$), there was a highly significant effect of time, as anticipated [$F(47, 1034) = 82.9, P < 0.001$]. Importantly, there was a highly significant interaction between group and time [$F(47, 1034) = 1.74, P = 0.002$] indicating that the 24 h profile of the FTD subjects was different from that of controls (Fig. 2). With activity onset plotted at 08.00, relative activity levels were lower in FTD subjects between 10.00–11.00 and immediately after 12.00, and they also declined sooner in the late evening from 21.00–23.30 (*post hoc* Scheffe's test).

Table 1 Summary of cognitive/behavioural scores and non-parametric measures of actimetric data by group (presented as mean \pm SEM)

Subjects	Age (years)	MMSE	ACE	CBI	Inter-day stability	Intra-day variability	L5 (total counts)	M10 (total counts)	Normalized Relative amplitude
Control ($n = 11$)	66.8 \pm 5.7	29.0 \pm 0.8	93.5 \pm 3.8	N/A	0.52 \pm 0.14	0.84 \pm 0.19	822 \pm 378	16420 \pm 7640	50.9 \pm 3.87
FTD ($n = 13$)	63.9 \pm 8.8	25.2 \pm 4.8	73.3 \pm 18.8	110.7 \pm 50.8	0.51 \pm 0.12	0.9 \pm 0.3	1035 \pm 529	16203 \pm 8276	48.2 \pm 1.65
Normal MRI FTD ($n = 6$)	64.4 \pm 5.3	28.3 \pm 3.6	86.7 \pm 9.2	95.2 \pm 57	0.487 \pm 0.09	0.787 \pm 0.27	883 \pm 657	17956 \pm 9682	45.8 \pm 2.15
MRI abnormal FTD ($n = 7$)	63.3 \pm 8.7	22.4 \pm 4.2	61.9 \pm 21	124 \pm 41	0.522 \pm 0.16	0.999 \pm 0.19	1166 \pm 396	14701 \pm 7291	51.5 \pm 2.16

FTD, frontotemporal dementia.

Normalized amplitude refers to M10–L5 counts/mean hourly activity level.

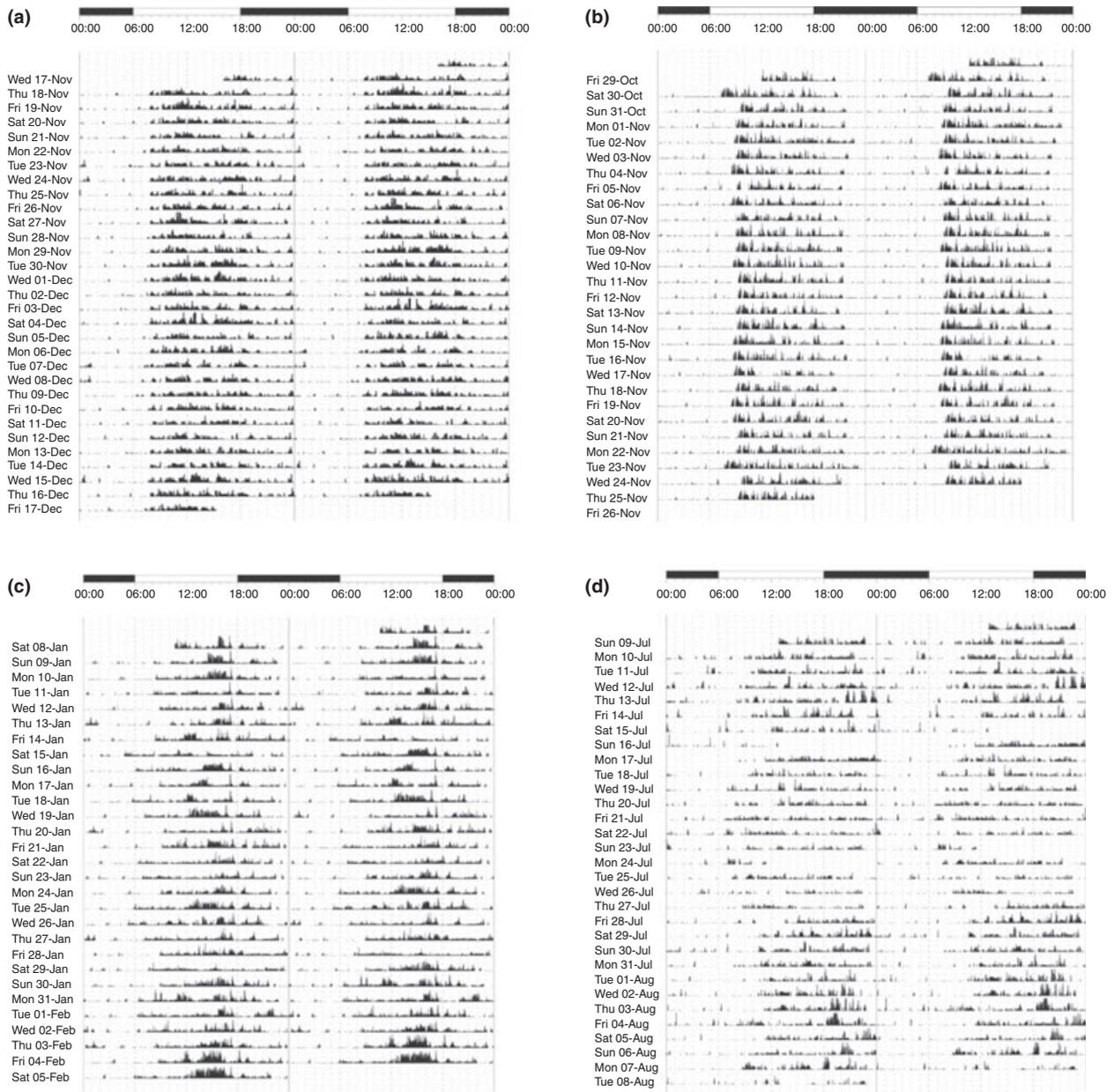


Figure 1 Representative actograms from healthy control (a) and frontotemporal dementia (FTD) subjects (b–d). Data from 28 consecutive days are double-plotted on a 48 h time base for clarity. Controls showed high activity during daytime hours and low night time activity. Activity onset and offsets are defined and consistent from day to day. Some FTD subjects had activity patterns similar to controls (b) but others had much lower amplitudes and more variable activity onset and offset (c–d).

The difference in 24 h profile between controls and patients was still present when the FTD patients were analysed as sub groups of progressive and non-progressive [three group comparison, time * group interaction, $F(47,987) = 1.35$, $P = 0.018$]. A direct (two group) comparison of progressive versus non-progressive FTD patients did not, however, show any significant difference [time * group interaction $F(47,517) = 0.86$, $P = 0.74$]. In summary, there was a

significant difference in daily distribution of rest and activity of all patients with FTD compared with controls but there was no significant difference between those with abnormal and normal MRI.

Non-parametric circadian rhythm analysis revealed that the stability, consolidation and peak/trough changes of activity in the control subjects were not significantly different to those of the FTD patients. This is shown in Table 1. Comparison was made between the

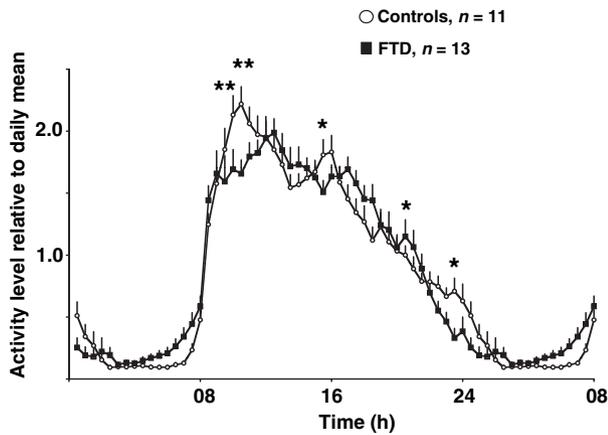


Figure 2 Group activity profiles (plotted as mean \pm SEM) for control and frontotemporal dementia subjects. The data are plotted relative to each individual's mean activity level and time of activity onset. *Indicates significantly different from age matched control by Scheffé's *post hoc* test ($P < 0.05$).

FTD subgroups (abnormal and normal MRI) and there was also no significant difference between these groups and the control subjects.

Sleep diary analysis

The data from the sleep diaries was combined with the actimetric data to study the percentage of sleep, sleep efficiency and sleep fragmentation in control and FTD subjects. FTD subjects had a reduced sleep efficiency (one tailed t -test $t = -2.6$, $P \leq 0.08$) and reduced percentage of sleep ($t = -1.99$, $P = 0.03$). Fragmentation of sleep did not, however, reach statistical significance ($P = 0.68$).

When FTD subjects were divided into MRI abnormal and MRI normal non-groups, the sleep efficiency was worse in the abnormal MRI patients and the difference was highly significant ($P = 0.008$). In summary, the sleep diary data suggest a significant difference between the two subgroups with patients having abnormal MRI, having less efficient night sleep.

Comparison between FTD and AD activity profiles

The relative activity levels were also calculated for an age-matched group of AD patients (previously published Hatfield *et al.* 2004). Previously patients with moderately severe (MMSE ≤ 19) AD demonstrated deranged activity profiles compared with age matched controls. The actimetric data from the FTD patients and the moderate AD group were standardized as before and then subjected to repeated measures ANOVA. Comparison between the FTD group and the moderate AD patients showed a highly significant interaction

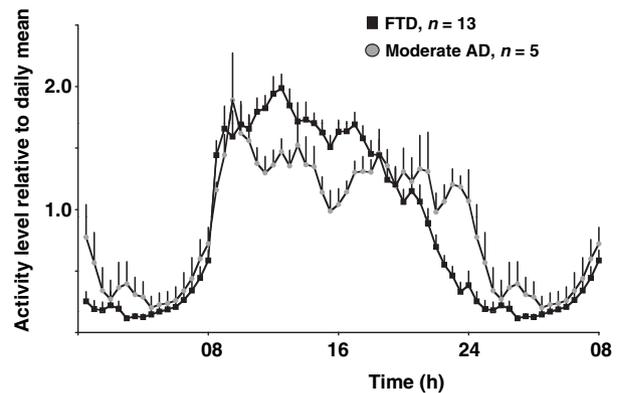


Figure 3 Group relative activity profiles (plotted as mean \pm SEM) for moderate Alzheimer's disease and frontotemporal dementia subjects. The data are plotted relative to each individual's mean activity level and time of activity onset. (point of first cross from below to above daily mean activity score).

between group and time [$F(46,736) = 3.22$, $P < 0.001$] (Fig. 3). The transition from rest to activity was not appreciably different between the groups, but the distribution of activity across the day and evening contrasted markedly, with the AD group having a far longer activity phase. The AD patients showed consistently less activity in the morning compared with the FTD group, but persisted in greater activity during the evening and into the night. This suggests that the nature of the sleep disturbance between the two groups is different. Clearly, further longitudinal analyses would resolve this issue in FTD patients.

Discussion

This study is the first to demonstrate significant sleep/wake disturbance in non-institutionalized FTD patients. This occurs throughout the course of the illness and the nature of the sleep disturbance is different to that seen with AD. These novel data suggest that early sleep disturbance may help to differentiate between FTD and AD.

Frontotemporal dementia was associated with disruption of the sleep-wake cycle compared with an age matched control population. The activity levels of FTD subjects were very variable but statistical analysis showed increased nocturnal activity and decreased morning activity levels compared with controls. In addition, sleep diary data confirmed decreased sleep efficiency and decreased total sleep in all FTD patients with a subgroup with abnormal MRI having the most marked impairment in sleep efficiency. This is in contrast to a previous study within our group showing no difference in sleep/wake patterns in those with mild AD but very marked disturbance in those with moderate disease [8].

Patients were carefully screened for other causes of sleep disturbance e.g. restless legs syndrome but polysomnography was not performed so it is not possible to completely exclude other sleep disorders contributing to sleep disturbance.

The increased sleep fragmentation in the sub group with abnormal MRI suggests increasingly disturbed sleep in this group. These results are based on small numbers but would justify further longitudinal analyses on larger subgroups to see if any difference in sleep/wake patterns became more variable between the two groups over time. There was no significant difference in the NPCRA in those with FTD compared with controls, this may reflect an inadequate sample size. Measures such as M10 or L5 may not show significant differences because of the more marked variability in daily activity between individuals with FTD compared with controls. This is in contrast to moderately severe AD where all patients had reduced activity levels.

There has only been one other study using actigraphy in FTD patients [20] which suggested a differential pattern of rest/activity disturbance in AD and FTD. AD patients showed a phase delay in their circadian rhythm and core-body temperature compared with more fragmented activity within FTD patients and a possible phase advance. Of note, these patients were institutionalized and were part of a cohort that had fulfilled the diagnostic criteria for AD in life then had a revised diagnosis based on their post-mortem pathology. This makes direct comparison with our study difficult, given that the behavioural phenotype of the patients in life must have been different.

All of the remaining literature using actigraphy in dementia has focused on probable AD. Marked disruption to the daily activity patterns of severely demented, institutionalized patients have been consistently reported [19,21]. The degree of activity disturbance can often be inversely correlated with the cognitive score [6,22]. Polysomnography studies have shown that moderately demented AD subjects living at home have fragmented nocturnal sleep and increased daytime napping [23] but that mildly demented subjects show little, if any, differences in their sleep-wake patterns compared with normal elderly controls. Actigraphic studies of those with probable AD have found few abnormalities in those with mild disease. In contrast many, although not all, of those with moderate dementia show significant disruption to their daily patterns [8,19,24]. In summary, these observations suggest that activity/rest disturbance increases in moderately impaired AD patients and tends to progress over time to become a common feature in the severely demented.

One difficulty that arises when comparing probable AD patients to those with FTD relates to measures

used to assess disease severity in FTD. Many patients with FTD have MMSE scores within normal limits yet have severely impaired behaviour. A wide range of cognitive assessments were used in both FTD and AD cohorts to give as much information as possible about the patients studied.

The disturbances of sleep within this cohort of FTD subjects is less marked than those with moderately severe AD but changes were present in the FTD group as a whole rather than those who only had more marked cognitive and behavioural impairment. This is distinct from the pattern of impairment seen in AD where only a subgroup with moderate or severe disease have sleep disturbance. This may reflect differential neuropathology affecting either the SCN directly or the pathways from the SCN that control sleep and wakefulness. Pathological studies in FTD have shown widespread, severe frontal and temporal neuronal loss extending into the orbital, frontal, basal forebrain and hippocampal structures [25]. These regions regulate sleep and wakefulness and it may be that direct pathological involvement of these arcs contributes to sleep fragmentation and disrupted sleep/wake patterns. There is overlap in many of the behavioural features of FTD patients with psychiatric disorders, notably mania. Interestingly, actigraphy performed on patients with bipolar disorder and mania has also shown a less stable and more fragmented appearance than age matched normal controls [26].

Over two-thirds of adult carers who look after those with dementia have disturbed sleep routines [27]. Carers find constant sleep disturbance one of the most difficult things to cope with on a daily basis and it is one of the commonest reasons for patient institutionalization [7]. It may well be that the sleep disturbance in FTD is under recognized and it is therefore important to highlight this to clinicians. Furthermore, the identification and classification of distinct phenotypes of sleep disturbance in different dementias may allow more targeted treatment of sleep disturbance to try and improve the quality of life for patients and carers.

In conclusion, we have demonstrated sleep-wake disturbance in non-institutionalized patients with FTD. This potentially disabling symptom deserves further study to try and improve diagnosis and treatment for patients and carers.

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