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Critical Flicker Fusion Threshold: A Potentially Useful Measure for the Early Detection of Alzheimer's Disease

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Critical Flicker Fusion Threshold (CFFT) is a psychophysical threshold and, in psychological terms, it is regarded as a measure of information processing capacity. CFFT has previously been shown to be a valid and reliable measure in young healthy volunteers and it also has a long history of use as a psychopharmacological measure in this group. Furthermore, the test satisfies many of the requirements of an 'ideal' measure for monitoring change, especially in a psychopharmacological context. Despite this, CFFT has been neglected as a research tool in elderly and Alzheimer's disease (AD) populations and was therefore investigated further in this regard. CFFT in community-based healthy elderly subjects was normally distributed, but CFFT and ascending and descending thresholds were not significantly correlated with age. The difference between ascending and descending thresholds was, however, significantly correlated with age and this relationship appeared to be due almost entirely to a change in the descending threshold. In addition, descending thresholds were found to be significantly greater than ascending thresholds in healthy elderly subjects. In contrast, patients with AD were found to have significantly lower CFFT and descending scores compared with healthy elderly subjects. Interestingly, descending thresholds were significantly lower than ascending thresholds in the patient group, a feature that may be a characteristic of AD. Mean CFFT and ascending and descending thresholds were found to have a high test–retest, split-half and inter-rater reliability, in addition to being significantly correlated with a number of psychometric measures, clinical scales and neuropsychological instruments commonly used to assess patients with AD. CFFT is a quick and simple measure to administer and patients had no difficulty completing the test. Because the measure is a psychophysical threshold, it is free from educational and cultural bias and there are no floor or ceiling effects. From the results of this work, CFFT appears to be a useful research tool in AD. It may be a suitable measure for monitoring cognitive change over time, either in community studies of AD or a clinical trial context, but further work is required. The technique might also contribute to the early detection of AD. This application would be particularly important because it would enable effective pharmacotherapies to be started early during the course of the illness before neuronal damage is too advanced and this would have significant benefits for patients.

KEY WORDS — flicker threshold; early detection; Alzheimer's disease

INTRODUCTION

In Alzheimer's disease (AD) and other forms of dementia, extensive and irreversible brain damage generally occurs before clinical symptoms become apparent. Products for the treatment of dementia have recently been licensed by the Food and Drugs Administration in the USA and by the CSM in the UK. In addition, many pharmaceutical companies are conducting research into products for the treatment of AD. The availability and development of drugs for use in AD will lead to a demand for early detection, ideally at a stage before memory disturbance is apparent. A number of studies which examined the effects of nicotine, hormone replacement therapy and non-steroidal anti-inflammatory drugs in patients with pre-clinical AD were found to reduce the risk of developing AD (Curran *et al.*, 1997). There is therefore a pressing need for a non-invasive, easy to use and inexpensive means of screening people at risk of developing AD which

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would help to facilitate the decision to commence treatment of AD at an early stage.

EARLY DETECTION OF ALZHEIMER'S DISEASE

There are a variety of possible ways of detecting pre-clinical or early AD (Touchon, 1997). Neuroimaging techniques will show alterations in brain structure (CT scan, MRI) or function (PET). However, CT scans show considerable overlap with the 'normal' elderly population and all scanning techniques are expensive and cumbersome to use on a large scale. They are only available to a very small proportion of patients with pre-clinical AD and, usually, in a research context. The costs of neuroimaging screening for pre-clinical AD, even if effective, would be enormous and this would not currently be possible with available resources. However, a recent study has demonstrated that in patients with very mild cognitive impairment, significant differences in hippocampal volume can be distinguished on MRI scan compared with controls (Convit *et al*., 1995). Various biochemical tests have been tried for AD. Lymphocyte membrane changes in acetyl choline receptor sites probably occur too late in the disease to be of use and monoamine oxidase activity increase is not sufficiently specific. Immunological methods of detecting abnormal proteins in cerebro-spinal fluid (CSF), using sophisticated enzyme-amplification methods, may offer some hope of developing early diagnostic markers for AD. However, this technique is also unsuitable for large-scale detection in a clinically 'healthy' population. Lumbar puncture is necessary to obtain a sample of CSF which is an invasive, uncomfortable, time consuming and potentially harmful procedure. There have also been exciting developments in molecular medicine and the molecular basis of early onset familial AD (Sherrington *et al*., 1995) and late onset AD (McLoughlin and Lovestone, 1994) is becoming clearer. Although these tests might indicate who is at risk of developing AD, they give no indication about *when* an individual is likely to develop the condition. Cognitive testing for early dementia is another possibility but, by definition, if cognitive changes are present, AD is already clinically apparent and the ideal point for intervention has already been passed. Critical Flicker Fusion Threshold (CFFT) may also have an important role in this regard (Curran, 1998).

CRITICAL FLICKER FUSION THRESHOLD (CFFT)

CFFT is a well established neurophysiological technique which has been extensively studied in young and elderly healthy volunteers. The neurophysiological basis of flicker perception is complex but well established (Gortelmeyer and Zimmermann, 1982). In particular, flickering light directly influences cortical activity (measured by EEG) and this has been demonstrated in a number of animal species and in man, where the first of these studies was conducted in the 1940s (Walker *et al*., 1944). Although changes were observed in several brain areas, they were most pronounced in the occipital region (Toman, 1941). Furthermore, Walker *et al*. (1944) examined the different components of the visual system in macaque monkeys, cats, dogs and man and were able to demonstrate that EEG activity recorded over the occipital cortex was synchronous with the frequency of retinal stimulation and, in macaque monkeys, this synchronisation peaked at 34 Hz (this was much lower than for other components of the visual system). Importantly, this is very similar to the CFFT observed in normal young healthy subjects and suggests that the occipital cortex is the principal determinant of the CFFT. The central nature of flicker perception is also supported by evidence that CFFT values are higher when measured with binocular vision rather than monocular vision (Ali and Amir, 1991) and that exposure of only one eye to flicker alters the threshold sensitivity of the other eye (Turner, 1968). The perception of flicker is thus an important and fundamental component of visual perception. Although flickering light is able to initiate neuronal activity in various parts of the visual system (from retina to cortex), the temporal resolution of CFFT appears to be determined by the occipital cortex.

MEASURING CFFT

In the studies described below, CFFT was measured using the Leeds Psychomotor Tester (Frewer and Hindmarch, 1988). The equipment is contained in an attaché case and is thus portable and simple to use. When open, a raised section has four red lights which enables CFFT to be measured. The push button used by the subject to stop recording is permanently attached to the investigator's console and is 1 m long.

The CFFT was measured using four red light-emitting diodes in binocular foveal fixation. The continuous psychophysical method of limits was employed to determine CFFT (Woodworth and Schlosberg, 1958). The lights were at eye level, and ambient illumination was diffuse without shadow or bright sunlight. When this pertains, ambient illumination has very little effect on the CFFT, except at the extremes of light or dark (Simonson and Brozek, 1952). This was achieved by closing curtains or blinds and using room illumination on all test occasions.

In the ascending mode, flicker was increased from 12 Hz at 1 Hz/s. The subject was required to press a button when flickering appeared to cease (ascending threshold). In the descending mode, flicker was decreased from 50 Hz at 1 Hz/s until flicker was just detected and registered by a button press (descending threshold). The starting points of 50 Hz and 12 Hz were default settings and were varied by the investigator to prevent subjects pressing the button press after a given time, and thus always seeming to get the same result (error of anticipation). Prior to testing, the subject was familiarised with the machine and the CFFT was the average of three ascending and three descending scores.

CFFT IN HEALTHY ELDERLY COMMUNITY BASED SUBJECTS (STUDY 1)

Patients

Subjects included in the study were all community-based and lived in their own homes under the care of two general practices (five GPs) in the same geographical area of Leeds (UK). Names and addresses of all patients aged 60 or above were supplied by the Family Practitioner Committee with the consent of the respective GPs. A total of 1420 patients were identified and a standard letter sent to each inviting them to take part in a general health screen.

Procedure

Assessments were carried out in patients' homes by three trained nurses under the day-to-day supervision of SC and included a general health screen, the Mini-Mental State Examination (Folstein *et al*., 1975) and CFFT determination.

Results

A total of 1420 patients aged 60 or above were identified, of whom 1035 (72·9 per cent) agreed to be seen by a research nurse and 79 (7·6 per cent) of the patients who agreed to participate could not be contacted despite repeated attempts to do so. Thus, a total of 956 patients (67·3 per cent of the target population) were actually seen. A further 312 patients were excluded because of medical problems known to interfere with CFFT, e.g. blindness. Thus 644 patients were analysed (45·4 per cent of the target population). This final sample included 229 (35·6 per cent) male and 415 (64·4 per cent) female patients with a mean age of 71·3 years (SD 6·97, age range 60–91 years). In the sample of 644 subjects, CFFT scores were normally distributed (Figure 1) and the CFFT scores are summarised in Table 1. Spearman Rank correlations are summarised in Table 2.

Conclusions

Scores were normally distributed. Descending thresholds were significantly greater than ascending thresholds, confirming findings from previous studies. CFFT, ascending and descending thresholds were not correlated with age. However, a significant correlation between age and the difference between ascending and descending

Table 1. Mean CFFT, ASD and DES thresholds (with SD and range) in 644 normal elderly subjects and Student's *t*-test between ASD and DES thresholds

Statistic	CFFT (Hz)	ASD (Hz)	DES (Hz)	*t*-value
Mean	24·6	24·2	25·0	–
SD	2·68	2·76	2·94	–
Range	17·7–32·7	16·2–33·2	17·5–39·9	–
t-test (ASD vs DES)	–	–	–	$t = -7{\cdot}04$ $df = 643$, $p < 0{\cdot}001$

ASD: ascending threshold; DES: descending threshold.

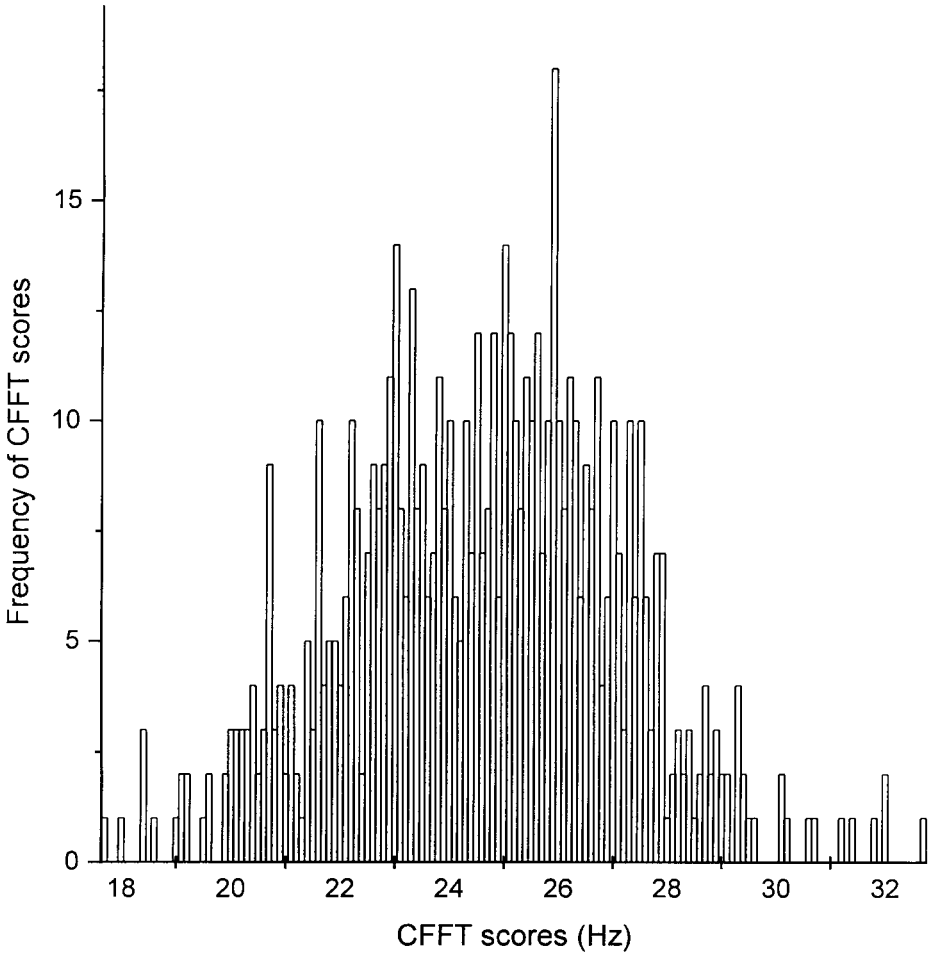

Figure 1. Distribution of CFFT scores in 644 normal elderly subjects

thresholds was observed. Since this correlation was negative, it suggests that ascending and descending thresholds converge with increasing age. The lack of a significant relationship between CFFT and age is important since if CFFT were correlated with age, this measure would probably be unable to distinguish change in cognitive function due to age or the disease process in a longitudinal context, e.g. as a screening instrument.

Table 2. Spearman Rank correlation coefficients; Critical Flicker Fusion Threshold, ascending and descending thresholds by age

1.	A vs Age	$r = 0{\cdot}004$, ns
2.	D vs Age	$r = -0{\cdot}066$, ns
3.	A–D vs Age	$r = -0{\cdot}131$, $p < 0{\cdot}001$
4.	CFFT vs Age	$r = -0{\cdot}051$, ns
5.	A vs D	$r = +0{\cdot}515$, $p < 0{\cdot}001$

A = ascending threshold; D = descending threshold.

CFFT IN PATIENTS WITH ALZHEIMER'S DISEASE (STUDY II)

Patients

The GPs involved with the community study were re-contacted and permission sought to visit their patients in eight Residential Homes in the same geographical area as the patients included in Study I. A research nurse assessed each person in the home that agreed to participate and administered the MMSE. Any patient who scored 23 or less on the MMSE scale then received a full medical (including dementia screen, and CT scan). The diagnosis of Alzheimer's disease was based on

Table 3. Structure of patients identified from residential homes

Number of subjects identified	203
Refused to be seen	8
Unable to administer MMSE	16
Number of patients assessed	178
MMSE $\leqslant$ or =23	110
Dementia (DSM-IIIR)	72
PDDAT (DSM-IIIR)	32
Excluded due to medication	3
Excluded due to blood tests	1
CT scan (excluded)	2
PDDAT meeting all criteria	26

DSM-IIIR criteria. Control subjects were identified as described in study I and were matched for age, occupational class and gender.

Results

Twenty-six patients with AD (three male) were identified from eight Residential Homes (Table 3) and patients had a mean age of 81·7 years (SD 6·05 years, range 67–89); controls 81·8 years (SD 6·13, range 67–89). Summary statistics are displayed in Table 4.

Conclusions

CFFT and descending thresholds were significantly lower in patients with AD compared with normal controls, but ascending thresholds were not significantly different in the two groups. In addition, in the patient group, ascending thresholds were also significantly higher than descending thresholds and this latter finding is a reversal of the situation seen in normal elderly subjects; this might be a characteristic feature of AD.

TEST–RETEST AND SPLIT-HALF RELIABILITY OF CFFT IN PATIENTS WITH ALZHEIMER'S DISEASE (STUDY III)

Patients

Patients were recruited into the study as described in Study II and met DSM-IIIR criteria for Primary Degenerative Dementia of the Alzheimer type (PDDAT) (APA, 1987). Testing sessions were separated by a period of one month (session I and session II).

Table 4. Summary statistics, 95 per cent confidence limits (CI_{95}) and *t*-values for CFFT, ascending and descending thresholds in patients with Alzheimer's disease and matched controls

	Normal subjects ($N = 26$)	Patients with AD ($N = 26$)
CFFT		
Mean	25·6	23·5
SD	2·13	2·32
Range	20·4–29·5	19·0–27·4
CI_{95}	24·8–26·4	22·6–24·4
t-value	$t = 2{\cdot}054$, $df = 50$, $p < 0{\cdot}0018$	
Ascending threshold		
Mean	25·4	24·5
SD	2·09	2·73
Range	20·8–30·4	19·4–30·1
CI_{95}	24·6–26·2	23·4–25·6
t-value	$t = 1{\cdot}363$, $df = 50$, $p < 0{\cdot}176$	
Descending threshold		
Mean	25·7	22·5
SD	2·39	2·28
Range	19·9–28·6	18·5–27·6
CI_{95}	24·8–26·6	21·6–23·4
t-value	$t = 4{\cdot}093$, $df = 50$, $p < 0{\cdot}0001$	

Results

Three male and 23 female patients were included in the study. Their ages ranged from 67 to 89 years with a mean age of 81·7 years $\pm$ 6·1 years. Summary data are detailed in Table 5 and the split-half and test–retest reliability coefficients are summarised in Table 6.

Conclusions

CFFT and ascending and descending thresholds were found to have a high split-half and test–retest reliability in AD patients. The test–retest reliability was examined over one month, but there are in fact an infinite number of test–retest reliabilities depending on the time interval chosen; one month was chosen because of practical considerations.

CONCURRENT VALIDITY OF CRITICAL FLICKER FUSION THRESHOLD IN PATIENTS WITH ALZHEIMER'S DISEASE (STUDY IV)

Patients

Patients were recruited into the study as described in Study II and met DSM-IIIR criteria for PDDAT (APA, 1987).

Table 5. CFFT, ascending and descending thresholds (mean, SD and ranges) for sessions I and II

Test procedure	Session type	Mean (Hz), SD and range
Critical Flicker Fusion Threshold	Session I	22·7, 2·29, 19·0–27·4
	Session II	22·7, 2·10, 19·8–27·1
	Even scores (Session I)	22·6, 2·26, 18·8–27·2
	Odd scores (Session I)	22·8, 2·31, 18·9–27·7
Ascending threshold	Session I	22·9, 2·34, 19·2–28·2
	Session II	23·1, 2·21, 20·2–28·2
	Even scores (Session I)	22·7, 2·35, 19·0–28·0
	Odd scores (Session I)	23·1, 2·34, 19·3–28·4
Descending threshold	Session I	22·4, 2·27, 18·7–27·3
	Session II	22·3, 2·14, 18·8–26·1
	Even scores (Session I)	22·4, 2·25, 18·6–27·3
	Odd scores (Session I)	22·4, 2·34, 18·5–27·4

Table 6. Split-half and test–retest (one month) reliability coefficients of Critical Flicker Fusion Threshold and ascending and descending thresholds in patients with Alzheimer's disease

Test procedure	Split-half reliability coefficient	Test–retest reliability coefficient
Critical Flicker Fusion Threshold	$r = 0{\cdot}87$, $p < 0{\cdot}0001$	$r = 0{\cdot}63$, $p < 0{\cdot}001$
Ascending threshold	$r = 0{\cdot}97$, $p < 0{\cdot}0001$	$r = 0{\cdot}89$, $p < 0{\cdot}0001$
Descending threshold	$r = 0{\cdot}97$, $p < 0{\cdot}0001$	$r = 0{\cdot}94$, $p < 0{\cdot}0001$

Materials

Although the criterion measure should be sensitive, reliable and conceptually sound (Parrott, 1991), one of the most difficult problems facing the investigator when evaluating the concurrent validity of a new measure in patients with AD is the lack of an agreed 'gold standard'. It was therefore decided in this study to choose a range of measures (clinical, neuropsychological and psychometric) known to be sensitive to cognitive impairment caused by cortical damage. The measures included:

Abbreviated Mental Test (AMT) (Hodkinson, 1972)
Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975)
Sandoz Clinical Assessment Geriatric scale (SCAG) (Shader *et al*., 1974)
Global Deterioration Scale (GDS) (Reisberg *et al*., 1982)
Digit Span (Wechsler, 1955)
Trail Making Test (TMT) (Reitan, 1958)
Digit Symbol Substitution Test (DSST) (Wechsler, 1955)
Word Fluency (WF) (Benton, 1968)
Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964)
Choice Reaction Time (TRT) (Hindmarch *et al*., 1988)

Results

Three male and 23 female community-based patients were included in the study. Their ages ranged from 67 to 89 with a mean of 81·7 years $\pm$ 6·1. Summary statistics are detailed in Table 7. CFFT and its subcomponents, ascending and descending thresholds, were significantly correlated with a number of other measures commonly used to assess aspects of cognitive and psychomotor function in patients with AD (Table 8).

Conclusions

CFFT and ascending and descending thresholds were found to be significantly correlated with a wide range of established clinical, psychometric and neuropsychological measures including TRT, AMT, GDS and RAVLT. In addition, CFFT and ascending threshold were significantly correlated with DSST. However, CFFT and ascending and

Table 7. Means, SD and ranges of individual assessments in patients with Alzheimer's disease

Variable	Mean	SD	Range
ASD (Hz)	24·6	2·84	19·4–31·7
DES (Hz)	22·3	2·22	18·5–27·6
CFFT (Hz)	23·5	2·34	19·0–28·2
TRT (ms)	1834·6	188·7	1518·0–2200·0
AMT	4·4	0·85	3–6
MMSE	17·7	3·5	10–23
GDS	4·3	1·05	2–6
SCAG	43·9	10·18	25–69
DF	5·2	1·61	2–7
DB	3·2	1·1	1–5
TD	8·4	2·5	3–12
TMT (ms)	144·8	92·9	50–360
DSST	5·9	5·8	0·0–19
WF	5·8	2·4	2·0–10·0
RAVLT	17·1	7·8	4·0–28

ASD, ascending threshold: DES, descending threshold; CFFT, Critical Flicker Fusion Threshold; TRT, total reaction time; AMT, abbreviated mental test; MMSE, Mini Mental State Examination; GDS, Global Deterioration Scale; SCAG, Sandoz Clinical Assessment Geriatric scale; DF digits forward; DB, digits backward; TD, total digits; TMT, Trail Making Test; DSST, Digit Symbol Substitution Test; WF, Word Fluency; RAVLT, Rey Auditory Verbal Learning Test.

descending thresholds were found not to be significantly correlated with a number of other clinical and neuropsychological measures including MMSE, SCAG, DF, DB, TD, TMT and WF. In addition, descending thresholds were not significantly correlated with DSST. While these data provide evidence that CFFT reflects cortical function in patients with AD, the strength of this conclusion depends critically on the specific criterion measures used. Present findings raise a number of important issues relevant to test development, particularly the issue of 'gold standards' and the enormous variability between different criterion measures.

INTER-RATER RELIABILITY OF CRITICAL FLICKER FUSION THRESHOLD IN PATIENTS WITH ALZHEIMER'S DISEASE (STUDY V)

Patients

Patients were recruited from two locations, an Old Age Psychiatry Day Hospital and a Dementia Assessment Ward serving the same geographical area in Leeds. Initially, all patients in both units were reviewed and subsequently all consecutive referrals over a six month period were assessed. Diagnosis of Alzheimer's disease was based on DSM-IIIR criteria (APA, 1987). Patients received a full medical and psychiatric assessment.

Method

Prior to commencing the study, the author trained the collaborating investigator in the measurement of CFFT and CFFT was measured as described above. Testing by the two investigators was separated by an interval of no more than 5 min and the investigators alternated who commenced testing.

Results

In total, 31 in-patients and 58 organic Day Hospital patients were identified and were further assessed. The patients not included in the study had a variety of diagnoses including the secondary causes of dementia, multi-infarct dementia (MID), mixed dementia (MID and AD) and rarer causes including hypoxic dementia. From a review of the case notes, discussions with nursing and medical staff, medical assessment by the author and review of laboratory investigations, 25 patients met DSM-IIIR criteria for PDDAT. Of these, four were unable to do the CFFT test and were excluded from the study. Thus, six male and 15 female patients with PDDAT were included in the study. The mean age was 78·8 years, SD 6·25 years (range 67–89). Pearson Product Moment Correlation Coefficients (r) were calculated to determine the inter-rater reliability of ascending, descending and Critical Flicker Fusion Thresholds. Summary data are provided in Table 9 and the three reliability coefficients are summarised in Table 10.

Conclusions

This study examined the inter-rater reliability of CFFT and ascending and descending thresholds in AD patients and results confirmed high inter-rater reliability of all three measures.

SUMMARY

CFFT has been widely used over the past 30–40 years to investigate the effects of psychoactive drugs and, in young volunteers, it has been shown to be correlate with a range of CNS

Table 8. Spearman rank correlation coefficients and significance levels in patients with Alzheimer's disease

	DES	CFFT	TRT	AMT	MMSE	GDS	SCAG	DF	DB	TD	TMT	DSST	WF	RAVLT
ASD	0·78 $p < 0·000$*	0·95 $p < 0·000$*	−0·82 $p < 0·000$*	0·56 $p < 0·003$*	0·13 $p < 0·52$	−0·16 $p < 0·001$*	0·09 $p < 0·96$	0·27 $p < 0·19$	0·28 $p < 0·16$	0·26 $p < 0·2$	−0·2 $p < 0·33$	0·48 $p < 0·014$*	−0·08 $p < 0·71$	0·43 $p < 0·03$*
DES		0·93 $p < 0·000$*	−0·58 $p < 0·002$*	0·71 $p < 0·000$*	0·17 $p < 0·42$	−0·59 $p < 0·000$*	0·09 $p < 0·65$	0·26 $p < 0·19$	0·21 $p < 0·31$	0·26 $p < 0·2$	−0·09 $p < 0·66$	0·31 $p < 0·12$	−0·06 $p < 0·79$	0·49 $p < 0·01$*
CFFT			−0·77 $p < 0·000$*	0·64 $p < 0·000$*	0·15 $p < 0·46$	−0·64 $p < 0·000$*	0·06 $p < 0·77$	0·24 $p < 0·24$	0·25 $p < 0·22$	0·24 $p < 0·25$	−0·19 $p < 0·36$	0·41 $p < 0·04$*	−0·07 $p < 0·74$	0·49 $p < 0·01$*
TRT				−0·56 $p < 0·02$*	−0·22 $p < 0·29$	0·47 $p < 0·02$*	−0·03 $p < 0·87$	−0·08 $p < 0·07$	0·05 $p < 0·81$	0·02 $p < 0·94$	0·3 $p < 0·13$	−0·42 $p < 0·03$*	0·17 $p < 0·41$	−0·49 $p < 0·01$*
AMT					0·43 $p < 0·03$*	−0·47 $p < 0·02$*	−0·11 $p < 0·58$	0·31 $p < 0·12$	0·12 $p < 0·56$	0·24 $p < 0·25$	−0·18 $p < 0·39$	0·11 $p < 0·58$	0·08 $p < 0·7$	0·62 $p < 0·01$*
MMSE						−0·39 $p < 0·05$*	−0·35 $p < 0·08$	0·08 $p < 0·71$	0·03 $p < 0·09$	0·09 $p < 0·67$	−0·47 $p < 0·02$*	0·19 $p < 0·35$	0·37 $p < 0·06$	0·48 $p < 0·01$*
GDS							0·28 $p < 0·17$	−0·13 $p < 0·54$	−0·19 $p < 0·34$	−0·11 $p < 0·6$	0·25 $p < 0·21$	−0·12 $p < 0·55$	0·17 $p < 0·41$	−0·31 $p < 0·13$
SCAG								−0·19 $p < 0·36$	−0·24 $p < 0·24$	−0·17 $p < 0·41$	0·02 $p < 0·91$	0·02 $p < 0·93$	−0·28 $p < 0·17$	0·02 $p < 0·92$
DF									0·65 $p < 0·000$*	0·94 $p < 0·000$*	0·16 $p < 0·44$	0·02 $p < 0·93$	0·14 $p < 0·5$	0·22 $p < 0·28$
DB										0·83 $p < 0·000$*	−0·01 $p < 0·95$	0·35 $p < 0·08$	0·39 $p < 0·05$*	0·15 $p < 0·95$
TD											0·09 $p < 0·68$	0·17 $p < 0·4$	0·27 $p < 0·18$	−0·01 $p < 0·46$
TMT												−0·23 $p < 0·25$	−0·14 $p < 0·49$	−0·26 $p < 0·2$
DSST													0·18 $p < 0·38$	0·16 $p < 0·43$
WF														0·25 $p < 0·22$

*Significant correlation.
ASD, ascending threshold: DES, descending threshold; CFFT, Critical Flicker Fusion Threshold; TRT, total reaction time; AMT, abbreviated mental test; MMSE, Mini Mental State Examination; GDS, Global Deterioration Scale; SCAG, Sandoz Clinical Assessment Geriatric scale; DF digits forward; DB, digits backward; TD, total digits; TMT, Trail Making Test; DSST, Digit Symbol Substitution Test; WF, Word Fluency; RAVLT, Rey Auditory Verbal Learning Test.

Table 9. Summary data for CFFT, ascending and descending thresholds (mean, SD and range) in patients with AD; comparison between two different investigators

Test procedure	Mean (Hz), SD and range for investigator I (JS)	Mean (Hz), SD and range for investigator II (SC)
Critical Flicker Fusion Threshold	25·1, 2·85, 21·1–31·4	25·7, 2·65, 21·1–30·6
Ascending threshold	26·7, 3·20, 21·1–34·9	27·4, 3·27, 22·0–33·8
Descending threshold	23·5, 3·61, 18·0–31·1	23·9, 3·22, 19·0–30·4

Table 10. Inter-rater reliability of ascending, descending and Critical Flicker Fusion Thresholds (CFFT) in patients with Alzheimer's disease

Descending threshold	$r = 0{\cdot}943$, $p < 0{\cdot}01$
Ascending threshold	$r = 0{\cdot}840$, $p < 0{\cdot}01$
CFFT	$r = 0{\cdot}903$, $p < 0{\cdot}01$

measures. It satisfies many of the features of an 'ideal' assessment instrument. It is valid, reliable and pharmacosensitive. There are no cultural or educational effects and it is economic, quick, and easy to administer. In addition, it does not have any floor or ceiling effects and it can be administered by staff with relatively minimal training. Consequently, it is now one of the most popular techniques in psychopharmacological research. Nevertheless, CFFT has not been systematically evaluated in AD patients and this has been the primary focus of these studies. The results show that, in healthy elderly subjects, CFFT scores are normally distributed and do not change significantly with increasing age. The latter point is important because a measure that was sensitive to changes in cognitive function due to age *and* pathology (e.g. AD) would make interpretation of results very difficult, especially during the early stages of the disease. CFFT is also significantly impaired in patients with AD compared with controls. The present results also show CFFT to be significantly correlated with a number of measures known to be sensitive to global cognitive impairment/brain damage in patients with AD, in addition to having a high test–retest, split-half and inter-rater reliability. Interestingly, in normal elderly subjects, descending thresholds are invariably higher than ascending thresholds and the opposite is seen in patients with AD. It is possible that this may be a characteristic feature of AD. CFFT may have an important role in identifying early cases of AD in a longitudinal context and a large community study to evaluate this is currently being planned. If CFFT is found to be useful in this regard it may be possible to commence treatment with an antidementia drug at a preclinical stage in the hope that this will delay or prevent the onset of the illness.

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