The pre-frontal cortex: links between neuropsychological performance and the sleep and wake EEG

THE PRE-FRONTAL CORTEX – LINKS BETWEEN NEUROPSYCHOLOGICAL PERFORMANCE AND THE SLEEP AND WAKE EEG

by

Clare Anderson

A Doctoral Thesis

Submitted in partial fulfilment of the requirements
for the award of
Doctor of Philosophy of Loughborough University

March 2003

ABSTRACT

The Pre-Frontal Cortex (PFC) has one of the highest Cerebral Metabolic Rates (CMR) during wakefulness (Braun et al , 1997, Maquet et al., 1990) and the lowest CMR during Slow Wave Sleep (SWS) at night (Maquet, 2000) Inasmuch that the PFC is a focus for low frequency delta activity (e g. Werth et al , 1996, 1997), generated directly by the cortex (Steriade et al. 1993a-c), it is argued, here, that this serves a localised function of sleep and is thus reflective of enhanced recovery. Given the PFC-delta activity link, Clark et al. (1998) assessed daytime regional cerebral blood flow (rCBF) and found increased 'brainwork' during the day resulted in increased delta activity at night, specifically in the (left) PFC. Although Clark et al provided a direct link between daytime PFC function and delta sleep, the extent to which the sleep EEG could be used to assess PFC neuropsychological performance had not been studied, in either young and older adults. Most research within this domain was based on either relationships between loss of sleep per se and behavioural measures of sleepiness (See Pilcher & Huffcutt, 1996) or used non-cortically specific areas/ tasks (e g. Bliwise, 1989; Crenshaw & Edinger, 1999; Edinger et al 2000) Therefore, if the focus were on the PFC with regard to task specificity and EEG recording sites, relationships between sleep EEG and performance may become apparent

Overnight, ambulatory sleep EEG's were performed on younger (19-23y) and older (61-75y) participants in addition to a neuropsychological test battery including tasks that predominately activate the PFC (e g Non-Verbal Planning and Verbal Fluency) Although total delta power showed no association with task performance, it was found that frontally dominant low frequency delta in the left PFC during the first NREM period was associated with better performance on (left) PFC specific tasks, for both younger and older age groups – Given that these associations were for both age groups it was argued that these associations were not at the behest of age, but specific to the PFC.

Finelli et al. (2000) had proposed that delta activity at night had functional similarities with daytime theta (5-8Hz) due to an underlying commonality Given the findings regarding the sleep EEG and PFC performance, the question was

raised whether low frequency delta identified here was also related to theta during the day, and if so, whether theta was also linked to PFC performance Further support for a possible relationship between these two indices came from recent findings regarding the waking EEG. Çiçek & Nalçaci (2001) found that alpha activity in the waking EEG was reflective of performance on the WCST, albeit that the measurements took place at separate times.

A laboratory study of eyes open/eyes closed conditions found that increased 7-8Hz activity during 'thinking' was related to PFC performance for the younger group. The methodology employed was problematic· Firstly, due the amount of artefact in the EEG there was a reduction in participants/epochs analysed, but secondly, it was questioned whether participants were actively following the protocol of the study and thus engaging in 'thinking' exercises. A second period of waking EEG was studied, the Pre-Sleep period: 'lights out' but preceding any signs of drowsiness It was found that 7-8Hz activity from the left PFC, during this period, was associated with PFC performance in both younger and older groups The 7-8Hz activity was thought to reflect 'thinking' due to its similarity to daytime 'thinking' EEG, the lack of external stimuli, participants' self reports, and numerous studies linking increased theta to thinking (e g. Kahana et al., 2001). 7-8Hz activity during both waking EEG recordings was shown to be associated with low frequency delta at night albeit that all recordings took place on separate days and so were not as a direct function of each other

In Summary, there was an association between low frequency delta during the first NREM period and 7-8Hz activity during wakefulness; an increment of both variables was associated with better performance on tasks orientated towards the PFC. These associations were specific to EEG recording site (left PFC) and task activation (left PFC) It is suggested that associations found are due to an underlying commonality between the sleep EEG, wake EEG and neuropsychological test performance

KEYWORDS. Pre-Frontal Cortex, Sleep EEG, Wake EEG, Low Frequency Delta, Theta Activity, Neuropsychological Performance.

ACKNOWLEDGEMENTS

I would like to thank Professor Jim Horne for his supervision and continued support, guidance and encouragement throughout the duration of this work. I would also like to thank Adrian Bailey and Dave Harris for their help with both computer-related and technical assistance

Thank you to friends within the Sleep Research Centre for their support and encouragement, especially to Stuart for years of listening, Pauline who did a great job proof reading, and Gill for her friendship

I thank all the participants who took part in this research for their continued time, commitment, and valuable contribution to this work.

Thank you to my best friend Ollie, for his humour, belief and for being there when the good times weren't. Special thanks for his support from all four corners of the globe during the preparation of this thesis.

Finally, thank you to all my family and friends, old and new, for their support throughout the years and especially so during recent times

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

BNF	British National Formulary
CBF	Cerebral Blood Flow
CCCF	Cattell & Cattell's Culture Fair Test
CMR	Cerebral Metabolic Rate
DLPFC	Dorso-Lateral Pre-Frontal Cortex
DSST	Digit Symbol Substitution Task
EEG	Electroencephalography
EMG	Electromyography
EOG	Electro-oculography
ESS	Epworth Sleepiness Scale
fMRI	Functional Magnetic Resonance Imaging
FFT	Fast Fourier Transform
KSS	Karolinska Sleepiness Scale
IQ	Intelligence Quotient
LPFC	Left Pre-Frontal Cortex
LPO	Left Parietal-Occipital
mg	Milligrams
MRI	Magnetic Resonance Imaging
mm	Millimetres
NREM	Non-Rapid Eye Movement (Sleep)
NVPT	Non-Verbal Planning Task
PET	Positron Emission Tomography
PVT	Psychomotor Vigilance Test
rCBF	Regional Cerebral Blood Flow
rCMR	Regional Cerebral Metabolic Rate
REM	Rapid Eye Movement (Sleep)
RPFC	Right Pre-Frontal Cortex
RPO	Right Parietal-Occipital
SWA	Slow Wave Activity
SWS	Slow Wave Sleep
TST	Total Sleep Time
U3A	University of the Third Age
WASO	Waking After Sleep Onset
WCST	Wisconsin Card Sorting Task

CHAPTER 1

LITERATURE REVIEW

1.1 PRELUDE TO THESIS

The work as described in this thesis was based upon three main research papers, which together posed the question of whether associations lay between EEG activity from the PFC and PFC performance. These papers were:

1) Werth et al. (1996)
2) Clark et al (1998)
3) Finelli et al (2000)

Werth et al (1996) studied the topography of slow wave activity in sleep concluding that low frequency delta (<2Hz) was indicative of recovery in that it was predominately found in frontal areas, specifically on the left side; an area showing the highest daytime metabolic rate. Clark et al (1998) demonstrated that daytime brainwork, as measured using functional imaging, was positively related to slow wave sleep at night, with the strongest association found in the PFC, once again, the left side was specified. Further work of influence was that of Finelli et al (2000) who showed that theta activity (5-8Hz) during daytime wakefulness was positively related to delta sleep (0.5-4.5Hz) at night, due to a similar underlying process

Therefore, given Werth et al. and Clark et al.'s work it would seem waking brainwork is related to night-time delta sleep arguably in a state of 'recovery' The extent to which daytime performance would be related to night-time delta sleep, that was specific to the PFC given its putative enhanced recovery need, is therefore questioned. As the sleep EEG may be related to PFC performance, then by considering the findings of Finelli et al. the waking performance of the PFC may also be related to the wake EEG due to an underlying commonality between daytime theta EEG and night-time delta EEG

This basic rationale leads to the investigation into associations between neuropsychological test performance and the sleep and wake EEG

1.2 FUNCTION OF SLEEP

A common and recurring theme in the world of Sleep Research is the question of 'Why do we sleep?' - A simple question that has yielded over half a century of study, debate and many sleepless nights for both the scientist and study volunteer alike. Extensive research during the late 20th century provided a wealth of knowledge regarding the function of sleep, and although (most) scientists now agree on why we sleep, the topic remains as intriguing and well researched as the onus moves towards the intricacies of such as a topic, namely the function of different sleep states and more recently, the investigation of a localised function of sleep.

1.2.1 Classification of Sleep States

Rechtschaffen & Kales (1968) first classified the state of sleep by dividing it into sleep stages, however, spectral measures of electroencephalographically measured sleep, distinguished in terms of amplitude (μV) and frequency (Hz), are now more widely used in sleep research. The Electroencephalogram (EEG) consists of silver-coated electrodes, placed on the scalp, that measure electrical potentials from the cortex The EEG not only allows the researcher to classify the style of sleep, as shown in Table 1.1, but due to the positioning of electrodes, also allows the researcher to assess the topography of different frequencies (e g. Landolt & Borbély, 2001; Werth et al., 1997)

Table 1.1: Classifications of EEG Defined Sleep

Sleep State	Frequency	Description	
Beta	>15Hz *(<10μV)*	Occurs in the alert, or anxious cerebrum	Alert
Alpha	8-11Hz	Typical of a cerebrum in relaxed wakefulness	
Theta	3 5-7 5Hz	Typical of drowsiness/light sleep	
Delta	<3 5 *(>75μV)*	Characteristic of Deep Sleep	Deep Sleep

The delta rhythm is responsible for making up around 20% of human sleep activity (Horne, 1988a) It is also termed Slow Wave Sleep (Slow Wave Activity, Delta Activity, Stages 3+4 – See Below for Clarification) because of its slow

frequency and has received much attention given the importance of this activity in the role of sleep, as highlighted in many experimental studies.

1.2.2 Slow Wave Sleep

Temporal Distribution

Slow Wave Sleep (SWS) predominates in the first two 90minute cycles of sleep (Bes et al , 1991) [sleep usually contains 5 cycles according to a standard hypnogram – Rechtschaffen & Kales, 1968] suggesting an immediate need for this sleep type. Studies that have challenged the temporal distribution of SWS and REM sleep conclude that REM sleep is both dispensable (to a degree) and adaptable, whereas SWS is necessary, in an immediate sense (Webb et al , 1967). Feinberg (1989) argued that SWS was focussed mainly within the first non-REM (NREM) period and later proposed that it saturated the first and second NREM periods when there was a high pressure for SWS, i.e after sleep loss (Feinberg et al , 1991). Studies such as these demonstrate that there is an increased need for SWS in comparison to other sleep stages.

Sleep Length: The Effect on SWS Times

The importance of SWS is also shown in the study of long- and short-sleepers in that regardless of habitual sleep length, SWS is stable across participants (Webb & Agnew, 1970) whereas there is less Stage 2 and REM sleep present in the sleep period Some researchers have stated "the absolute amount of SWS seems to be one of the most constant needs of the human organism since both intra- and inter-individual studies have shown a consistency of SWS amount within a habitual range of the previous wakefulness" (Benoit et al., 1980, p 482) Bliwise & Bergmann (1987) extended the investigation into individual differences in stages 3 and 4, and concluded that SWS was stable across participants when stage 3+4 were added, but that stage 4 alone showed individual variation. An interesting aspect of this work was their admission that two male subjects of nearly identical age, demographics, sleep habits and health should differ so widely in the EEG cortical activity. They claimed this was a '*frank mystery*'. The work described in this thesis may make a unique step in understanding the implications of such differences in a neuropsychological sense, and therefore disputing the work of

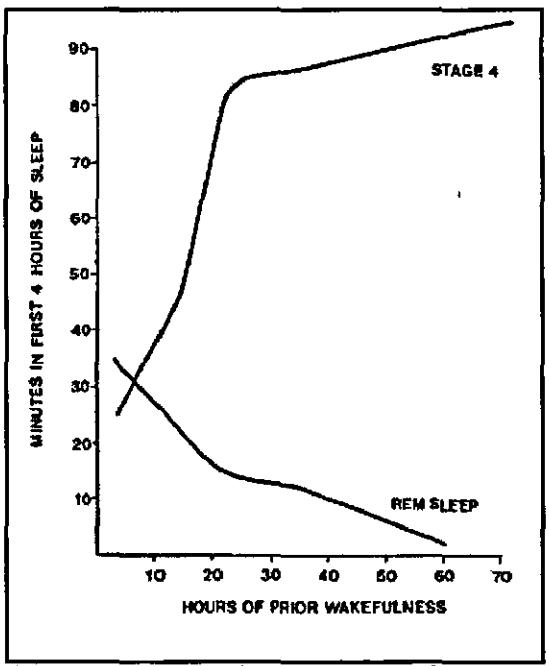
Spiegel et al. (1986) who claimed the clinical significance of SWS may be limited, in that the individual differences have no functional meaning.

Studies utilising normal long- and short-sleepers are an excellent example of the stability of SWS: the experimental manipulation of sleep times also shows the stability of SWS since reducing Total Sleep Times (TST) from 7.5hours to only 4hours does not alter SWS levels (Johnson & Macleod, 1973).

SWS Rebound

The general consensus is that SWS is stable Not only is it stable, it is also obligatory: It has been shown that following sleep loss, 30% of total sleep is regained which is made up of *all* the lost Stage 4 sleep, *half* of lost REM sleep and little or none of lost stages 1+2 sleep (Kales et al., 1970; Horne, 1985). More importantly, the rebound of Stage 4 takes precedence over any other sleep stage (Horne, 1983).

Slow Wave Sleep & Cerebral Restitution



As hours of wakefulness increase, the amount of SWS increases due to the increased need for cerebral restitution (via SWS) following prolonged wakefulness.

Note the decrease in REM sleep as the due to the precedent of SWS.

Figure 1.1: The relationship between Stage 4 sleep (SWS) and prior wakefulness (Adapted from Webb & Agnew, 1971). Reprinted From Horne (1988a) pp. 144 with permission from the author.

It is well established in sleep research that sleep is predominantly for the cerebrum as the effects of sleep deprivation are far more debilitating on the brain than on the body (c f. Horne, 1988a) Early direct evidence for SWS as a restorative measure came from Webb & Agnew (1971), who found the amount of SWS during the night was linearly related to amount of prior wakefulness (See Figure 1 1) suggesting the function of SWS was to recuperate the cerebrum from the 'wear' and 'tear' of wakefulness

Of course, the nature of SWS as 'recovery[1]' and/or 'restorative[2]' is open to debate A recent study by Stickgold et al (2000) suggests SWS has an information-processing function However, the study shows that learning was not evident unless 6hr of sleep was undertaken, and that learning was proportional to the amount of sleep in excess of 6hr, which suggests the information processing to be more attributable to REM sleep Although the authors used a modelling technique to determine the extent to which REM and SWS were together responsible for consolidation, it is difficult to decipher from this a) how SWS was alone responsible for learning consolidation, b) whether the lack of elarning was due to a loss of SWS or TST and c) whether SWS is indeed a 'recovery' state, and without 'recovery' performance is diminished that is separate to any consolidation of learning. The Stickgold et al study is used here to present an argument that SWS is not globally considered in a 'recovery' role, however, given the wealth of research that looks at SWS/SWA as 'recovery'(e.g. Achermann & Borbély, 1997; Achermann et al , 2001; Werth et al , 1997) and the influence these papers have on the research into SWS/SWA/Delta activity, the argument of a 'recovery' role of SWS/SWA remains strong.

Although Webb & Agnew refer to SWS in their work linking daytime wakefulness to night-time sleep, their concept supports the model of sleep regulation proposed by Borbély (1982) in his 'Two-Process model of Sleep' referring to the effect of prior wakefulness on Slow Wave Activity (0.5-4.5Hz).

[1] Used to refer to a reversal of daytime effects, a sense of 'rest and revival'
[2] Used to refer to a healing aspect, and thus seldom used in this thesis

The Two-Process Model of Sleep

This model of sleep regulation (Borbély, 1982) attempts to explain how the physiological need for sleep (sleep pressure) increases during the day as an interaction between prior wakefulness and circadian influences. These two process are termed '*Process C*' and '*Process S*' Process S increases during the day, to a high sleep pressure whereby sleep onset occurs, and decreases exponentially during the night as the pressure for sleep reverses. Borbély et al 's earlier study (Borbély et al., 1981) showed that following sleep deprivation there is an increase in slow wave activity (SWA) <1Hz in the first NREM period that is a reflection of the exponential decline of sleep propensity whose initial need is built up in the preceding extended hours of wakefulness[3]

Slow Wave Sleep: The Variables

The two-process model of sleep demonstrates how process S (or SWA) is subject to other variables, namely prior wakefulness. However, SWA can also be affected by the *quality* of prior wakefulness: Horne & Minard (1985) found that after a behaviourally 'active' day, such as visiting cities, zoos, museums etc., there was an increase in SWS An earlier study (Horne & Walmsley, 1976) found similar, albeit not as strong, findings in that increased visual load appeared to increase SWS levels. Although some researchers point to the increase of SWS being due to exercise (e g. Adam, 1980), there is strong scientific evidence that SWS increases after exercise due to increased heat (Horne & Staff, 1983; Horne & Moore, 1985), similar to the idea that increased brainwork, and thus heat, during the day results in increased SWS at night This theme of daytime brainwork shall be expanded in later sections (e g. 1.4 The relationship between the waking/Sleeping PFC)

The term 'SWA' has been used to refer to frequencies 0.5-4.5Hz, which is considered the delta band Spectral analysis is able to be more specific in the reference to different frequencies, such that the traditional band 0.5-4 5Hz is considered relatively wide.

[3] Recent developments have shown a second marker of sleep propensity (Finelli et al , 2000) –See Section 1.10. The Significance of the Waking EEG?

1.3 CLARIFYING THE SLOWER FREQUENCY WAVES

The delta band has traditionally covered 0.5-4Hz, but studies (e g. Jobert et al., 1994) are now referring to the delta band in terms of its slow (0 5-2Hz) and fast components (2-4Hz). The use of separate delta bands was utilised by Benoit et al. (2001) who found that slow delta and fast delta showed different relationships to alpha, theta and beta rhythms They demonstrated that the fast delta waves increased from drowsiness to the start of SWS, whereas slow delta increased during the SWS period Benoit et al. argued that as they found a relationship between slow delta with theta, and fast delta with alpha, this reflected a different origin of the slow and fast delta waves. Therefore, evidence would suggest that the frequencies within the traditional band 0 5-4Hz are neurophysiologically distinct, and therefore should be regarded separately.

Ferrara et al. (2002) supported Benoit et al.'s conclusion that slow and fast delta activity was distinct. Ferrara et al. assessed regional differences in the SWS-rebound following selective SWS-deprivation. They deprived young adults of SWS through the use of auditory tone, and suppressed SWS on two consecutive nights They found that during the SWS-deprivation nights, there were large decreases in EEG power at the fronto-polar, central and parietal derivations in all the frequency ranges (delta, theta & alpha) However, only slow frequency delta activity (0.5-2Hz) was decreased in the frontal derivation together with a large increase during the recovery sleep; Interestingly, 3-4Hz activity did not show these trends Therefore, they argued that these two frequencies were functionally distinct, and due to this and the recent advance in neurophysiology with respect to cortically-generated rhythms (See below), they argued for a "re-examination of the functional role of EEG rhythms during sleep" (pp. 11).

1.3.1 Low Frequency Delta – A New Frequency?

In addition to Ferrara et al.'s reference to 0.5-2Hz, Werth et al (1996) looked at specific frequency components over a normal nights sleep and found an increase of 2Hz activity in the frontal regions during NREM sleep A follow up study (Werth et al , 1997) looked in more depth at the topography of sleep EEG power

throughout the night and focussed on the low frequency delta (0.25-2Hz) The authors confirmed that this frequency had most power in the frontal regions during NREM sleep but also that it declined over successive NREM periods at a faster rate in the frontal regions, than the rest of the cortex. The authors suggest that low frequency delta (<2Hz) supports the notion that the frontal parts of the cortex have a specific involvement in the function of sleep. They also related their findings to the two-process model of sleep, in that Process S declines at a steeper rate during NREM in the frontal regions Therefore not only does the brain exhibit localised sleep function (i.e. increased delta activity in frontal regions) but also a localised sleep regulatory system (due to localised decrease of Process S)

The localisation of low frequency delta activity was again highlighted in Achermann et al.'s (2001) study involving the enhancement of delta activity through prior sleep deprivation. They found that low frequency activity 1.25-1.5Hz (they excluded frequencies below 0.5Hz) was enhanced in the left anterior derivation (as well as higher delta frequency EEG power). They highlighted the low frequency range because:

- It had the largest increase in power during recovery sleep.
- It was dominant in the frontal regions during baseline/recovery sleep
- Coherence (reflecting hemispherical communication) was only evident in this frequency range

Studies commenting on the low frequency delta rhythm, including Achermann et al , suggest that the presence of low frequency delta is an indication of higher recovery need of the frontal cortex. This idea is given neurophysiological significance with the work describing frequencies <1Hz.

1.3.2 <1Hz Activity

The neurophysiological significance of low frequency delta has been increasing ever since Steriade et al. (1993a) identified a low frequency of around 1Hz, in the thalamo-cortical system (reciprocal information transfer system from the thalamus to the cortex) of the sleeping cat. Further work saw this frequency in human sleep

(e g. Steriade et al , 1993b, Steriade & Amzica, 1998) subsequently proposed to be generated by the cortex[4] itself and reflected the cortex's generation of its own recovery frequency. Furthermore, Steriade & Amzica (1998) found this cortically generated low frequency delta to be prevalent in the Pre-Frontal Cortex (hereafter referred to as the PFC)

Although low frequency delta has recently gained recognition, it is not entirely new: The work by Borbély et al (1981) first highlighted frequencies <1Hz They found that EEG power from <1Hz did not decrease from the first to the second NREM period after sleep deprivation, as other delta frequencies do Achermann & Borbély (1997) extended research on the low frequency delta originally identified by Steriade et al., by claiming its peak was 0.7Hz (range 0 5-0.95Hz) and arguing that it was functionally distinct to frequencies higher than 2Hz, since it did not decline over subsequent NREM periods as >2Hz activity did. The authors proposed an inverse relationship between frequencies above and below 1Hz, which is highlighted and supported, through studies by both Werth et al (1997) and Benoit et al. (2001) as discussed Further evidence for distinct slow and fast delta components comes from a study administering a benzodiazepine hypnotic. Although this decreases delta/theta activity, it caused an increase in activity <1Hz (Trachsel et al , 1990) signifying these rhythms were not the same.

Activity <1Hz may have been masked in earlier research due to filters placed on the EEG recordings (Achermann et al , 2001), more advanced filters now allow the study of this low frequency activity with minimal risk of artefact, and therefore the research into the low frequency range is becoming more frequent. The importance of low frequency rhythms would appear to be in constant development in the field of sleep research. The generation of the rhythm by the cortex, and its predominance in frontal regions, would suggest a heightened cortical recovery during SWS periods. Studies concerning the relationship between the waking and sleeping PFC would add to this concept as the cerebrum

[4] Proposed to be generated by the cortex since it is still present after the removal of the thalamus (Steriade et al. 1993c) and yet disappears in the thalamus in decorticated animals (Timofeev & Steriade, 1996)

is hypofrontal[5] during SWS, reflected by low frequency delta activity, and hyperfrontal[6] during the day as discussed below

1.4 THE RELATIONSHIP BETWEEN THE WAKING/SLEEPING PFC

1.4.1 Functional Imaging

Functional imaging studies, using positron emission tomography (PET), have shown that the PFC is one of the most active parts of the cortex during the day (e g. Maquet et al , 1990; Braun et al , 1997) Braun et al 's extensive study carried out PET scans ranging from pre-sleep states, throughout sleep, to the following day of wakefulness It was found that the PFC during wakefulness (both pre-sleep and post-sleep) had an increased regional cerebral blood flow (rCBF) suggesting that the PFC worked hardest during the waking state in comparison to other brain regions. Interestingly, Braun et al. demonstrated that during periods of intense delta activity, there was a global reduction in cerebral blood flow (CBF) [26%] that was more evident in the PFC. This supported earlier work that found a 23% reduction of rCBF, with the most marked areas of reduction being in the frontal cortex (Buchsbaum et al , 1989).

Other studies have supported Braun et al 's finding in that the PFC is one of the least active areas during periods of SWS [stages 3+4] (e g. Hofle et al., 1997; Maquet et al , 1997; Maquet 1999, 2000) Maquet carried out extensive functional imaging studies relating to the SWS period and in his early study found that SWS resulted in lower CBF globally (Maquet et al , 1997) Later studies were more specific and he highlighted that the marked reduction in blood flow was most apparent in the frontal regions (Maquet, 1999) especially during SWS (Maquet, 2000).

[5] When the frontal part of the cortex is one of the 'least' active areas.
[6] When the frontal part of the cortex is one of the 'most' active areas.

In summary, it is clear that the PFC works hardest during the day and becomes least active at night, especially during periods of SWS. During this time it is arguably in a state of increased cortical recovery as the low frequency delta waves (<2Hz) reflect a greater degree of disengagement from surrounding stimuli and thus a more profound resting state. However, the extent to which the PFC is activated during wakefulness is changed following prolonged sleep deprivation

1.4.2 The Neurophysiological Effect of Sleep Deprivation

Imaging studies during sleep deprivation have been carried out in order to pinpoint areas affected by a loss of sleep. Thomas et al (1998) carried out PET scans after normal sleep and then at 24, 48, and 78hours of prolonged wakefulness Compared to baseline, CBF was markedly reduced, especially in frontal areas, decreasing at a rate of 7% for each day of sleep deprivation. During recovery sleep, CBF reduced by 26% during SWS with the greatest reduction in the PFC. Further work by Thomas et al found that after twenty-four hours of prolonged wakefulness, rCMR [regional cerebral metabolic rate] was decreased in the PFC (Thomas et al., 2000).

Drummond et al. (2000) extended this work and performed brain-imaging techniques on subjects undergoing verbal tasks after 35hours of prolonged wakefulness. The authors found that after sleep deprivation, areas that were activated during verbal fluency in baseline trials (e.g the PFC) were even more activated under sleep loss conditions, suggesting that the brain (specifically the PFC) was working harder to maintain performance during task completion. Although the finding is, in itself, interesting, the authors found an unexpected twist as the parietal lobe was activated in an apparently compensatory effort.

The literature discussed would therefore suggest that the most active brain region (e g the PFC) becomes less active under prolonged wakefulness (unless during PFC task completion whereby its makes an 'apparent' compensatory effort). Given that the PFC is also a focus for low frequency delta, it would indicate that the lack of sleep and/or low frequency delta results in the PFC being unable to work as efficiently as it would under optimal conditions, thereby suggesting low

frequency delta to provide some aspect of 'recovery'. The relationship between the wake and sleep PFC is evident through the use of functional imaging as discussed, this is supported by similar findings through studies utilising electroencephalography.

1.4.3 Electroencephalography

Exhaustive research has been carried out looking at the topography and frequency of EEG during wakefulness and sleep in the PFC. The finding are interesting and provide compelling evidence that the PFC undergoes an enhanced form of recovery during periods of increased delta activity.

A recent study (Clark et al , 1998) assessed the relationship between delta sleep at night and afternoon CBF. Basing their research on the idea that SWS increases with prior wakefulness (Borbély, 1982) and following increased brainwork (Horne & Minard, 1985), they hypothesized that increases in waking CBF would be positively associated to SWS at night. Not only did the authors find that increased CBF was related to increased SWA, they also found that the association was stronger in the PFC. Unfortunately, no neuropsychological tests were undertaken (it would have been interesting to assess the extent to which performance on the tasks during the day was related to SWS at night), however, it does suggest that waking function is related to SWS at night, especially in the PFC. The extent to which the use of SWS, through the use of sleep staging, may mask some important concepts is questioned, and whether the separate analysis of slow (0.5-2Hz) and fast (2-4Hz) delta activities may reflect different relationships to daytime CBF since they are thought to reflect different origins (Benoit et al , 2001).

As the PFC works hardest during the day it is expected, given that delta may serve some recovery function, that a regional analysis of the EEG should exhibit increased delta activity in the PFC in comparison with other brain regions (Lanquart et al , 1996; Sekimoto et al., 2000). Once again sleep deprivation studies provide an interesting aspect to this area in that the enhancement of SWA (0.75-6.5Hz) through prior sleep deprivation is most pronounced in frontal areas

during recovery sleep (Cajochen et al , 1999) and that the normal decline of SWA (0 5-4.5Hz) over the NREM periods (Dijk et al , 1990, 1993) is also more pronounced in the frontal regions (Cajochen et al , 1999).

Achermann et al. (2001) utilised the experimental paradigm of Cajochen et al. by assessing the *hemispherical* differences of delta power during recovery sleep but focussed on the delta range, specifically the lower frequencies. They found that although TSD increased power within the range 0.75-10.75Hz, delta power (1 25-1.5Hz) increased not only in the PFC, but more importantly, it was significantly increased in the left PFC. These data therefore imply that both sleep regulation and recovery is localised with reference to the left PFC.

Ferrara et al. (2001), as discussed earlier, found that the PFC was more resistant to the auditory suppression of SWS (herein classified as the appearance of two waves $\leq$ 4Hz, > 75μV). The authors attribute this 'resistance' to SWS deprivation in the lower frequency as an indication of a greater need for sleep in the frontal areas. This papers goes as far as to suggest that a re-evaluation of the function of sleep should be incurred, with the acknowledgement of local functions of sleep

1.5 SLEEP AND NEUROPSYCHOLOGICAL PERFORMANCE

Given the evidence of the relationship between the metabolism of the sleeping brain and waking brain, in particular the PFC, one could speculate that the sleep EEG may hold properties for predicting neuropsychological test performance predisposed towards the PFC. However, the literature concerning the relationship between sleep and performance, especially of a localised nature is, as yet, unpublished

Most studies of sleep and performance are concerned with sleep restriction or short-term sleep deprivation and the effect this has on tests that are long, boring, monotonous and sensitive to the behavioural implications of sleep loss (c.f Pilcher & Huffcutt, 1996) Studies that have looked at sleep per se and the effect it has on neuropsychological functioning have generally focussed on sleep problems and the manifestation of the problem on daytime behaviour (e.g. Hayward et al ,

1992) The study by Hayward et al aimed to assess neuropsychological functioning and sleep patterns in the elderly. However, their rationale of carrying out such a study was not particularly encouraging, plus the sleep parameters used were centred around sleep duration, waking after sleep onset (WASO), time of wakening etc. The literature concerning the relationship between sleep and neuropsychological function would indicate that performance on neuropsychological tests would have more impact on spectral measures of sleep, and that the sleep variables chosen here are more likely to be related to tasks sensitive to daytime sleepiness caused through sleep disturbance and not tasks of a higher function. Unsurprisingly, they concluded that sleep disturbance was not related to neuropsychological performance

Crenshaw & Edinger (1999) had a much stronger rationale behind their work, but whilst choosing spectral measures of sleep, they used reaction time (RT) as their performance index. The authors concluded that delta activity (2-4Hz) was not related to reaction time in normal subjects, although older (60y+) insomniac patients with slow reaction times did show a decrease of power in the 2-4Hz frequency. The main concern with this finding is a) the extent to which both are affected by the confounding variable of age and b) the extent to which RT is affected by a possible confounding effect of sleepiness due to the insomniacs' symptoms They did speculate that more research was needed, and indeed they followed this up with a later study (Edinger et al , 2000) Edinger et al looked at the relationship between RT and delta activity, this time amongst healthy sleepers aged 40-59yrs, and concluded that physiological parameters other than 2-4Hz activity may determine performance on the RT task The conductance of these studies is surprising given the wealth of research that has consistently shown that RT is more likely to be affected by parameters, such as sleep duration, than delta activity for instance (e.g. Gillberg & Åkerstedt, 1994).

The studies in this area that have proven to be interesting centre on the idea of improving neuropsychological functioning in the elderly through the enhancement of SWS. Dustman et al (1984) first demonstrated that aerobic exercise in 55-70year olds, over a period of 4 months, significantly improved neuropsychological test performance than controls (engaged in stretching programme) Although the

authors fail to relate the improvement to SWA or make an attempt to measure this; the results still remain interesting A more ambitious study was carried out by Naylor et al. (2000), that was the first study to show that low intensity activity in older people not only increased their SWS levels (sleep staged according to Rechschaffen & Kales) but also improved memory function, especially working memory. Although the authors attribute the results to exercise altering circadian rhythmicity (and therefore increasing sleep quality), the study does indicate a relationship between SWS and neuropsychological test performance It is thought that a predisposition toward the use of spectral measures of delta activity may have given results an increased neurophysiological and theoretical basis, as opposed to using older sleep staging methods.

1.5.1 Effect of Sleep Deprivation

Most studies looking at sleep and neuropsychological test performance, have been concerned with a loss of sleep. The longest sleep deprivation period undertaken was that by 17-year old Randy Gardner spanning 264 hours (11days), an achievement which has since been well documented (e g Ross, 1965; Gulevich et al , 1966). Dement (1972) commented on the surprising lack of psychological and physical impairment, especially given the extent of the neurological impairments as Gardner found increasing difficulty in attention, speech and memory functions. a clear sign of a neuropsychological deficit (Horne, 1988a).

Given the idea that low frequency delta is produced by the cortex, and is thought to reflect an enhanced form of recovery for the frontal areas, it is thought that a loss of this type of sleep would result in a reduction in the efficiency and ability of this area. This would certainly be the assumption made from numerous studies on long-term sleep deprivation. The loss of sleep in excess of 32 hours has consistently shown decrements to performance, with regards to speech (e g Harrison & Horne, 1997, 1998; Bard et al., 1996; Morris et al , 1960), Temporal Memory (Harrison & Horne, 2000a), divergent, flexible thinking (Harrison & Horne, 1999; Wimmer et al., 1992) and decision making (Harrison & Horne, 2000b) Although all these would suggest a decrement to the cerebrum following sleep loss, the finding that convergent tasks are not affected by sleep loss (Milner

& Petrides, 1984; Stuss & Benson, 1985; Fuster, 1989) would appear to be contradictory. However, the former functions mentioned (speech, temporal memory and flexible divergent thinking) are all functions of the PFC. It would therefore appear that human sleep loss is more detrimental to the function of the PFC which would be concurrent with the findings regarding the function of delta activity and functional imaging studies of the waking PFC under prolonged wakefulness.

1.6 THE PRE-FRONTAL CORTEX (PFC)

1.6.1 Anatomy

The PFC lies anterior to the primary motor and premotor cortices and includes the dorsolateral and orbital frontal regions, Broca's area and the frontal eye fields (Kolb & Wishaw, 1985) As the PFC is the largest cortical region (Rezai et al., 1993) and has extensive connections with other cortical regions, it is not surprising that the range of deficits associated to PFC damage is wide (Shimamura, 1995) The function of the PFC has been assessed through years of study ranging from lesion studies to the more modern functional imaging studies

1.6.2 Function

The exact, and numerous, functions of the PFC are unknown, but generally the PFC is involved with the maintenance of wakefulness, the enlistment of other cortical areas and non-specific arousal (Fuster, 1989, Stuss & Benson, 1986). In his review of the PFC, Horne (1993) lists other functions mediated by the PFC, including planning, sensory discriminations, the direction and maintenance of novel, goal directed behaviours, speech and decisions for actions By localised damage one can assess the behavioural consequences and thus make assumptions on the original function of the affected brain region, therefore traditional studies that promote the understanding of the PFC come from studies of lesions in the PFC caused by head injury, tumours and surgery.

A classic deficit in PFC damaged patients is their inability to temporally organise behaviour, due to deficits in attention and memory (Fuster, 1989) This is evident in their poor ability to perform tests looking at recency (e g. Butters et al , 1994; Milner et al., 1991), which has attributed to a dysfunction of the left PFC (Milner et al., 1991) Damage to the PFC has also resulted in deficits in decision making due to the inability to assess future consequences (Bechara et al , 1994; 1998) Taking into account the divergent, flexible thinking the PFC is involved with, together with a memory for contextual details and temporal order (See Milner & Petrides, 1984 for review), it is expected that the ability to make decisions would be affected through a PFC impairment.

Further implications of the impaired PFC lie in planning ability (e g Milner et al., 1985, Fuster, 1989) and the perseveration of actions, mainly due to the inability to inhibit an obvious response (Luria, 1973) Due to the location of the speech centre Broca's area, lying within the PFC, speech impairment is often associated with localised damage in the frontal regions, in that it becomes less articulated, less innovative, contains shorter sentences and is often accompanied by a flat tone (Horne, 1993).

The PFC has no unitary function but is involved in a variety of executive functions e g temporal memory, perservation, planning, inhibition, speech and the initiation/maintenance of novel goal directed behaviour The idea that PFC decrements are caused through a loss of (slow wave) sleep is highly supported (e.g Harrison & Horne 1996, 1997), however, recent developments exemplify that the broad bandwidth of the delta rhythm (0 5-4.5Hz) may be masking specific sub-activities within this range, and therefore the idea that sleep serves a global process, is becoming not only topographically specific (in regards to the PFC) but also frequency specific in that not all activity 0.5-4.5Hz may be equally reflective of increased recovery for the PFC during sleep but the focus turning towards lower frequency delta waves.

1.7 PFC IMPAIRMENT THROUGH SLEEP LOSS

With prolonged wakefulness therefore, one can expect decrements, similar to those described above, which are characteristic of an individual with an impairment of the PFC The literature on sleep deprivation and performance can be split into two categories, the first, and perhaps most common, deals with behavioural aspects of sleepiness (c f. Pilcher & Huffcutt, 1996), i e. vigilance or reaction time, which can be overcome through motivation (Horne & Pettitt, 1985) or countermeasures to sleepiness (Bonnet & Arand 1994a, 1994b) The second category deals with physiological detriments of long-term sleep loss (>36hours), and it is this type of sleep deprivation that gives insight into the sleep for cerebral restitution debate. Given that long-term sleep loss affects functions such as planning, speech, inhibition and temporal memory, the tasks described below are all affected by sleep loss due to the demands they make on the PFC. Table 1.2 summarises a selection of studies that have found the following tasks sensitive to sleep loss

Table 1.2: A summary of studies specifying sleep loss decrements on tasks proposed to rely on the integration of the PFC.

	WCST	NVPT[7]	Stroop Test	Verbal Fluency[8]	Torrence Test	Haylings Sentence Completion	Temporal Memory
Harrison & Horne 2000a	-	-	-	-	-	-	✓
Harrison et al. 2000	-	-	-	✓	-	✓	✓
Binks et al 1999	×	-	×	×	-	-	-
Harrison & Horne 1998	-	-	-	✓	-	✓	-
Randazzo et al 1998	✓	-	-	-	-	-	-
Harrison & Horne 1997	-	-	-	✓	-	-	-
Naëgelé et al. 1995	✓	✓	✓	✓	-	-	-
Horne 1988b	-	✓	-	✓	✓	-	-

×= No Significant Effect of Sleep Loss ✓ = Significant Effect of Sleep Loss

The use of the WCST in studies of sleep loss is rare, possibly due to the inconsistency of findings regarding the activation of the WCST (e.g Anderson et al , 1991). However, a study that involved sleep-restricting (5h) children (aged 10-14y) found decrements in performance on the WCST and Verbal Creativity tasks

[7] Tower of London or Tower of Hanoi Used
[8] Verb to Noun Generation or Thurstone's Word Fluency Used

(Randazzo et al , 1998) They attributed the decrements to the inability to maintain higher cognitive functions, even in the presence of motivation that overcame sleepiness related impairments on other tasks (i e Psychomotor tasks) However, the extent to which this was related to a PFC impairment is questioned due to the lack of adequate sleep deprivation involved Binks et al. (1999) also suspected the validity of the WCST in the detection of a sleep induced PFC impairment as they found 34-36hours of sleep loss did not impair performance on the WCST. However, studies conducted on sleep apnoea patients found a marked reduction in the performance on the WCST (Naëgele et al., 1995). Although sleep apnoea is thought to affect the functioning of the PFC, the extent to which this is due to sleep loss and/or pathology associated with the disorder is still being researched (e g. Engleman et al , 2000).

Although Horne (1988b) found that sleep loss (>32hrs) had a significant negative effect on planning time during the Tower of London and also a sleep loss decrement on the Torrence test of creativity (verbal and figural) in comparison to controls, the subsequent use of these tasks in sleep research has been sparse. However, a task that is more common in studies of sleep research is the verbal fluency task. Not only have many sleep deprivation studies highlighted the change in the sound/formation of speech, such as monotonic, simple sentences (e g Horne, 1993), but they have also found a significant decrease in the ability to produce words at a given prompt (Harrison & Horne, 1997, 1998) Harrison & Horne are the pioneers in this work, and conclude that a sleep loss of 36 hours produces deficits of a PFC nature (i e reduced verbal fluency) even though tasks were short, novel and interesting, and caffeine was administered to remove any masking effects of sleepiness (Harrison & Horne, 1998)

Morris et al. (1960) also commented on the effect sleep loss had on speech as they found sleep deprivation caused changes in tone, rhythm and the clarity of the voice. In the study by Harrison & Horne (1997), not only did they find reduced verbal fluency on the Thurstone verbal fluency task, they also noted the articulation of subjects' voices changed as their tone became dull, flat and monotone.

Although Naègelé et al. (1995) found the Stroop task to be sensitive to a PFC impairment, whether due to the loss of sleep or decreased executive function due to the apnoeic condition, Binks et al. (1999) reported the task was insensitive to the effects of sleep loss. However, Binks et al. reported that neither the WCST, Stroop test nor verbal fluency were sensitive, which is surprising given the extent to which others support them as a marker of PFC impairment through sleep loss and therefore their findings are viewed with caution.

A recent sleep loss study (Harrison & Horne 2000a) found that 36hrs of sleep loss did not impair the ability to recognise a face, but did impair the ability to recall 'when' it had been seen in terms of time. Therefore, sleep loss had a significant debilitation effect on the ability to make a recency judgement, despite conditions promoting optimum performance (such as caffeine and motivation) Similarly, Harrison & Horne (1998) confirmed that the Haylings Sentence completion was impaired through sleep loss in that sleep deprived subjects gave more incorrect answers on the incongruent conditions (that is they failed to inhibit a known response) and the latency to provide an incongruent response increased under sleep loss conditions The Haylings task, in addition to the other tasks mentioned here, activates the PFC and is also negatively affected by sleep loss. The neurophysiology of the PFC during sleep loss, as discussed, shows why these tasks might be affected

1.8 PFC IMPAIRMENT ASSOCIATED WITH HEALTHY AGEING

Neuropsychological evidence

Horne & Harrison extended their work of sleep loss induced PFC decrements with a study designed to compare the effects of sleep loss to PFC impairments associated to healthy ageing (Harrison et al , 2000) The rationale behind this work lay in the reasoning that as the PFC seemed to work hardest, it may be more vulnerable to deterioration through natural ageing or through loss of sleep Given that previous research had shown both sleep deprived young people, and healthy older people (60+) to be sensitive to PFC orientated tasks, Harrison et al's study aimed to assess the extent to which these two similarly impaired groups were comparable The authors found that all the PFC measures taken (Verbal Fluency,

Temporal Memory and Haylings Sentence Completion) were significantly affected by age, and interestingly, that the amount of PFC impairment induced by 36hrs of sleep loss was similar to the deficit shown in a healthy 65 year old The authors were keen to stress however, that an 'aged' brain was not a 'sleepy' brain as careful measures were taken to ensure normal sleep in this older group.

Moscovitch & Winocur (1995) proposed that the memory ability of an elderly person corresponds to a deficit seen in those with frontal lobe and hippocampal lesions (i e. impaired working memory and/or temporal order) Many other researchers have also found memory performance to be consistently impaired in older people (e g Daum et al , 1995; Parkin & Lawrence, 1994) Parkin & Walter (1991) found that performance on the Brown-Peterson task (a task of free call using Short-Term Memory) was impaired in older groups, but also, that scores on the Brown-Peterson technique corresponded to scores on frontal tasks (i e. WCST, verbal Fluency) The memory decrements associated to older age have therefore been attributed to hippocampal dysfunction (i e. Geinisman et al., 1995) since the hippocampus is linked to memory function (Kolb & Wishaw, 1985) However, research shows that the rCBF in the hippocampus is equal in older and younger age groups during recollection, whereas rCBF in the PFC was bilateral for the younger group with the older adults showing posterior frontal lobe activation only (Schacter et al , 1996). The authors concluded that differences in frontal activation reflected age-related changes in memory ability and not hippocampal function.

A recent study by Corey-Bloom et al. (1996) provided more evidence for age-related reduction in PFC performance. They found Verbal Fluency to be especially sensitive to ageing effects, whereas other language tasks that are not so specialised to the PFC (e g. Boston Naming Test) showed no effects Daum et al. (1996) gave 50 right-handed subjects four tasks WCST, Verbal Fluency, Temporal Memory and a word recall task. They found all tasks were affected by age, apart from the recognition component of the temporal memory (which is not a PFC-specific function). They also found all the tasks inter-related supporting the involvement of the PFC.

There is no unitary function of the PFC that is common to all tasks, therefore understanding the relationship between ageing and PFC function can sometimes be confusing and conflicting due to various literature findings. Also, tests that are sensitive to a PFC impairment may not always be inter-correlated: For instance, some studies have reported that the WCST and Verbal Fluency are inter-related (e.g. Craik et al., 1990; Daum et al., 1996) whereas others have found the two tests are not related (Fabiani & Friedman, 1997) Interestingly, the latter work found no relation of Verbal Fluency with age, only an effect of age on the WCST and Temporal memory. They attributed this to the WCST relying on different aspects of PFC function and/or that the Verbal Fluency Task (Thurstone's Verbal Fluency[9]) was too easy.

The PFC function theory in relation to cognitive ageing is a complex one, the complexity being summed up in the review by West (1996) as he attempts to draw the numerous models of frontal lobe ageing together to form a unified concept. As Parkin (1997) show normal ageing does reflect in a loss of function associated to the PFC, but as the PFC has no unitary function the resulting behavioural deficits are multifaceted and difficult to segregate

Neurophysiological evidence

Biological studies of PFC function with regard to healthy ageing, provide a much clearer assessment of areas negatively affected by the healthy ageing process. Martin et al. (1991) carried out PET scans on thirty volunteers aged 30-85 years and found that there was an age-related reduction in rCBF in the left PFC Further support came from a recent study by Raz et al. (1999) who conducted MRI scans on eighty-five participants ranging from 19-77 years, and found the volume of the DLPFC reduced with age, and that this reduction was related to performance of working memory The use of MRI in the assessment of frontal lobe damage in the healthy aged population has consistently shown that the frontal lobe is more prone to the effects of ageing as the deterioration here is more advanced than other brain regions (Cowell et al.,1994; Coffey et al., 1998).

[9] Thurston's Verbal Tasks is considered much easier than the Verb-to-Noun Verbal Fluency task

As the PFC is therefore becoming less 'hard-working', to use Harrison et al.'s terminology, during the ageing process, surely we can therefore expect a reduced amount of delta activity in older people, since the increase in delta activity is in response to the increased metabolism of the PFC.

1.9 DELTA ACTIVITY AND HEALTHY AGEING

It has been well documented that sleep changes throughout the ageing process (See Bliwise 1993 for review) Although older people show increased sleep onset latency, increased stage 1 sleep and increased waking after sleep onset (e g. Landolt et al., 1996, Bliwise, 1993; Dement et al., 1982), the area of concern is with regards to changes to SWS, or more specifically delta activity, with age The most consistent finding, with regard to sleep and ageing, has to be the reduction of delta activity (e g. Feinberg, 1974, Mourtazaev et al., 1995). However, most of these studies are dated since they investigated SWS by means of staging sleep and/or SWS parameters based on Rechtschaffen & Kales' method. This is not considered as robust as current spectral analysis methods especially given the recent findings regarding the slow and fast delta frequency components. An area of concern when using sleep stages in the older population is that the EEG amplitude is reduced (See Fig. 1 2) and one of the requirements of Stage 3 and 4 sleep is an amplitude exceeding 75μv (Rechtschaffen & Kales, 1968).

However, studies conducting a spectral analysis of the EEG have also shown a reduction of delta activity (e g Ehlers & Kupfer, 1989; 1997; Larsen et al., 1995a; Landolt et al , 1996) The reduction of SWA[10] is thought to begin at 20years of age, reducing to half its peak level by the age of 40 years (Feinberg et al., 1983; Dement et al , 1985).

Interestingly, this decline in SWS, although a uniform phenomenon throughout the cortex, does show both topographical and temporal changes in that the reduction of delta activity is most evident in the first NREM period (Ehlers &

[10] The decline of SWA with age is claimed to be affected by sex differences (e g Dijk et al 1989) although this is rebuked by others (e g. Brenner et al 1995) Most studies control for this

Kupfer, 1989) and is prevalent within the PFC (Carrier et al., 2001; Landolt & Borbély, 2001).

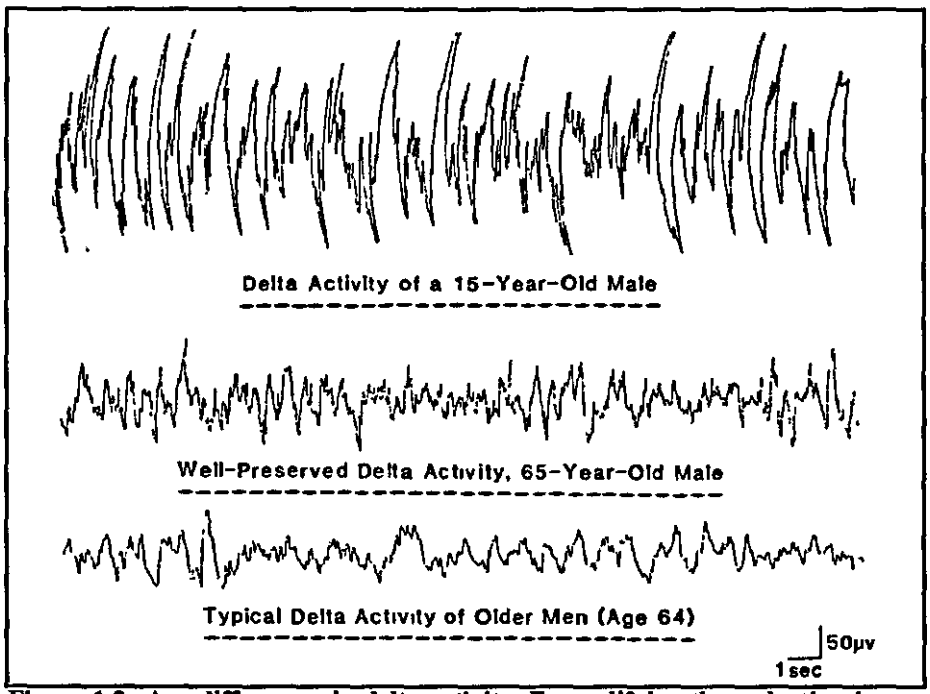


Figure 1.2 Age differences in delta activity. Exemplifying the reduction in amplitude with age (Zepelin, 1983 -taken from Chase & Weitzman (1983) pp 433)

Landolt & Borbély (2001) assessed topographic changes in the sleep EEG in young (22.3y) and older (62.0y) people. Although they confirmed basic parameters known to be associated to ageing (i.e reduced SWS, Stage2, sleep efficiency etc), they did find that for frequencies 0.75-2Hz, the anterior dominance of such frequency was only significant in the younger age group, which is contrast to the posterior regions which were similar for both age groups. Therefore, older people do not demonstrate hyperfrontality with regards to low frequency delta This study is currently the only study to compare the topography of EEG frequencies as a consequence of age, and more specifically the only study to refer to low frequency delta in an older population.

As low frequency delta is generated directly by the cortex, and is a focus for the PFC, the loss of low frequency delta through the effects of age, may reflect impairment in older people, whether this is a cause or effect of age-associated PFC decrements. The reduction of delta activity has been attributed to both a reduction of sleep need (e.g Reynolds et al , 1985; Carsakadon & Dement, 1985)

and biological changes with age, such as metabolism (Bliwise, 1997) or mild brain pathology (e g Benson et al , 1997).

1.10 THE SIGNIFICANCE OF THE WAKING EEG?

Early research on waking EEG shows it was once an area for contention as the sleep EEG is now As the waking and sleeping PFC has been linked metabolically, it is thought this may also be apparent in studies comparing EEG activity across the waking state

The Zurich laboratory responsible for identifying the two-process model of sleep and the extensive literature regarding low frequency delta, have recently turned their attention to the waking EEG As described earlier, Process S builds up during the day and decreases during the night, reflected in SWA (0.75-4 5Hz). Finelli et al (2000) aimed to identify what waking EEG frequency may account for the increase in Process S during the day as SWA reflects its decrease at night. They found that during prolonged wakefulness, EEG power in 5-8Hz bandwidth best reflected the increasing Process S, and given that this activity was significantly correlated to following SWA (0 75-4 5HZ), they concluded that the waking EEG could also be used as a marker for sleep propensity. Interestingly, both the rise rate of waking theta and subsequent decline in delta sleep were both predominant in the anterior areas Inasmuch that this may simply be a reflection of increasing sleepiness, the interesting aspect lies in the idea that these two frequencies are part of an underlying common process (Finelli et al., 2000).

This is supported by the work of Ehlers et al. (1998) who assessed the differences in the waking and sleep EEG due to age They found that increasing age was associated to a decrease of delta (0.75-4 5Hz) in the waking EEG, which is similar to the sleep EEG. This is interesting since the same study reported that the sleep EEG and wake EEG were functionally related as one was related to the other. Therefore, this would support the work of Finelli et al. (2000) in that the waking EEG and sleep EEG are part of an underlying process.

However, it is not only with reference to performance that theta is making a comeback; The study of the waking EEG, and the implication of the theta rhythm, is summarised by the article "theta returns" by Kahana et al. (2001) They describe how the theta range is becoming intriguing as it reveals associations between brain oscillations and cognitive processes The study of the waking EEG and cognitive processes is interesting, especially when the relationship starts to be localised to (left) frontal regions.

1.10.1 Waking EEG and Cognitive Test Performance

Vogel et al. (1968) prematurely attempted to assess whether the waking EEG could be used to predict performance. Although the findings were not particularly impressive, they did show a very weak relationship between the EEG (beta) and waking performance on simple tasks (such as counting) Mundy-Castle's (1957) earlier work was much more encouraging as it showed that the theta rhythm was increased by mental arithmetic or visual imagery. The theta rhythm Mundy-Castle identified may well have been the 'Kappa rhythm'.

The Kappa rhythm was once renowned for being associated to thinking as it was produced during a problem solving exercise (Kennedy et al , 1964). The term 'Kappa Rhythm' was seldom used for distinction of EEG activity, however, the phenomena associated with it (i e. thinking) still gained recognition. Ishihara & Yoshii (1971) carried out a study of EEG and mental activity and concluded that theta activity in the frontal region appeared during mental activity and continued during sustained attention tasks Interestingly, they report that this frontal 'theta' was most frequent during the Digit Symbol Substitution task (DSST), the only task they used that relied mainly on the integration of the frontal lobes due to its reliance on working memory. They concluded that theta activity during mental performance seemed to originate in the frontal area and tended to appear on tasks that required continuous concentration of attention Findings such as these are interesting since theta is normally associated with a drowsiness (See table 1 1) whereas in these circumstances it is associated with increased mental effort, thinking, and tasks that require sustained attention.

The relationship between the waking EEG and performance has recently received much attention following an absence of several decades since the work of Mundy Castle, Chapman etc. Many studies have implicated the theta rhythm as an indication of increased brainwork (e g Gundel & Wilson, 1992, Ramos et al., 1993; Jensen & Tesche, 2002) Recent developments have shown the waking EEG can be used as a marker of performance. Hoptman & Davidson (1998) argued that the resting EEG was reflective of cognitive or emotional behaviours, and therefore attempted to find a relationship between neuropsychological test performance and waking EEG: Due to verbal fluency being regarded as highly specific to the left frontal cortex they argued that this test would be related to a left-sided activation over anterior scalp positions. With regard to the Tower of London, the authors predicted this would cause bilateral frontal activation Thirty-two participants underwent the neuropsychological tests on the first session, and the waking EEG on the second whereby delta (1-4Hz), theta (4-7Hz) and alpha (8-13HZ) bandwidths were examined. They found in the alpha band that verbal fluency was associated with power density in the left central region, with performance on the task being correlated with this activity. The number of attempts at the Tower of London task problems was associated with (alpha) activity in the left parietal region The authors conclude that waking EEG could be used to predict test performance on the verbal fluency task, but not the Tower of London

Recent research by Çiçek & Nalçaci (2001) has shown that low alpha frequency (8 6-10.2Hz) from the left frontal regions was associated with better performance on the WCST. Interestingly, the EEG measures taken at rest and not during task completion indicate an underlying commonality between the generation of the EEG and areas involved in performance of the WCST. Çiçek & Nalçaci focussed their research on younger individuals, but as the waking EEG changes with age, such as a reduction in peak alpha frequency (e g Roubicek, 1977), the relationship may be different with an older age group. McEvoy et al (2001) found that younger subjects (18-25y) demonstrated an increase in frontal theta during task completion whereas the older group (42-56y) did not. Due to the older population performing less efficiently on the WCST (See above) and also showing changes in the waking EEG, the study of Çiçek & Nalçaci would be interesting if performed on older participants.

1.11 SUMMARY

- Sleep is for the recovery of the cerebrum. Evidence includes
  - Sleep Loss results in neuropsychological deficits.
- The aspect of sleep thought to be important is SWS, due to:
  - The immediate need for SWS during the night
  - The stability of SWS in short-sleepers, natural or experimental, at the expense of stages 1 and 2, and REM sleep
  - The rebound of SWS following sleep deprivation
  - The relation between length of prior wakefulness and SWS levels at night.
- SWS is used to refer to 0.5-4.5Hz activity New research splits the delta range into its slow (0 5-2Hz) and fast (2-4 5Hz) components as it is argued to be functionally distinct.
- The 'recovery' value of delta activity has been re-examined proposing that low frequency delta has an enhanced recovery process in the PFC, as:
  - Activity <2Hz is prominent in the PFC.
  - Activity <2Hz is decreased during sleep loss, with a focus in the PFC
  - Activity 1 25-1 5Hz has the largest increase in power during recovery sleep, particularly in the PFC.
  - Activity <1Hz is generated by the cortex itself, and is prevalent in the PFC
- Sleep would appear to have localised functions, particularly in reference to the PFC. Evidence for this is includes:
  - Sleep loss in excess of 36hours results in behaviour characteristic of a PFC impairment.
  - The PFC has the greatest reduction in rCBF during prolonged wakefulness
  - Not only does the PFC show greatest CMR during the day, it shows the greatest fall in CMR at night, particularly during SWS.
  - The EEG is of a higher frequency in the PFC during the day, and the lowest during SWS periods at night suggesting this area to be more active during the day and yet in an enhanced state of rest during the night.
  - Healthy aged people show a reduction in delta activity (0.5-4 5Hz) and also low frequency delta (<2Hz). Neuropsychological research also shows that older people to perform less efficiently on tests orientated towards the PFC in comparison to younger counterparts

- Daytime CBF is related to night-time SWS, with the strongest association being in the PFC.

➢ Delta activity also appears to be lateralised:
- Recovery of delta activity is more pronounced in the left PFC
- Low frequency delta is enhanced in the left PFC.

➢ Although there is a wealth of evidence concerning the waking and sleeping PFC, no study has attempted to assess the extent to which one can use the delta sleep EEG to predict performance of the PFC. Studies that have been conducted are limited:
- Studies concern sleep variables, as opposed to spectral analyses.
- Studies have also focussed on non-cortically specific recording sites and/or tests (i e. RT), but have been inconclusive
- It has been shown that by experimentally increasing delta activity in older people, memory performance improves

➢ The waking EEG has been shown to reflect sleep EEG at night, as both are possibly due to the same underlying mechanism

➢ The Waking EEG, and its association with performance has been given moderate attention. Findings show:
- Increased thinking results in more frontal theta activity.
- Some tasks (e g WCST/Verbal Fluency) have been linked to wake EEG activity

1.12 AIMS

The aims of this thesis are to investigate possible associations between the waking and sleeping EEG and performance, with a focus on the Pre-Frontal Cortex: ***Associations Between PFC Performance and the Sleep EEG in Healthy, Older People.***

Given that the PFC is a focus for the cortically-generated low frequency delta, which is reduced with healthy ageing, and that PFC performance is also reduced, incidentally or otherwise in an older population (e g. West, 1996), a possible relationship between the indices of neuropsychological test performance and low frequency delta in healthy older people is hypothesised. Specific research questions were thus

- Is delta activity related to PFC performance?
- Is low frequency delta activity related to PFC performance?
- Is this relationship unique to frontal activity?
- Is this relationship unique to PFC orientated tasks?

Waking EEG, and its association to the Sleep EEG and PFC Performance in Older Adults

Given that the waking EEG and sleep EEG are thought to be stable the use of the waking EEG will be studied to assess the extent to which there is an association between the wake and sleep EEG, and PFC performance Specific research questions are thus:

- Is the wake EEG related to the Sleep EEG, specifically low frequency delta?
- Is this relationship unique to frontal areas?
- Is there an association between wake EEG and PFC performance?
- Is the wake EEG a more suitable predictor of PFC performance than the sleep EEG?

Associations Between PFC Performance and the Sleep/Wake EEG in Younger Adults

This section deals with the investigation of whether the relationship between PFC performance and sleep EEG is specific to older people, given a possible underlying commonality associated with ageing Similar associations between delta activity and neuropsychological test performance will be investigated with a younger sample Specific research questions are thus:

- Is delta activity related to PFC performance in a younger group who are not thought to be impaired on PFC tasks?
- Is low frequency delta a focus for this association?
- Is the relationship unique to the frontal areas, with regard to both task and delta activity?
- Is low frequency delta related to waking EEG?
- Is waking EEG also a marker of PFC performance?

CHAPTER 2

GENERAL METHODOLOGIES

2.1 AIMS

The aim of the research in this thesis was to investigate the relationship between waking performance and EEG activity, during both sleep and waking conditions, in both young and older sleepers. Subjects were screened to ensure they were normal, healthy sleepers, and selected to undergo a battery of neuropsychological tests, two nights of Sleep EEG recording and a Wake EEG recording.

The methodology as described in this chapter provides details for the methods employed for all subsequent experimental chapters (Chapters 3-6)

2.2 PARTICIPANTS

Participants were within two age bands: Young, aged 19-23years and Older, aged 61-75years The young participants were selected from respondents to recruitment posters at Loughborough University and the older participants were selected from the University of the Third Age (U3A); an organisation that promotes social activities after retirement All participants were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971)

All participants were paid for their involvement in the experimental studies, and gave informed consent (See Appendix 1) to take part in the studies described

2.2.1 Criteria for Healthy Sleepers

Interview

Volunteers underwent a structured interview to detect any sleep-related problems and general health status (See Appendix 2) All participants were:

- Healthy, with no social, emotional or physical problems that might affect their sleep, such as anxiety or severe arthritis/rheumatism.
- Not impaired in their sight and hearing (with/without glasses/hearing aids)

- Free from any sleep-related disorder, such as insomnia or heavy snoring
- Free from medication other than anti-inflammatory agents (e g those on anti-depressants, hypnotics etc, were excluded, as was any medication with a possible side-effect of daytime sleepiness as listed in the BNF)

Participants were also interviewed to assess their general sleeping habits This ensured that all participants were:

- Healthy, undisturbed sleepers, with an habitual sleep length of 8hours ± 1hour
- Classified as 'Non-Nappers' (naps < twice per month)
- Had a regular sleeping pattern.
- Had scores within the normal range (≤10) on the Epworth Sleepiness Scale (Johns, 1991 – See Figure 2.1).

The Epworth Sleepiness Scale

How likely are you to fall asleep in the following situations? Please indicate, using the following scale, which is most appropriate given the situation.

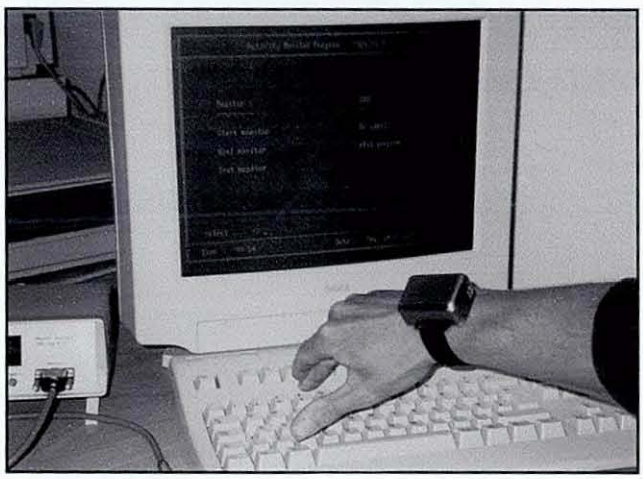
0 = Would *never* doze
1 = *Slight* chance of dozing
2 = *Moderate* chance of dozing
3 = *High* chance of dozing

Situation	**Chance of Dozing**
Sitting and Reading	.. . .
Watching TV	....
Sitting inactive in a public place (e g. theatre/meeting)	. . ..
As a passenger in a car for an hour without a break	. . ..
Lying down in the afternoon when circumstances permit	.. . .
Sitting and talking to someone	. . ..
Sitting quietly after lunch without alcohol	....
In a car, while stopped for a few minutes in the traffic	....
	TOTAL ....

Figure 2.1: The Epworth Sleepiness Scale (Johns, 1991)

Screening

All participants were asked to wear a Swiss, Gaehwiler-type actimeter (See Figure 2.2) to ensure they had normal, undisturbed sleep. Actimeters were worn on the dominant wrist and were set to record movements in 30-second epochs (Sampling rate: 8Hz), providing a frequency score for each epoch. Data was collected and transformed into binary data (0 for an epoch containing no movement and 1 for an epoch containing movement). Sleep Onset was calculated using the algorithm 14/10 epochs (Horne et al., 1994) so sleep onset is five minutes (10 epochs) into a period of seven consecutive minutes (14 epochs) of inactivity. Sleep offset was the commencement of a period of activity. This method was used to ensure participants were regular 8-hour sleepers ± 1hour.



Dimensions of the actimeter are:

Size: 51x36x21mm
Weight: 68g

Figure 2.2: Gaehwiler Actimeter worn on the wrist

Actimetry was also used to assess sleep disturbance to ensure night-time sleep disturbance was not causing daytime sleepiness, particularly in the older age group. Actimetry data was visually examined for sleep onset/offset markers, sleep disturbance and any periods of inactivity during the daytime that may be indicative of napping (See Appendix 3).

All participants were required to rate their sleepiness, every hour, throughout the day for three consecutive days to ensure no excessive daytime sleepiness. This was done using the Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990 - Figure 2.3). An easy-to-use form (See Appendix 4) was given to all participants to complete.

The KSS scale is considered a sensitive measure of sleepiness: a study assessing the validity of the scale showed that is more sensitive to changes in sleepiness than physiological changes; the EEG only signifying sleepiness when the KSS rating reached 7 or above (Åkerstedt & Gillberg, 1990) Therefore, in this thesis, the KSS was considered the most sensitive measure of daytime sleepiness.

The Karolinska Sleepiness Scale

1	Extremely alert
2.	Very alert
3.	Alert
4	Rather alert
5.	Neither alert, nor sleepy
6	Some signs of sleepiness
7	Sleepy, but no effort to keep awake
8	Sleepy, some effort to keep awake
9	Very Sleepy, great effort to keep awake, fighting sleep

Figure 2.3: The Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990)

2.3 EXPERIMENTAL DESIGN & PROTOCOL

A repeated measures design was used, whereby participants underwent both neuropsychological testing and EEG recordings. These were performed on days separate from each other, in order to minimise any interference. For instance, increased brainwork during the day can increase SWS at night [a major variable in this research] (Horne & Minard, 1985). Neuropsychological testing, and all waking EEG recordings, were undertaken in the laboratory, between 10 30h and 12.00h when participants felt most alert (See Figure 2.4) whereas sleep recordings were undertaken in the home All participants reported wake-up times that had a range of about 1 hr; therefore any differences in wake-up time are not a confound[1] of the correlations between EEG and performance reported later.

[1] It should be noted that PFC performance is unlikely to be affected by such variances, since PFC decrements are not alleviated with caffeine and/or motivation (See Harrison et al , 2000)

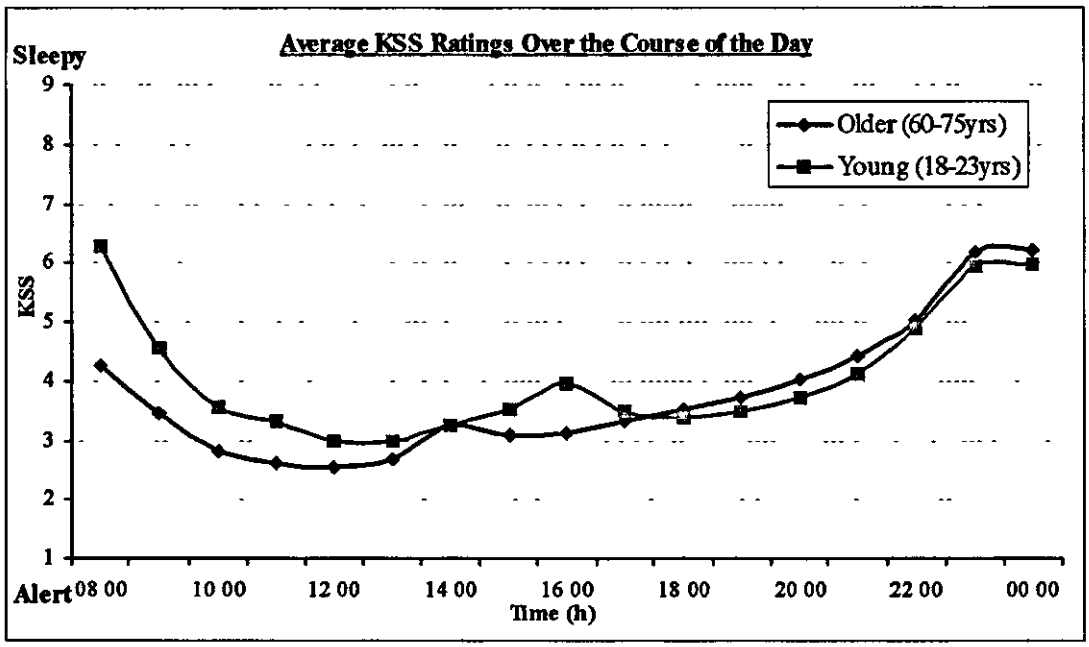


Figure 2.4: Average Karolinska sleepiness scale ratings throughout the day for both young (n=12) and older (n=24) groups.

2.4 GENERAL PROCEDURES

After 18 00h on the night prior to neuropsychological testing, all EEG recordings and days involving KSS measurements, participants abstained from caffeinated drinks (including strong tea) and alcohol. All participants undertook neuropsychological test measurements and sleep EEG recordings (old n = 24; young n = 12), whilst all young participants (n = 12) and half the older group (n = 12) performed waking EEG recordings

2.4.1 Neuropsychological Testing

Participants arrived at the laboratory at 10 00h where they were required to fill in sleep diaries (See Appendix 5) to ensure they had a normal nights sleep the night before (compared against initial interview data and actimetry). Test administration was 10 30h to 12.00h. Test order was counterbalanced to remove fatigue effects, although this was deemed slight due to the novel, short and interesting nature of the tests. All test sessions were kept under 90 minutes to keep fatigue and/or boredom to a minimum. This allowed time for the tests with a five-minute break in between each task. All tests were explained on a prior familiarisation day, but

were not practiced, due to the novel prerequisite attributed to PFC tasks (Lowe & Rabbitt, 1997). All tests were short in duration, and participants were encouraged to apply maximal effort.

Testing consisted of a selected number of established frontally activating tasks to assess PFC performance (in addition to non-frontally specific tasks) The tasks were selected based on:

- Brain activation during completion
- Literature reports of sensitivity to PFC decrements.
- Ease of administration and understanding for the participant.
- All similar in terms of interest and length

The four main tasks used for assessing PFC performance were. the Wisconsin card sorting task, a verbal fluency task, a non-verbal planning task and a temporal memory task. Tasks such as reaction time and IQ were used to gauge global slowing and/or general cognitive ability, in addition to anagrams or self-ordered pointing to complete the test battery by using task that were less frontally specific Although no task is wholly frontally specific it is thought that the four main PFC tasks all rely on the integration of the PFC. Each chapter will specify the tasks in use

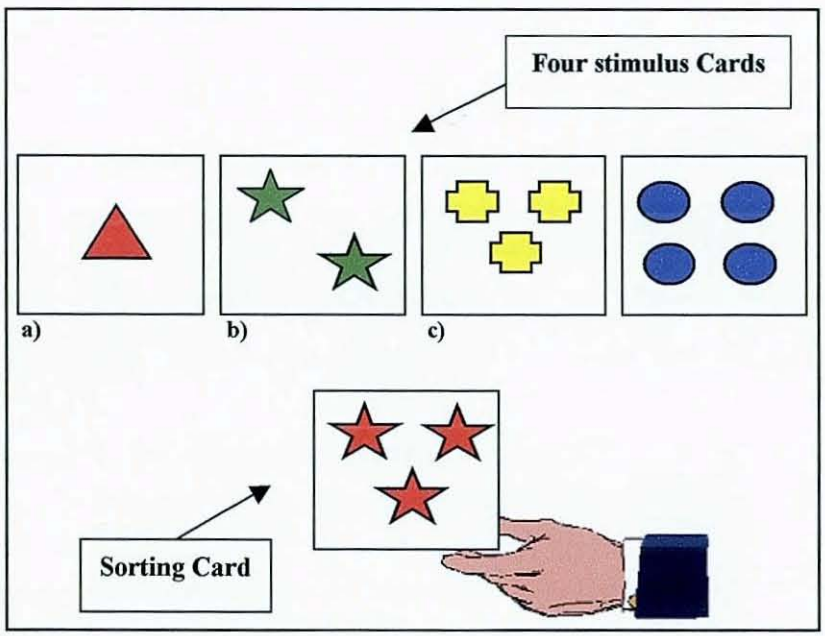
WCST

Perhaps the most widely used test in the assessment of frontal lobe impairment is the Wisconsin card sorting task (WCST); a test of perseveration through the sorting of cards to changing rules The test gained validation from the early work of Milner (1963) and since then many recent studies have confirmed the use of the WCST in the assessment of PFC dysfunction (e g Robinson et al , 1980, Goldberg et al , 1987) Milner (1995) found lesions to the dorsolateral PFC (DLPFC), usually on the left side, led to a difficulty in set shifting characterised by perseveration (a deficit unmasked by the WCST). In support of this, Raz et al. (1998) found the volume of the DLPFC (established via MRI) was significantly correlated to the number of perseverative errors on the WCST.

Volz et al. (1997) provided support for the WCST as a frontal task as their results indicated an activation of the frontal area Although the authors went on to specify the lateralisation of the task lay on the right-hand side, this was in opposition to Rezai et al. (1993) who concluded activation was on the left-hand side. However, the most consistent finding regarding localisation would appear to be the bilateral activation of the PFC during the WCST (Mentzel et al., 1998; Nagahama et al., 1996; Cantor-Graae et al., 1993). The use and validity of the WCST as a tool for assessing frontal lobe damage has been questioned due to the conflicting nature of findings regarding the localisation of activation the task produces (Barcelo, 2001; Chase-Carmicheal et al., 1999; Anderson et al., 1991). Nevertheless, this task is consistently used in frontal lobe studies, validating its use here.

PROCEDURE

Four stimulus cards and a deck of 64 cards are presented to the participants. They are instructed to sort the 64 sorting cards by selecting each card and placing it underneath one of the four stimulus cards where they believe it matches (See Figure 2.5).



The participant is required to place the 'sorting card' underneath one the 'stimulus cards' to where he/she believes it matches: **Example:** This stimulus card could be placed at location **a)** by sorting to colour; location **b)** by sorting to form or location **c)** by sorting to number. The experimenters response of 'correct' or incorrect' should determine their next response.

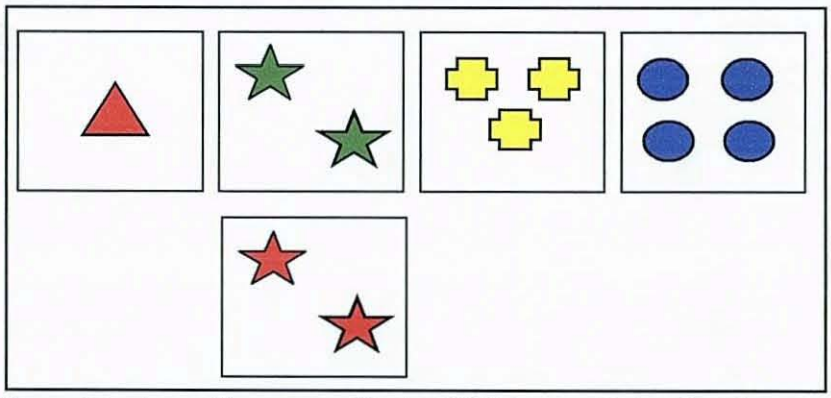
Figure 2.5: The Wisconsin Card Sorting Task.

Upon placing the card they are told by the experimenter whether the response is 'correct' or 'incorrect'. The first sorting category is colour, and they place the card underneath the stimulus card of the same colour, number or form. If the card is

incorrect they leave the card where it is and take the next card in the deck and choose an alternative location. Once they hear a 'correct' response they carry on sorting to that sorting rule (colour), that is, until ten correct responses are made.

Once ten responses are made, the experimenter changes the sorting rule to form (unbeknown to the participant), the participant should then realise that the rule is no longer 'colour' due to the response being 'incorrect' and therefore develop a strategy to determine the new rule. The extent to which the participant reverts back to an old rule, regardless of the 'incorrect' response is known as 'perseveration' or a perseverative response.

The measure taken for this thesis was the number of 'perservative errors', however, it should be noted that not all perseverative responses are perseverative errors since some cards are ambiguous (See Figure 2.6). The experimenter kept a record of all responses using the WCST response sheet (See Appendix 6).



Scenario: The previous sorting rule was '*form*' and is now '*number*'. This is perseverative as it is still sorted to '*form*' (if in a row) but is not an error as it also matches to '*number*'.

Figure 2.6: An ambiguous card in the WCST exemplifying that the perseverative response is not always a perseverative error.

This test was administered and scored according to the manual (Heaton, 1981) although the standard test uses 128 sorting cards (two identical packs of 64). Due to all other tasks being short in nature, it was deemed necessary that the WCST should also be short and novel. Therefore, the application of the WCST has been varied slightly in accordance with other studies (e.g. Grant & Berg, 1948; Grant et al., 1949; Fey, 1951; Loranger & Misiak, 1960; Robinson et al., 1980) in that only the first 64 cards were utilised. The criterion for analysis/discontinuation was the

completion of three categories [colour, form and number] (Tarter, 1973) or after 64 cards were sorted, whichever came first.

Test Duration: Approximately 12 minutes.
Measurement Used: Perseverative Errors

NVPT (Tower of London)

The ability to plan and sequence behaviour relies on the functioning of the PFC (Stuss & Benson, 1984). The Tower of London was originally designed to test planning abilities of PFC lesioned patients (Shallice, 1982), as this task was able to identify those with left frontal damage as the test requires those performing it to plan a sequence of events involving moving coloured beads to a target pattern. A study by Morris et al. (1993) sought to assess the activations produced by the Tower of London task by use of rCBR. They concluded that planning was associated to frontal lobe activation, with significantly higher levels of activity in the left frontal region, namely the DLPFC and the superior PFC. Many other studies have also found a PFC activation during the Tower of London task (e.g. Ward et al., 1999 [MRI]; Lazeron et al., 2000 [fMRI]; Dagher et al., 1999 [rCBF]) and although most studies conclude that the Tower of London predominately activates left frontal regions, Rezai et al. (1993) reported it to be bilateral in nature.

PROCEDURE

The non-verbal planning test used here was the Tower of London (Shallice, 1982). The task comprises three pegs of different lengths (short, medium and long) and three beads of different colours (red, green and blue) as seen in Figure 2.7.

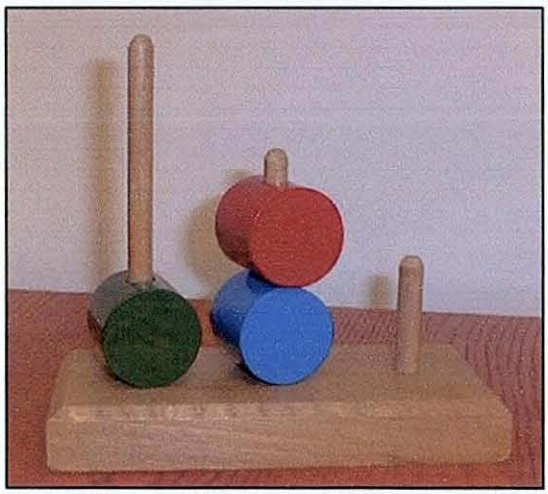


Figure 2.7: The Non-Verbal Planning Test Used

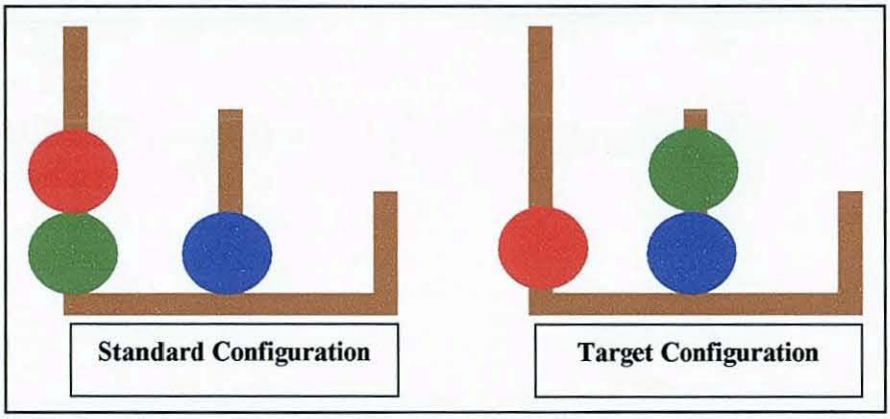
The beads are presented to the participants in the standard pattern (See Figure 2.8) and they are required to move the beads in a specific pattern from the standard pattern to the same as that shown on the target pattern card within a set number of moves. The test has strict guidelines for this process:

i) Only one bead can be moved at a time

ii) The bead must only be moved from one peg to another. This means the participant is not allowed to put a bead on the table, nor have more than one bead in their hand at any one time.

iii) Three beads are allowed on the long peg, two beads on the medium peg, and only one bead on the short peg. If this rule is followed the apparatus is stable at all times in that all beads are firmly in place.

A practice test is given first and repeated until the participant fully understands the requirements of the task. There are twelve different configurations (See Appendix 7) that each participant attempts, each with a different number of moves ranging from two to five, the test becoming more difficult as it progresses. Each problem is different, and requires a flexible approach, and effective planning to be successful.



This problem would require moving the red to the short peg (1), moving the green onto the middle peg (2) and then moving the red back to the long peg (3).

Figure 2.8: An example of a three-move problem in the Non-Verbal Planning Task (Tower of London).

The task was recorded on a tape recorder (in addition to a standard stop-watch for quality control) and played back through the computer programme Cool Edit 95 so that each click on the apparatus could be digitally timed. The experimenter would say *"this is problem 1 and can be solved in two moves"*. The time from the word "moves" to the first click of the apparatus was recorded as '**planning time**' and the time from the first click to the last click was known as '**subsequent execution time**'. Both these times made up '**Total Completion Time**'. All miscellaneous clicks were recorded at the time of occurrence (i.e. a bead click that was not a move) and the clock was stopped when the apparatus was being moved back to the starting position (Standard Pattern) in the event of an error. Participants were allowed three attempts at each problem, after three attempts the problem is abandoned and they move onto the next problem. Once a participant is aware of a mistake, the clock is stopped, the apparatus moved back to the standard configuration and the next attempt is initiated.

Test Duration: Approximately 10 minutes.
Measurement Used: Mean Total Completion Time.

Verbal Fluency

This task requires the initiation and production of verbal responses (e.g. associated verb or word beginning with ...) following a prompt (e.g. noun or 'S' respectively). The Verbal fluency task has consistently been shown to activate the PFC, and more specifically the left PFC, though studies using fMRI (Phelps et al., 1997), rCBF (Cantor-Graae et al., 1993), MRI (McCarthy et al., 1993) and PET

Scans (Petersen et al , 1988; Frith et al., 1991; Friston et al , 1991). This task is perhaps the most consistent task in functional imaging to highlight the involvement of the frontal lobes. A recent multi-centre European experiment assessed the reproducibility of PET activation during the verbal fluency tasks (Poline et al , 1996) and concluded that the verbal fluency was highly consistent in activating the left PFC, with some further, but less significant, activation in temporal areas.

PROCEDURE

Participants were given orally a noun as a prompt and asked to generate orally as many verbs that were directly linked to that noun as they could within one minute They were given the example: "If I say APPLE, you might say, peel, eat, chew, bite, crunch etc " Pilot studies had been run to determine nouns that elicited about 8-10 verbs each within one minute. The selected nouns comprised of four unambiguous common objects (Pencil, Shirt, Cake and Fish), a concept (Game) and a location (Cinema). The first noun served as a practice and participants were encouraged to ask questions if they did not understand The remaining 5 nouns were given under test conditions: The participant sat alone[2] in a soundproof room with the timed pre-recorded tape of the five nouns playing through a set of headphones with an attached microphone recording their responses.

Responses were transcribed into a random order and were assessed by two judges, independently, to produce an inter-rater reliability of 95% They had to reject responses that were.

i) Not a verb

ii) Not related in any obvious way to the noun prompt

iii) A repeat of a previously given verb.

This form of verbal fluency test (noun-to-verb) is thought to be more demanding that verbal fluency test that require generation of words from a given letter prompt (i.e. Thurston's FAS Verbal Fluency task) and as a result can be influenced by educational attainment Although all young participants were of the same educational level, the older group were varied in their educational attainment and

[2] It was thought that the presence of an experimenter would inhibit the natural flow of responses

so were split into two groups: Those with no education beyond 16 years of age, and those who had received college/university/work-related education beyond 16years.

Test Duration: Approximately 8 minutes
Measurement Used: Mean total correct responses

Temporal Memory

This task is relatively new, especially compared to the WCST, Tower of London and Verbal Fluency, when referring to tasks that are sensitive to PFC impairment. Developed by Parkin et al. (1995) for the study of ageing, it was found that frontal lobe impairments interfere with the ability to identify '*when*' something occurred This is supported by work that lesions to the (left) PFC do impair the ability to make recency judgements (Milner et al., 1991) although this work did centre on verbal recency judgements

PROCEDURE

Participants were visually presented [via an overhead projector] with twelve faces, each for 10seconds, known as *List A* After a five-minute interim period they were presented with a second set of twelve faces, each for 10seconds, known as *List B.* After a second interim period of five-minutes, Participants were then shown a random sequence of forty-eight faces, twenty-four, which they had already seen, and twenty-four unseen faces ('foils') Participants were required to state, using the temporal memory score sheet (See Appendix 8) whether they had previously seen the face (**"Recognition"**) and if so, whether it came from List A or List B (**"Recency"**). The scoring method used Parkin et al. (1995) was utilised (Recency Sensitivity) which accounted for the number of recognised faces when assessing recency, that is:

$$z = (r-x)/SD$$

r = number discriminated correctly (recency)
p = probability of discriminating recognised item correctly by chance
n = number recognised
x = n * p
SD = Square root of (n * p * q)
q = (1 – p)

During the five-minute interim periods between sets, participants were given eighty-four anagrams of six letter nouns of similar frequency in the English

language, presented on an A4 sheet of paper in order to stop rehearsal. They were asked to complete as many as possible in any order they wished

The test also utilised an auditory version, with an identical procedure whereby sentences were presented via a tape player instead of faces.

Test Duration: 18 minutes
Measurement Used: 'Recognition' and 'Recency'

Haylings Sentence Completion

This task requires an inhibition of a well-known response, and substitution with a novel word as an expected sentence ending is substituted for an incongruent word in the second condition of the task. The Haylings tasks is a relatively new task in the study of PFC impairment, however, a recent functional imaging study, using PET, showed this task to produce activation predominately in the PFC, even more so under suppression (incongruent) conditions (Nathaniel-James et al, 1997) Inhibition of strong impulses depends on the integration of the PFC, and so it is expected that this task would activate parts of the PFC.

PROCEDURE

This task, designed by Burgess & Shallice (1996) requires participants to complete a sentence with an incongruent word, when there is a strong tendency to provide a more obvious completion Participants were given twenty sentences [taken from Bloom & Fischler (1980) which have a probable ending of >0 85] and were required to complete the sentence when the final word was omitted. They were then given another set of twenty sentences (same probability endings) but this condition required them to complete the sentence with an incongruent response, for instance, the weather is normally hot at this time of [year] ...and they might say *"pineapple"*. All sentences were presented through a set of headphones, and all responses were recorded through an attached microphone and latencies electronically timed (Cool Edit Pro ©) Responses were transcribed, randomly and blindly, and then rated by two judges, independently. In addition to the timing of response latency, scoring of congruency was also carried out in accordance with that proposed by Burgess & Shallice (1996) – See Table 2.1.

Table 2.1: Scoring for the Haylings Completion Task as proposed by Burgess & Shallice (1980)

Response		Score
[a]	A Meaningful Ending	5
[b]	A synonym of [a]	3
[c]	Not [b] but the same semantic category as [a]	2
[d]	Not [a], [b] or [c] but the sentence is syntactically correct with an obvious association between the keys words even though the sentence is meaningless overall	1
[e]	None of the Above	0

Possible responses for these categories:

Example:

"Father carved the turkey with a ....."

[a] knife – highly probably response (>0 85) according to Bloom & Fischler (1980).

[b] blade; [c] fork; [d] word [e] camera.

Although it has been suggested that participants can be given the scoring criteria before the task, the test was done blind here merely stating an 'incongruent' response was necessary. This was deemed more appropriate as it was feared indication of the scoring criteria may be problematic in terms of comprehension.

Test Duration: 8 minutes

Measurement Used: Response Latency and Score of Congruency.

Reaction Time

Not considered to rely on the PFC, this task was used as a measure to gauge the extent to which global slowing may be affecting performance on tasks relying on speed i e. the NVPT.

PROCEDURE

The Psychomotor Vigilance Test [PVT] (Dinges & Kribbs, 1991) was utilised to assess reaction time. Participants sat in front of a computer screen and pushed a response button with the index finger as fast as they could when they saw a digital millisecond clock appear on the screen. The faster they responded, the smaller the counting number reached expressing their reaction time and thus giving feedback on results. The programme was set so a stimulus would appear randomly between 2 and 12 seconds. The mean reaction time (excluding lapses >500msecs) was established from these responses A one-minute practice was given prior to administration, although an increased practice would have removed any practice effects, it was thought that this task should be given novel in accordance with the other tests

Test Duration: 10 minutes

Measurement Used: Mean Reaction Time

Fluid Intelligence (CCCF)

An ongoing debate concerns the extent to which fluid intelligence relies on the frontal lobes. Extensive work by Duncan et al. (2000) found the Cattell & Cattell Culture Fair (CCCF) test to produce activation's in the bilateral PFC, However, this study only utilised categories 3 and 4 which were proposed to be high in *g* (general intelligence). Fluid intelligence, such as that measured by the CCCF is likely to reflect frontal integrity due to issues such as the attention demands and goal-directed behaviors the IQ test makes (Duncan 1995) However, due to the complexity of the PFC, and that most of the PFC is insensitive to cognitive demands of some IQ tasks (Duncan & Owen, 2000), fluid intelligence can remain fully functional following frontal lobe damage (See Duncan et al., 1995) and also following sleep loss (Horne, 1993). The CCCF was therefore used in this thesis as a measure of general cognitive ability.

PROCEDURE

This is a non-verbal measure of fluid intelligence that minimises the influence of verbal fluency, educational attainment and culture (Cattell, 1963). It is divided into four sections involving four different perceptual abilities: 'Series, Classification, Matrices, and Conditions' (See Figure 2.9) The test comprises two forms, Test A and B, which serve as a measure of consistency as they are of the same format. In accordance with standard test procedure, both Test A and B were given with an interim break and the scores added and converted to an Intelligence Quotient (IQ) score

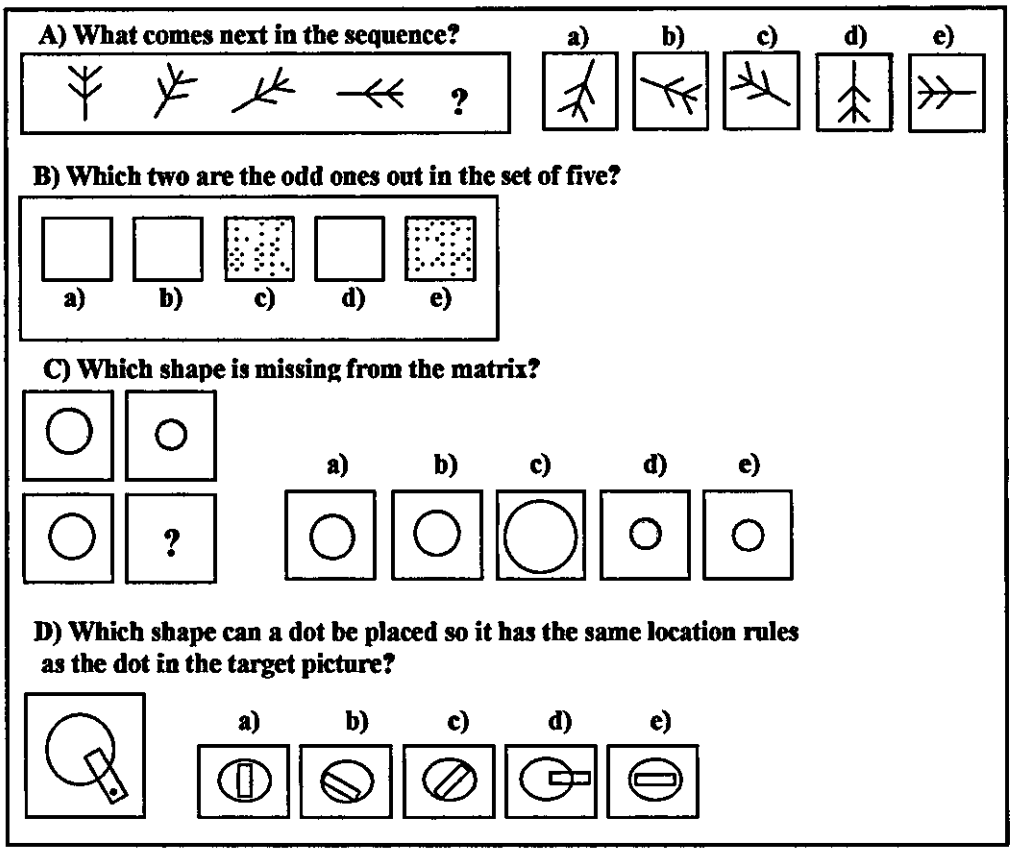


Figure 2.9: An example of the four sets of non-verbal perceptual abilities measured by the Cattell & Cattell Culture Fair Test.

Test Duration: 2 x 12.5 minutes

Measurement Used: IQ Score.

2.4.2 Waking EEG

Participants arrived at the lab at 09.30h and filled in the sleep diary. Electrodes were attached (see section 2 5 2) and subjects sat in a soundproof booth, following instructions on the screen (Part A) and through the set of headphones (Part B) The monitor and headphone output were split, so that the experimenter (outside the sound-proof booth) could see and hear the instructions at the same time, thus being able to indicate on the on-line EEG recording periods for subsequent analysis in addition to recording comments in real-time using the waking EEG form (See Appendix 9) An intercom allowed the confirmation of the subjects' understanding and their rating of sleepiness, using the KSS, to ensure they remained alert during the session. The session comprised Parts A and B: Part A was an Eyes Open Condition, and therefore relied on visual instructions through

the monitor, and Part B was an Eyes Closed condition, and therefore relied on instructions through the headphones.

Participants were first asked to follow the instructions on the screen (some examples of this can be seen in Figure 2.10.) before being asked to put on the headphones to follow the auditory instruction. Testing commenced at 10.30h and lasted between 24-30 minutes. The condition order for all participants was as follows:

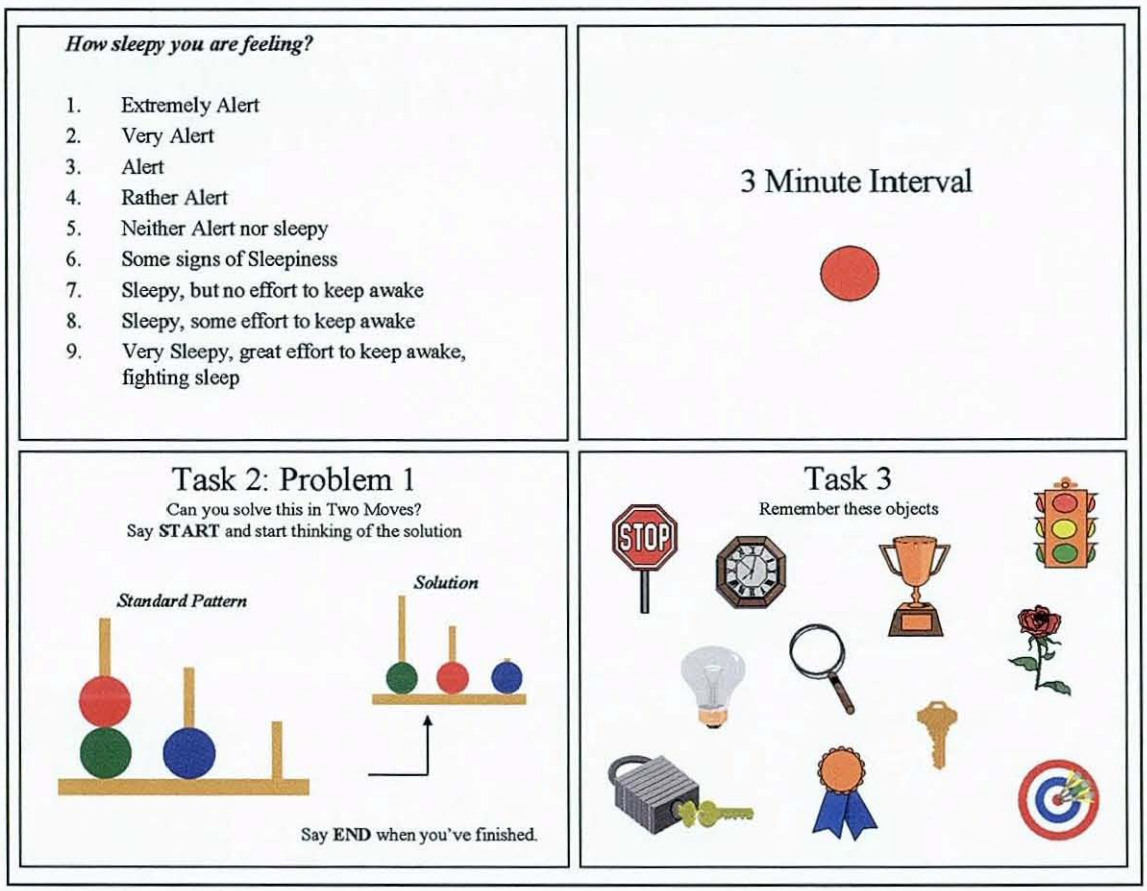


Figure 2.10: Examples of the screen display during the Waking EEG Recording - *Top Left:* **KSS Rating Display**; *Top Right:* **Eyes Open (1);** *Bottom Left:* **NVPT Problem (2);** *Bottom Right:* **Object Location (3).**

PART A

1) Eyes Open Condition – Participants were required to remain focussed on a red dot. *Duration: 3 minutes*
2) Non-Verbal Planning – Participants were required to manipulate the blocks of the Tower of London, in their minds, to complete the puzzle

(See Section 2.4 1 – The Tower of London for task details). *Duration: Self-Paced – Approximately 3 minutes*

3) Object Location – Participants were asked to focus on a group of objects (eyes open) and then to try to remember the location of those objects (eyes closed). *Duration: 2 minutes*

PART B

4) Eyes Closed – Participants were required to close their eyes and try to free their mind of any thought. *Duration – 3 minutes*
5) Verbal Fluency[3] – Participants were given a noun, and they were required to think of as many verbs that were linked to that noun without saying them out loud. Five verbs were used, these were: Book, School, Car, Picture and Holiday. *Duration – 5 x 1 minute*
6) Journey - Participants were asked to think of the journey they had to the laboratory that morning. *Duration – 2 minutes.*
7) Song – Participants were asked to think of a song, and sing it in their head *Duration – 2 minutes*
8) Yesterday – Participants were asked to remember everything they had done on the day prior to the trial. *Duration – 3 minutes.*
9) Experiment – Participants were asked to remember everything that had happened to them over the test bout, i e. to try and remember the tasks in order. *Duration – 3 minutes.*

2.4.3 Sleep EEG

All Sleep recordings were ambulatory, as opposed to being carried out in the laboratory as it was found that participants generally preferred to be at home, especially the older age group. Home recordings also reduce the need for extensive adaptation to laboratory surroundings and it was thought the recording should be as normal as possible Two nights of sleep EEG was recorded: The first night was for adaptation purposes, and the second night was used for analysis In the older age group, one in four participants were selected for a third night

[3] This is a different condition to the verbal fluency performance measures – no performance measures were taken here but was merely to encourage 'active' thinking.

recording to assess the night-to-night stability of the EEG recordings taken This was thought more essential in the older age range, as the younger group appeared less inhibited by the equipment used.

Participants refrained from consuming alcohol or caffeinated drinks after 18.00h on the nights selected for EEG recordings. All participants completed sleep diaries to ensure the previous night sleep was not disturbed, as this would affect the following nights sleep. Electrodes were fitted at 19 00h according to the standard 10-20 international system and recording montage selected (See Section 2.5 4). The application took between 45minutes-1hour Afterwards the participants were able to move around as normal, and go through their 'normal' evening/nightly routines. Electrodes were removed at 08.00h the following morning, and taken back to the laboratory for download and analysis in order to compare to the neuropsychological tests.

2.5 ELECTROENCEPHALOGRAPHY (EEG)

2.5.1 Equipment and Set-up

Sleep EEG recordings were made with an ambulatory 8-channel polygraph (Embla ™ - Flaga hf. Medical Devices, Iceland See Figure 2 11), and waking EEG recordings using the Embla™ system operated in the on-line mode EEG time constants were set at 0.3 seconds and a high frequency filter set at 45Hz[4] to remove any noise from the EEG (i e that caused by nearby electrical equipment) EEG data were sampled at 100Hz[5] and spectrally analysed in 30-second epochs (sleep EEG) or 5-second epochs (waking EEG) using Somnologica software (Version 2.0, Flaga hf Medical Devices). Band-pass filters were used to select specific frequencies that were subjected to spectral analysis in order to establish EEG power (μV^2) for a given frequency band

[4] This is automatic setting associated to a 100Hz sampling rate. A notch filter of 50Hz or 60Hz are only applicable if the sampling rate is above 100Hz
[5] EMG was sampled at 200Hz

Due to frontal electrodes being sensitive to eye movements, and some of the EEG sample periods being close to sleep onset, a quality check was carried out to ensure that slow eye movements were not evident on the EEG, in that the EOG channels were in phase (due to the EEG being recorded on the EOG channels) and not phase-reversed which are indicative of slow eye movements (due to upper and lower outer canthus sites). Slow eye movements associated to sleep are usually <0.3Hz (Rechtschaffen & Kales, 1968) and thus were removed by the band-pass digital filters, since the lowest frequency used in the thesis was 0.5Hz.

All artefacts were manually removed from the EEG recording, equally across all frequencies, and channels, by averaging either side of the affected epoch.

2.5.2 Sensors

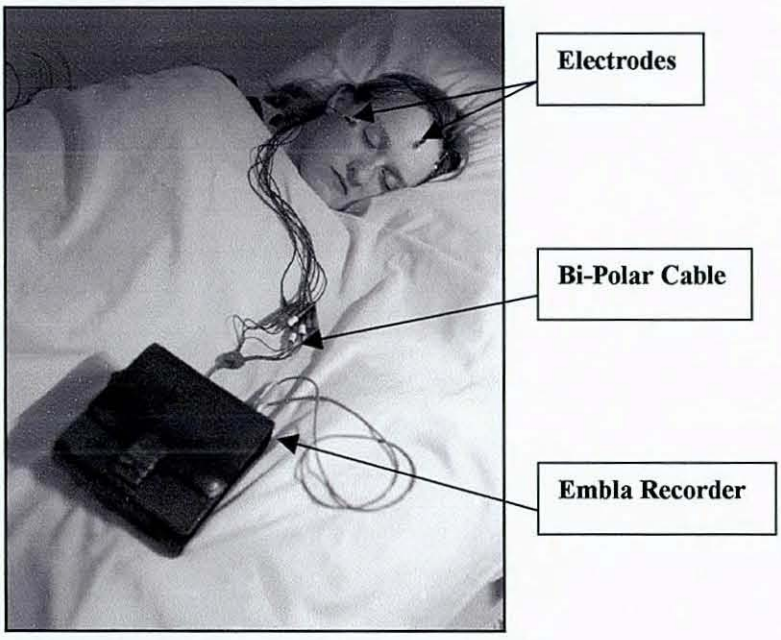


Figure 2.11: The Ambulatory Embla ™ Recorder – Flaga hf. Medical Devices, Iceland.

EEG, EOG and EMG signals were collected using silver chloride cup electrodes. The chloride (AgCl) is replaced after each use via a 20-minute soak in Sodium Hypochlorite solution to ensure electrical signals pass from the skin to the electrode consistently. Electrodes are attached to the scalp using collodion glue with ten-20 used as the conductor, and attached to facial areas using double-sided adhesive tabs and a conductance gel (SLE). All EEG electrode impedances were

maintained at <5kΩ and EOG/EMG were maintained at <10kΩ using an impedance tester (Oxford XI-1). See Figure 2.11 for sensors.

2.5.3 Calibration

The Embla recorder is a digital system and so signal acquisition does not change over time once calibrated in the workshop (unlike analogue recorders). Once electrode impedances are checked and are accurate, given that all electrodes are equally placed, and comparisons made are intra-individual and not inter-individual (i.e. between brain location and not between participants) calibration is less problematic. However, to ensure the signal remained consistent throughout testing a known signal of 50μV/5Hz, using a Calibration system (XC-90-B, Oxford), was passed through the electrodes, Embla System, and downloaded on Somnologica (See Figure 2.12).

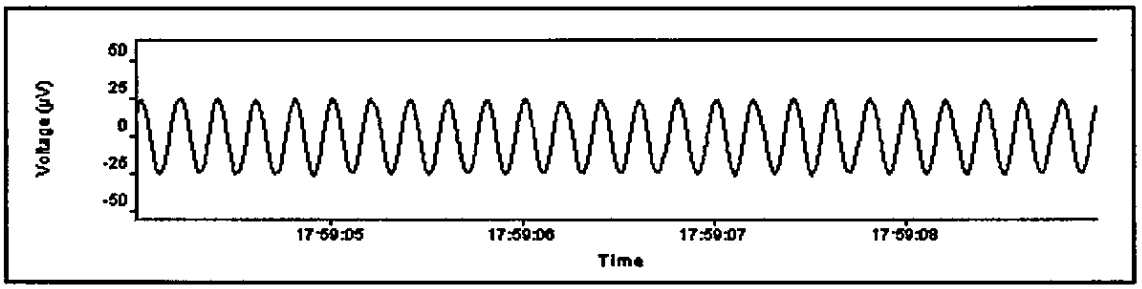
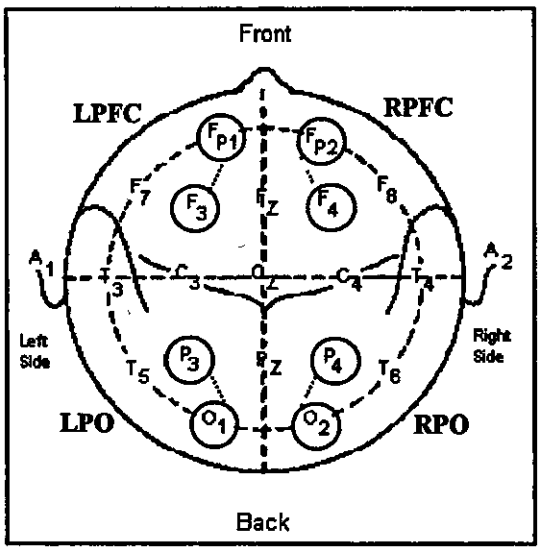


Figure 2.12: Calibration results of a known signal of 50μV/5Hz passing through the Embla and Somnologica System

2.5.4 Recording Template

Electrode placement was determined using the standard 10-20 International System, and consisted of 16 electrodes. The EEG Montage divided the cortex into quadrants as determined by: Fp_1-F_3, Fp_2-F_4, O_1-P_3 and O_2-P_4 (See Figure 2.13). For the purpose of identifying Sleep Onset, REM Sleep etc., four additional channels were used according to standards set for identifying stages of sleep (Rechtschaffen & Kales, 1968), these were: C4-A2, Two EOGs (1cm above left outer canthus and 1cm below right outer canthus) and a bi-polar submental EMG. Within participants the four bipolar electrode distances were the same (due to the international 10-20 measurement system).



The four sets of Bi-polar electrodes circled, divide the cortex in quadrants. These are:

Fp_1-F_3 – Left Pre Frontal Cortex (LPFC)
Fp_2-F_4 – Right Pre Frontal Cortex (RPFC)
O_1-P_3 – Left Parieto-Occiptal (LPO)
O_2-P_4 – Right Parieto-Occiptal (RPO)

Figure 2.13: The EEG montage used for all Sleep EEG and Waking EEG Recordings

2.5.5 EEG Analysis

The whole nights sleep EEG was recorded, but the analysis centred around the first NREM period because:

i) It is a period of intense delta activity (e g. Braun et al, 1997; Maquet 2000; Maquet et al., 1997; Borbely, 1982)

ii) It is least likely to be disrupted than other NREM periods, especially in the older age groups (Bliwise, 1997)

iii) Any variance in delta levels due to ageing are evident in this period (Feinberg, 1989; Webb & Dreblow, 1982)

The second NREM period was analysed as a secondary measure, in addition to a period of REM sleep

Standardisation

There can be marked difference in the EEG amplitude of men and women, merely due to anatomical differences such as skull thickness (Dijk et al, 1989). In younger adults the difference is relatively small due to the signal being strong enough to penetrate the skull layers easily. However, as one ages the amplitude of delta activity reduces (Dijk et al, 1989), making any difference more noticeable. Therefore, to account for gender differences that may be attributable to an anatomical difference, the EEG had to be standardardised:

EEG power in the frequency range of 1-3Hz (mid-delta range) was downloaded and averaged into 3minute epochs. It was then standardised using an adapted[6] standardisation technique as used by Horne & Reyner (1996), which removes individual differences in the EEG power levels This was done using the equation·

$$\text{Standardised EEG} = \frac{\text{Av 3min power in NREM} - (\text{Av Total REM Power})}{\text{St Dev (Av. 3min Power in NREM} - \text{Av. Total REM Power)}}$$

Upon completion of standardising the data the method was soon found to be unsuitable for this type of analysis. The standardised technique was effective at showing the change of EEG over time (when accounting for individual differences) but this thesis aimed to investigate delta power for the whole first NREM period, and the standardardisation procedure was not sensitive enough for slight changes in delta power. However, this technique was found to be effective for the identification of the first NREM period. A common identification of sleep stages has been the Rechtschaffen & Kales (1968) method, and it was initially thought this would be used to identify the first NREM period. However, the standardised procedure described above was deemed more suitable (especially since Rechtschaffen & Kales is becoming less common in today's sleep EEG analyses) since·

- It controls for any individual differences in amplitude due to being based on baseline amplitude (REM)
- It keeps the process of identifying NREM periods standard across all ages without having to adjust for frequency and amplitude.

A small pilot study was carried out to determine the effectiveness of the standardisation procedure for this purpose. Figure 2.14 shows the comparison of Rechtschaffen & Kales' traditional method and the standardisation procedure.

[6] Adapted by using longer epoch length due to increased recording time, and also standardised to REM sleep, as opposed to a baseline waking EEG.

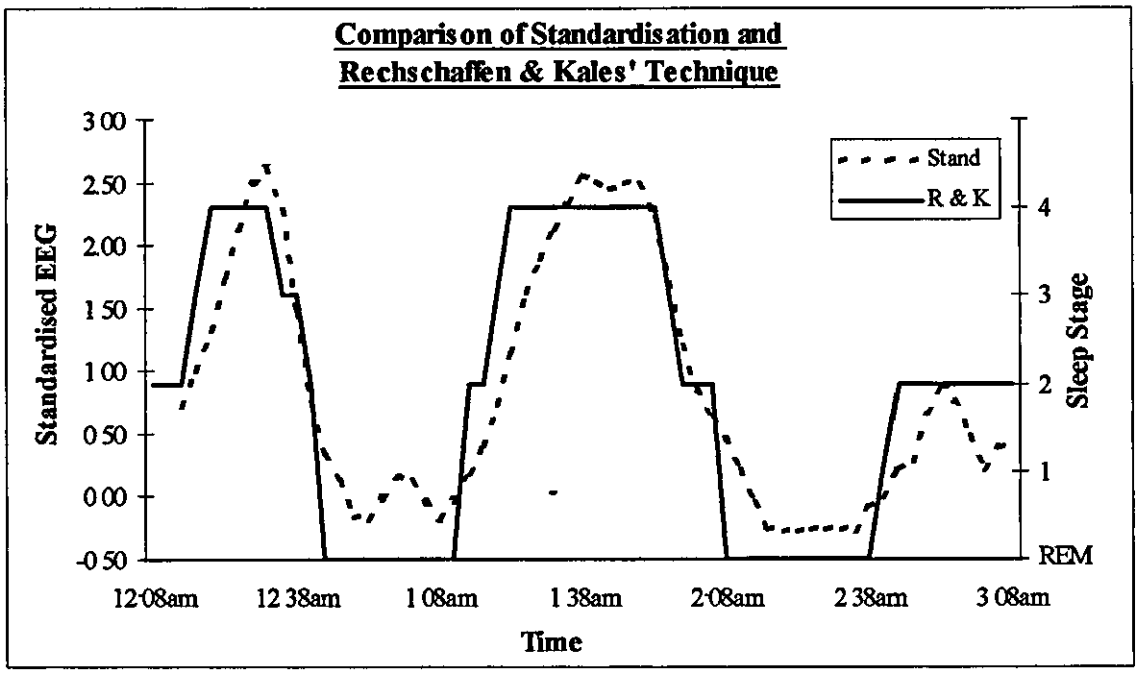


Figure 2.14: The comparison of the Standardisation method and Rechtschaffen & Kales' method for determining the first NREM period.

The standardisation procedure is also favoured as it avoids the inclusion of eye rolling since the selection is slightly further into the NREM period. All identification of NREM periods, for all participants, shall be done via this method, using 1.0 as the start and end of the NREM period.

The analysis of the EEG still had to be standardised across participants [to remove possible confounding variables attributable to anatomical differences], therefore, the EEG shall be downloaded and expressed as relative data (as opposed to absolute data) by being converted to a percentage of an overall power range within-subjects. For example, if one is looking at the delta range 0.5-4 5Hz, each frequency bin (within that range) will be represented as a percentage of the total range for each participant, for each channel. Details on frequency bins selected will be described in the chapters to follow.

Sleep Parameters

Sleep parameters, such as Total Sleep Time and Time spent in Stages 1,2,3,4 and REM sleep were identified using the rules as set out by Rechtschaffen & Kales (1968).

Spectral Analysis

Spectral analysis is currently the most commonly used method of analysing the EEG signal. It allows us to describe the EEG in terms of frequency and amplitude for a given time. This thesis aims to spectrally analyse the EEG to determine the extent to which power in a given frequency range (to be established) can be used to predict neuropsychological test performance, thus establishing the extent to which the EEG is related to PFC neuropsychological test performance.

CHAPTER 3

SLEEP EEG & NEUROPSYCHOLOGICAL TEST PERFORMANCE IN HEALTHY, OLDER PEOPLE

3.1 INTRODUCTION

The majority of sleep research has been concerned with younger adults, and certainly the extensive studies assessing the possible recovery values of delta activity have been based on young adults. However, the older population hold many interesting facets for study. Delta activity not only deteriorates as one gets older (see Bliwise 1993 for review) but PFC performance also diminishes (e g. Corey-Bloom et al , 1996). Therefore, there is currently studies assessing the association between delta activity and ageing, and also ageing and PFC performance, but no study has been performed that directly investigates the association between delta activity and PFC performance in this age group However, it is not only the extent to which these two variables are inter-linked, but also the reason why: Whether reduced delta activity is due to impaired PFC function, whether reduced PFC function results in less delta sleep, or indeed whether they are both due to the same underlying process, such as reduction in PFC volume (e g Parkin & Walter, 1991; Cowell et al., 1994).

Delta activity has been shown to diminish with increasing age, but most research has focussed on SWA encompassing frequencies 0.5-4 5Hz The difference between slow (0 5-2Hz) and fast (2-4 5Hz) frequencies has been highlighted by several recent studies (e g. Benoit et al., 2001). Low Frequency delta has been proposed to hold recovery properties during sleep (Werth et al., 1996, 1997), particularly that of a localised function due to its predominance in the frontal region. However, this predominance shifts with increasing age (Landolt & Borbély, 2001) as activity 0.75-2Hz did not show a frontal dominance in older healthy participants, as it did for a younger group. The first, and currently the only, study to look at low frequency delta in older people suggested that the advanced recovery properties are either no longer needed or mechanisms that would normally generate them are deteriorating (Landolt & Borbély, 2001) Inasmuch that low frequency delta is generated directly by the cortex, and is thought to be in response to high metabolism of the PFC during the day, the idea that older people show a reduction in PFC metabolism (Martin et al , 1991) may result in both reduced low frequency delta and reduced PFC performance, thus providing a basis for a link between these two indices

The suspicion of a relationship between PFC performance and low frequency delta is also enhanced considering the relationship between the waking and sleeping PFC The use of the PFC during the day is, in young healthy adults, increasingly activated (Maquet et al , 1990, Braun et al , 1997) together with an increase in delta sleep at night in this region (Lanquart et al., 1996, Sekimoto et al , 2000). However, in the older population delta sleep at night is reduced (e g. Larsen et al , 1995a; Landolt et al., 1996) with the reduction being most apparent in the frontal areas (Carrier et al , 2001, Landolt & Borbély, 2001). The PFC during sleep therefore has less delta activity, but the extent to which this is a reflection of daytime PFC performance is unknown.

The loss of delta activity would therefore be expected to manifest itself in a deficit on PFC tasks, as opposed to less cortically specific tasks such as vigilance type tasks. Corey-Bloom et al. (1996) concluded that old people over the age of 85years were seriously impaired on the verbal fluency task, a task that strongly relies on the PFC (e.g. Frith et al , 1991). Although this might be expected for such an age category, Daum et al. (1996) also demonstrated age-related changed in executive function throughout an age range of 20-60years suggesting age impairments are evident by 60years They used the WCST, the verbal fluency and temporal memory as measurements of executive function (PFC) and found them all to diminish with age They attributed the findings to a frontal dysfunction, further supported by an inter-relation of tasks.

Further support for a PFC involvement in ageing has come from studies utilising functional imaging methods: Raz et al (1999) found that there was a reduction in volume of the DLPFC using MRI in older participants, but more specifically, Martin et al. (1991) found a reduction in rCBF in the left PFC in this age group. As Clark et al (1998) has shown that rCBF during the day is directly linked to SWS at night, then one could speculate that those older people in Martin et al.'s study would also show reduced SWS due to the reduced rCBF in the PFC area. This link provides a strong indication that those people who perform badly on PFC tasks (for whatever reason) are likely to have lowered rates of SWS/SWA during the night. The extent to which this is more focussed toward the lower delta frequencies is yet to be determined.

Given the prior literature, it seems logical to assume that the examination of sleep and performance, in this manner, would be undertaken. However, studies looking at the effects of sleep and performance in older groups, have been concerned with sleep problems and the extent to which they affect daytime functioning (e g Hayward, 1992; Crenshaw & Edinger, 1999) Hayward looked at sleep disturbance at night and assessed whether this could predict performance on neuropsychological scores, which demonstrated an age-related decline. However, it is argued that the effect of sleep disturbance is more likely to cause decrements in reaction time (Gillberg & Åkerstedt, 1994) and not decrements in executive function which are more likely to be caused by an underlying PFC deficit (Rabbitt, 1997). It is argued that the use of more cortically specific tasks and recording sites would yield more interesting findings and add further insight into the sleep function debate

Successful and interesting findings in the field of delta activity and performance in the elderly have been found Naylor et al (2000) found that an increase in low intensity aerobic activity in the elderly (66-92yrs) resulted in an increase in delta activity and a subsequent improvement in memory functioning Although the authors attribute this to a change in circadian timing of sleep, and thus improved sleep, it is difficult not to note the possible delta activity-performance link. If a prior study had shown a link between delta activity and performance, followed by this subsequent study concerning increasing delta activity to improve memory function, this would appear a logical progression of research. Nevertheless, the research by Naylor and colleagues is interesting, and provides much optimism for a link between delta activity and performance in the older age range

3.1.1 Aims

As rCBF has been directly linked to delta activity at night, with a direct focus for the PFC (Clark et al., 1998), it is assumed that as rCBF in the PFC is reduced in an healthy older group (Martin et al., 1991), then both delta activity and PFC performance will be negatively affected as a result The extent to which these two variables are related is the main topic of concern for this chapter. However, further perspective is added with the interest in low frequency delta, which is proposed to

be generated directly by the cortex (Steriade et al., 1993a, 1993b), and as a result is most affected by age in the PFC where this activity is greatest (Steriade & Amzica, 1998). Low frequency delta is shown to diminish with age (Landolt & Borbély, 2001) as does PFC performance, possibly due to an underlying commonality This forms the hypothesis that there will be associations between low frequency delta and performance, localised to the PFC in healthy older people.

Research Questions

- Can the sleep EEG be used to predict PFC performance in older people?
- Is low frequency delta associated with PFC performance?
- Is this relationship unique to PFC tasks?
- Is this relationship unique to the LPFC?

3.2 METHODOLOGY

Twenty-four right handed participants (14 female,10 male) with an age range of 61-75years (mean. 67 9 years, SD: 3 5years) took part in the study All were normal healthy sleepers as determined through sleep diaries and actimetry, and none suffered from extreme daytime sleepiness as determined by ESS and KSS (See Chapter 2). All were considered appropriate for the study through screening as set out in chapter 2 which ensured participants were:

i) Free from sleep problems, or problems affecting their sleep.
ii) Non-Nappers (<2 times a month)
iii) Free from medication affecting the CNS
iv) Satisfactory in eye sight and hearing (with/without glasses/hearing aids)

All participants undertook both parts of the study· A neuropsychological test battery and two nights of sleep EEG recording One in four participants were assigned to a third night of sleep recordings to check the night-to-night stability of EEG results

Neuropsychological Tests

The neuropsychological tests used in the test battery were three tasks known to activate the PFC during completion:

- The Wisconsin Card Sorting Task (WCST)
- Non-Verbal Planning Task (NVPT)
- The Verbal Fluency Task[1]

Two further tasks were used, they were

- Reaction Time
- Cattell & Cattell Culture Fair Task (CCCF)

The reaction time was used as a gauge to global slowing, and the CCCF was used as a guide to general cognitive ability.

Sleep Recordings

Sleep recordings took place on nights separate to neuropsychological tests, two nights of sleep EEG, 5-7 nights apart, were recorded (a third night for six participants for quality checks) The analysis centred on the first NREM period since most age-related changes are evident here (Webb & Dreblow, 1982). Analysis of the second NREM shall be conducted if deemed appropriate

Chapter 2 describes the procedures for the neuropsychological test battery and sleep EEG recordings.

Statistical Analyses

All statistical analyses are concerned with assessing the relationship between an independent variable (Delta activity) and the dependent variables (Neuropsychological test performance) Therefore, Pearson r Correlation Coefficients shall be determined, with the use of partial Correlation Coefficients and Bonferroni Adjustments where applicable.

Any analyses concerning differences, such as female/male test scores, will use the (un)related t-test or the One-Way ANOVA for multiple variables The significance level is set at 5% unless otherwise stated

[1] The verbal fluency was considered to have an educational bias, and therefore only participants who had received education post-16yrs were used (n=16). See Chapter 2 for details

In order to compare groups and/or databases for distribution, "box and whisker" plots will be used. The box plot consists of a lower "hinge" (25th percentile) and an upper "hinge" (75th Percentile), the centre of these being the median value The "whiskers" of the plot represent the "fence" range of values, these fall within 1.5 times the value between the appropriate hinge and the median. Any values falling outside of this range are represented by an asterisk (*) and are termed "outliers".

3.3 RESULTS

3.3.1 Participant Characteristics

All participants fulfilled criteria as set out in Chapter 2, which is evident in Table 3 1, showing the characteristics of all participants used. As seen, the mean scores between age, Epworth Sleepiness Score (ESS), and Time in Bed (TIB) are similar for male and female participants

Table 3.1: Participants characteristics for the current study

Ss	Sex	Age	ESS	TST (hrs)	Ss	Sex	Age	ESS	TST (hrs)
FEMALE					MALE				
1	f	64 00	3.00	8 43	3	m	61 80	6 00	8 25
2	f	67 10	6 00	8 56	4	m	68 00	9 00	9.16
7	f	64.11	8 00	7.32	5	m	68 80	5 00	8.16
9	f	63.40	4 00	8 11	6	m	66 40	3.00	7.33
10	f	67 20	3 00	8 02	8	m	64 60	4 00	8.32
11	f	66 80	1.00	7.44	14	m	68.70	3 00	8.42
12	f	68 30	5 00	8 51	15	m	62 00	5 00	8 36
13	f	70.20	1 00	9 05	16	m	71 70	6.00	7.59
18	f	66 20	3 00	8.06	17	m	69 50	5 00	8.04
20	f	67 40	0 00	7.22	19	m	70.30	2 00	7.17
21	f	72.20	6 00	8 51	-	-	-	-	-
22	f	74.00	0 00	8 14	-	-	-	-	-
23	f	75.40	2.00	7.16	-	-	-	-	-
24	f	71 20	9 00	8 55	-	-	-	-	-
Mean		**68.39**	**3.64**	**8.27**	**Mean**		**67.18**	**4.80**	**8.27**
SD		**3.72**	**2.84**	**0.63**	**SD**		**3.40**	**1.99**	**0.58**

3.3.2 Daytime Sleepiness Score

Participants were required to rate their feelings of sleepiness, using the KSS, every hour for three days. This average score is given in Figure 3.1. As can be seen,

there is a marked increase in alertness following awakening, to a peak of alertness around 10 30h, which is when neuropsychological testing took place (10 30h-12 00h). Daytime alertness levels in this sample group were considered extremely important in ensuring neuropsychological tests were carried out during maximal alertness to remove any possible confounding variable of sleepiness. Although wake-up times were all within a one hour range, the fluctuation in daytime sleepiness, as determined by KSS, was considered a more robust measure of individual daytime sleepiness propensities

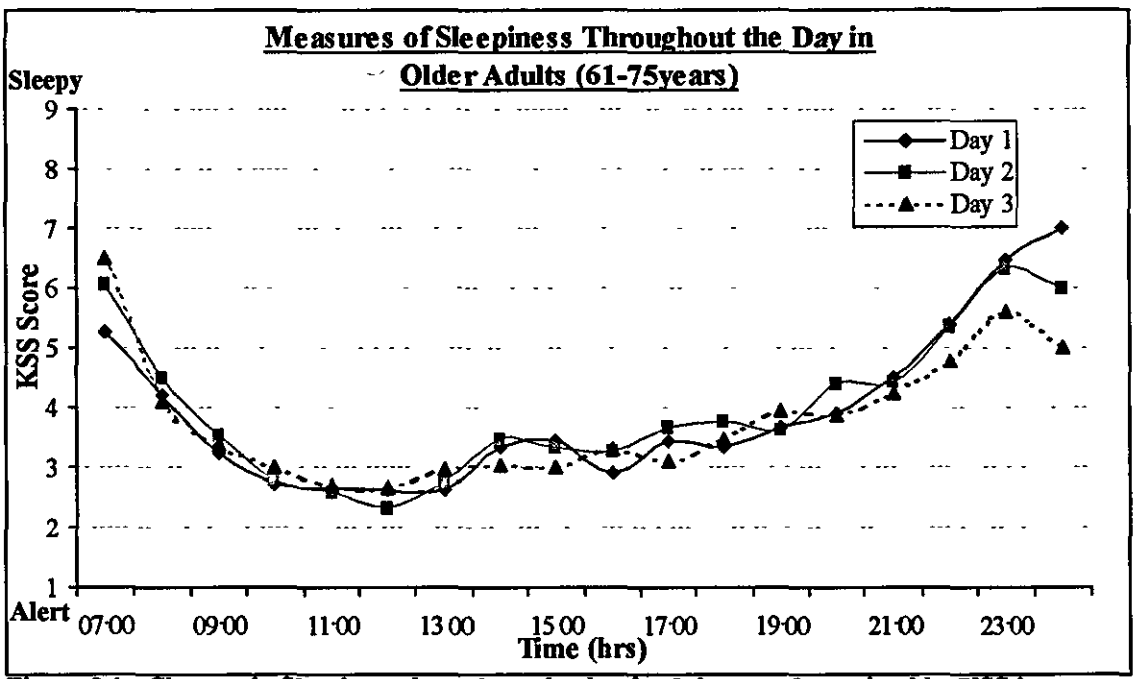


Figure 3.1: Changes in Sleepiness throughout the day for 3 days, as determined by KSS in a healthy, older sample.

3.3.3 Neuropsychological Test Performance

Table 3.2 shows the mean scores on all neuropsychological tests used.

A One-Way ANOVA revealed no significant sex differences for any performance data ($F < 4.2$ [d.f. 1, 22], $P > 0\ 05$) therefore, male and female data were combined and treated as one group.

Table 3.2: Neuropsychological Test Performance. A Mean Comparison

Ss	WCST	NVPT	RT	IQ	VF*	Ss	WCST	NVPT	RT	IQ	VF*
FEMALE						MALE					
1	5 00	13.23	361.21	119	11 50	3	2 00	13 26	302 83	114	9 67
2	8 00	41.58	319 10	**	9 00	4	2.00	16 81	340.60	81	10 83
7	3.00	25 79	284 10	104	10 17	5	7 00	30 94	309 40	126	5 83
9	2 00	15 84	322.80	96	6 50	6	3 00	24 26	346 50	81	8.17
10	4 00	26.45	356.99	98	-	8	10 00	52.18	338 60	91	7.00
11	7 00	27.60	284 80	80	-	14	5 00	17.94	294.10	93	-
12	10.00	27 30	425 60	**	-	15	5 00	27 15	351 40	104	7 33
13	11 00	31.93	323.20	101	-	16	4 00	16 20	302 83	103	-
18	8 00	23.86	283 41	76	-	17	2.00	31.00	329.04	109	5 00
20	7.00	27 59	340 96	88	11.83	19	3 00	17 90	287 65	117	9 83
21	4 00	24 31	395.72	88	7 33	-	-	-	-	-	-
22	9 00	27.92	325 22	100	**	-	-	-	-	-	-
23	10.00	26 17	342 43	98	4 83	-	-	-	-	-	-
24	5.00	32 25	326.58	70	5 67	-	-	-	-	-	-
Mean	**6.64**	**26.56**	**335.15**	**93.17**	**8.35**	**Mean**	**4.30**	**24.76**	**320.30**	**101.90**	**7.96**
SD	**2.84**	**6.78**	**40.80**	**13.50**	**2.67**	**SD**	**2.58**	**11.53**	**23.47**	**15.21**	**2.05**

* Verbal Fluency is based on n = 16

** No Data (Loss)

Inter-Relation of PFC Tasks

Table 3 3 shows the correlation matrix for all neuropsychological tests in an attempt to assess the inter-relation amongst tasks that are all thought to be PFC activating The significance level is set at 1% to reduce the possibility of a Type I error.

Table 3.3: Correlation matrix showing the relationship between task performance

	WCST	NVPT	Verbal Fluency	Reaction Time	IQ
WCST	-	0 59*	-0 23	0 17	-0 12
NVPT	-	-	-0.45	0.11	-0.22
Verbal Fluency	-	-	-	-0 10	0.08
Reaction Time	-	-	-	-	-0 08
IQ	-	-	-	-	-

* Significant at 1%

As the matrix shows, NVPT and the WCST were inter-related in that increased perseverative errors on the WCST was associated with increased time taken to complete the NVPT. This can be seen in Figure 3.2. Although NVPT shows a trend with Verbal Fluency, this was not significant No other task performance indices were related, this is important when considering NVPT and Reaction Time

since in an older group it is important to ensure performance on tasks relying on speed (i e NVPT) is not an effect of 'global slowing'.

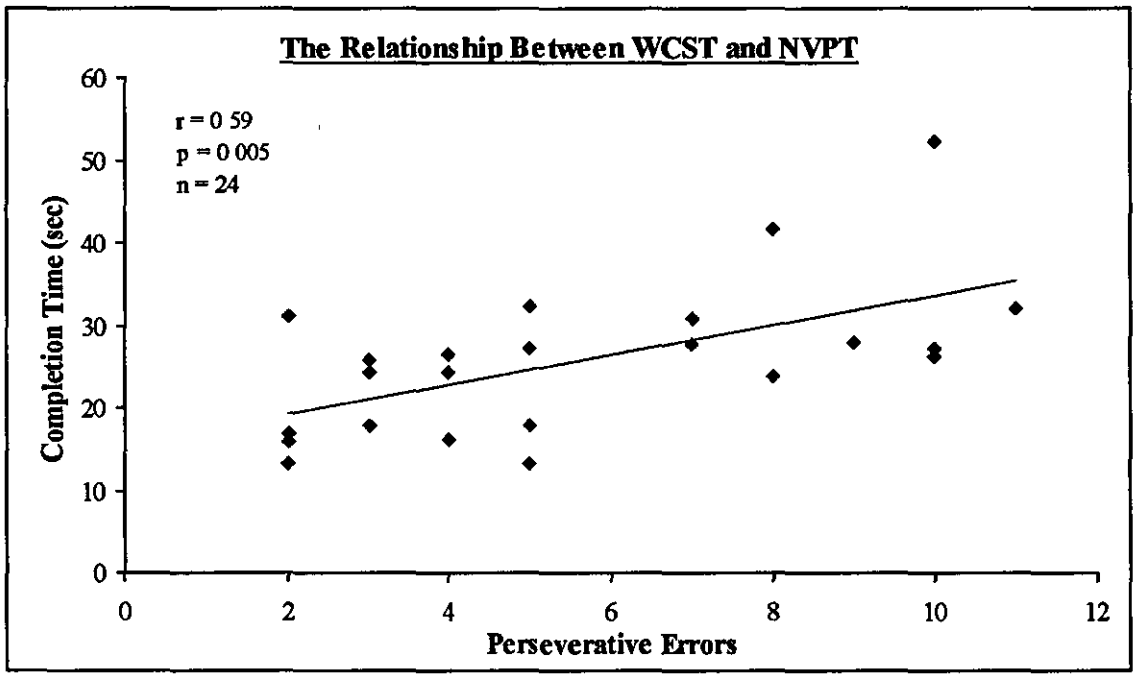


Figure 3.2: The relationship between perseverative errors on the WCST and Completion Time on the NVPT

Age Effects

Due to literature suggesting older people are impaired on executive functioning, the tasks were assessed to see if they demonstrated an age effect. Using a one-tailed criteria (as it was hypothesized task performance would be affected by age given the literature), it was found that NVPT, RT and IQ did not demonstrate an effect of age ($r < 0.15$ [d f. 23] $p > 0.1$), nor did the verbal fluency task ($r = -0\ 40$, [d f. 15], $p = 0\ 06$) However, the WCST was just significantly associated with age ($r = 0\ 35$ [d.f. 23] $p = 0.05$), using the one-tailed criteria.

3.3.4 Analysis of the EEG

Total Delta Power

Before any bandwidth analysis took place, total mean delta was compared across hemispheres to ensure no dominance of total delta power. Total delta power was summated for each channel, for each participant, and the group total was expressed as a percentage of all four channels. This is shown in Table 3.4. A One-

Way repeated measures ANOVA found no significant differences between the four channels for total delta power ($F = 0\ 42$ [d.f. 3, 92] $P > 0.5$), demonstrating total delta power was stable across all quadrants

Table 3.4: A Quadrant Analysis of Mean Total Delta Power (%)

	LPFC (%)	RPFC (%)	LPO (%)	RPO (%)
Average	25 43	25 87	24 44	24 27
Standard Deviation	5 77	6.45	6 32	4.88
Standard Error	1.18	1.32	1 29	1.00

Specifying the Frequency

The analysis of the EEG began with a probe of the delta range with a specific interest on frequencies less than or equal to 2.5Hz. All frequency bins were expressed as a percentage of total delta power (0 5-4.5Hz) to ensure data was relative. All analyses will begin on the left PFC (Fp_1-F_3). The WCST was used to establish whether any of the frequency bands should be further examined. The correlation between the frequency bins and the WCST are graphically represented in Figure 3.3

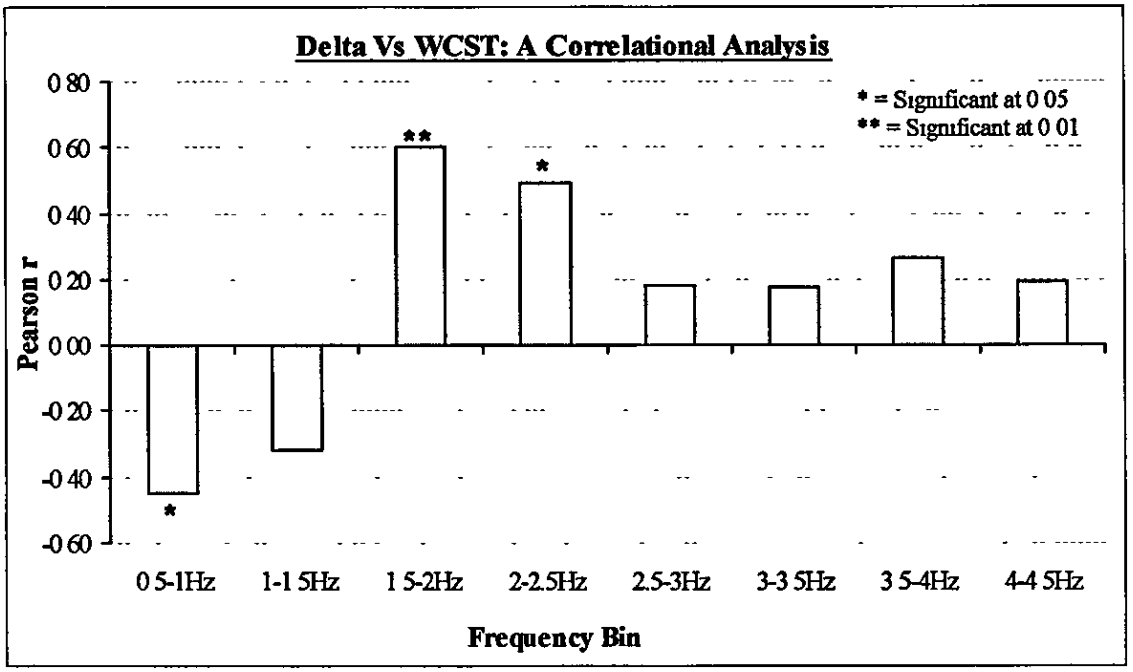


Figure 3.3: A Graphical representation of the correlation between perseverative errors on the WCST and eight delta frequency bins.

As evident from figure 3.3, there are three frequency bins that relate to the WCST. However, it is thought 2-2.5Hz is an artefact from 1.5-2Hz due to the overlap of

the EEG. This is confirmed with a partial correlation since the relationship between WCST and 2-2.5Hz, when partialling for 1.5-2Hz, becomes insignificant ($p > 0.5$). Therefore, there are two frequencies, both in opposite directions that have an association with the WCST. It was suspected that these two frequencies were inversely related, which is confirmed in Figure 3.4. The strength of the relationship is highly significant, with 62% of the variance in one frequency being explained by the other.

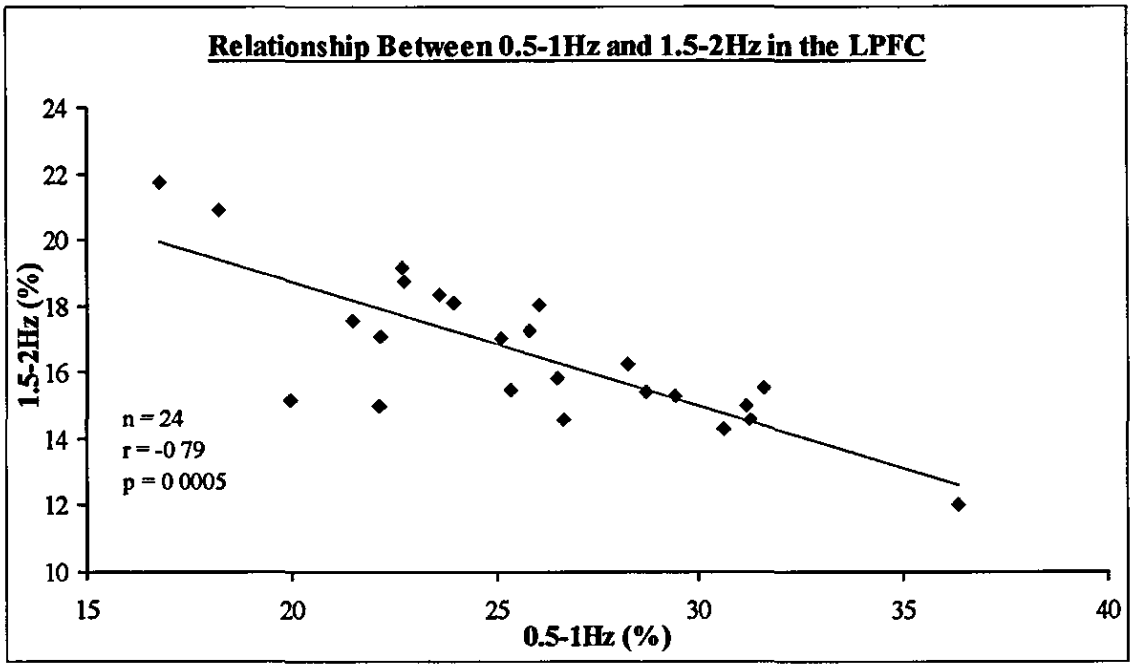


Figure 3.4: The relationship between 0.5-1Hz and 1.5-2Hz in the LPFC.

Due to the correlational nature cause and effect cannot be attributed so it is not known if the lower frequency is driving the higher one or vice versa, or indeed, whether they are both driven by an external source. Nevertheless, it is thought both these frequencies are important in recovery sleep; inter-hemispherical analysis may give insight into the distribution of these frequencies, and therefore may specify one for investigation

Hemispherical Analysis

The literature would suggest that SWA should be more dominant in frontal regions, more specifically the left frontal region Therefore, the distribution of both these frequencies was expressed in a box plot for examination This is shown in Figure. 3.5.

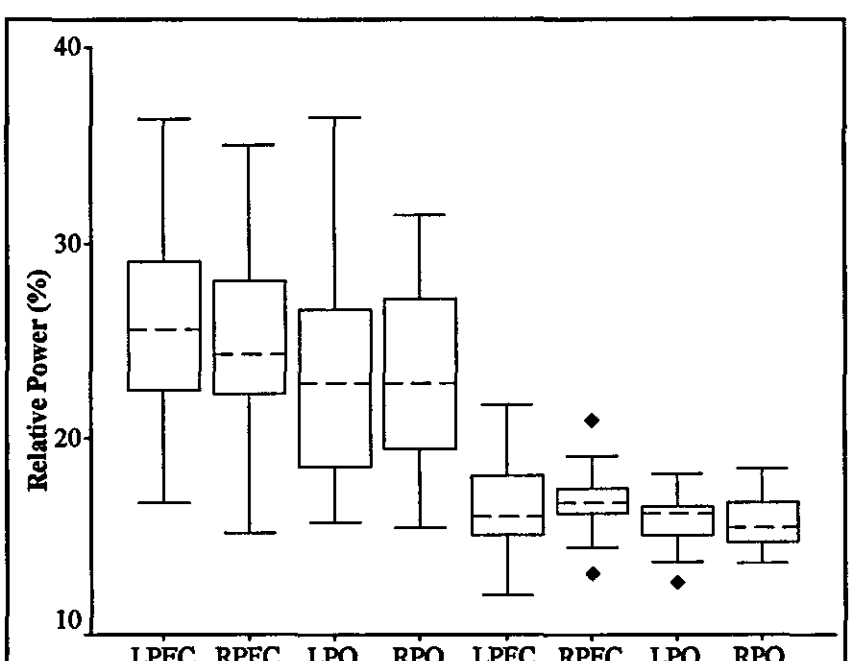


Figure 3.5: A Box plot to show the distribution of data for 0.5-1HZ and 1.5-2Hz

As the box plot shows, distribution is relatively equal amongst all channels for both 0.5-1Hz and 1.5-2Hz. However, it does appear that for 0.5-1Hz, there is a frontal dominance, albeit not predominately left. A One-Way ANOVA confirms that none of the quadrants show dominance for either 0.5-1Hz ($F = 1.678$ [d.f. 3, 92] $p > 0.1$) or 1.5-2Hz ($F = 1\ 165$ [d f. 3, 92] $p > 0.1$). However, when data was combined to enable a frontal Vs parietal comparison, the means indicate a frontal dominance for 0 5-1Hz (See table 3.5), However, a t-test confirms that both frequencies show frontal dominance ($t > 2.0$ [d f. 23] $P < 0\ 02$)

Table 3.5: Mean relative power for frontal and parietal regions: A Frequency Comparison

		Frontal	Parietal
0.5-1Hz	Mean	25 06	23 23
	St Dev	*4 96*	*4.88*
1.5-2Hz	Mean	16 98	16 03
	St Dev	*2 00*	*2 14*

It is still impossible to unravel the two inverse frequencies for selection, so a cross-correlation of the EEG was carried out to see if this gave more insight into these two frequencies. Table 3 6 shows the results of the cross-correlation of the EEG for both 0 5-1Hz and 1.5-2Hz.

Table 3.6: Cross-Correlation of relative power for 0.5-1Hz and 1.5-2HZ

0.5-1Hz

	LPFC	RPFC	LPO	RPO
LPFC	-	0.89**	0 33	0.38
RPFC	-	-	0 35	0 38
LPO	-	-	-	0 92**
RPO	-	-	-	-

1.5-2Hz

	LPFC	RPFC	LPO	RPO
LPFC	-	0 87**	0 53*	0 44*
RPFC	-	-	0 67**	0 62**
LPO	-	-	-	0 79**
RPO	-	-	-	-

As seen in Table 3.6, activity 0.5-1Hz shows strong inter-hemispherical correlations, whereas 1 5-2Hz demonstrates strong correlations between hemispheres, within hemispheres and also contra lateral correlations. It is therefore argued that 1.5-2Hz shows a more global function since during SWS it has strong correlations to all quadrants. For low frequency delta (0.5-1Hz) there are strong correlations between hemispheres, but not within. Of course there are greater distances between pairs of electrodes intra-hemispherically than inter-hemispherically, although the strong correlations for all channels for 1 5-2Hz would also show this if the lack of correlation for 0 5-1Hz was due to electrode distance. Therefore, it is proposed that 0 5-1Hz has a localised function as it shows only inter-hemispheric correlations

The recovery properties of both 0.5-1Hz and 1 5-2Hz are apparent and it is difficult to unravel the two frequencies due to the strong relationship between them. However, due to cross-correlation of the EEG, and due to the strong literature of <1Hz data coupled with the fact that activity less than 1Hz is produced by the cortex itself, the frequency band 0 5-1Hz shall be used to assess the extent to which low frequency delta can be used to predict performance on tasks specific to the PFC.

3.3.5 Delta Sleep Vs Neuropsychological Test Performance

WCST

Low Frequency delta (0.5-1Hz) from the left frontal region was correlated against WCST to see if this activity was associated with perseverative errors This relationship is shown in figure 3.6 As shown, as low frequency delta increases, perseverative errors decrease, Therefore, better performance was significantly associated with increased low frequency delta from the left frontal region

Interestingly, this relationship between the WCST and low frequency delta is only significant for the left frontal channel, although the right frontal channel came close to significance ($r = -0.36$ [d.f 22] $p = 0.08$). Neither posterior channel gave any association ($r < -0.15$ [d f. 22] $p > 0.5$) to WCST performance

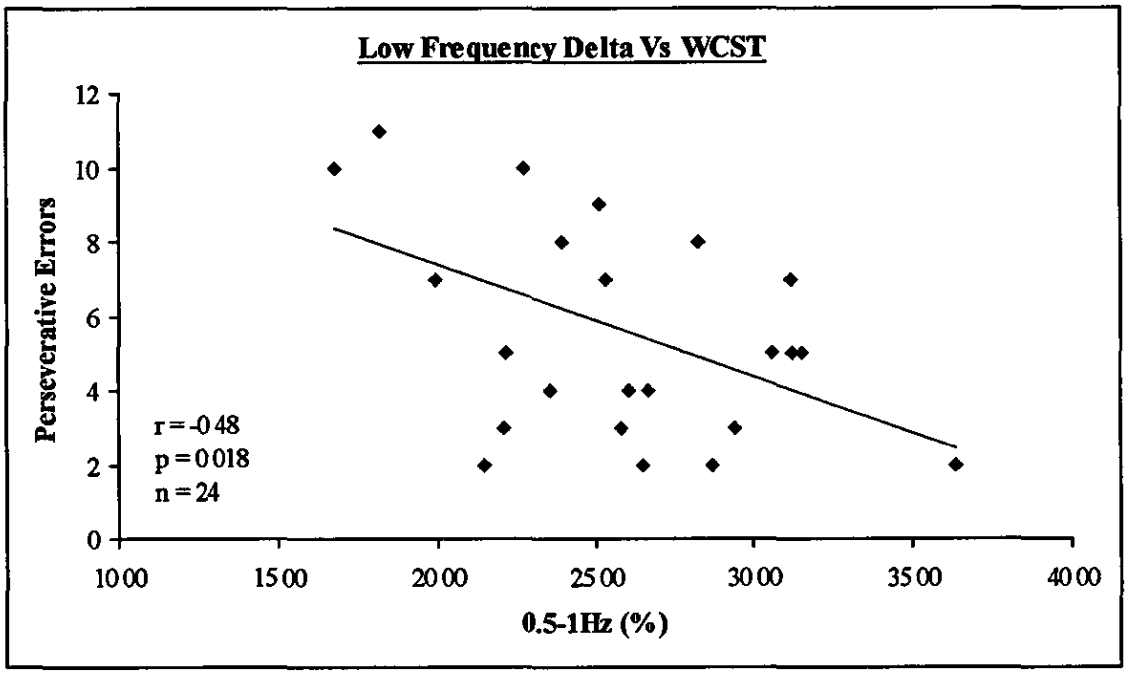


Figure 3.6: The relationship between relative power in low frequency delta (0.5-1Hz) from the left frontal region and perseverative errors on the WCST.

It was discussed in section 3.1 how age has an effect on the delta EEG, specifically low frequency delta, in that as one becomes older, the low frequency delta is most vulnerable to the age effect (reduction) as shown by Landolt & Borbély (2000) Therefore, age shall be partialled out from all correlations between performance and low frequency delta.

Although this affects the correlation as expected, the correlation for the left frontal channel remains significant (-0.40 [d.f. 21] $p = 0.03$). The WCST is also affected by age (Fristoe et al., 1997), this was shown in the current data as preservative errors were significantly associated with age using the one tail criteria ($r = 0.35$ [d f 22] $p = 0.05$). This exemplifies the importance of controlling for age effects by partialling them out in the correlation between WCST and low frequency delta.

NVPT

As low frequency delta from the left frontal region was significantly associated with performance on the WCST, it was then compared to the NVPT. The finding shows that as low frequency delta from the left frontal channel increased, time taken to complete the NVPT decreased, thus once again, low frequency delta was associated with better performance. The correlation between NVPT and low frequency delta in the right frontal channel was significant (r = -0 46 [d.f. 22] p = 0.025) albeit smaller than for the left frontal channel (r = -0.60 [d.f. 22] p = 0.002) as seen in Figure 3.7. Neither posterior channel demonstrated a relationship with NVPT (r < -0.2, [d.f. 22], p > 0 3). Partialling out age marginally improved the correlation for both left (r = -0.63, p = 0 001) and right (-0 45, p = 0 015) frontal channel correlations with NVPT.

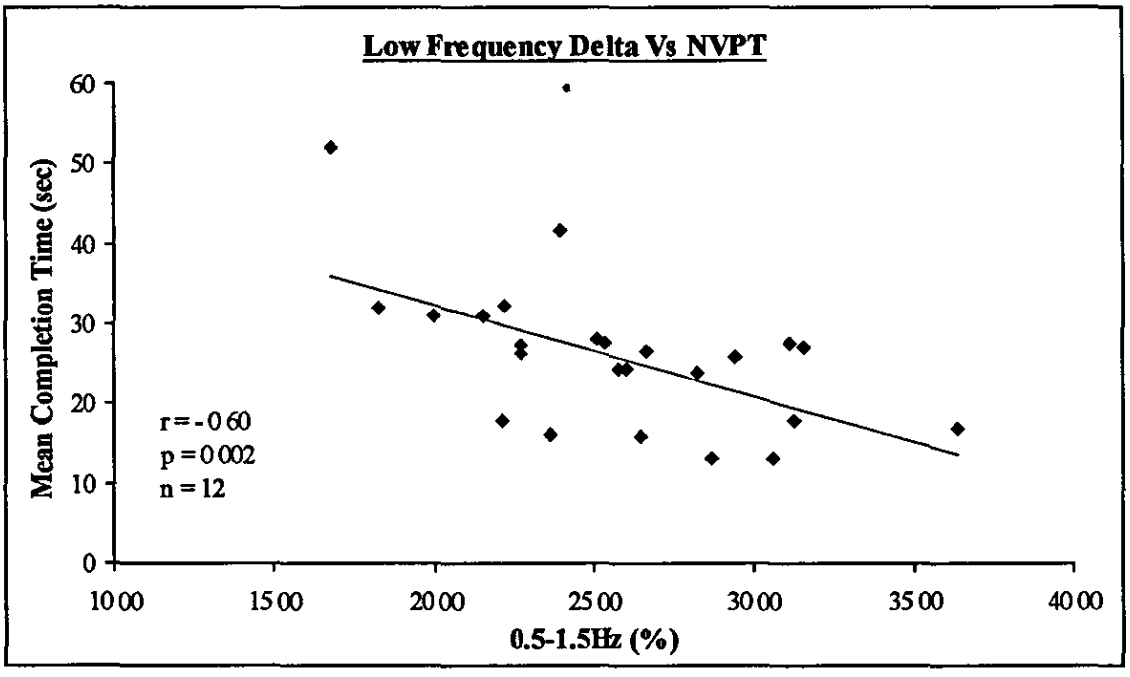


Figure 3.7: The relationship between relative power in low frequency delta (0.5-1Hz) and mean completion time on the NVPT.

The statistical correlation between NVPT and low frequency delta power in the left PFC appears strong, however, the graph depicts that a possible outlier might be affecting this correlation. A box plot to show the distribution of data confirms this (see Figure 3.8), although removal of the outlier does not alter the significance of the relationship between low frequency delta and completion time (r = -0.48 [d f. 21] p = 0.018). Leverage values between NVPT and low frequency delta

were computed, and the leverage for this outlier was 0.16. As a rule of thumb a leverage value of less than 0.2 is deemed to be safe. The reason for this subject being an outlier is unknown since he/she has no outlier result on any other test (although worse performance is consistent across tasks) nor EEG data, due to this and the leverage result it is therefore considered a genuine result and not an artefact for removal

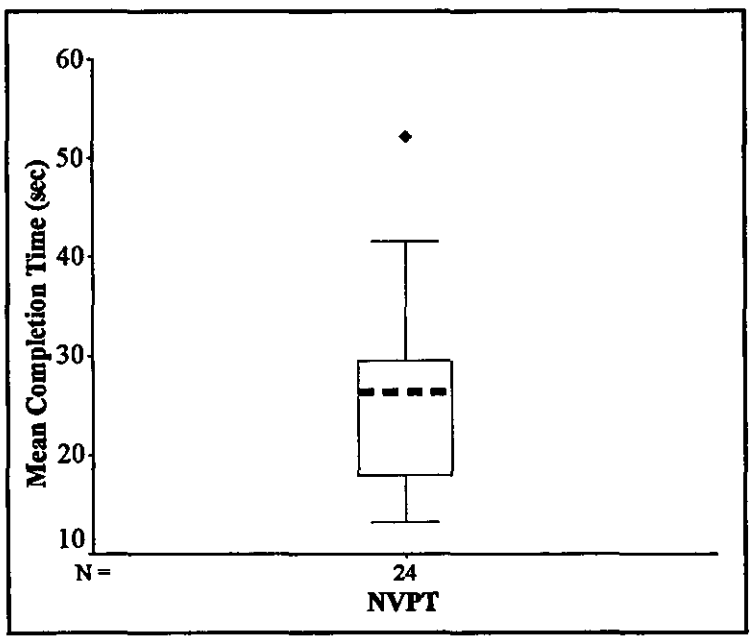


Figure 3.8: A box plot showing the distribution of mean completion time on the NVPT

Due to the time nature of the NVPT, some researchers might argue that global slowing would account for variance on this task. However, there was no relationship between mean completion time on the NVPT and reaction time ($r = 0.11$ [d f 22], $p > 0.5$). Therefore, slow completion times were not simply due to a slowing associated with ageing.

Verbal Fluency

Due to educational influences on the verbal fluency task, this task was only analysed with those participants who had received post-16yrs education, whether through school, further education or work related The relationship between verbal fluency and low frequency delta from the left frontal region was also significant in that as low frequency delta increased, the number of responses generated also increased (See Figure 3.9) This relationship was significant for both the left ($r = 0.57$ [d.f.14] $p = 0.021$) and right ($r = 0.50$ [d f 14] $p = 0\ 046$) frontal channels.

The relationship was not significant for either posterior channel ($r < 0.35$, $p > 0.1$) or for the smaller group ($r = 0.37$, $p > 0\ 1$). The verbal fluency showed no age effect ($r = -0.40$, $p > 0\ 1$), but nevertheless age was partialled out of the equation since delta is thought to be affected by age. However, the correlation remained significant for both the left ($r = 0.49$, $p = 0.03$) and right ($r = 0\ 45$, $p = 0.04$) frontal channels after age had been taken into consideration.

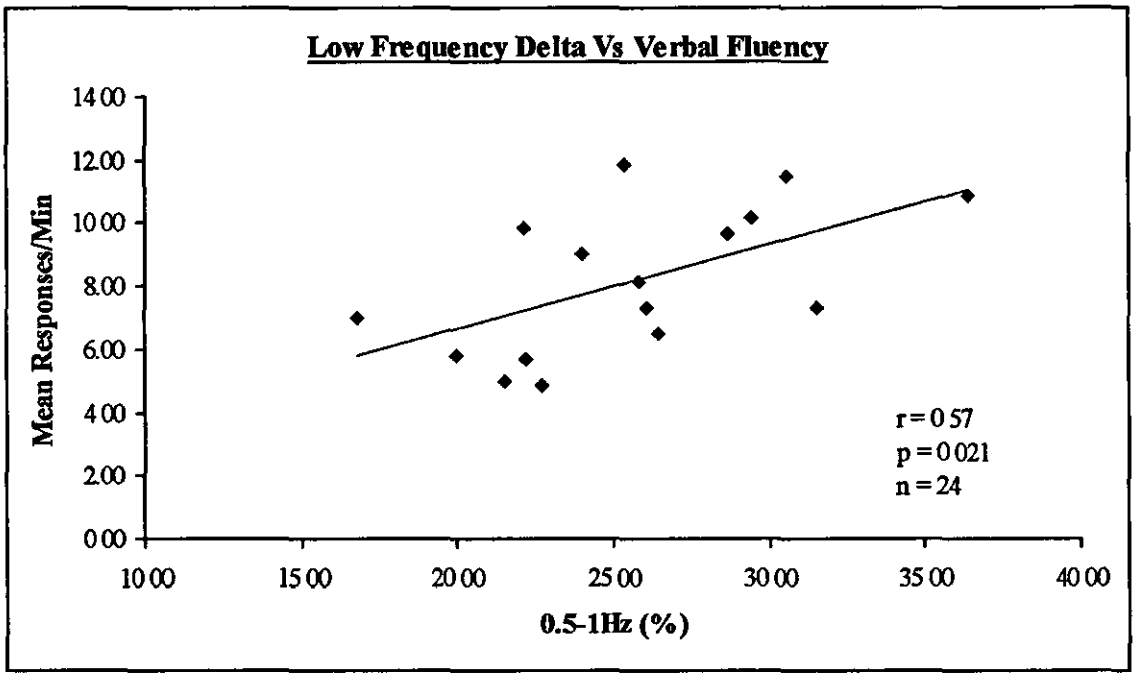


Figure 3.9: The relationship between low Frequency delta from the left frontal channel and mean responses per minute generated on the verbal fluency task.

There was no relationship between reaction time and low frequency delta for any quadrant ($r < 0.1$, $p > 0.5$). Although IQ did not show a relationship with the low frequency delta within the left frontal channel ($r = -0.20$, $p > 0.1$), it did show a significant association to the right frontal channel ($r = -0.49$, $p = 0\ 014$). The posterior channels were not associated with IQ ($r < -0.2$, $p > 0\ 3$).

Low Frequency Delta: The Effect of Age

Age has been accounted for throughout the chapter as it is claimed that low frequency delta reduces with age (Landolt & Borbély, 2000). The relationship between age and low frequency delta in the left frontal channel can be seen in figure 3.10, and so the partialling out of age throughout the chapter is justified The correlation between age and low frequency delta is significant for the left

frontal channel using a one-tailed criteria (r = -0.40, [d f. 22] p = 0.02) and just misses significance for the right frontal channel (r = -0.30, [d f. 22] p = 0.07), however, both posterior channels demonstrated no age effect (r < -0.11, p > 0 3).

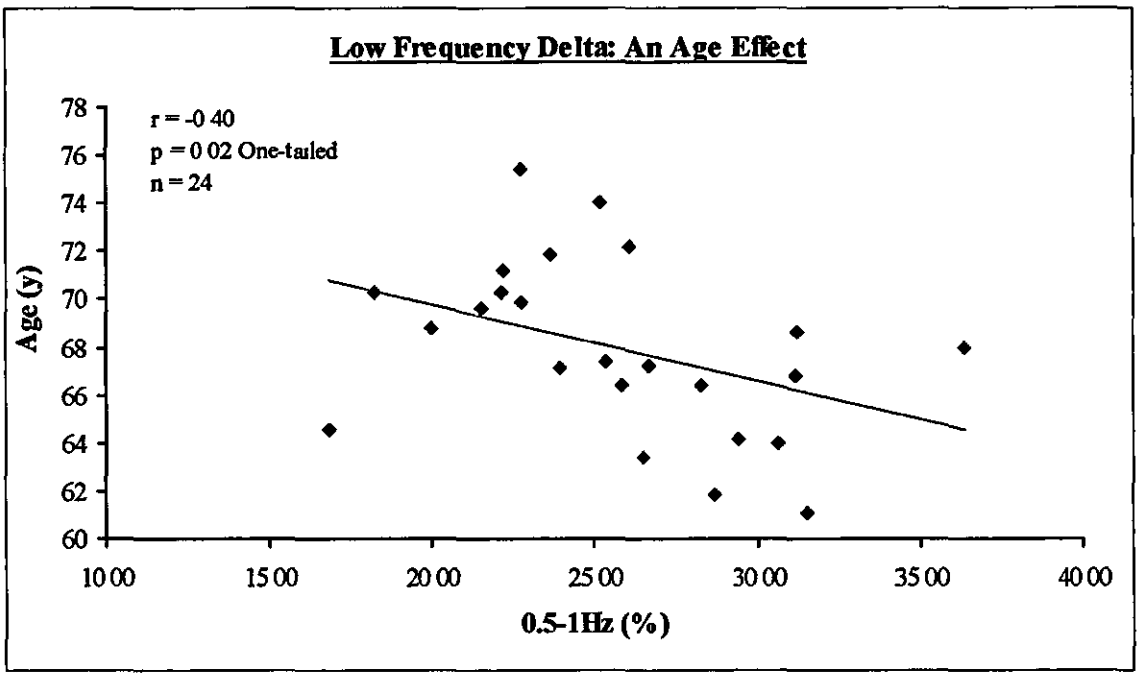


Figure 3.10: The relationship between relative power in low frequency delta (0.5-1Hz) and age.

3.3.6 Night-to-Night Stability of Low Frequency Delta

To validate the low frequency delta, and to assure that this was representative of a normal nights sleep, one in four participants underwent a third night recording The results confirm that night-to-night stability was high for all channels (r > 0.72 [d.f. 4] p < 0 05) especially in the left frontal region (r = 0.89 [d f 4] p = 0.008).

3.3.7 Breaking Down Frequencies <1Hz

The bandwidth 0.5-1Hz is a large bandwidth, in terms of time, as it covers waves from 2 seconds (0.5Hz) to 1 second (1Hz). Therefore, to make speculation on frequencies less than 1Hz, the frequency 0.5-1Hz was spectrally analysed in 0.1Hz bins and expressed as a percentage of the 0.5-1Hz range. The frequency associated with increased performance was 0 6-0 7Hz from the left frontal channel, showing correlations with the WCST (r = -0 47 [d f.22] p = 0.02) and the NVPT (-0.57

[d.f 22] p = 0 004). This was only considered a pilot analysis for future work regarding the lower frequency range in the left frontal channel

3.3.8 Analysis of the 2nd NREM Period

An analysis of the second NREM period was attempted but this showed no interesting trends with neuropsychological test performance, and the period was also more problematic in terms of artefact due to increased disturbance.

3.4 DISCUSSION

It was found that low frequency delta (<1Hz) in the first NREM period was associated with neuropsychological test performance on tasks specific to the PFC. This relationship, between tasks that activated the (left) PFC and low frequency relative EEG power, was unique to the left PFC recording site. No association between tasks performance and delta EEG was found for posterior sites.

3.4.1 The Effectiveness of the Sleep EEG

The work described in this chapter was the first study to assess the extent to which the sleep EEG reflected PFC performance. Hoptman & Davidson (1998) attempted to assess whether EEG asymmetry during the waking EEG was reflective of waking performance, but correlations were low, and both the rationale and discussion of results were different in that the authors attributed the findings to basic EEG-performance links. The current study takes an approach whereby the issue of sleep function is addressed in addition to the relationship between EEG and performance. Hoptman & Davidson (1998) point to a problem of artefact with the EEG, and so the relatively artefact free sleep EEG is an opportune and efficient method of measuring clean brain activity.

3.4.2 The Analysis of the EEG

The first NREM period was selected for analysis: Delta activity during this time is most profound (e g Werth et al , 1996,1997), less disturbed, particularly with an

older sample group (Bliwise, 1997); and the decline of delta due to ageing is more prominent during this period (Webb & Dreblow, 1982) The analysis of the second NREM period was attempted but this was considered problematic in terms of disturbance All analyses were standardised due to the possible confounding variable of sex, due to anatomical differences for instance (Dijk et al , 1989), which the present study aimed to control for.

Before any analysis of the EEG took place total delta power was assessed to ensure no localised dominance, particularly in the frontal regions, and therefore any assumptions or conclusions on the properties of localised low frequency delta were not a result of an initial hyperfrontality of total delta power. As total delta power did not demonstrate a frontal dominance, it is suggested that the total delta range is not a localised sleep function, and therefore supports the decision to split the delta range into its low and high frequency components as some researchers now suggest (e g Benoit et al , 2000). It is thought that low frequency delta is concerned with a localised sleep function as it is frontally dominant, especially so in the left frontal lobe/region which is consistent with Werth et al. (1996, 1997) However, a study incorporating older adults found that low frequency delta 0 75-2Hz was only frontally dominant in the younger age group and not the older group (Landolt & Borbély (2001) In the current data, the distribution of data did not reveal strong frontal dominance but a t-test of frontal and parietal regions did show that low frequency delta was still significantly frontally dominant. This is surprising given the fact that Landolt & Borbély's older subject group were similar (mean age 62.0), should the group have been much older, the diminished frontal dominance of low frequency delta would have been expected

The results showed a strong inverse relationship between frequencies above and below 1Hz supporting the findings of Werth et al. (1997) Both Werth et al. and Benoit et al. (2001) proposed that the slower and faster delta waves were functionally distinct, this would support the fact that total delta does not indicate test performance due to the combination of different frequencies, but when the delta range is split in accordance with previous work identifying the importance of the lower frequencies, a relationship becomes apparent. This work would

therefore further suggest that the functional difference in frequency within the delta range should be considered in future sleep research.

The results describe the relationship between low frequency delta (<1Hz) and PFC test performance, in that an increase in frequency <1Hz being associated with increased PFC performance This association is given a neurophysiological basis due to the fact that low frequency delta (<1Hz) is generated directly by the cortex (Steriade et al., 1993a, 1993b, 1996) These findings presented here may therefore indicate a greater role that the sleep EEG may have in reflecting the function of sleep, particularly a localised function. The sleep EEG may be a window on waking PFC function due to the fact that low frequency delta has enhanced recovery properties for a region that works hardest during the day since all associations were unique to this area, thus the low frequency delta is possibly in response to the efficiency of the PFC.

3.4.3 Neuropsychological Test Performance

The WCST

The WCST is renowned for its use in a clinical setting to determine those with a frontal impairment (Milner 1995). The literature regarding the activation of the WCST is inconsistent, although most studies now find it produces bilateral activations of a pre-frontal nature (e g Mentzel et al., 1998; Nagahama et al., 1996; Cantor-Graae et al , 1993) The WCST was found to show a significant correlation with low frequency EEG recorded from the left frontal channel with the finding for the right frontal channel being close to significance. This would suggest the sleep EEG has a localised sleep function, in that it is related to daytime performance on a task that relies on integration of the efficiently recovered region.

The NVPT

This finding is also attributable to the NVPT. The NVPT is highly specific to the left PFC, and findings demonstrated that low frequency delta was associated with better performance on this task, specifically in the frontal regions. The relationship was also evident in the right frontal region albeit not as strong. The NVPT has

been shown to activate the left frontal PFC, and thus if the sleep EEG in the left PFC is related to performance on a task that has strong left PFC reliance, then it is suggested that low frequency delta sleep has a function local to this area The use of the NVPT task is effective since it is culture free, is not educationally biased and is short, interesting and novel to complete. The sensitivity of the task in assessing PFC performance is evident in the consistent functional imaging results. Low frequency delta during the first NREM period has now been shown to be able to identify PFC performance on this task, in addition to current functional imaging methods.

Verbal Fluency

The verbal fluency task has been extensively referred to as a measure of PFC function in functional imaging studies (e.g. Cantor-Graae et al , 1993), in studies of sleep loss (Harrison & Horne, 1997, 1998), and studies assessing the effects of ageing (Harrison et al , 2000). Given the findings from the previous two tasks, it was expected this task would show a strong relationship to low frequency delta in the left frontal regions, which was indeed the case. It was found that as those people with higher levels of low frequency delta produced a greater number of responses on the verbal fluency task. Once again, this relationship was specific to the frontal channels, especially the left.

It has been suggested that the ageing population should not be considered as homogenous, and on some tasks, including verbal fluency, one should account for educational level (Ylikoski et al , 1999). It is argued that those with more vocabulary will perform this task more effectively than those with less vocabulary regardless of PFC function Simple vocabulary differences would mask any deficits in the initiation and production of words to a given stimuli that is considered to be PFC specific. Therefore, for this analysis only those with post-16 years education were included in the analysis, and it was found that those people who generated more responses, had higher levels of low frequency activity during the night, possibly in an increased state of recovery

Brain imaging studies of waking individuals has shown that the NVPT and verbal fluency have a stronger tendency to activate the left PFC, than the more bilateral

nature of the WCST. Coincidentally or otherwise, the relationship between low frequency delta and task performance is a stronger correlation for the NVPT and verbal fluency than the WCST. The WCST and NVPT both show either significant, or near significant, correlations with the right PFC. The finding of a relationship for left and right associations may be explained in that studies have reported the WCST (Mentzel et al., 1998; Nagahama et al , 1996, Cantor-Graae et al , 1993) and the NVPT (Rezai et al., 1993) to produce bilateral activations However, the verbal fluency has consistently shown to predominantly activate the left hemisphere, namely the left PFC (Poline et al., 1996), and so the relationship this task has to the right PFC may be explained by the high interhemispheric correlation of low frequency delta during the NREM period.

IQ

Although IQ is thought to depend on the PFC, the lack of finding between IQ and <1Hz activity from the left frontal derivation is interesting, especially given the debate for the reliance of IQ (fluid intelligence) on the PFC (given the left might be dominant) However, the current study did find that IQ was significantly associated with right low frequency delta. Major research by Duncan has provided evidence of the role of the PFC in IQ; Duncan et al. (2000) found that the CCCF test produced bilateral activation of the PFC. As the CCCF test was also used in this study it may be questioned as to why this did not show a correlation to EEG power given that EEG was related to other PFC orientated tasks. One such suggestion is that Duncan et al 's work only administered categories 3+4 that are thought to be high in '*g*', or general intelligence, due to increased difficulty It is not inferred here that the CCCF test does not rely on the PFC merely due to an absence of a relationship with the low frequency delta within the left PFC, the maintenance of attention and novel, goal directed behaviour needed during this task would implicate the PFC. However, it is suggested that the initial categories of the CCCF test were easy for the subjects in this study and thus overall scores were not high in '*g*'. Tasks of increasing difficulty are likely to cause more problems for the older population, whereas low '*g*' may be performed to a satisfactory level. The relationship IQ has with activity in the right frontal channel is interesting, especially given further inspection of Duncan et al.'s (2000) neural analysis of IQ. Non-verbal tasks measuring '*g*' showed no differences between

left and right sides (verbal IQ was highly left specific), however, when the data was not corrected for multiple comparisons (but with the threshold lowered to $p<0\ 001$), the right PFC showed increased activation. This is only speculation, due to the uncorrected nature of data, but nevertheless it may hold important value for the finding discussed here.

Further evidence for a localised sleep function is the lack of finding for other brain regions and the lack of significance for tasks that were not specific to the PFC. The consistent findings for the left PFC in conjunction with (left) PFC specific tasks may, in part, be supported by the findings of studies that locate low frequency delta as not only frontally dominant but also specific to the left side, proposing that the function of sleep is localised (Werth et al , 1997). If low frequency delta in this region is a localised sleep function, it is plausible that a reduction of recovery sleep would be associated with reduced performance in this region. Whether both aspects are due to an underlying reason, or whether they cause/affect each other is unknown However, the concept remains that the sleep EEG is effective at predicting performance on these tasks and further supports the localised sleep function theory.

3.4.4 The Neuropsychological Tests Utilised

Although the WCST, the NVPT and verbal Fluency are all found to activate frontal regions, the inter-relation between the tasks was limited in this study, with only the WCST and NVPT reaching significance. The PFC is the largest cortical region and has no unitary function, and as such, many studies have supported the claim that frontal tasks are not always likely to be inter-related (e g. Fabiani & Friedman, 1997) The complexity of the PFC is highlighted by West (1996) and it is because of this complexity that the lack of task inter-relation is reported, it would be naïve to expect all tasks of a frontal nature to be inter-related due to some commonality.

3.4.5 Age Effects

Neuropsychological Test performance

Due to the frontal nature of the tasks, it might be expected that age effects would be evident However, only the WCST showed a relationship with age. The lack of age effects is attributed to the relatively short-age range of the participants used. This was not designed to be a study of ageing that would make assumptions of the effects of age based on PFC task performance, but was merely an attempt to link sleep and performance in an older age range which would show more variance on both neuropsychological test performance and low delta sleep EEG.

Interestingly, Fabiani & Friedman (1997) found the WCST to show an age effect whereas the verbal fluency did not. However, their study utilised a comparison of young (22-28yrs) and old (65-88yrs) groups whereas this study was not a study of ageing and had no comparison younger group as it was not an ageing study. Nevertheless, the current study also found WCST to show an age effect, even with the small age range, whereas the verbal fluency did not.

In a study comparing the effects of age to that of younger people, both sleep deprived and controls, Harrison et al (2001) found a 65 year old performed similarly to that of a sleep deprived person However, the authors were keen to stress an aged brain was not a sleepy brain as sleep length was adequate in all groups. However, the current study goes to show what may be accounting for the similar decrement in performance; given that rCBR (in the PFC) is reduced during both sleep deprivation (e g. Thomas et al , 1998, 2000) and ageing (e g. Martin et al., 1991), the PFC is perhaps not working optimally In the older group this may be reflected in low frequency delta as shown in this study.

Low Frequency Delta

The unobtrusive and non-invasive EEG technique was accepted by the older participants as it was able to measure sleep in their home keeping all other factors constant, such as normal sleep time, nightly routines, normal sounds, normal sleeping habits etc. This is reflected in the high night-to-night stability analysis which showed low frequency delta was consistent on a third night in a

representative sample. This supports the finding of Larsen et al. (1995b) who found the correlation between spectral measures of EEG to be extremely high Although using older people in studies can be problematic, this was not the case in this study, since the sample selected were good, healthy sleepers, and did show night-to-night stability.

As discussed above, the EEG did not show an absence of frontally dominant low frequency delta, but it did show a relationship to age, unlike the neuropsychological tests (bar the WCST). The lack of age effect on the tasks has been attributed to the short age range, which is not considered wide enough to determine age effects (although a comparison to a younger group would). However, low frequency delta still shows an age effect over this relatively short age range in that the younger participants had more <1Hz activity than the older participants. It is therefore suggested whether low frequency delta within the first NREM period is sensitive enough to show an age effect over 15years which is considered too small to be detected by PFC specific tasks.

3.4.6 The Advantage of the Sleep EEG

It has already been suggested that the sleep EEG is advantageous over waking EEG methods in assessing brain activity as the waking EEG can be prone to noise. Following the findings from this study, the sleep EEG is able to make a prediction of PFC test performance, due to significant associations between low frequency delta and PFC performance. Therefore, the use of the sleep EEG in assessing performance is an important breakthrough in the field of sleep research, since other measures used to assess the function of sleep and/or performance have been functional imaging methods, which are extremely costly. Both fMRI and PET scans can only take snapshots of the sleeping/waking brain, whereas the sleep EEG is a continuous recording in a natural setting, that does not disturb sleep, unlike the noise generated from the MRI scanner and the head restraint accompanying it.

3.4.7 Further Research

As the sleep EEG can be used to determine neuropsychological test performance, that is orientated towards the PFC, this research provides evidence for a practical use of the EEG in determining PFC function. However, it is questioned the extent to which the sleep EEG is the only period that may depict PFC function The waking EEG would be considered a more efficient measure due to short recording times, time of day and also the ability to monitor recordings online. The use of the waking EEG, and the suspicion that this may be a period of interest lies in studies that have shown a relationship between the wake and sleep EEG (e g. Ehlers et al , 1998) but more importantly a recent study that has suggested a possible relationship between the wake EEG and neuropsychological test performance (Hoptman & Davidson, 1998)

3.5 CONCLUSIONS

Summary

1) Total delta power showed no frontal dominance, and was not considered an indication of localised recovery sleep.
2) Low Frequency Delta Activity (0.5-1Hz) was selected for analysis. This was thought to reflect enhanced recovery Due to:
   a) An evidence of frontal dominance as frontal areas require more recovery sleep (Werth et al., 1996, 1997).
   b) A seemingly local function that was specific to frontal areas as found during a cross-correlation of the EEG.
   c) This activity is generated by the cortex itself (Steriade, 1993a, 1993b) and so is considered an advanced recovery system for the advanced PFC.
3) Activity 0.5-1Hz showed an inverse relationship with activity 1.5-2Hz, supporting previous work that had demonstrated this, but also exemplifying the distinct frequencies contained within the delta range.
4) Low Frequency delta was found to be associated with three tasks of PFC function, in that those participants who performed better on tasks of a PFC nature, had significantly more low frequency delta.

a) This relationship was specific to the left frontal channel (with the NVPT also being associated with the right albeit not as strong).
b) This relationship is specific to the PFC tasks No relationship was found for the non-cortically specific reaction time.

5) The performance tasks were not sensitive enough to reveal age effects over the small age range of 15years. However, the low frequency delta was related to age within this small gap, suggesting it may be more sensitive than the performance measures in assessing age.
6) A pilot analysis of frequencies less than 1Hz revealed that, more specifically, frequencies 0 6-0.7Hz were related to increased performance.
7) The findings support a localised function of sleep, as the sleep EEG is associated with performance of the PFC - the hardest working cortical region during the daytime that requires more recovery low frequency delta at night.
8) Although the sleep EEG is shown to reflect PFC function, it is suspected that the waking EEG may also show a relation to PFC function given the similarity between the wake and sleep EEG, and also recent findings of a possible relationship between wake EEG and neuropsychological test performance.

Conclusion

The sleep EEG in the left frontal channel can be used to predict PFC performance that is specific to the left PFC, in that an association between PFC performance and low frequency delta was found This study supports a localised function of sleep since a frequency that is generated by the cortex as a reflection of recovery, is associated with waking PFC performance that is specific to the left frontal region – an area with the highest daytime CMR. The lack of findings for total delta power and inverse relationship between slow and fast delta frequencies highlight the importance of distinguishing the delta range The association between low frequency delta and PFC performance is apparent but cause/effect cannot be attributed. The extent to which the relationship between the two indices of EEG and neuropsychological test performance is specific to the sleep EEG is questioned, and further research will establish whether more efficient daytime recordings also show this relationship or whether the sleep period is more robust in the association to PFC performance.

This Chapter was financially supported by The Wellcome Trust Foundation

The work as described in this chapter is published as:

Anderson, C. & Horne, J A. (2003). Pre-Frontal Cortex: Links Between Low Frequency Delta EEG in Sleep and Neuropsychological Performance in Healthy, Older People *Psychophysiology.* In Press.

CHAPTER 4

WAKE EEG & NEUROPSYCHOLOGICAL TEST PERFORMANCE IN HEALTHY OLDER PEOPLE

4.1 INTRODUCTION

The previous chapter assessed the extent to which the sleep EEG relates to PFC performance in a healthy older group, given the relationship between waking PFC activity (CMR/CBF) and delta sleep at night in this region. The focus of this thesis is an investigation into associations between EEG and performance, not just the sleep EEG, but also the waking EEG. It is thought that the waking EEG may be more efficient due to it being less time consuming and taken during a more convenient time for testing. Therefore, the use of the wake EEG and its relation to neuropsychological test performance will be examined to investigate the efficiency of this period and also to establish whether this relationship might be evident across the sleep/wake cycle or whether it is specific to the sleep EEG as previously found It is suspected that the waking EEG will also relate to PFC performance, due to the literature linking waking EEG with both task performance and the sleep EEG.

Given the relationship between rCBF in the PFC during wakefulness and delta activity during sleep (e g Braun et al , 1997), it is proposed that sleep has a localised function for recovery. Similarly, it has been shown that EEG frequencies during the day are faster in the PFC (Mathew, 1989 - frequency being positively correlated with CMR), with this region exhibiting more delta activity during NREM sleep at night (e g Lanquart et al , 1996). However, the extent to which daytime and night time frequencies are related is still a topic for discussion. It is argued that if the PFC works harder during the day, indicated by faster frequencies, then this should be positively correlated to delta activity at night as a reflection of recovery due to this increased work.

The extent to which faster frequencies are a reflection of brain work is questionable· The *beta* rhythm is characteristic of an alert, active, awake individual and encompasses frequencies between 15Hz and 30Hz Frequencies above 30Hz are classed as *'gamma'* waves and are thought to be reflective of the integration of a variety of stimuli (e.g Tallon-Baudry et al , 1997). Just below the beta rhythm is the *'alpha'* rhythm, a slower EEG that is characteristic of a relaxed wakeful cerebrum. As soon as cognitive stimulus is given, the alpha rhythm

ceases and a return to the beta rhythm commences, termed '*alpha blocking*'. Given this trend of a reduction of alertness from beta through to alpha activity, it is expected that the slower frequency '*theta*' will result in a further reduction of alertness Although this is the case, there is an interesting twist.

The theta rhythm has been associated with sleep onset, REM sleep, hypnagogia, hypnosis, and of course, as expected, drowsiness (Stern et al , 2001). Researchers have consistently and successfully used the theta rhythm in the EEG as marker of sleepiness (e g Belyavin & Wright, 1987; Torsvall & Åkerstedt, 1987, Cajochen et al., 1995). Cajochen et al. found that theta activity (6.25-9.0Hz) progressed over periods of 3, 10, 27, and 34 hours of prolonged wakefulness, thus concluding theta was a direct indication of increasing sleepiness.

However, the theta rhythm holds an extraordinary 'dual' purpose. Schacter (1977) suggests that there are actually two types of theta rhythm: Firstly, there is theta activity associated with decreased levels of alertness as mentioned, whereas secondly, it is associated with increased attention, and the efficient conductance of cognitive tasks. This latter concept, that is the increase of theta through cognitive task performance, has been reported during a number of studies (e g Gundel & Wilson, 1992, Ramos et al, 1993; Smith et al , 1999). Jensen & Tesche (2002) clarified the theta band to a more specific focus and concluded that 7-8 5Hz activity from the frontal region was a reflection of memory maintenance during a task to recall sets of digits since theta increased during digit retention

Gevins et al. (1979a, 1979b) assessed EEG correlates of what they term "higher cortical function" by assessing EEG during tasks such as serial addition, mental rotation blocks, Koh's block design, and letter substitution They found that theta increased during all three tasks, especially in frontal areas, and concluded that higher function resulted in an increased activation of theta The authors proposed that this activation of theta was not task specific, but was associated with more global processes such as attention

The increase of theta during thinking has been researched for over half a century. Early findings from Kennedy et al (1949) and Mundy-Castle (1957) indicate that

theta increases during problem solving and thinking. Kennedy et al referred to this rhythm as the *'kappa'* rhythm. The kappa rhythm is an alpha like EEG activity which has been reported during both waking (Chapman et al., 1962) and SWS (Sewitch et al, 1978). Chapman & Colleagues investigated the kappa rhythm during wakefulness and found that kappa and alpha were independent of each other, in that kappa was produced frontally, increasing during hard tasks Chapman et al. labelled kappa as activity as 7-12Hz that was functionally distinct when produced frontally, and claimed it to be 1 cycle/second (1Hz) slower than alpha activity. Although Mundy-Castle (1957) investigated EEG changes in theta during task performance, there was never any reference made to theta in the frontal area. The referral of the kappa rhythms ceased but the phenomenon associated with it did not becoming referred to and investigated as frontal theta. Ishihara & Yoshii (1976) not only found theta activity originated in the frontal area during task performance, they also found it appeared most during the digit symbol test which is interesting since this task is the only task they used (out of 15 others) that relied on the frontal lobes due to its working memory component. Therefore, this may suggest that the waking EEG and its relation to performance may be specific to frontal regions.

Çiçek & Nalçaci (2001) investigated the alpha rhythm (low· 8.6-10.2Hz, High. 10.9-12.5Hz) during both a task (WCST) and relaxed wakefulness and how this was related to performance on the WCST. They found that low alpha activity in the left frontal region correlated with performance on the WCST, not only during task performance, but also with the EEG taken during rest. These findings are significant to the current study since they provide indication that the EEG can be used to assess performance on tasks, especially localised. The notion that the EEG can be measured during relaxed wakefulness and still correlate to performance, taken during a separate time, indicates an underlying relation between performance and EEG. Hoptman & Davidson (1998) also found that the waking EEG had properties for assessing localised performance, in that verbal fluency was related to alpha activity in left central regions, and the Tower of London was related to alpha in the left parietal region. However, correlations were low ($r < 0.35$) and the authors fail to discuss the localisation implications The question, therefore, is why activation in a particular area, is related to a particular task.

Tucker et al.'s (1985) finding may give insight into this as they found theta activity was focussed in the left frontal region during a word fluency task, whereas this trend wasn't evident for other frequency bands This is interesting given the reliance of verbal fluency on the left frontal region (e g Frith et al , 1991)

Suetsugi et al (2002) extended literature on the study of the relationship between the wake and sleep EEG. They investigated two groups: one showing frontal theta and one without frontal theta The differences between the wake and sleep EEG between these two groups indicated that the frontal theta group showed more theta during task performance and during sleep, in frontal and central regions. The authors concluded that activities during a mental task and during sleep correlate with each other. Given the findings from the previous chapter, that the sleep EEG is a reflection of PFC performance due to the localised role of sleep, then one could predict that waking EEG during task performance would also be a marker of performance, with the strong possibility of this association also being localised

The relationship between the sleep EEG and waking EEG has produced interesting findings. Finelli et al. (2000) found that daytime theta correlated to night time delta activity concluding that daytime theta activity was a secondary marker of sleep propensity Although it is thought increasing theta (reflecting sleepiness – especially given recordings took place under sleep loss conditions) would be correlated to depth of sleep at night, the findings that the topographic distribution of both frequencies is similar (i e. largest rise of theta & delta in PFC) is an important finding since it suggests both are due to an underlying process, and thus, gives insight into a possible association between the sleep and wake EEG. A similar finding was proposed by Ehlers et al. (1998) who found delta activity at sleep onset was related to delta activity during sleep, once again, they attribute this to the two process model of sleep in that the increased delta during wakefulness and sleep reflects the homeostatic nature of process S Similarly, the finding shows that the spectral properties of an individual's EEG is stable across the sleep/wake cycle. The waking EEG may therefore hold interesting properties as the sleep EEG did (in chapter 3) with regards to task performance thus validating the wake EEG as a tool for assessing performance.

The studies described examining the relationship between waking EEG and task performance have focussed on healthy, young adult groups. However, given that older people exhibit changes in both PFC function and (sleep and wake) EEG activity, coupled with the findings from the previous chapter, the research between EEG and performance with advancing age becomes an increasingly interesting topic for consideration. Literature has shown that the wake EEG is also subject to age-related changes: There is an apparent reduction in power in the delta and theta bands (e g Polich, 1997; Duffy et al , 1993), an increase in power in the beta band, a decrease in alpha amplitude (Dustman et al , 1983) and a slowing of the peak frequency in the alpha band (e g Woodruff & Kramer, 1979, Roubicek 1977)

As discussed, the PFC shows many age-related changes in particular a reduction in rCBF (Martin et al., 1991), and a reduction of volume (Cowell et al , 1994), which incidentally or otherwise has been shown to be linked to working memory performance (Raz et al., 1999), a strong indicator of PFC function As Çiçek & Nalçaci (2001) found that daytime EEG was reflective of PFC performance in younger people, it is suspected that an older sample group who perform less efficiently on tasks of a PFC nature, due to the changes mentioned above, would demonstrate this in their waking EEG activity

McEvoy et al. (2001) examined neurophysiological changes during a working memory task due to age They found that younger subjects (mean 22years) displayed more frontal theta during task completion than older subjects (mean 69years) and also that younger adults showed increased theta activity with task complexity whereas older participants did not The authors attributed the findings to changes in the frontal networks that are used during working memory, with increasing age, and that whilst younger adults utilise posterior sites as task complexity increases, older group rely on the controlled and effortful frontal networks. As the frontal part of the cerebrum is showing age-related changes, the older group are unable to use strategies using other cortical regions and so depend on the ageing PFC resulting in impaired performance.

4.1.1 Aims

Due to the relationship between low frequency delta and performance, this chapter aims to establish the extent to which the waking EEG is related with performance The waking EEG may hold similar properties to the sleep EEG since studies have reported stability of spectral measures across the sleep/wake cycle (Ehlers et al , 1998; Suetsugi et al , 2002). Inasmuch that the sleep EEG reflects changes in PFC performance due to a probable localised function of sleep, it is argued that baseline measures of waking EEG will also be related to the sleep EEG, and therefore PFC performance Studies have already shown the waking EEG is reflective of performance on cognitive tasks, albeit in a younger age group, (e.g. Gevins et al , 1979a, 1979b; Çiçek & Naçaci, 2001), although this relationship has never been localised nor related to sleep. McEvoy et al (2001) show that older subjects show reduced working memory performance and also reduced theta levels due to dependence on frontal networks that are showing age-related decrements This chapter aims to bring all the concepts together to assess the relationship between sleep EEG, waking EEG and task performance, whilst retaining the focus on the PFC, in an attempt to validate the use of the EEG in assessing PFC performance, and provide further evidence of a localised sleep function in the healthy, older people.

Research Questions

- Is low frequency delta during the night related to daytime theta (thinking) when recorded on separate days?
- Can the waking EEG be used to assess PFC performance in healthy, older people?
- Is the use of waking EEG more efficient than the sleep EEG?
- Can the waking EEG be recorded under controlled, artefact-free conditions?

4.2 METHODOLOGY

Twelve[1] right-handed participants (6 female, 6 male) with an age range of 61-74years (mean. 67 9years, SD: 4 29years) took part in the study. All were normal healthy sleepers who had previously undergone two nights of Sleep EEG recording and a battery of neuropsychological tests. The sample was recruited from the twenty-four participants who had previously taken part in the study in chapter 3. All subjects had given prior consent of waking EEG and so selection was not biased towards self-selected elite. The sample of 12 was randomly chosen and balanced for sex and age.

The Neuropsychological Tests in use for this chapter for this age range were:

- The Tower of London
- The Verbal Fluency Task[2]
- Wisconsin Card Sorting Task
- Reaction Time and IQ (Non-Cortically Specific)

EEG analysis began with preliminary analyses of the waking range 3-10Hz, with a specific interest in the theta range 4-8Hz produced frontally EEG power spectra was calculated in 5 second epochs, and power within each 1Hz frequency bin was expressed as a percentage of the full waking range 3-15Hz in order to standardise the data. Wake EEG was analysed to assess the association with both neuropsychological test performance and low frequency delta during sleep at night. Data was carefully selected to ensure only artefact free epochs were used.

4.2.1 Experiment 1

Waking EEG was recorded during a time of optimal alertness (late morning) and subjects were asked to undergo a series of 'thinking' scenarios under controlled conditions in the laboratory

[1] 3 participants were removed, and replaced (matched for age and sex) due to artefact across the trial – See Discussion

[2] Verbal fluency was considered to have an educational bias, and therefore, only participants who had received education post-16yrs were used (n=8)

All eyes closed conditions were spectrally analysed: Power spectra were calculated for 5-second epochs for the first 60seconds of each condition (verbal fluency only first 30seconds analysed, as verb generation dries up after this time – Harrison & Horne, 1997) This comprised twelve continuous artefact free epochs. Any data that failed to show the first six epochs to be artefact free were not analysed. Therefore, the number of participants varied for each condition

See Chapter 2 for full procedures: Neuropsychological Testing and Waking EEG Recordings.

4.2.2 Experiment 2

The selection of EEG was the 5-10minutes following "lights out", and was required to be a minimum of 12 epochs (1minute) of clean EEG The absence of eye rolling was considered imperative since this affects the EEG from the fronto-polar channels, and also, it was important in the study to control for drowsiness in the assessment of theta

See Chapter 2 for full procedures: Neuropsychological Testing and Sleep EEG Recordings since the wake EEG selection was made using the Sleep Recording montage, protocol etc.

Statistical Analysis

All statistical analyses are concerned with assessing the relationship between an independent variable (Wake EEG) and the dependent variables (neuropsychological test performance and low frequency delta EEG). Therefore, Pearson r correlation coefficients will be determined, with the use of partial correlation coefficients, if and when applicable Any analyses concerning differences, such as female/male test scores, will use the (un)related t-test or the One-Way ANOVA for multiple variables. The significance level is set at 0 05 unless otherwise stated

In order to compare groups and/or databases for distribution, "box and whisker" plots will be used. The box plot consists of a lower "hinge" (25^{th} percentile) and

an upper "hinge" (75th Percentile), the centre of these being the median value. The "whiskers" of the plot represent the "fence" range of values, these fall within 1 5 times the value between the appropriate hinge and the median. Any values falling outside of this range are represented by an asterisk (*) and are termed "outliers".

4.3 RESULTS – Experiment 1

4.3.1 Participant Characteristics

All participants fulfilled the criteria as set out in chapter 2, with the sample being matched for age and sex. This can be seen in table 4.1.

Table 4.1: Characteristics of Participants

FEMALE				MALE			
Ss	**Age**	**ESS**	**TST (hrs)**	**Ss**	**Age**	**ESS**	**TST (hrs)**
7	64 11	8	7.32	3	61 8	6	8 25
9	63.4	4	8 11	8	64.6	4	8 32
10	67.2	3	8 02	15	62	5	8 36
11	66.8	1	7.44	16	71.7	6	7 59
21	72.2	6	8 51	17	69 5	5	8 04
22	74	0	8 14	19	70 3	2	7.17
Mean	**67.95**	**3.67**	**8.09**	**Mean**	**66.65**	**4.67**	**8.15**
SD	**4.29**	**3.01**	**0.46**	**SD**	**4.39**	**1.51**	**0.49**

4.3.2 Daytime Sleepiness Scores

Hourly values for the Karolinska Sleepiness Scale (KSS) were taken for 3 days to ensure the subject sample showed a normal distribution of sleepiness, and also to ensure waking EEG was taken at a time of maximal alertness. The average fluctuation of daytime sleepiness, as measured by the KSS, is shown in Figure 4.1. As seen alertness was maximal during the testing session, and the normal distribution of sleepiness throughout the day was evident.

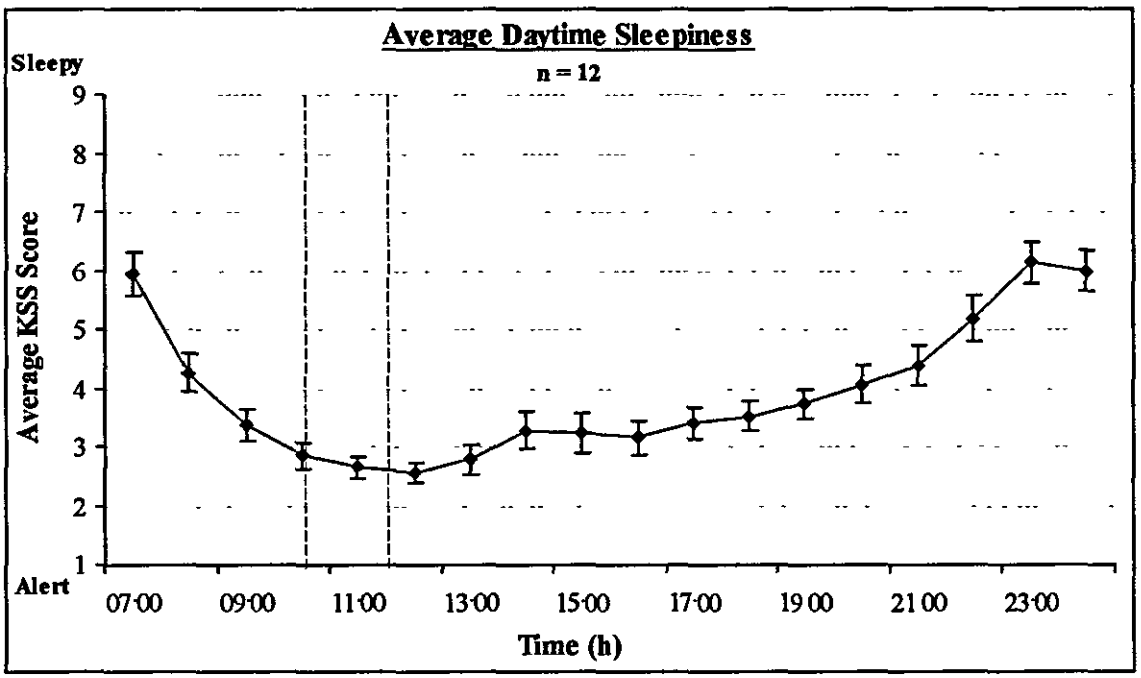


Figure 4.1: The fluctuation in daytime sleepiness, as measured by the KSS. Average values over 3 days, inclusive of standard error. Testing times are indicated by the vertical dotted lines.

4.3.3 Sleepiness During the Trial

Due to the focus being on theta, it is imperative that theta activity is not due to sleepiness but thinking during test conditions. Therefore, throughout the trial, between each condition, participants were required to rate their feelings of sleepiness using the KSS It has been shown that the KSS is extremely sensitive to objective measurements of sleepiness, and that EEG characteristics of sleepiness are evident at a scale of 7, "Sleepy, but no effort to keep awake" (Åkerstedt & Gillberg, 1990). Therefore, at a given point of 7, the trial was aborted. The average rating of sleepiness throughout the trial is shown in Figure 4 2

Although sleepiness increased over the duration of the session, average reports remained below a KSS of 6 ("Some signs of sleepiness"). One subject indicated a score of 8 towards the end of the trial, the trial was therefore aborted and only conditions whereby the rated KSS was less than 7 were included As the experimenter recorded, and assessed, the on-line EEG recording, a secondary measure also ensured that no signs of EEG/EOG measured sleepiness was evident (i e. eye rolling) None of the participants showed physiological signs of sleepiness as determined through the EEG/EOG.

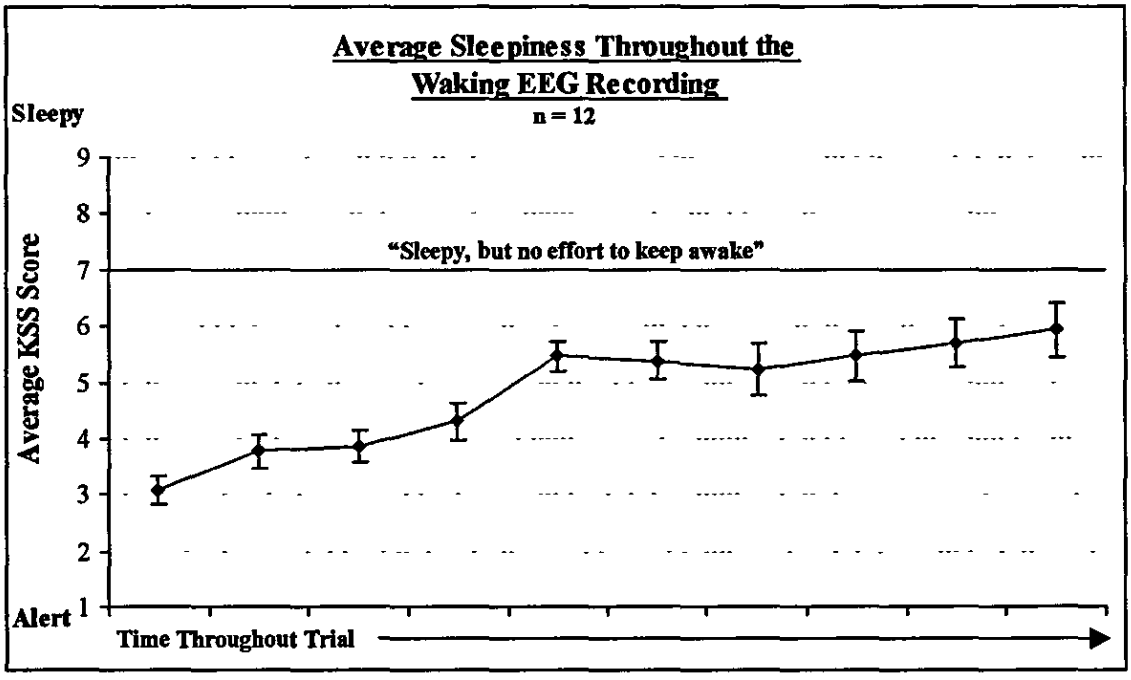


Figure 4.2: The fluctuation of sleepiness throughout the waking EEG recording session. Average KSS and Standard Error are shown.

4.3.4 Analysis of the Waking EEG

The eyes open conditions were not analysed due to this portion of the EEG being prone to noise with frequent bursts of artefact due to eye blinking (0.2Hz) and eye movements (ranging from 0 6-2 5Hz). Although the band-pass filter would remove this artefact, the eyes open was still avoided as eye movements interfered with the frontal channels throughout.

All eyes closed conditions were spectrally analysed· The first 12 continuous epochs of clean EEG for each condition were analysed (6 continuous for verbal fluency): Any data that failed to show the first twelve/six epochs artefact free were not analysed Therefore, number of participants varied for each condition This is shown in table 4.2.

Table 4.2: Number of Participants displaying clean artefact EEG for the first twelve (six) continuous 5-second epochs. Total number of analysed epochs are also indicated.

	n =	no. epochs =
Eyes Closed	12	144
Verbal Fluency[3]	12	216
Journey	10	120
Yesterday	7	84
Experiment	10	120
Song	12	144
Thinking (See Below)	12	144

The three thinking conditions (journey, yesterday, experiment) had few total subjects due to artefact and it was thought that these conditions could be combined (i.e 1min of clean EEG from each and expressed as relative power like other conditions) to form one condition thus increasing the number of participants. The distribution of the EEG ranging from 3-10Hz for the left frontal channel is shown in figure 4.3.

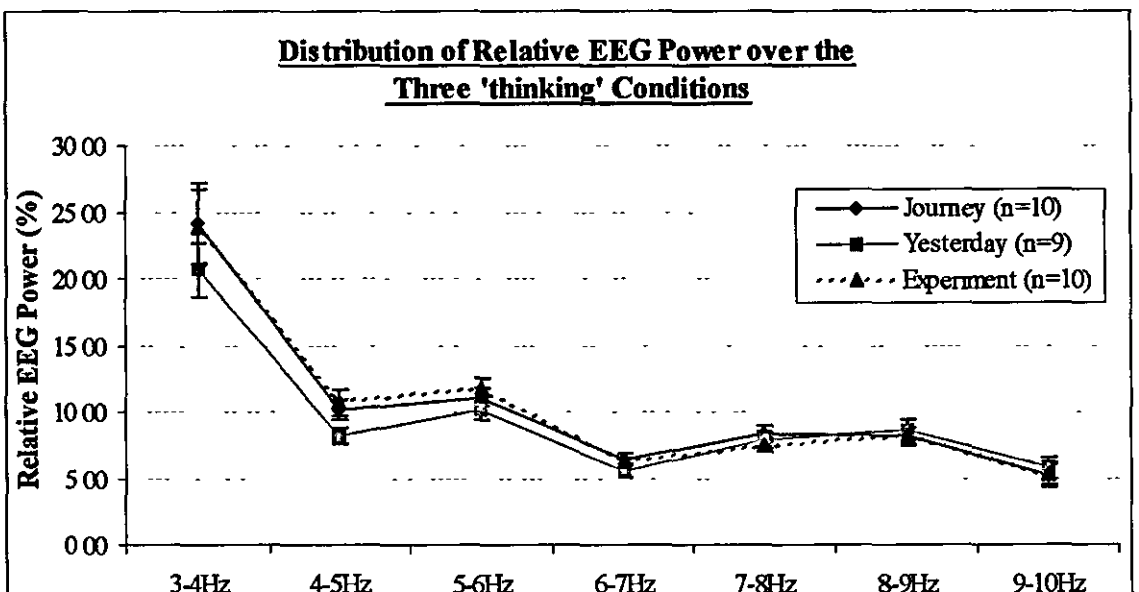


Figure 4.3: Distribution of EEG activity in the left frontal region to show the similarity of the three 'thinking' conditions.

[3] This is not a performance measure, and is distinct from the verbal fluency task measures reported – This condition is merely to encourage 'active' thinking.

As can be seen, the distribution is equal as the conditions are very similar. All quadrants demonstrated the three thinking conditions were equally distributed. It is argued that thinking of a journey, of what happened yesterday, and of the experiment, would all involve similar processes in that they all·

- Involve visual thoughts
- Involve memory retrieval

Given the equal distribution of these three conditions, they will be combined as proposed and termed 'thinking' for the remainder of the study, thus increasing the number of participants to 12, and the epochs analysed to 144 (See table 4 2).

4.3.5 Wake EEG Vs Low Frequency Delta

Given the findings of Finelli et al. (2000), the extent to which theta during the daytime was a marker of low frequency delta was assessed. There was no significant relationship between waking EEG and sleep EEG for the eyes closed condition ($r < 0\ 15$ [d f 11] $p > 0\ 5$), verbal fluency condition ($r < 0\ 44$ [d f. 11] $p > 0.1$), or the song condition ($r < 0.43$ [d f.11] $p > 0.1$). However, there was a relationship between low frequency delta and waking 7-8Hz activity ($r < 0\ 68$ [d f. 11] $p < 0\ 02$) in the thinking condition which is graphically represented in Figure 4 4 This relationship remains significant when partialled for age at the 5% level ($r = 0\ 61$ [d f. 9] $p < 0.05$). Interestingly, the higher correlations between delta sleep and daytime frontal theta were all in the 7-8Hz range (for verbal fluency and the song condition), with other frequency bands showing $r < 0\ 30$

All other bins (4-7Hz) showed no relationship with low frequency delta from the left frontal region ($r < 0.46$, $p > 0.2$).

This relationship between 7-8Hz activity and low frequency delta at night was not significant for any other region ($r < 0\ 35$ [d f.11] $p > 0\ 1$) and thus was specific to the left frontal region.

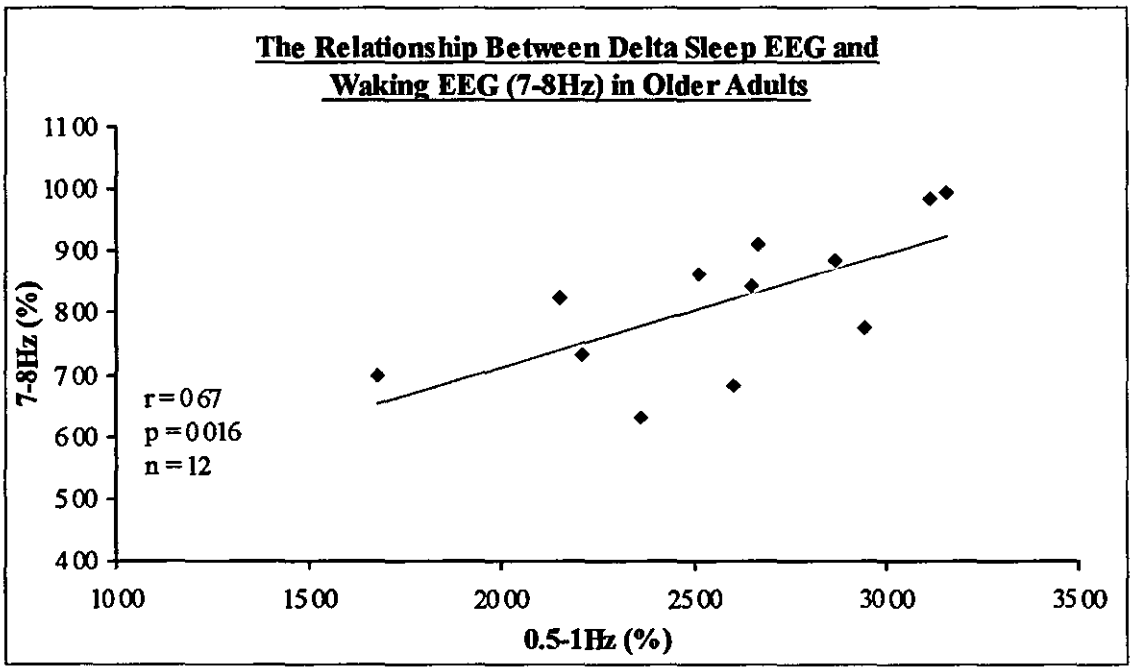


Figure 4.4: The relationship between relative EEG power in low frequency delta range (0.5-1Hz) during sleep, and relative power 7-8Hz during an alert thinking exercise. This relationship is unique to the left frontal region.

Although sleepiness was strictly controlled for, it was questioned whether an association between night-time sleep and daytime wake EEG might be due to sleepiness/relaxation/time on task as opposed to underlying traits in the EEG as proposed Although time on task was relatively small (1minute) two small analyses were conducted:

i) A partial correlation accounting for individual propensity for sleepiness (ESS)

ii) A time on task analysis

i) Partial Correlation

The relationship between low frequency delta and daytime 7-8Hz activity, whilst controlling for trait sleepiness (ESS scores) increased the correlation somewhat ($r = 0.78$, d f. 9, $p < 0.004$). Therefore, it was thought this relationship was not due to trait sleepiness, but due to a trait in the EEG.

ii) Time on Task Analysis

This comprised of splitting the wake EEG recording into its first and second half temporal components, and performing the same correlation with low frequency delta for each half respectively. It was thought that if the effect was due to time on

task, the correlation for the second half would be higher. Results indicate that the relationship is evident for both the first half (r = 0 67, p = 0 018) and second half of the task (r = 0 62, p = 0 03), and is therefore *not* a reflection of time on task

4.3.6 Wake EEG Versus Neuropsychological Test Performance

Mean task performance did not differ between male and female participants. These results are listed in Table 4.3. An Independent Samples t-test confirmed that males and females did not differ (t < 0.47 [d f 10] p > 0 05) and so males and females were treated as one group.

Table 4.3: Mean Task Performance: A Comparison of Sex

		NVPT	VERBAL FLUENCY	WCST	RT	IQ
Male	*Mean*	**26.28**	**8.25**	**7.77**	**318.73**	**106.33**
n = 6	*Stdev*	*14 39*	*1 65*	*2.02*	*24.66*	*9.29*
Female	*Mean*	**24.65**	**7.96**	**8.00**	**328.27**	**94.33**
n = 6	*Stdev*	*4.51*	*2 05*	*1.92*	*43.02*	*8.80*

N: B – Verbal Fluency (male n = 5, female n = 3)

The EEG from the left frontal channel[4] for each condition was assessed independently to the NVPT, as there were seven correlations for each condition, the accepted level of significance was 1% to minimise the possibility of a type I error A special interest was paid to the frequency bin 7-8Hz given its association with low frequency delta.

Eyes Closed Condition

NVPT was not associated with relative power within any frequency bin, in the left frontal channel (r < 0 45 [d.f. 11] p > 0 1).

Verbal Fluency Condition

NVPT was not associated with relative power within any frequency bin, in the left frontal channel (r < 0 45 [d.f. 11] p > 0 1) The strongest associations were in the delta range, but these proved insignificant

[4] Left frontal will be analysed first as it is thought any interesting link will be found in this channel primarily given the findings from Chapter 3

Song Condition

Once again, NVPT was not associated with relative power within any frequency bin, in the left frontal channel ($r < 0.25$ [d.f 11] $p > 0.1$).

Thinking Condition

NVPT was not associated with relative power within any frequency bin, in the left frontal channel ($r < 0.26$ [d.f. 11] $p > 0.3$).

Due to the NVPT showing no relationship with daytime waking EEG it is thought the other tests would not demonstrate a relationship, due to the NVPT being the most sensitive to relative EEG power in the previous chapter.

4.4 RESULTS – Experiment 2

The waking EEG results, although demonstrate a relationship to delta sleep at night, fail to show any associations to neuropsychological test performance Given that the aim is to investigate possible links between the wake EEG and neuropsychological test performance, this will be explored further The rationale behind the hypothesis that such an association may exist is that:

- Delta sleep EEG is associated with PFC performance as shown in the previous chapter.
- The PFC has a faster frequency (higher metabolism) during the day and slower frequency (lower metabolism) during SWS: If the slow waves are reflective of PFC performance due to a need for recovery then are the faster waves during the day also reflective given the relationship between the fast and slow frequencies (and/or high/low metabolism)
- Previous studies have shown a link between waking EEG and task performance (See Introduction 1.10.1).

It is argued that the EEG data from Experiment 1 are difficult to analyse given the amount of noise in the data. Daytime waking EEG recordings are problematic due to the presence of artefact caused by blinking, sweating etc especially on the frontal channels. Therefore, a secondary experiment was carried out to assess the

waking EEG under optimum conditions whereby participants are classified as 'awake' but are quiet and relaxed with minimal sensory input and a reduced amount of artefact This period is the pre-sleep period

All participant data is the same as that presented for Experiment 1; Only the independent variable, wake EEG, is different in that it is recorded after lights out but prior to eye rolling associated to drowsiness.

4.4.1 Sample Information

The sample of the time taken varied between participants but criteria of a minimum of 12 clean epochs (1 minute) was adhered to for all participants. The mean sample taken for the group and time before sleep onset can be seen in Table 4.4.

Table 4.4: EEG Sample Information for pre-sleep wake EEG

		Sample Taken		Time to Sleep Onset	
		Minutes	Epochs	Minutes	Epochs
Old	*Mean*	4 24	50 83	22 75	273.00
	St. Dev.	1.58	18 96	15.73	188 78

4.4.2 Pre-Sleep Theta Activity – Relation to the Wake EEG

Due to the study by Ehlers et al and the problem of artefact in the waking EEG, the study aimed to assess waking EEG whilst still alert, and possibly 'thinking' when external stimuli is minimal. Therefore, comparisons were made between daytime alert wake EEG and pre-sleep wake EEG to assess if theta (4-8Hz analysed in 1Hz bins) was evident prior to sleep onset due to increased thinking

For the four frequency bins, all (bar 4-5Hz) demonstrated high correlations to daytime EEG ($r < 0\,87$ [d f 11] $p < 0.05$) As 7-8Hz was shown to be the frequency bin of interest in Experiment 1, and also is less associated with sleepiness than frequencies 4-7Hz, this shall be used in the comparison to neuropsychological test performance and delta sleep The left frontal channel will

be assessed primarily before the rest of the quadrants as it is argued that any links will be evident here.

7-8Hz Activity

Given that an older age group with a 15 year age range was being used it was thought necessary to control for age A correlation showed that although the left and right frontal areas were not significantly related to age (left: r = -0 42, p = 0.16; Right. r = -0.09, p = 0.7), the parietal areas were significantly related to age (Left: r = -0.57, p = 0 05; Right r = -0 67, p = 0 018) Therefore, age was partialled out of all correlation statistics involving wake EEG

The relationship between 7-8Hz activity during the two wake conditions (daytime and pre-sleep) was compared for all four quadrants: It was found that both frontal channels exhibited an association, especially the left frontal (r = 0.72 [d f. 11] p < 0 008) which remained significant after the partialling out of age (r = 0 65 [d f. 9] p = 0 03) Although the right frontal was significant (r = 0 65 [d f 11] p = 0.02), the data did demonstrate an outlier, which when removed caused the relationship to be insignificant (p > 0 1). The parietal channels did not show a relationship between daytime 7-8Hz activity and pre-sleep 7-8Hz activity (r < 0.47 [d f.11] p > 0 1) The only relationship in the left frontal channel is shown in Figure 4.5.

This graph shows the strength of the relationship between 7-8Hz activity during alert thinking with that taken during the pre-sleep period. As seen, those who exhibit greater levels of 7-8Hz activity during a controlled thinking condition also show greater levels of 7-8Hz activity after "lights out" possibly due to enhanced thinking during this time. As these recordings took place on separate days, it suggests an underlying commonality in the production of this activity.

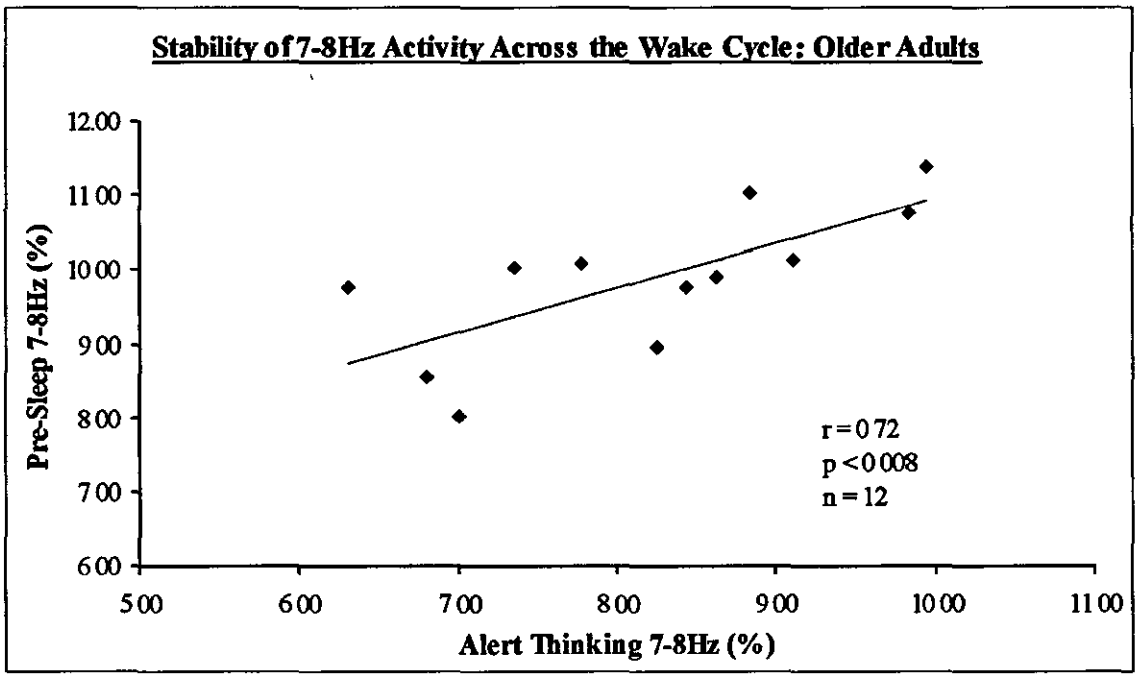


Figure 4.5: The relationship between 7-8Hz activity during the daytime and 7-8Hz activity during the pre-sleep period in the left frontal channel.

4.4.3 Pre-Sleep 7-8Hz Activity – Relation to Low Frequency Delta

It was found that pre-sleep 7-8Hz activity was significantly associated with delta activity (0.5-1Hz) during the first NREM period ($r = 0.81$ [d.f. 11] $p < 0.001$) in the left frontal channel. This remained significant after partialling out age ($r = 0.77$ [d.f.9] $p = 0.005$). Delta activity was not associated with any other frequency bin in the theta (4-7Hz) range ($r < 0.39$ [d.f. 11] $p > 0.1$). This relationship between low frequency delta and pre-sleep 7-8Hz activity in the left frontal region prior to sleep onset, during the settling down period, is shown in Figure 4.6.

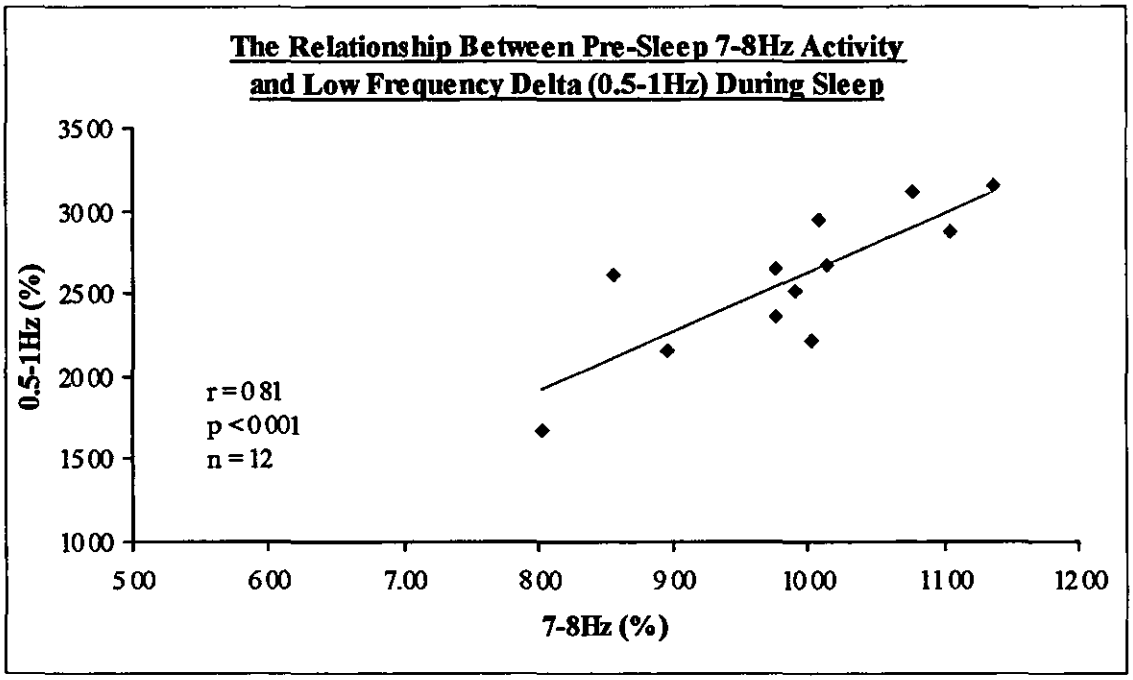


Figure 4.6: The Relationship between 7-8Hz activity prior to sleep onset (at settling down) and delta sleep (0.5-1Hz) in the left frontal region during the first NREM Period in older adults.

The relationship between low frequency delta and pre-sleep 7-8Hz activity was not related in the right frontal channel nor left parietal channel ($r<0.35$ $p > 0.1$) but, surprisingly, was significantly related in the right parietal channel ($r = 0.46$, $p = 0.04$), however, this was not significant after age was partialled out ($r = 0.54$ [d.f.9] $p = 0.08$)

4.4.4 Pre-Sleep 7-8Hz Activity Vs Neuropsychological Test Performance

It was found that pre-sleep activity 7-8Hz was significantly related to performance on the NVPT for both the left frontal ($r = -0.65$ [d f. 11] $p = 0.03$) and the right frontal ($r = -0.64$ [d.f. 11] $p < 0.03$) Interestingly, both these correlations became stronger when partialled out for age, especially the left frontal association (left: $r = -0.75$, $p < 0.007$; Right: $r = -0.65$, $p = 0.03$). However, neither parietal channel demonstrated this relationship ($r< -0.36$, $p > 0.1$)

Although the WCST and NVPT were significantly related ($r = -0.65$, $p < 0.02$), there were no significant correlations between performance on the WCST and 7-8Hz activity in any quadrant ($r < -0.35$, $p > 0.2$) Although there were only 8

participants who undertook the verbal fluency task (due to controlling for education) a correlation between performance and 7-8Hz activity was performed, However, this also showed no relationship existed for any quadrant ($r < 0.47$, $p > 0.2$).

4.4.5 Expansion of the Pre-Sleep Database

Given that the pre-sleep wake EEG shows stronger associations with the sleep EEG, in comparison to those with the daytime wake EEG, it is thought that this period of wake EEG is preferential especially when considering the reduced problem of artefact and the lack of external stimuli present. The analysis on the pre-sleep period has only encompassed twelve participants since the two wake conditions were being compared and it was important to have a repeated measures design. The pre-sleep period will now be compared to low frequency delta and the neuropsychological tests using twenty participants to see if the associations are still apparent with increased subjects which is thought to give more reliable results regarding any associations.

Sample Information

Twenty participants (10 female; 10 male) with an age range of 61-75years (mean· 67 6years; SD· 3.3years) were used. Sample information is as shown in Table 4 5

Table 4.5: EEG Sample Information for pre-sleep wake EEG in twenty participants.

		Sample Taken		Time to Sleep Onset	
		Minutes	Epochs	Minutes	Epochs
Old	*Mean*	4 43	56 65	31 09	373 05
	St. Dev.	2.14	25 63	27 51	330.16

The use of twenty participants was considered more robust and the sample information shows that there was little difference between the use of twelve versus twenty participants in terms of both sample taken and also time before sleep onset. This was confirmed with a repeated measures t-test which showed no difference in the sample taken ($t = -0.68$ [d.f. 30] $p > 0.1$)

In these 20 participants, it was established whether 7-8Hz activity was related to age. This was found to be insignificant for both frontal channels ($r < -0.36$, $p > 0.1$) but remained significant for both parietal channels (Left: $r = -0.50$, $p < 0.03$, Right: $r = -0.51$, $p < 0.03$). However, when looking at the graphical depiction of the left frontal 7-8Hz activity and age association (See Figure 4.7) this indicates a possible relationship if it were not for two probable outliers.

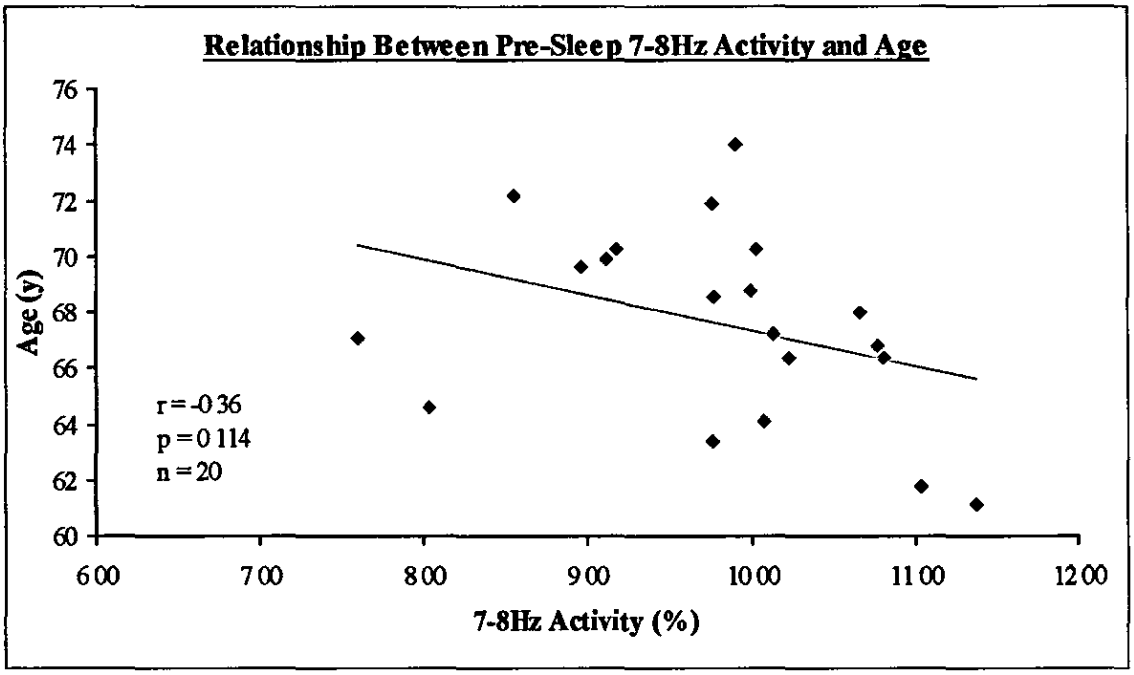


Figure 4.7: Relationship between 7-8Hz Activity in the left frontal channel and age. Two datapoints suggest a high leverage.

As two points on the left hand side of the graph suggest they may be rendering an association insignificant, the data was checked for leverage Results revealed that both points carried high leverage values in that they both exceeded 0.2. Therefore, with these points removed from this analysis the correlation was significant ($r = -0.68$, $p = 0.02$) as shown in Figure 4.8. However, the correlation to the right frontal remained insignificant even when accounting for points of high leverage.

The relationship between 7-8Hz activity and age (for all quadrants) demonstrates the importance of partialling out age from correlations to ensure any significant correlations are not a factor of an underlying variable (i e. age).

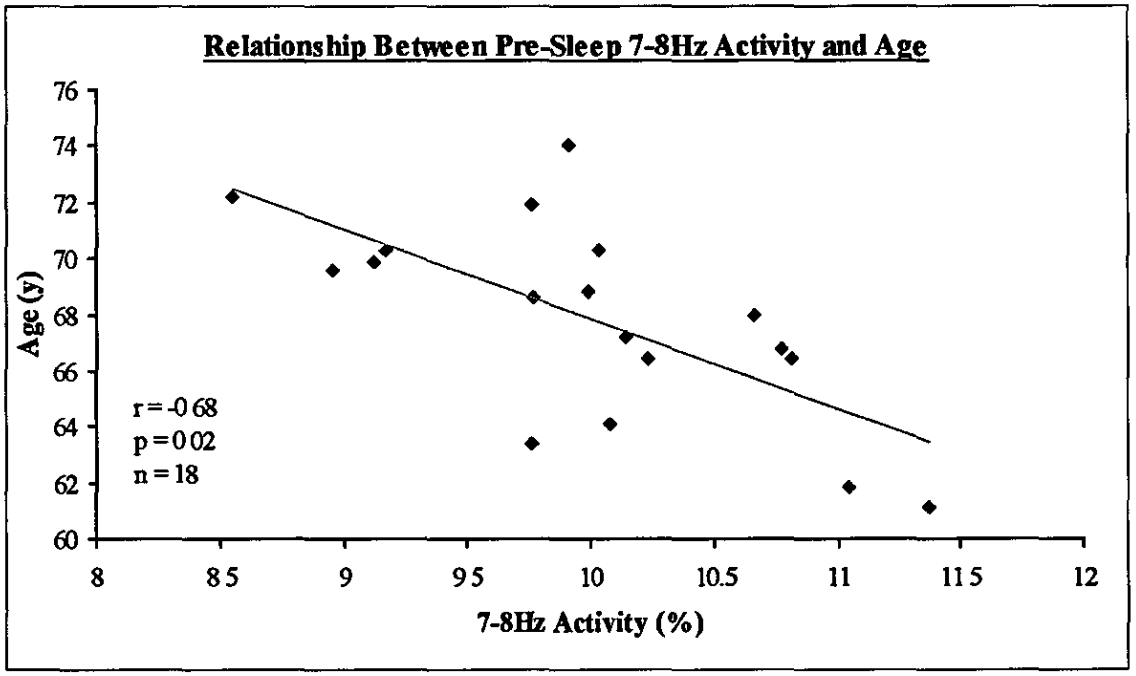


Figure 4.8: Relationship between 7-8Hz Activity in the left frontal channel and age. Correction of high leverage points.

7-8Hz Versus Low Frequency Delta

For twelve participants the relationship between pre-sleep theta and delta sleep EEG from the left frontal region was strongly significant as seen in Figure 4 9.

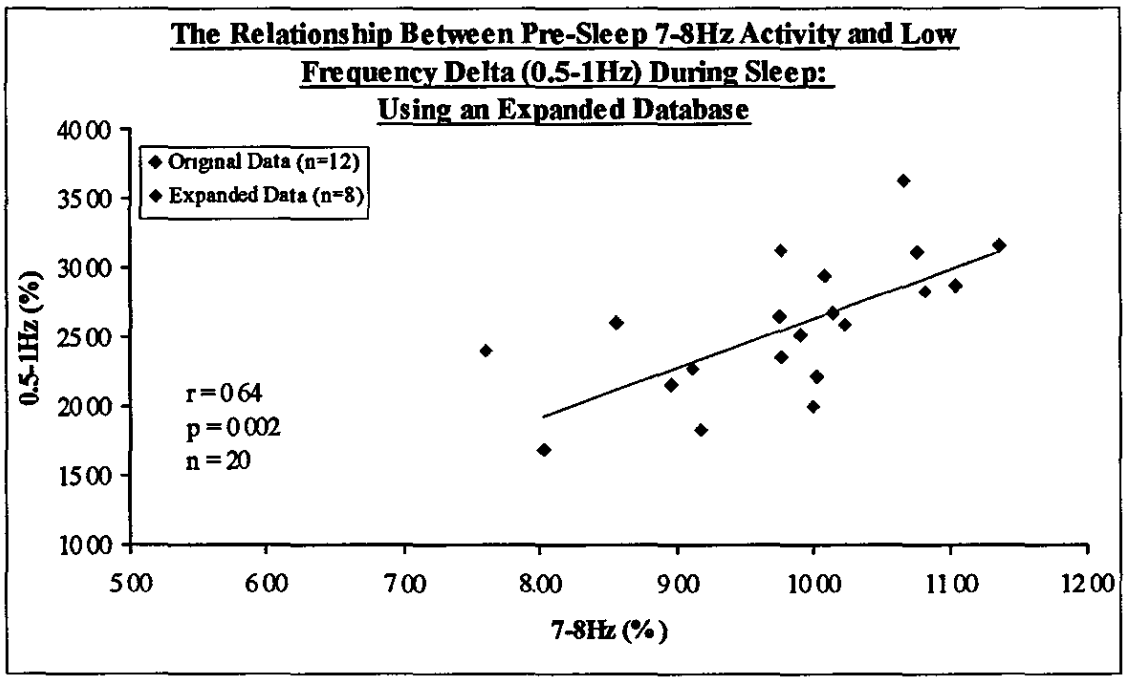


Figure 4.9: The Relationship between 7-8Hz activity prior to sleep onset and delta sleep (0.5-1Hz) during the first NREM Period in older adults. The use of twenty participants is considered more robust and further demonstrates the association between the two indices, *(the original 12 are shown as dark grey and the expanded 8 shown in light grey).*

The graph shows how the extra 8 subjects fit into the existing database. As seen, the use of twenty participants retains the strong significance although the correlation coefficient is reduced. This correlation remains significant after the partialling out of age ($r = 0.60$, $p = 0.007$). Interestingly, this relationship was not evident in any of the other quadrants, with or without age partialled out ($r < 0\ 37$, $p > 0\ 1$).

7-8Hz Activity Versus Neuropsychological Test Performance

WCST

It was found that performance on the WCST was not related with pre-sleep theta activity ($r = -0\ 38$ [d f. 19] $p > 0\ 1$) from the left frontal derivation even with an increased participant number. This relationship was close to significance for the right frontal ($r = -0\ 43$ [d f.19] $p = 0\ 057$), whereas for the left and right parietal areas, there were no associations ($r < -0.15$, $p > 0\ 5$)

NVPT

The relationship between relative pre-sleep 7-8Hz activity and NVPT was significant for both frontal channels: left frontal ($r = -0\ 70$ [d f. 19] $p = 0\ 0005$) and right frontal ($r = -0\ 67$ [d f 19] $p = 0.001$), both gaining increased significance after age had been partialled out (Left: $r = -0.77$, $p < 0\ 0005$; Right: $r = -0.68$, $p = 0.001$). Figure 4 10 shows the correlations between 7-8Hz activity in the left frontal region and NVPT. Neither of the parietal channels demonstrated a trend ($r < -0\ 33$, $p > 0\ 1$) even with age partialled out ($r < -0.40$, $p > 0.05$).

This correlation between NVPT and pre-sleep theta in the left frontal region also remains significant when partialling out RT ($r = -0\ 71$, $p < 0\ 001$) demonstrating that this relationship is not at the behest of global slowing.

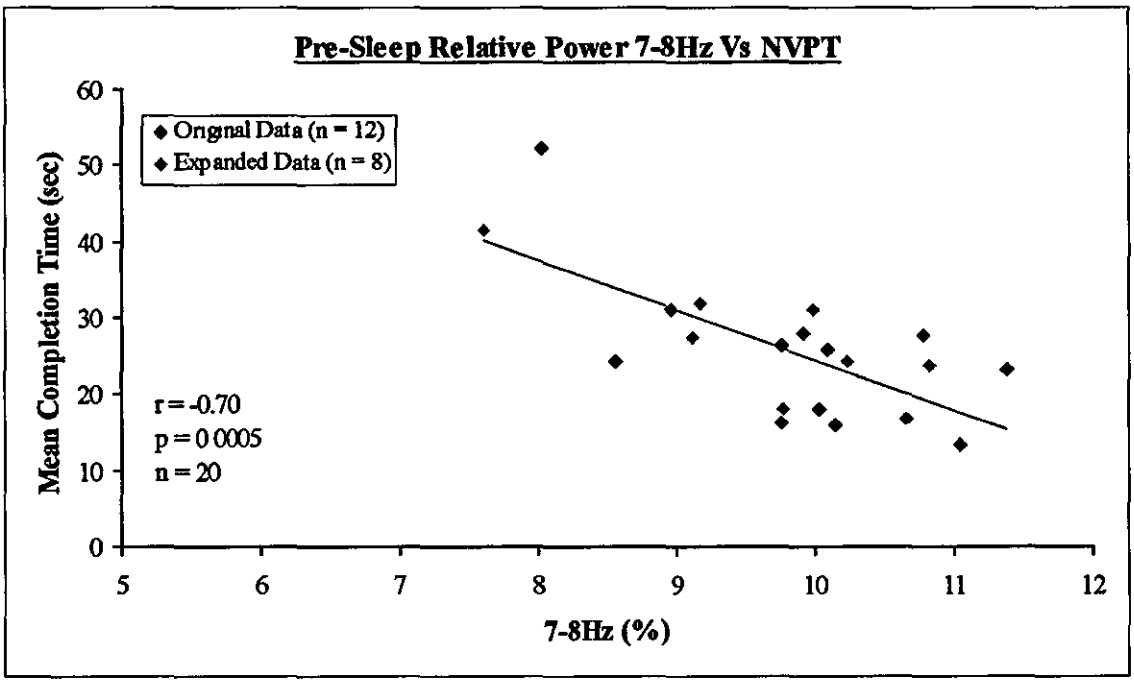


Figure 4.10: The relationship between relative power 7-8Hz in the left frontal channel and performance on the NVPT in older adults ***(the original 12 are shown as dark grey and the expanded 8 shown in light grey).***

Although it would appear that this graph contains two outliers, possibly holding the correlation, a boxplot of the data (See Figure 4.11) confirms that neither of these two points are outliers and thus removal from the database is not supported.

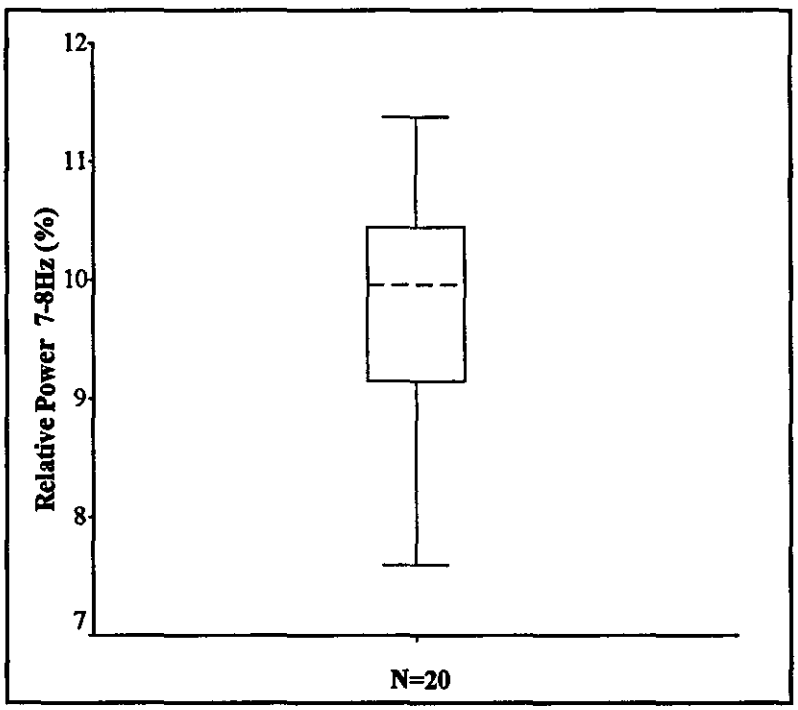


Figure 4.11: A box plot to show the distribution of the mean completion time on the NVPT for the older group.

VERBAL FLUENCY & NON-SPECIFIC TASKS

There was no relationship between verbal fluency and 7-8Hz activity for any quadrant ($r < 0.30$ [d.f. 9] $p > 0.1$). However, reaction time was associated with activity in the left ($r = -0.46$, $p = 0.039$) and right ($r = -0.47$, $p = 0.035$) parietal regions, but not frontal regions ($r < -0.35$, $p > 0.1$). There was no relationship between IQ and EEG from any quadrant ($r < 0.18$ [d.f. 17] $p > 0.4$).

4.4.6 7-8Hz Activity – A 'Sleepy' EEG?

To determine whether this particular activity (7-8Hz) is simply indicative of sleepiness, a spectral analysis over the range 3-11Hz was carried out for two separate samples: (i) The pre-sleep period discussed – Three minutes after lights out when the EMG becomes relaxed indicating 'settling down' but prior to signs of drowsiness[5] indicated by eye rolling; (ii) Three minutes of artefact free EEG immediately before the onset of stage 1 sleep (Rechtschaffen & Kales, 1968). The comparison of power within each frequency bin is evident in figure 4.12.

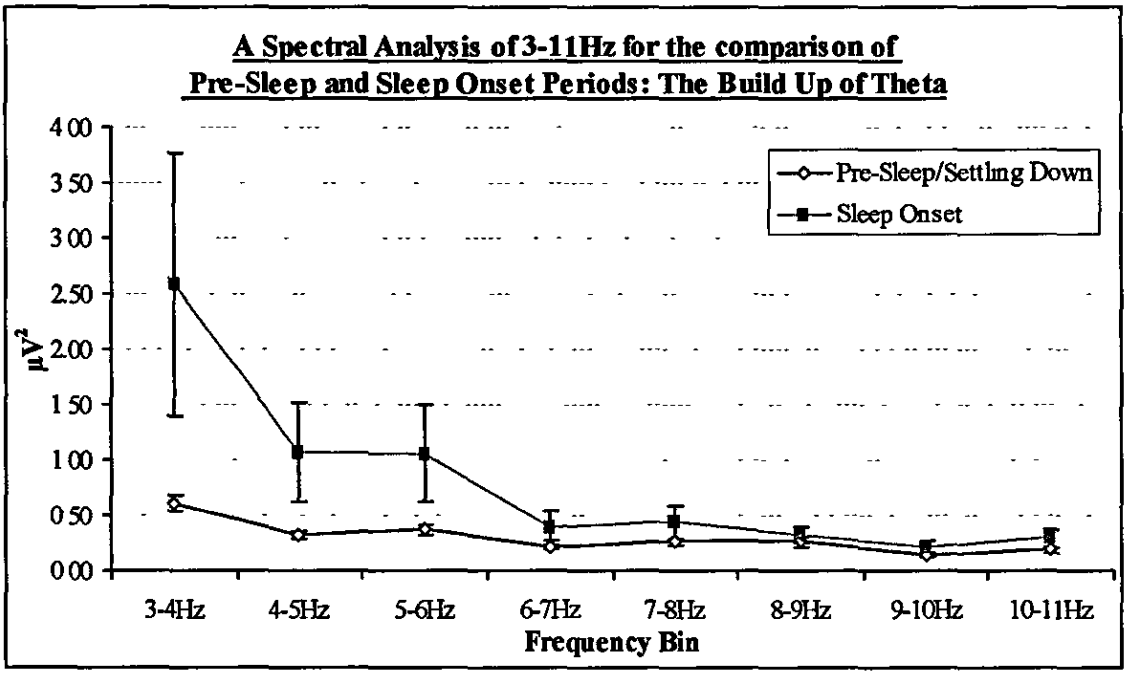


Figure 4.12: Spectral analyses of 3-11Hz power for two conditions: A clean period of EEG taken after lights out but prior to drowsiness and a period of clean EEG taken immediately before sleep onset.

[5] Although drowsiness maybe evident here, this was too low to be picked up by eye movements and/or KSS responses.

As seen from Figure 4 12, theta power that is indicative of sleepiness (that is immediately prior to sleep onset) is associated with the lower theta (3-6Hz) range, not 7-8Hz and provides further evidence that this is not en effect of sleepiness.

4.5 DISCUSSION

The findings show that waking 7-8Hz activity, during both alert 'thinking' conditions and pre-sleep conditions is associated with low frequency delta during the first NREM period Pre-sleep 7-8Hz activity was also shown to be associated with performance on the NVPT, the relationship being specific to the left frontal region The pre-sleep condition was considered a more reliable portion of wake EEG given a reduction of artefact and a lack of external stimuli. 7-8Hz activity generated after "lights out" was thought to reflect thinking given that it was strongly associated with daytime thinking conditions and also participants reported thinking after the lights had been turned out.. Therefore, 7-8Hz activity during the pre-sleep period, reflective of thinking, was associated with both low frequency delta (recovery sleep) and PFC performance. These relationships were unique to the left frontal PFC, which is known to have a higher metabolism during the day, and also lower during the night reflective of an increased recovery state. This provides support for the previous chapter that suggests a localised recovery function of sleep predisposed toward the low frequency delta range that was specific to the left frontal region.

4.5.1 Theta as reflective of increased thinking

The Issue of Sleepiness

Theta activity has consistently been linked to feelings of drowsiness (e g Cajochen et al., 1995). However, in this chapter the interest lay in the thinking properties also associated with theta activity (e g. Ramos et al., 1993; Jensen et al., 1993) whilst controlling for sleepiness. Experiment 1 assessed waking EEG in a controlled, laboratory setting. Although subjective sleepiness increased over the duration of the trial it was shown that KSS scores remained below 7 "Sleepy, with no effort to keep awake". This point was shown, in a study to validate the KSS, to be associated with changes in the EEG reflecting sleepiness (Åkerstedt & Gillberg

(1990), therefore, the KSS was considered to be a sensitive indicator of sleepiness. In addition to this, the online recording of the EEG and EOG made early identification of sleepiness possible, with the trial terminating and any remaining conditions being excluded from analysis should signs of sleepiness, either through the EEG/EOG and/or high KSS scores becoming apparent.

The KSS was acquired at the end of each condition and as participants had their eyes shut for 3minutes, KSS scores were considered higher than they might have been preceding the conditions after instructions had been given. Therefore, KSS scores were probably maximal, and yet still did not reflect high levels of sleepiness. The maintenance of alertness was considered in the design of the experiment and each condition was kept both short and interesting and the room was air-conditioned to give a standard air temperature that would not induce feelings of sleepiness. The timing of EEG was during the late morning, and as KSS scores given over three days show, this was the time of optimum alertness for older people. Sleep diaries prior to waking EEG ensured a normal nights sleep prior to the trial. In addition to this, the partialling out of trait sleepiness (ESS) only increased wake and sleep EEG associations, and accounting for time on task also revealed that the correlation was evident for the first and second half of the task If this effect was due to sleepiness caused by time on task, it would be expected that the second half would show a higher correlation which was not deemed to be the case here.

The issue of sleepiness was adequately dealt with in Experiment 1 with methodological considerations, such as time of day and KSS scores. Although Experiment 2 overcame many of the pitfalls of Experiment 1, namely the reduction of artefact, it did highlight the issue the sleepiness. Of course, it is accepted that sleepiness is higher during pre-sleep periods than late morning recordings, however, it is still thought that sleepiness was not highly influential given that the period taken was after "lights out" but before any sign of drowsiness Additionally, the 7-8Hz activity discussed was not thought to be associated with increasing sleepiness spectral analyses showed that increasing sleepiness was associated with activity in the lower theta range (3-6Hz). Nevertheless, this period should be studied with care, and it is imperative that any

recordings are taken prior to drowsiness, since the rolling eye movements can affect the EEG, especially those in frontal derivations (Teece, 1972)

The period of analysis taken in Experiment 2 was between lights out and drowsiness. This was not only to avoid artefact in the EEG during drowsiness but also to avoid the hypnagogic[6] period which is usually linked to drowsiness/sleep onset/light sleep (c.f. Schacter, 1976). Although sleep onset is linked to hypnagogia, recent findings have indicated that the sleep onset marker is not until Stage 2 sleep (e.g. De Gennaro et al , 2001a) whereas hypnagogia does not start until stage 1 sleep (Morikawa et al., 1997). Hori et al. (1994) identified nine stages of hypnagogic activity; the frontal activity taken during this study (7-8Hz) is compatible with their stages 1 and 2, which they mark as 'wake'

Evidence of Thinking

As the literature suggests that increased levels of theta are associated with thinking, it was thought that theta would therefore increase during 'thinking' conditions compared to the eyes closed condition. This was not found to be the case The stipulation of an individual being involved in thought processes can only be introspective, it can never be absolutely stated that someone is 'thinking', although it is thought given the instruction that most participants would participate in the given exercise. However, for eyes closed condition, even though asked to "clear their mind of any thought", this is deemed much more difficult to carry out, especially under novel experimental conditions, and thus it is unlikely that this was the case Therefore, this is critical of studies that have compared baseline eyes closed conditions to 'thinking' scenarios, due to the introspection involved, and also the likelihood of someone 'thinking' during eyes closed 'free mind' conditions.

Although it can be argued the extent to which participants were thinking, during the daytime the thinking was controlled (if participants adhered to instructions), and during the night it is proposed that people normally think after lights out (Also, both waking conditions were strongly associated in 7-8Hz activity). A

follow up telephone interview was carried out with a selection of participants to find out what they thought about after turning the lights out. All those interviewed gave answers, with no one reporting not thinking at all. Answers included:

- Visually thinking of grandchildren, family etc.
- Visually thinking of what they had done during the day
- Visually think of what they were doing the following day
- Think of falling asleep – focus on body extremities
- Visually think of happy scenario/role play in mind

4.5.2 Associations Between the Sleep and Wake EEG

It was shown that 7-8Hz activity was strongly related to the sleep EEG when taken during waking daytime recordings and also the pre-sleep period The sleep EEG sample used was that as presented in Chapter 3 and was thought to reflect greater cerebral recovery due to its frontal dominance, uniqueness to the left frontal region, and relation to task performance The relationship between waking EEG and the sleep EEG is strong and supports findings of previous studies that have linked the wake and sleep EEG (Finelli et al., 2000, Ehlers et al., 1998). Finelli et al. (2000) showed that an increase in daytime theta (5-8Hz) was related to an increase in night-time SWS (0 5-4.5Hz). However, the EEG recording was taken over 42hours of prolonged wakefulness, thus allowing the researchers to comment that the increase in theta was homeostatic reflecting sleep propensity. The 7-8Hz activity in the current study does not reflect sleepiness, and is not proposed to be a marker of sleep propensity, but a marker of thinking/performance, and that increased thinking (7-8Hz) is reflected in the increased need for recovery sleep (low frequency delta).

Ehlers et al. (1998) showed that the spectral signature of an individual was stable across the waking and sleeping EEG for all the frequency bands, the strongest association being for theta and beta frequencies. As with Ehlers et al , Suetsugi et

[6] A period leading up to sleep onset that is drowsy and contains lots of visual imagery (e g. Tanaka et al , 1996, Hori et al , 1990)

al (2002) studied the relationship between wake and sleep EEG, performing comparisons within frequencies, and concluding delta activity during the daytime is related to delta at night, as was theta, alpha and beta with the respective same frequencies The studies do not report on correlations across frequencies, such as theta versus delta. The findings presented here argues that the scientific rationale behind the use of night-time delta and daytime theta is strong, since brainwork during the day (reflected by frontal theta) would be related to recovery sleep at night (reflected by low frequency delta) The lack of theta-delta findings for Ehlers et al. may be based on the fact they only took EEG from central derivations, and that this relationship between 'thinking' activity and 'recovery' activity is localised to the frontal parts of the brain as the current study would suggest.

Ehlers et al. (1998) also fail to mention how close the wake sample was to sleep onset. If this sample was taken too close to sleep onset, such as after the onset of drowsiness, the theta and delta values are likely to be increased and thus a product of sleepiness. This was controlled in the current study, and therefore the issue of sleepiness/drowsiness was always given a priority thus avoiding findings being attributed to the homeostatic need for sleep Although Ehlers et al. never made an attempt to address the findings with reference to the recovery properties associated with delta sleep but focussed their conclusions towards an argument for a homeostatic drive for sleep, as Finelli et al. (2000) did, they did provided a valuable platform for which the current study was based.

The localisation of the relationship between waking EEG and low frequency delta adds more evidence to the debate of a localised function of sleep, since the areas that tend to work hardest during the day (e g. Maquet et al., 1990) and those which are involved in sustained attention (Kolb & Wishaw, 1985) have more low frequency delta. The current study supports this in that higher amounts of frontal theta, associated with thinking (e g. Smith et al , 1999) were related to higher amounts of low frequency delta, which is thought to be restorative (e g. Werth et al., 1996, 1997). This relationship was localised to the left PFC, thereby supporting the findings of Clark et al. (1998) who found higher levels of daytime CMR were related to SWS in the left PFC. Therefore, the current study and that of

Clark et al , both propose that daytime 'thinking' is associated with night-time delta sleep (recovery) in the left PFC

Although the associations between sleep and wake EEG were predominately localised to the left PFC, there was an association between pre-sleep wake EEG and delta activity (0.5-1Hz) in the right parietal region This finding does not support the main argument that daytime performance and night-time delta sleep is linked in the PFC due to the localised enhanced workload/recovery of the PFC. Most studies concerning the waking and sleeping PFC utilise younger adults, whereas older adults may exhibit changes in this relationship due to the age-related changes in the PFC. An interesting paper by Drummond et al (2000) may give insight here Drummond et al. reasoned that through sleep deprivation the PFC, as it becomes impaired, would be less activated. However, the authors found that not only did the PFC become more activated, in an apparently compensatory effort, but also that it recruited other areas namely the right parietal to further compensate for its decreasing function. Although this is shown through sleep deprivation, it might be argued that with healthy ageing, the aged PFC recruits other brain regions as it does during prolonged wakefulness due to a similar reduction in metabolism in the PFC for both sleep deprivation (e g. Thomas et al , 2000) and healthy ageing (e g. Martin et al , 1991). Therefore, if this is the case, as the right parietal was working harder during the day than normal, in an effort to compensate for the PFC, it was showing a relationship with low frequency delta at night in the right parietal region. This is, of course, at present speculative.

Even if this speculative idea was to be the case, there was no relationship between EEG activity in the right parietal region and neuropsychological performance This lack of finding may be explained by the fact that the neuropsychological performance is not specific to the right parietal area. Even if the right parietal region had been activated during task completion, due to reasons above regarding compensation, the effect would not have been strong enough to relate to the EEG The ability to use the sleep EEG to predict task performance relies on the sensitivity of the task in question as seen in Chapter 3 as the sleep EEG was associated only to tasks that predominantly activate the PFC.

Of course the issue of age effects on varying recruitment sites cannot be addressed with such a small age range, this is merely an observation that may describe the relationship with the right parietal region Drummond et al 's method would be interesting to assess the extent to which an older person recruits other brain regions during task completion However, this would have to be a longitudinal study, and one that would be extremely hard to control, in addition to the large time scale involved.

4.5.3 7-8Hz Activity Versus Neuropsychological Test Performance

Daytime wake EEG showed no relation to task performance, whereas activity 7-8Hz during the pre-sleep period showed strong relations to the NVPT. The lack of finding during daytime levels may be that the older adults used in this study displayed less theta during 'thinking' conditions similarly to that found by McEvoy et al. (2001) that older adults (mean 69years) displayed less theta on tasks of a frontal nature. Nevertheless, the use of the pre-sleep period was considered more robust in the association to performance due to:

- A lack of artefact in the EEG
- A lack of external stimuli
- An increased number of participants (although still related for reduced)
- Enhanced theta activity prior to sleep onset

The finding that the NVPT was significantly associated with pre-sleep 7-8Hz activity during the day would support the findings of Çiçek & Nalçaci (2001) who found the low alpha rhythm (8 6-10.2Hz) correlated to performance on the WCST. Both Çiçek & Nalçaci and the current study's findings show that this relationship is local to the left frontal region, which is interesting considering tasks utilised by both studies are frontally activating tasks. Both studies also show that the waking EEG is taken at a separate time, and thus reflects an underlying process common to both EEG generation and task performance within the frontal regions, and thus these associations are due to a trait in the EEG. Tucker et al. (1985) also localised their changes in theta during task performance to the left anterior hemisphere taken during a word fluency task. This study had taken theta during a thinking task

and so this may reflect localised functional changes within the left anterior region, thus explaining its uniqueness to this area Whereas Çiçek & Nalçaci's study provided evidence for the EEG in predicting performance, Tucker et al.'s provided evidence that the EEG changes during task performance, and that interestingly, these changes are to the left frontal area

7-8Hz activity that was associated with NVPT in this study was slightly lower than that proposed by Çiçek & Nalçaci (2001), that is 8 6-10 2Hz. However, the extent to which these two findings are the same is questioned· The current study suspects the rhythm identified may be that of the kappa rhythm which ranges from 7-12Hz (Mundy-Castle, 1957) and is linked to 'thinking'. The authors also found that this relationship was also evident in the EEG when taken separately from recordings, similarly to the current study suggesting an underlying commonality. Therefore, the activity identified here (7-8Hz) and that proposed by Çiçek & Nalçaci (8.6-10 2Hz) may in fact *both* be the same rhythm, that is the kappa rhythm

The findings presented here, and also that of Çiçek & Nalçaci, may both be explained, in part, by the findings of Clark et al (1998) who found that daytime cerebral blood flow was related to SWS at night Clark et al 's findings suggest that daytime brainwork is related to delta sleep at night. This is significant to the findings in this study since it is thought brain work in the form of thinking, signified by theta (kappa) activity, is not only related to delta sleep, it is also associated with PFC performance.

However, associations between PFC performance and pre-sleep theta were only evident for the NVPT. The WCST is not as sensitive as the NVPT in identifying PFC function, especially given the reduced associations in Chapter 3, and also the inconsistent findings from functional imaging studies that have thrown the task into disrepute for assessing PFC performance (e g Anderson et al , 1991) Although the Verbal Fluency is a task that is sensitive to PFC impairment given its activation of left frontal regions (e g. Frith et al., 1991), the reduced amount of participants, due to having to control for educational attainment, may have affected the results here

4.5.4 The Effectiveness of the Methodology

The use of the waking EEG is an important concept to consider especially when assessing the validity of the EEG in assessing PFC performance. However, the recording of waking EEG can be problematic. Artefact is a common problem encountered during waking EEG recordings as emphasised in Experiment 1. Due to the use of front-polar electrodes; sweating, eye blinks, frowns etc can affect the activity picked up by the fronto-polar electrodes located on the forehead. Therefore, some conditions were not analysed due to noisy data thereby reducing the subject total, and making any relationship difficult to find.

Although twelve participants underwent a daytime waking EEG recording, three initial participants were replaced Of these three participants two displayed hippus[7], which was particularly evident on the frontal channels as they are sensitive to the muscle movements around the eye due to the amplification of the EEG. It has been suggested that 3 in 10 people would show hippus (Ukai et al , 1997), which is similar to this finding of 2 in 12. The origin of hippus is normally unknown, and although it has a frequency of around 0 2Hz, it can have a wider frequency spread Due to this and the idea that it can be associated with sleepiness (Ukai et al , 1997), these two subjects were removed from the study The final participant removed was a contact lens wearer, and as a result blinking was increased more than other subjects to the point where even eyes closed conditions resulted in blinks more than once in every five seconds, thus in every epoch. These are just some examples of the problems encountered during waking EEG recordings.

External sources may also affect the wake EEG; although someone is asked to take part in a thinking exercise, it is only introspection that allows us to make judgements of whether they actually took part in the conditions. Although the testing took part in a soundproof booth, some low frequency noises would still get through such as the loud banging of doors Also, there is a novelty concerned with the testing scenario, which has been shown to affect delta sleep, and therefore, the possibility remains that theta would also be affected given the relationship

[7] A rhythmic variation in the size of the pupil caused by a tremor in the iris (Bouma & Baghuis, 1971) that results in artefact across the EEG.

between these two variables, albeit that this is, as yet, unknown. A more natural setting without external stimuli, and during minimal noise and novelty is thought to be advantageous over the daytime laboratory methods employed It is argued that the pre-sleep period would evoke thought processes that would be more internally generated, and thus reflective of 'thinking'. Ehlers et al. took their waking recording at sleep onset, which is interesting given their findings that the wake EEG and sleep EEG are stable in terms of the spectral composite of the EEG. Therefore, Experiment 2 aimed to use this pre-sleep period in order to minimise the problems encountered with artefact in Experiment 1

The pre-sleep waking EEG was a useful marker of PFC performance, albeit not as reliable as the sleep EEG, Nevertheless, this period should be studied with care. It is imperative that any recordings are taken prior to drowsiness, since the rolling eye movements can affect the EEG, especially those in frontal derivations (Teece, 1972) Also, drowsiness will affect the EEG since theta is associated with sleepiness (Cajochen et al , 1995). For future waking EEG recordings, the use of the pre-sleep period is suggested, however, it should be ensured that the selected period is after 'lights out' but preceding any drowsiness signals, in particular, eye rolling. If this is adhered to then artefact from the eye movements and any associations to the hypnagogic period would be avoided, rendering the use of the pre-sleep as reliable

4.5.5 Future Work

The aim of the thesis is to investigate possible associations between neuropsychological test performance and the sleep and wake EEG; This has been carried out with a healthy, older group and it has been shown that the both the sleep and wake EEG show associations to neuropsychological test performance that are specific to the left PFC, possibly due to an underlying commonality This commonality may be concerned with age, in that as one ages the PFC becomes less efficient resulting in decreased performance and putative recovery based activities. The remainder of this thesis will therefore examine whether this relationship is only evident in older, healthy people who show more variance in PFC performance and delta/theta levels, or whether associations between

neuropsychological test performance and the sleep/wake EEG is common across young and older people alike.

4.6 CONCLUSIONS

Summary

Experiment 1

1) Theta during the trial was thought to be reflective of increased performance/attention and not sleepiness because.
   a) KSS Scores showed the waking EEG recording time was during a time of maximal alertness
   b) Tasks were of short duration and were interesting and novel.
   c) KSS and EEG/EOG throughout the trial remained alert, and if not, the trial was aborted
2) There was no relationship between neuropsychological test performance and daytime waking EEG
3) There was an association between low frequency delta sleep and waking 7-8Hz activity.
4) The methodology used was considered problematic as the EEG was prone to noise, and participant numbers were only kept maximal due to the integration of similar categories.

Experiment 2

5) The pre-sleep period was found to be artefact free and more reliable than laboratory recordings The EEG was clearly classified as 'wake' and was taken after "lights out" but before any signs of drowsiness.
6) Pre-sleep 7-8Hz activity was strongly associated with waking 7-8Hz activity even though recordings were taken on days separate to each other. It is argued that both are due to 'thinking' (kappa or frontal theta activity) since there is a strong correlation and also participants reported thinking after the lights had been turned out.
7) Pre-sleep 7-8Hz activity was associated with low frequency delta: This correlation was stronger than that found for the daytime theta activity. This finding that daytime 'thinking' is related to night-time delta sleep is consistent

with imaging studies related daytime 'brainwork' with night-time delta sleep (e g. Clark et al , 1998)

8) Pre-sleep 7-8Hz activity was associated with NVPT - This was unique to the left PFC, and suggests 7-8Hz activity is a possible marker of recovery need.
9) There was no association between pre-sleep 7-8Hz activity and the WCST which was proposed to be due to the reduced specificity of the WCST, and also the verbal fluency, proposed to be due to low sample sizes.
10) The 7-8Hz activity identified as important in its relationship with low frequency delta was argued to NOT reflect sleepiness, but that sleepiness was associated with activity in the lower theta range (3-6Hz)
11) The use of the pre-sleep period (Between "lights out" and prior to drowsiness) for a sample of waking EEG is considered more reliable than laboratory waking EEG recordings due to a lack of artefact and external stimuli, but not as valid as the sleep EEG in its association to PFC performance.

Conclusion

It has been shown that 7-8Hz activity during the day (possibly reflective of thinking) is related to recovery sleep at night and is localised to the left frontal region However, the methodology was not considered robust due to the presence of artefact in the EEG and so the waking EEG was recording after "lights out" but before any signs of drowsiness. 7-8Hz activity during this time was strongly related to that found during daytime thinking conditions, and thus possible reflects thinking, but was also associated with the sleep EEG This supports the argument of a localised function of sleep, since those areas active in putative thinking (frontal theta) display more recovery sleep (SWA) at night due to an underlying process (not direct since different days) This finding was specific to the left frontal region which has previously been shown to work harder during the day and also have more recovery sleep at night. Pre-sleep 7-8Hz activity was related to performance on the NVPT, a task highly dependent on the integration of the PFC. Therefore, the wake EEG could also be used to predict PFC performance, albeit not as strong as the sleep EEG.

The use of healthy, older participants is considered important for this study since, firstly they show variance in delta levels and PFC performance, and secondly

findings are often different to those concluded with the use of younger adults Although this is not a comparison of age, the extent to which the sleep EEG and wake EEG can be used to assess PFC in younger adults has not been studied. The remainder of the thesis will therefore aim to investigate possible associations between the (sleep and wake) EEG and neuropsychological test performance in young adults to establish whether these associations are evident for older and younger adults alike, and not simply at the behest of age.

This Chapter was partly financially supported by
The Wellcome Trust Foundation

The work as described in this chapter is to be published as:

Anderson, C. & Horne, J.A. (2003) Frontal Cortical EEG Links Between Waking "Thinking" and Sleep "Recovery" Activities in Older People. *Sleep.* Under Review.

CHAPTER 5

SLEEP EEG & NEUROPSYCHOLOGICAL TEST PERFORMANCE IN YOUNGER PEOPLE

5.1 INTRODUCTION

The work described in this thesis has shown that the sleep and wake EEG are both associated with performance; this relationship being unique to frontal areas. However, these associations were made using an older population who show both reductions in delta activity at night (e g. Bliwise, 1993) and PFC performance (e g West, 1996). Therefore, the remainder of this thesis aims to establish whether these associations are found in a younger population, and thus, whether the association between EEG and performance are unique to the PFC or unique to ageing.

Chapter 3 described how a reduction in low frequency delta during the first NREM period reflected a reduction in PFC performance as measured by the WCST, a non-verbal planning task and verbal fluency. It was argued that low frequency delta was indicative of enhanced recovery since this was frontally dominant, and those who performed less efficiently on PFC tasks had less recovery sleep at night possibly due to the efficiency of the PFC The association between delta sleep and PFC performance is interesting, however, it is questioned whether this is due to the two elements of ageing as previously mentioned or whether delta in younger adults is also reflective of their PFC performance, and thus the association is found across ages but is specific to those areas that work harder during the day and are a focus for delta activity at night, that is, the PFC.

Much of sleep research has been concerned with younger adults, in particular sleep deprivation studies It has been shown that sleep loss in younger adults results in a similar deficit on PFC tasks as those seen in a 65 year old (Harrison et al., 2000) However, these older individuals were not sleep deprived since this study ensured all older people were normal, healthy 8h sleepers However, given the findings from the previous chapter it may be argued that older people are performing inefficiently on these tasks due to a loss of low frequency delta and/or an underlying effect of age causing both apparent age-related impairments. Causality of the association between PFC performance and delta sleep is not attributed, however, if a reduction of low frequency delta is affecting the ability to

use the PFC (or vice versa) then this relationship would be specific to the PFC, and thus should still be evident in a younger population

Although, sleep deprivation causes a PFC deficit (e g Harrison & Horne, 1997, 1998), the extent to which this is due to a loss of SWA (0.5-4 5Hz) or whether this is due to a loss of more specifically low frequency delta is questioned. The suggestion that sleep deprivation effects, namely PFC decrements, are possibly due to a loss of low frequency delta is due to previous findings linking low frequency delta with PFC performance, but also because of recent literature suggesting the delta range (0 5-4.5Hz) is not consistent in that slower (<2Hz) and faster frequencies (2-4.5Hz) are functionally distinct (e.g Benoit et al , 2000). The recent argument that <2Hz activity serves as enhanced recovery for the cerebrum has been debated by many researchers due to the frontal dominance of this activity (Werth et al , 1996); its increase in frontal areas during recovery sleep (Achermann et al., 2001; Ferrara et al., 2002) and the resistance of <2Hz activity to deprivation (Ferrara et al., 2002, Werth et al., 1996).

Research is now centring on low Frequency delta, especially that of <1Hz since Steriade et al. (1993b) proposed that <1Hz was generated by the cortex itself, and furthermore, this activity is prevalent in the PFC region (Steriade & Amzica, 1998). As an extension to these studies, the study described in Chapter 3 also highlights the importance of low frequency delta (<1Hz) and argues that this frequency is reflective of an enhanced recovery need for the PFC, and thus is associated with the performance of this region.

The relationship between low frequency delta and PFC performance has yet to be studied in younger adults. Studies that have looked at sleep and performance in younger people have tended to centre on actual sleep loss or sleep disturbance and the effect this has on subsequent behaviour (Pilcher & Huffcutt, 1996) Studies that have looked at neuropsychological test function have used either non-cortically specific recording sites, such as C4-A2 (Bliwise, 1989) or tests, such as Reaction Time (e g Crenshaw & Edinger, 1999, Edinger et al , 2000), which are not cortically specific. Recent studies utilising functional imaging during periods

of sleep loss also give insight into possible associations between recovery sleep and PFC performance in younger people

Functional imaging during sleep deprivation has confirmed the deterioration of the PFC during prolonged wakefulness. Balkin et al. (1998) demonstrated that the largest reductions in rCBR were in the PFC whereas Drummond et al. (2000) found, during task performance under sleep loss conditions, that the PFC increased its activation over baseline levels, which the authors argued was possibly due to an effort to overcome any decrements caused by prolonged wakefulness. There is much evidence relating the PFC to delta sleep during the night, and yet studies relating delta activity with waking PFC performance have not, as yet, been carried out.

Hayward et al. (1992) made an attempt to relate neuropsychological performance with sleep patterns, which was based on a weak rationale, since parameters such as total sleep time are expected to be associated with behavioural manifestations of sleepiness (Gillberg & Åkerstedt, 1994) and not to neuropsychological test performance. As one would expect, the findings yielded no significant results It is suggested that the area of interest is not sleep parameters such as TST, WASO etc, but that sleep analysis should be focussed on an analysis of the delta rhythm, or SWA, given its strong relation to the PFC and possibly neuropsychological test performance as discussed above.

5.1.1 Aims

Given that low frequency delta is related to PFC performance in healthy older people, the extent to which this was also applicable in a younger population was raised. In a younger population the PFC is most active during the day and is also a focus for low frequency activity (<2Hz) during the night. Although the younger population perform optimally well on PFC tasks, and the level of delta activity is at a level higher than that of older people, it is still thought that an association will be evident given the PFC-Delta links discussed The finding in a previous chapter (3), that low frequency delta and PFC performance are related, may be unique to ageing in that they are both caused by underlying ageing effects The use of a

younger population would therefore ascertain whether this relationship is consistent over age groups, in that it is specific to the PFC and reflective of general properties of low frequency delta and/or the function of the PFC This study will therefore assess performance of healthy young people on neuropsychological tests known to activate the PFC, and to assess the extent to which this performance is associated with spectral measures of sleep EEG, with a specific focus on Low Frequency Delta (<2Hz)

Research Questions

- Is the delta activity in the sleep EEG associated with neuropsychological test performance?
- Is Low Frequency delta important in the relationship between sleep EEG and performance?
- Are these relationships localised to the frontal regions?
- More specifically, are these relationships predisposed to the left PFC?
- Does any possible relationship give insight into the localised function of sleep?
- Is the EEG a useful tool in assessing neuropsychological test performance in younger people?
- Does this relationship differ to that found in the older age group, and if so how?

5.2 METHODOLOGY

Twelve right-handed participants (6male; 6female) with an age range of 19-23years (mean. 21.12years; SD: 0.10years) took part in the study All were normal, healthy sleepers as determined by sleep diaries and actimetry and did not suffer from extreme daytime sleepiness as determined by ESS and KSS. All participants were thoroughly screened, according to that described in Chapter 2, to ensure that they were:

i) Free from sleep problems or problems affecting their sleep.

ii) Non-Nappers (<2 times a month)

iii) Free from medication affecting the CNS

iv) Satisfactory in eye sight and hearing

All participants undertook both parts of the study: A neuropsychological test battery and two nights of sleep EEG recording.

Neuropsychological Tests

The neuropsychological tests used in the test battery were three tasks known to activate the PFC during completion:

- Non-Verbal Planning Task (NVPT)
- The Verbal Fluency Task
- The Temporal Memory Task

Two further tasks were used, they were:

- Reaction Time
- Cattell & Cattell Culture Fair Task (CCCF)

Sleep Recordings

Two nights of sleep EEG recordings took place on nights, 5-7 days apart, separate from neuropsychological testing, the first night being for adaptation purposes. The second recording night was used for analysis, with a focus on the first NREM period extending to the second NREM period if deemed necessary. EEG analysis will focus on the low frequency EEG (1Hz) before a wider analysis ranging from 0 5-4.5Hz will take place

As the older participants showed large night-to-night stability in the EEG measures employed, it was thought that the younger group would show greater stability given that it has been proposed that older people show a greater 'first night effect' (Webb & Campbell, 1979). The second night recordings were considered a robust reflection of 'normal' sleep EEG especially given that night-to-night stability of computer-measured frequencies is high (e g. Tan et al., 2000) even in an older age group (Tan et al , 2003)

Chapter 2 describes the procedures for the neuropsychological test battery and sleep EEG recordings.

Statistical Analyses

All statistical analyses are concerned with assessing the relationship between an independent variable (delta activity) and the dependent variables (neuropsychological test performance). Therefore, Pearson r correlation coefficients will be determined, with the use of partial correlation coefficients where applicable.

Any analysis concerning differences, such as female/male test scores, will use the (un)related t-test or the One-Way ANOVA for multiple variables The significance level is set at 5% unless otherwise stated.

In order to compare groups and/or databases for distribution, "box and whisker" plots will be used. The box plot consists of a lower "hinge" (25^{th} percentile) and an upper "hinge" (75^{th} Percentile), the centre of these being the median value. The "whiskers" of the plot represent the "fence" range of values that fall within 1.5 times the value between the appropriate hinge and the median. Any values falling outside of this range are represented by a marker (*) and are termed "outliers".

5.3 RESULTS

5.3.1 Participant Characteristics

Table 5.1 shows the participant characteristics. As seen, all are right-handed, have normal ESS scores (<10) and sleep for 8hours ± 1hours each night. All participants completed both parts of the study: Neuropsychological testing and Sleep EEG Assessment

Table 5.1: Characteristics of participants

	Sex	R/L Hand	Age	ESS Score	TST (hrs)
1	F	R	21 40	2	8 66
2	F	R	20 30	9	7 46
3	M	R	22 00	9	7.52
4	M	R	22.00	8	8 36
5	F	R	19.70	10	9 04
6	F	R	21.10	8	9.11
7	M	R	22.10	2	8 51
8	F	R	21.70	9	7.59
9	M	R	20.90	3	7.38
10	M	R	21.70	4	8 46
11	F	R	19 80	10	8 29
12	M	R	21 60	5	8 43
Mean	-	-	21.1	6 6	8.5
StDev	-	-	0.1	3.15	0.55

5.3.2 Daytime Sleepiness Scores

The mean hourly KSS scores are shown in Figure 5.1. As seen, there is little variation over the three days, and low scores (indicating alertness) are consistently found during the late morning. Therefore, testing for all neuropsychological tests was done during this time (10 30h-12 00h).

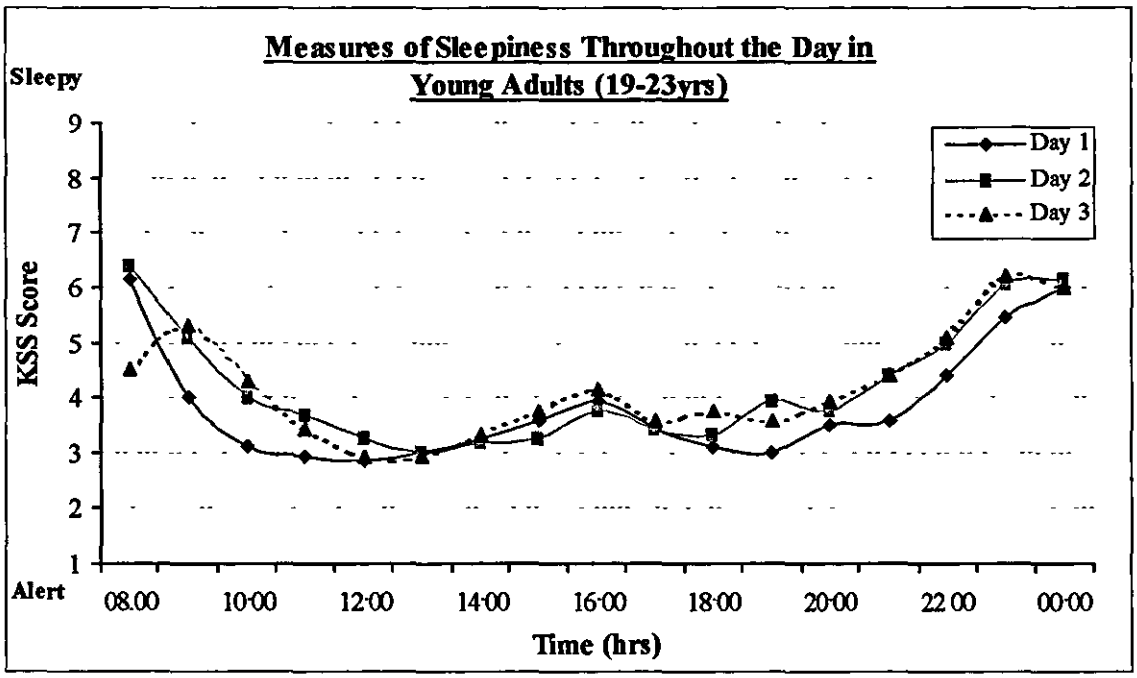


Figure 5.1: Changes in sleepiness throughout the day, as determined by KSS, reflect increased alertness during the late morning when neuropsychological testing took place.

5.3.3 Neuropsychological Test Performance

Table 5.2 shows the mean performance scores for all neuropsychological tests indicating that there is very little difference between male and female test performance. A One-Way ANOVA confirmed that there were no significant differences between males and females ($F < 1.4$, $p > 0.1$) for any performance scores, and so males and females were treated as one group.

Table 5.2: Mean Performance on Neuropsychological tests: A Comparison of Sex

Ss	Non-Verbal Planning	Verbal Fluency	Temporal Memory Faces	Temporal Memory Sentences	Self-Ordered Pointing	IQ
MALE						
3	12 00	7 33	2 45	2.04	1 40	137
4	23.30	8 67	0.92	3 21	1.47	103
7	21 10	7.17	0 82	1.25	-	137
9	20.14	8 33	0.42	1 63	2 01	131
10	11 36	9.33	1.25	4.13	0 46	131
12	11.07	11 67	3 42	0	5.59	116
Mean (m)	**16.49**	**8.75**	**1.55**	**2.04**	**2.19**	**125.83**
St Dev (m)	**5.60**	**1.65**	**1.15**	**1.46**	**1.98**	**13.57**
FEMALE						
1	19 91	9 67	1 22	0.41	1 47	117
2	16.54	5 50	2.18	4 13	1.50	131
5	22 07	8 50	2.18	1.67	5 63	117
6	26.85	4 17	1.28	4 37	3.51	116
8	16 69	12 33	0.83	2 08	3.38	116
11	15.10	7 00	3 42	4.08	5.50	116
Mean (f)	**19.53**	**7.86**	**1.85**	**2.79**	**3.50**	**118.83**
St Dev (f)	**4.40**	**2.95**	**0.94**	**1.64**	**1.83**	**5.98**
Total Mean	**18.01**	**8.31**	**1.70**	**2.42**	**2.90**	**122.33**
Total St Dev	**5.06**	**2.33**	**1.01**	**1.53**	**1.93**	**10.65**

5.3.4 Analysis of the EEG

Total Delta Power

Before any bandwidth analysis took place, the distribution of absolute delta power over the four quadrants during the first NREM period was checked. Total delta power (0.5-4.5Hz) was summated for each channel, for each participant, and each of these values was then expressed as a percentage of the sum of all channels. This was to ensure there was no dominance of total delta power, particularly in frontal

regions. Group[1] mean percentages are shown in table 5 3. A One-Way repeated measures ANOVA revealed no significant difference between these values (F = 1.25 [d f 3,40] P > 0.1).

Table 5.3: Group mean percentages for total delta power.

	LPFC (%)	RPFC (%)	LPO (%)	RPO (%)
Average	28 40	25.32	21.62	24 66
Standard Deviation	9.57	9.48	4 78	8 08
Standard Error	2.77	2 74	1 38	2 34

Recent literature concerning low frequency EEG and findings from the previous chapter suggest that the area of interest may be <1Hz activity. Therefore, the first analysis of the EEG was a spectral analysis of the lower frequency range 1Hz (± 0.5Hz) Data was downloaded and bandwidth filtered before analysing 0.5-1.5Hz. Due to differences in skull size, etc, the data were standardised to relative data, whereby 0.5-1.5Hz power was expressed as a percentage of power 0.5-10Hz within each participant. Standardised data showed no sex differences using an unrelated t-test ($t < 0.8$, $p > 0.4$) Initial analyses will concentrate on the left frontal channel (Fp_1-F_3) since this was deemed to be the channel of most interest given the literature and prior findings. Follow up analysis of other channels was carried out when necessary.

Comparison of Low Frequency Delta to Neuropsychological test Performance

Low frequency delta activity (0.5-1.5Hz) was related to NVPT as seen in Figure 5.2. Although the relationship is significant (r = 0 73 [d f. 11] p = 0.007), the graph does indicate two outliers that might have leverage on this statistic.

[1] This analysis was based on 11 participants, due to a faulty electrode on channel O_2-P_4 for one subject. All further analyses concerning the right-parietal channel (O_2-P_4) will be for 11subjects only.

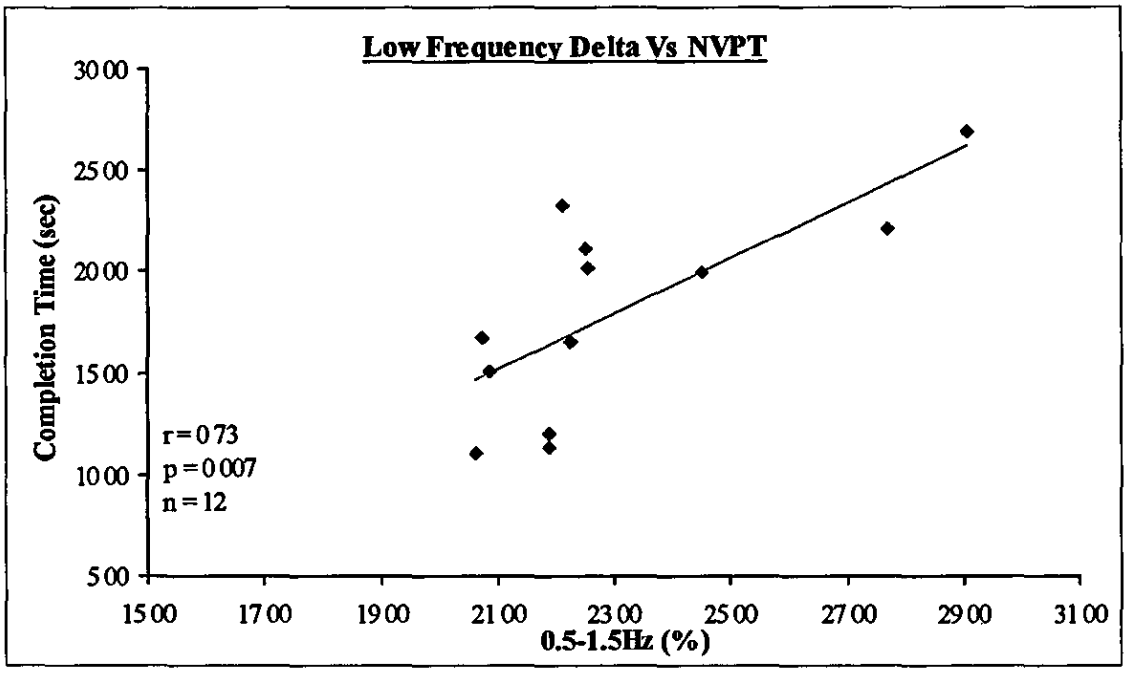


Figure 5.2: The relationship between low frequency delta and Completion Time on the Non-Verbal Planning Task.

Although this relationship appears strong, firstly, the association is not in the expected direction, that is increased delta associated with increased PFC performance, and secondly this may be due to a possibility of two outliers. Therefore, this data was put into a 'boxplot' to show the distribution of data, this can be seen in Figure 5 3

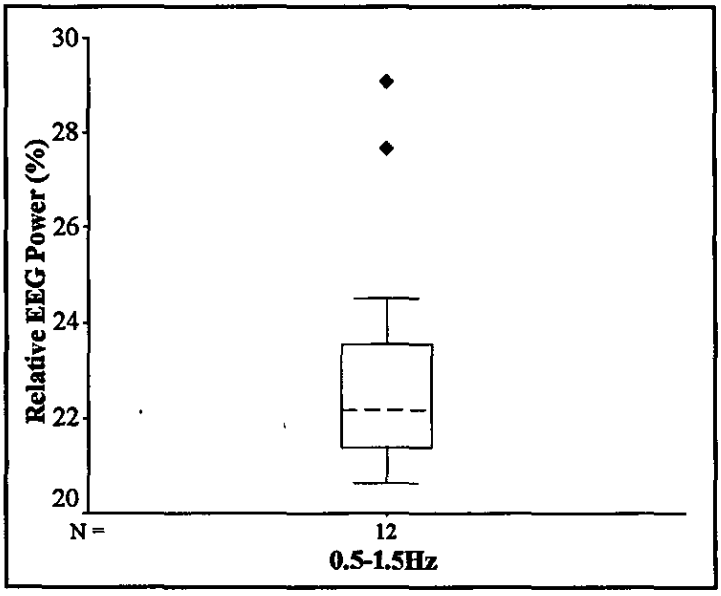


Figure 5.3: A Box plot to show the distribution of low frequency delta data. This demonstrates two outliers within the data, and the necessity to account for these in any analyses.

The boxplot demonstrates that these two points are outliers; therefore, the data was re-analysed with only ten points. However, this resulted in both NVPT and Verbal Fluency not being related to Low Frequency delta 0 5-1.5Hz ($p > 0.1$) To summarise, low frequency delta around 1Hz (±0.5Hz) does not show any relationship to neuropsychological test performance in young adults. Therefore, analyses were expanded to look at the full delta range, with a specific interest still on the lower frequencies (<2Hz)

The Delta Range (0.5-4.5Hz)

The EEG was spectrally analysed in 0.5Hz bins, from 0 5Hz to 4.5Hz with each bin expressed as a percentage of the whole range (0.5-4.5Hz). These data were then compared with the robust test. NVPT. The correlation results are graphically depicted in Figure 5 4.

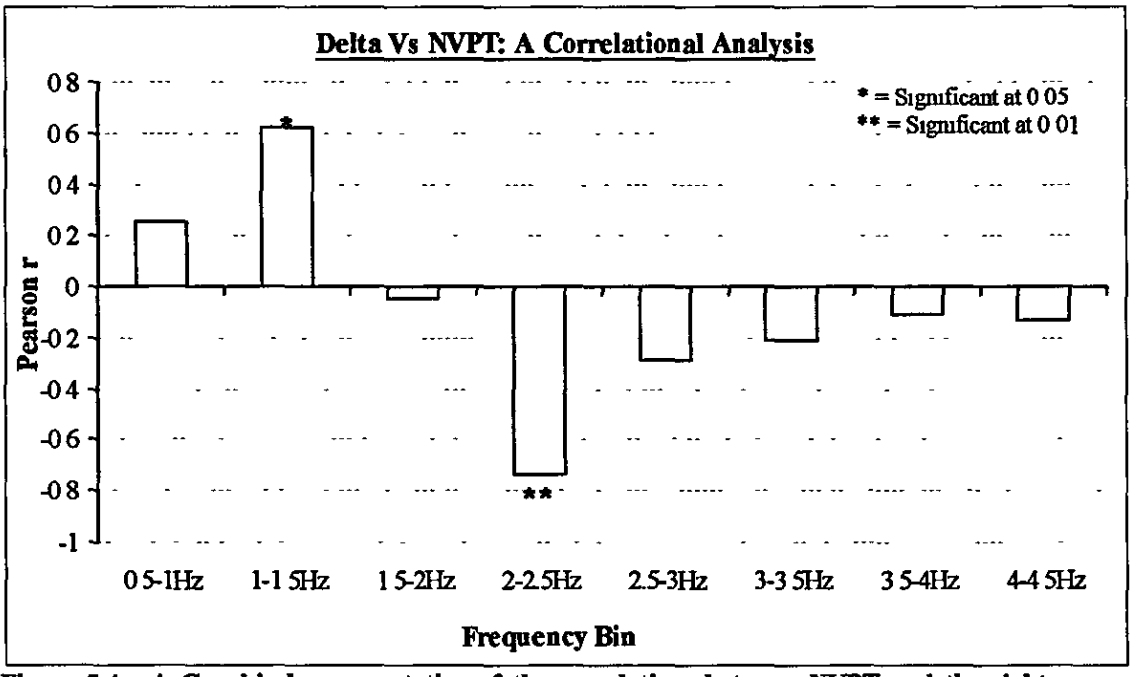


Figure 5.4: A Graphical representation of the correlations between NVPT and the eight delta frequency bins

It would seem that NVPT is related to both 1-1.5Hz and 2-2 5Hz, but due to the opposite nature of these two correlations, it is thought these two frequencies may be inversely related. A partial correlation indicates this since the relationship of both frequencies with NVPT becomes insignificant when partialling out the other frequency. The inverse relationship of these two frequencies can be seen in Figure 5.5.

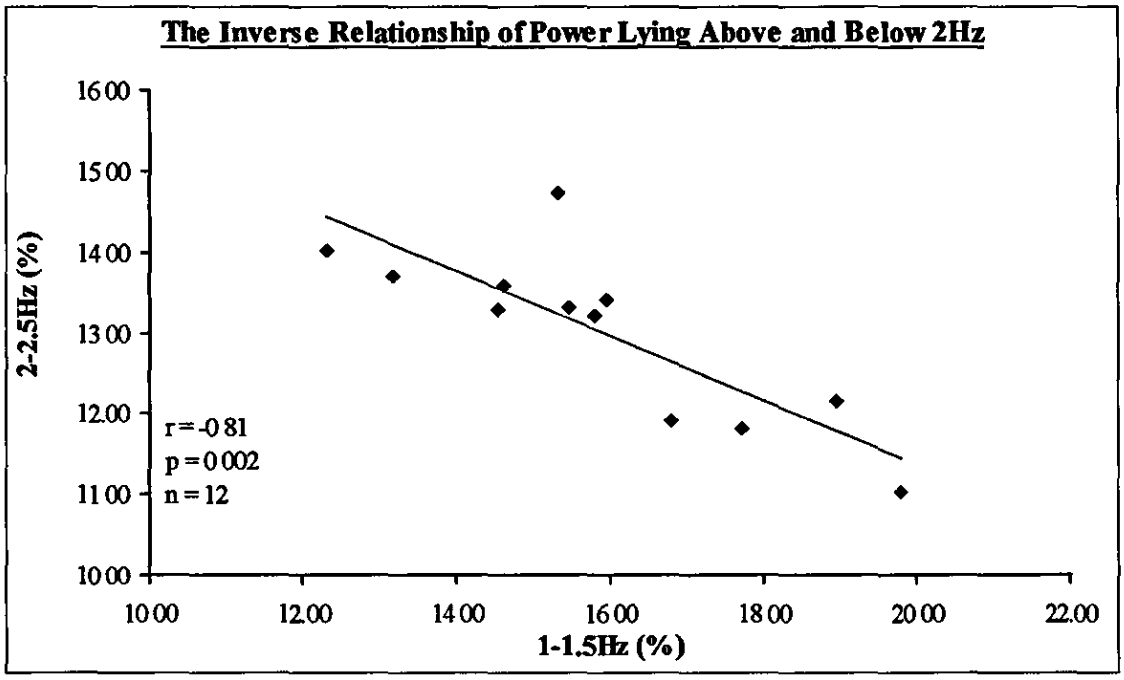


Figure 5.5: The Inverse relationship between relative power within 1-1.5Hz with relative power 2-2.5Hz

It is not possible to determine cause or effect, thereby establishing which is the definite 'driving' frequency. Before comparing these frequencies to the neuropsychological test performance, more analysis of the frequency bands is necessary to determine which may be of interest, given that there are two frequencies, inversely related, that are both related to the NVPT. An examination of hemispherical trends was carried out for further insight.

Hemispherical Analysis

The literature regarding low frequency delta would suggest that the recovery aspect of delta is more prominent in the frontal regions, and more specifically the left frontal regions. Therefore, from looking at mean relative power across hemispheres, this may give an indication of which of these frequencies is reflective of recovery and therefore of interest here.

The inverse relationship between 1-1.5Hz and 2-2.5Hz is consistent in all quadrants ($r > 0.80$, [d.f. 22] $p < 0.002$). A One-Way ANOVA showed that both 1-1.5Hz and 2-2.5Hz relative power showed differences over the quadrants (**1-1.5Hz:** $F=11.032$ [df: 3,43], $p = 0\ 0005$; **2-2.5Hz:** $F = 14.116$ [df 3,43], $p = 0\ 00005$). These differences are reflected in Figure 5.6.

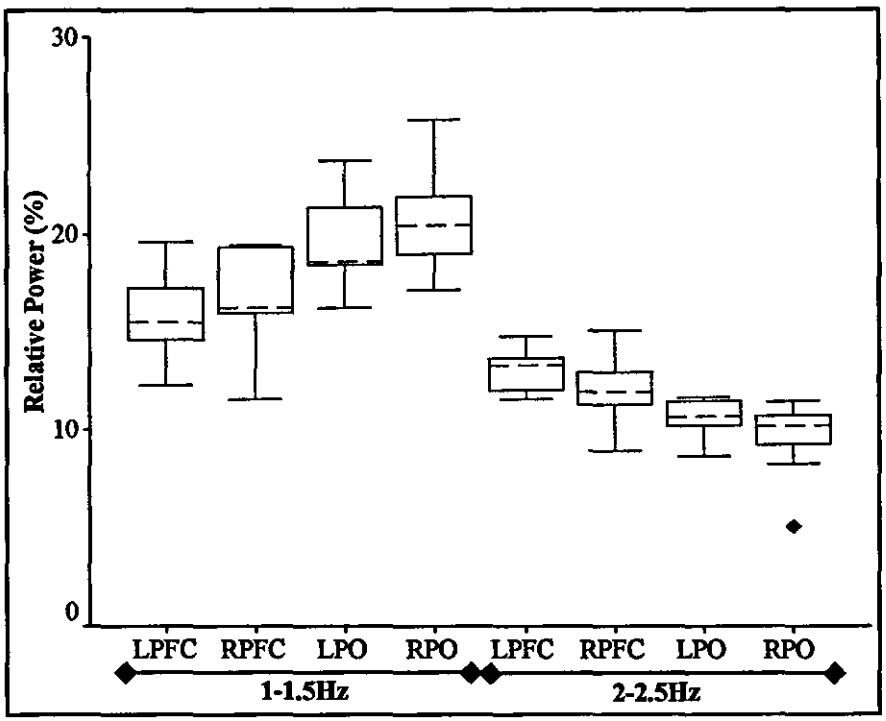


Figure 5.6: A Box plot showing the distribution of Relative EEG Power Across Quadrants for 1-1.5Hz and 2-2.5Hz

This boxplot not only demonstrates the equal distribution of data within data sets (apart from one outlier on the right posterior channel) it demonstrates two important points: Firstly, the difference between anterior and posterior derivations for both frequencies is apparent and secondly, although 1-1.5Hz would appear to be the dominant frequency (which might be expected due to being a wider bandwidth[2]), when looking at each frequency independently and assessing the differences over quadrants, it is evident that relative power 2-2.5Hz is not only dominant in frontal regions, it is more dominant in the left frontal channel. On combining the left and right sides, both for the anterior and posterior sites, a t-test confirmed that for 2-2.5Hz activity, the frontal areas had predominately more relative low frequency delta (t = 7 02 [d.f.10] p = 0.0001). More specifically, the left PFC had significantly more relative power than the right PFC (t = 2.45 [d.f. 11] P < 0 02).

[2] Although 1-1 5Hz and 2-2.5Hz are both 1Hz bins, 1-1 5Hz is a larger bandwidth when considered on a time basis as it has a bandwidth of 0 4sec compared to 0.1sec.

This would suggest that for 2-2.5Hz activity, this may have some enhanced recovery function due to it being dominant in the frontal, specifically left frontal region, which Achermann et al. (2001) thought may reflect 'recovery' sleep. Given this rationale, 2-2 5Hz activity was compared to neuropsychological test performance.

5.3.5 Delta Sleep EEG Versus Neuropsychological Test Performance

NVPT

It was found that low frequency delta activity (2-2.5Hz) in the left frontal region was related to NVPT ($r = -0.74$, [df 22], $p = 0.006$) This can be seen in figure 5.7.

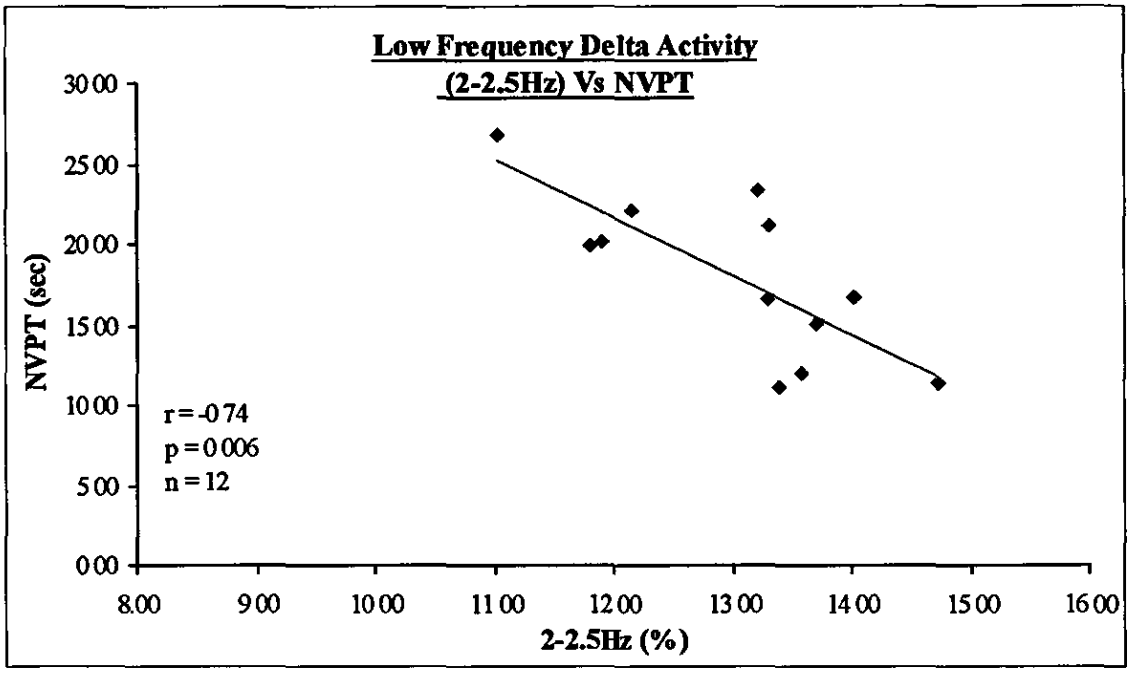


Figure 5.7: The relationship between relative power 2-2.5Hz from the left frontal derivation and performance on the NVPT.

Interestingly, NVPT was not related to 2-2.5Hz in any other quadrant ($r < 0.16$, $p > 0.5$) and thus the relationship was specific to the left frontal region

VERBAL FLUENCY

It was found that low frequency delta (2-2.5Hz) was not related to verbal fluency Although there was a trend showing increased low frequency activity (2-2 5Hz) was associated with an increased number of responses (See Figure 5.8), this

finding was not significant (r = 0 34 [d.f 22], p > 0.1). Verbal fluency was not related to relative power in this frequency range in any other quadrant (r < 0 35, p > 0.1).

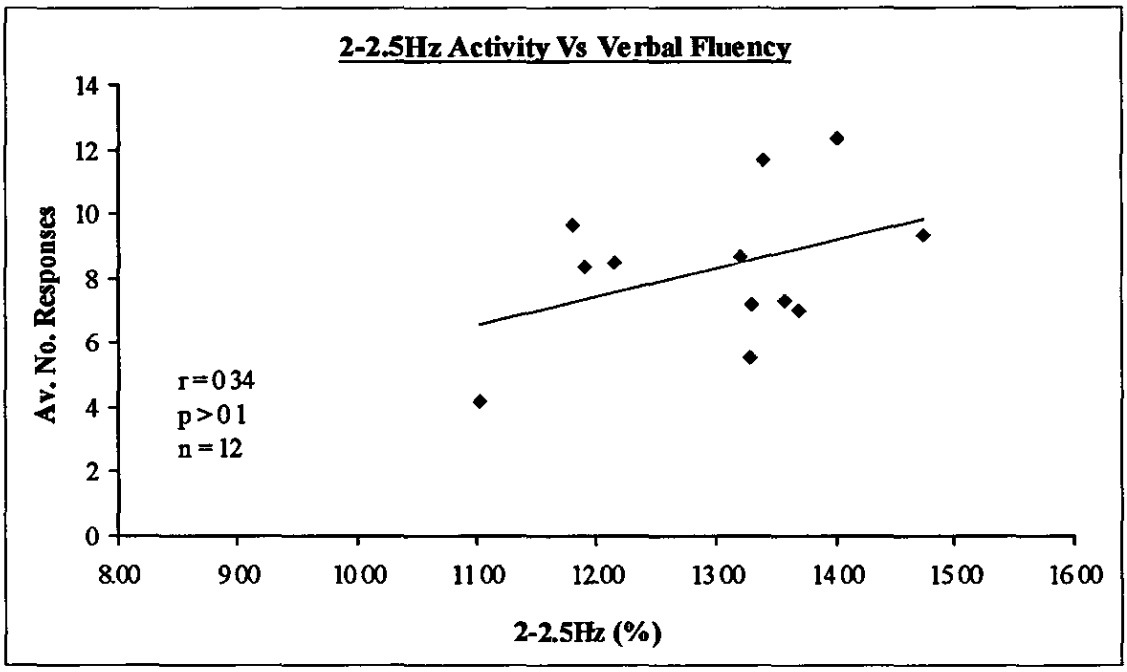


Figure 5.8: The relationship between relative power 2-2.5Hz (%) with the average number of correct responses on the verb-to-noun verbal fluency task

TEMPORAL MEMORY

No relationship was found between low frequency delta and performance on temporal memory for any quadrant either for the faces or sentences method (r < 0.24, p > 0.1).

NON-PFC SPECIFIC TASKS

There were no relationships between tasks not orientated towards the PFC and low frequency delta activity (2-2.5Hz) for any quadrant.

5.3.6 Analysis of the 2nd NREM Period

Following on from the first NREM analysis, the second NREM period was analysed. In terms of relative power distribution, the first and second NREM periods were the same as confirmed with a one-way ANOVA that showed there was no difference between the first and second NREM period in terms of power

distribution (F = 0.24, p > 0 5) However, the second NREM period revealed no interesting results with regard to the neuropsychological tests, as no relationships were evident.

5.3.7 Comparison to an Older Age Group

As the data used in Chapter 3 and the current chapter both deal with the sleep EEG in terms of percentage, in order to express relative data, it is not possible to compare the young and old EEG since this would compare in terms of distribution only and would be misleading. For example, it would appear that the older population have more percentage of delta in the low frequency range compared to that of the younger group (25 85% versus 9.71%). However, an independent t-test confirms that total delta power is significantly larger for the younger group (t = - 0 38 [d f 34] p < 0 0004), demonstrating that any comparison of relative data, between ages, should be done with caution if at all, and therefore, only relative data should be compared

The data from the older group was therefore converted to relative power based on the younger group: The mean power in the older participants was plotted in each frequency bin as a percentage of the mean power in the younger participants, as used by Landolt & Borbély (2001) This can be seen in Figure 5.9.

As seen, the black line represents delta power in the younger group (at 100%), with the older group displaying less delta across all frequency bands for all quadrants (bar 4-4.5Hz activity in parietal regions). However, interestingly the low frequency range (<1Hz) is almost 80% of the younger power suggesting a lesser age effect than other frequencies This was confirmed with a One-Way ANOVA which showed that the younger group displayed significantly more absolute delta power in all frequency bins above 1Hz (F > 6 345 [d.f. 34] p < 0.003), whereas 0.5-1Hz bin was not significantly different (p > 0.1).

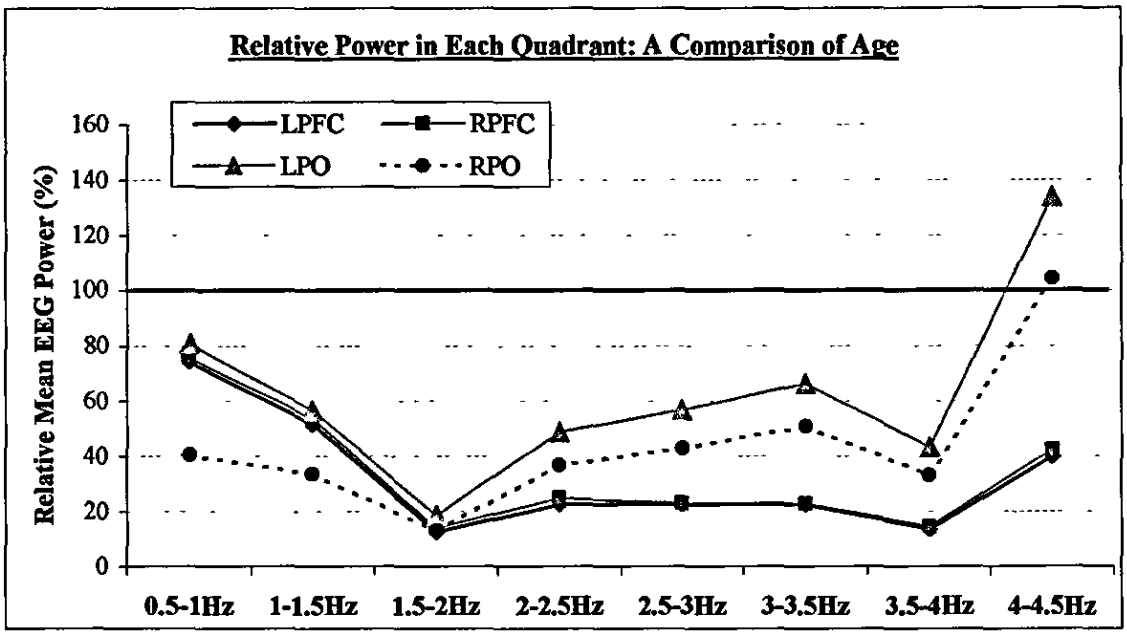


Figure 5.9: The mean power for each frequency bin in older participants expressed as a percentage of power in the younger participants (indicated by a black line at 100%).

5.4 DISCUSSION

Findings show that the frontally dominant relative power in the 2-2.5Hz range is associated with neuropsychological performance on a task that is known to strongly activate the left PFC, that is the NVPT (Morris et al, 1993). This association was only evident in the left frontal region, as all other quadrant analysis revealed insignificant findings. Also, no association could be made between task performance on non-cortically specific tasks and this low frequency EEG.

5.4.1 The Importance of Low Frequency Delta

Preliminary analysis of the EEG indicated total delta (0.5-4.5Hz) power showed no frontal dominance during sleep in normal, healthy young sleepers Most early research on SWA centred on the full delta range, and it is only recently that research has begun to split the delta frequencies in the 'sleep as a localised process' debate There has been overwhelming evidence that frequencies at the lower end of the delta range are most reflective of recovery sleep, and interestingly, it is in this lower region of delta that the results of this study proved worthwhile of assessment.

The low frequency delta in this study (2-2.5Hz) demonstrated a frontal dominance, which is in accordance with the findings of Werth et al. (1996) who conducted a spectral analysis of a normal nights sleep and found 2Hz activity was dominant in frontal regions. Werth et al. assigned this to the idea that activity around this area was indicative of recovery sleep as the PFC requires more recovery due to increased activity in this area during the daytime. The findings from the work of Werth et al (1996, 1997) and the current study show that activity around 2Hz is not only frontally dominant but was also specific to the left side Given that this activity may reflect a degree of 'recovery' as low frequency delta (<1Hz) did for the older group, this was compared with data from the neuropsychological tests, to establish whether this was associated with performance.

5.4.2 Sleep EEG Vs Neuropsychological Test Performance

It was shown that participants who had more delta power in the 2-2.5Hz range (as a percentage of total delta power) performed better on the NVPT. Once again this finding was specific to the left frontal region. Since 2-2.5Hz was dominant in the left frontal derivation during the night, and also provided an insight on performance on a task known to activate the (left) PFC, the results provide support for the debate on the localised function of sleep similar to that found in Chapter 3 for the older age group

However, unlike the older group, NVPT was the only task that showed an association to delta power in the younger age group. Although the Verbal Fluency indicated a trend of better performance to increased relative delta power, the result was not significant. This findings may be, in part, explained by the type of tests in use. Although both tasks are shown to be highly specific to the left PFC, studies have rarely found consistency in the inter-relation of PFC tests (e g Fabiani & Friedman, 1997), possibly due to the complexity of the PFC. It is thought that the NVPT makes specific demands on the PFC without being affected by external variables, and thus, although the verbal fluency task is highly specific, it is affected by educational level/type, since those who have more verbs in their vocabulary will perform better on this task regardless of their PFC

ability/workload The older group may also be more valid in that they were distinguished in terms of educational attainment, and although the younger group were of similar educational attainment they were of different background in that some were aware of nouns/verbs whereas others were not Regardless, the verbal fluency has not been disregarded and it is questioned whether increased participants would result in a significant finding, given the existing trend.

There was no association between delta power (2-2.5Hz) and temporal memory (sentences nor faces method). This may be due to the sensitivity of the temporal memory task, in that it is not as specific as the NVPT and verbal fluency in the activation of the PFC (See Parkin et al , 1995) The fact that no association was found between delta sleep EEG and IQ or Reaction time shows support for the localised sleep function since the (low frequency) delta sleep EEG is only associated with performance on tasks known to activate the left PFC. The extent to which IQ is a marker of frontal function is a topic for debate for researchers. Duncan et al. (1995) argue that IQ is a marker of frontal function. Given the sustained attention involved in the task, it is thought that this task must implicate the frontal areas, however, in comparison to tasks such as the NVPT, the activation may not be as specific and therefore the task not as sensitive in identifying frontal lobe performance per se.

The Haylings Sentence Completion task was carried out in this study but was not included in any analyses due to a concern regarding the reliability of the task: Upon the transcription of responses, it was found that participants were not generating a novel response to sentences but were seeking items around the room and replacing them This was not thought to be particularly strenuous for the PFC since it did not require inhibition of a common response or generation of a novel response. Therefore, further studies presented in this thesis will remove the Haylings Sentence Completion from test procedures. It is recommended that the Haylings Sentence Completion Task should either be

i) Administered under 'blind' conditions
ii) The scoring criteria should be adapted to account for such responses.
iii) Participants are made aware of the scoring criteria before completion.

It would appear, in this chapter, that the test is important when comparing PFC performance with low frequency delta It is proposed that the test should be highly specific to the PFC, and should be free of educational bias The test that was related to low frequency delta for the older group in Chapter 3 was the WCST, a test of perseveration that is shown to activate frontal regions during task completion (e g Rezai at al., 1993) However, the WCST was not used in the current study using a younger age group as it was thought that this task would create ceiling effects given that it is quite easy A small pilot study was undertaken with a group of 4 participants (mean age 20.65y), it was shown that perseverative errors were minimal and the task was easily performed. This may explain why Binks et al (1999) failed to find a significant effect of sleep deprivation in their study, even though this task is particularly vulnerable to the PFC decrements associated with healthy ageing (e g. Daum et al , 1996).

5.4.3 Sleep as a Localised Function

In support for the findings in Chapter 3, this chapter shows that sleep may serve an enhanced recovery function that is localised to the PFC, more specifically the left PFC, to a greater degree than other brain regions The data shows that the 2-2 5Hz range, is not only dominant in the frontal regions, but also in the left frontal regions, which, in turn, is associated with waking performance on the NVPT. This supports the work of Clark et al (1998) who showed the relationship between daytime CBF and delta sleep EEG was stronger in the left PFC.

Studies that have linked night-time sleep activity with daytime waking activity have performed the two recordings/trials on the same day. Therefore, given the fact that SWA is in response to workings of the brain during the day, this would be expected. The study described in this chapter conducted EEG and test performance on separate days, since it did not wish to measure EEG changes in response to an increased PFC workload, but it wished to measure sleep and test performance under 'normal' separate conditions As the sleep EEG was related to test performance, this was thought to be reflective of sleep function, since the function of sleep is to ensure daily efficient cerebral work, and indeed sleep was shown to be related to efficiency on the PFC tasks.

5.4.4 The Significance of the First NREM Period

The current study initially assessed the first NREM period since it contains the greatest amount of delta activity (e g. Braun et al , 1997, Maquet 2000, Maquet et al , 1997; Borbely, 1982). Of course, these studies look at SWA in the whole delta range (0.5-4.5Hz); however, the dispersion of low frequency delta over successive NREM periods was carried out by Werth et al. (1997) They found that 0 25-2Hz activity also had a steeper decline between the first and second NREM periods, whereas faster delta activities did not. This is in addition to Achermann and Borbély (1997) who found activity below 1.95Hz demonstrated a decline from the 1st NREM period to the 2nd NREM period. In support of these two findings, the data presented here showed this trend, although the result was insignificant. Nevertheless, given that the activity studied here was above 2Hz, and thus possibly different to that referred to by Werth et al (1996) for example, an analysis was performed relating activity in the second NREM period to neuropsychological test performance. However, this did not yield any significant associations Werth et al.'s finding would suggest the first NREM to be of most interest since most low frequency could be found here (plus if this an enhanced recovery function, it will be more apparent in the earlier stages of sleep). The current data would support this, since the first NREM was linked to performance whereas low frequency delta power in the second NREM period proved to be of little interest

5.4.5 Low Frequency Activity

Although a lot of recent research has centred around the frequency of 1Hz (e g. Steriade, 1993a, 1993b) claiming it to be important in terms of recovery sleep, this study found this frequency was not as specific as the 2-2.5Hz when using previous research in the clarification of what constitutes recovery sleep. However, there was shown to be an inverse relationship between 1-1.5Hz and 2-2.5Hz, which is consistent with the findings of Achermann & Borbély (1997) and Werth et al. (1997). The two frequencies are impossible to unravel in this thesis since a correlational analysis does not attribute cause or effect, therefore, the 'driving' frequency was unknown Nevertheless, as these two frequencies demonstrated an

inverse relationship, by making assumptions based on the frequency 2-2.5Hz, then this will possibly infer frequencies around 1-1.5Hz. The use of 2-2 5Hz is based on a rationale of recovery sleep, and was therefore considered as a better reflection of recovery sleep than 1-1.5Hz for reasons specified in the results section, i e. a (left) frontal dominance The frequency range that is associated with PFC performance in older people is slower, which maybe expected due to the slowing of the EEG associated with healthy ageing (Bliwise, 1993).

As noted in Chapter 3, the lower frequency associated with PFC performance, when more specific analyses were carried out, was 0.6-0 7Hz. It is therefore proposed whether there is an activity lower than 0.5Hz that is associated with PFC performance in a younger adult population, for instance around the 0.3Hz mark. Although the difference between 0 3Hz and 0 6Hz seems slight, it is a large difference when considering the frequency in terms of time as there is a difference of 1.66seconds (3.33seconds Vs 1 67 seconds), which in the context of EEG is large. However, it was not considered robust to go below 0.5Hz due to the possible inclusion of noise (e g. sweating) in the signal at these lower frequencies when running spectral analyses. Therefore, 0 5HZ remained a cut-off for all subject groups.

5.4.6 Comparison to an Older Age Group

Although the two frequencies of interest were different for each age group, they were considered of similar function as: both reflected a (left) PFC dominance; both were associated with performance on tasks known to activate the (left) PFC; and both were involved in an inverse relationship between slow and fast delta frequencies, supporting Achermann & Borbély (1997) for example. The faster frequency (2-2.5Hz) identified here in the younger group as reflective of 'recovery' sleep, when compared to that found for the older group (0 5-1Hz), is considered plausible given the fact that the EEG shows with age (Bliwise, 1993)

There was shown to be an age effect for each delta band (above 1Hz), which is expected given the reductions in delta with age. As the absolute delta power shows, the difference between young and old groups is immense, and so without

standardising the data it is impossible to compare these groups. As the EEG analysis used here is based on percentages to standardise this data, an age comparison of the percentage data used is not acceptable: the comparison of total delta power shows how the two age groups differ which in turn will affect the percentage based data

However, there was no age difference in absolute power throughout the delta range apart from activity <1Hz when standardising the older data to the younger data (as used by Landolt & Borbély, 2001). This is interesting since Landolt & Borbély (2001) found that activities below 2Hz demonstrated an age effect. However, as stated in Chapter 3, the older participants used here possibly differed from those in Landolt & Borbély's study since they still showed hyperfrontality of low frequency delta whereas Landolt & Borbély's didn't, even though the mean age was smaller (mean 62 0y) Given that low frequency delta (<1Hz) is not an effect of age, it is thought that the associations with neuropsychological performance in Chapter 3 are therefore *not* at the behest of age, but that the relationship(s) are specific to the PFC.

With regard to further age-related comparisons it is thought that the represented data should not be compared since the aim is not compare different age groups, and make assumptions on the rate of ageing. The aim is to investigate the association between neuropsychological test performance and the EEG. The comparison of younger and older adults here is used merely to investigate further whether this relationship is age-specific or PFC-specific. However, although the absolute data or percentage based relative data cannot be compared, the phenomenon associated with them can be, that is associations between 'recovery' sleep and neuropsychological test performance This will be discussed further in Chapter 7 (General Discussion).

5.4.7 Further Research

Low frequency delta has been shown to be associated with PFC performance in both older and younger healthy people The sleep EEG is thought to hold interesting and exciting ties to PFC performance given the recovery properties

associated with low frequency delta. Chapter 4 detailed how the waking EEG may be more efficient in the assessment of PFC function, if associations with PFC performance were present This was indeed the case for an older group, and given that the younger group also display associations between PFC performance and the sleep EEG, this would suggest that the associations are PFC specific and not age specific. Therefore, future work should assess the waking EEG in a younger age group to see if they, firstly overcome the pitfalls of artefact found in the older group, secondly, if the waking EEG is more strongly associated with PFC performance, and thirdly, whether the relationship between the sleep and wake EEG is consistent for older and younger age groups alike

5.5 CONCLUSIONS

Summary

1) Total delta power (0 5-4.5Hz) showed no dominance in any quadrant.
2) It was thought 2-2 5Hz activity indicated a recovery aspect of sleep due to:
    a. Frontal dominance of activity – Studies show the PFC has slower EEG and less CBF during the night in response to increased CBF and faster EEG during the daytime, indicating increased restoration at night.
    b. A left PFC dominance – based on studies that have shown the left PFC to be more activated during the daytime, and less active during SWS.
    c. A reduction from the 1st NREM to the 2nd NREM - the temporal distribution showing the immediate need
3) The relative power within 2-2.5Hz in the left PFC was found to be associated with performance on the NVPT, and a trend was apparent for the verbal fluency Both tasks activate the left PFC in functional imaging studies.
4) The relationship between delta activity (2-2.5Hz) and neuropsychological test performance was unique to the left PFC, providing support for a localised function of sleep.

5) The frequency identified (2-2.5Hz) was faster than that identified for the older group (0.5-1Hz) to reflect 'recovery' sleep. This is accepted given the slowing of the EEG found in healthy ageing
6) Low Frequency delta (<1Hz) does not show an age effect whereas frequency above 1Hz does, this is argued for support that the finding in Chapter 3 is a relationship unique to the PFC that is not at the behest of age.

Conclusion

The Sleep EEG in the left PFC is associated with neuropsychological test performance on a task known to activate the (left) PFC. This study not only supports the use of the EEG as a tool for assessing PFC performance but also supports the current theory of a localised function of sleep The association between low frequency delta and PFC neuropsychological test performance was confirmed in the younger adult population, albeit not as strong as the older group. Therefore, this association is thought to be specific to the PFC, and not unique to ageing, which was further supported by an age comparison of <1Hz activity. The extent to which this is specific to sleep, or EEG across the sleep/wake cycle will be investigated for the remainder of the thesis

CHAPTER 6

WAKE EEG & NEUROPSYCHOLOGICAL TEST PERFORMANCE IN YOUNG PEOPLE

6.1 INTRODUCTION

This thesis has demonstrated that low frequency delta in the sleep EEG is associated with PFC performance in both younger and older age groups, suggesting that this relationship is specific to the PFC as opposed to a product of healthy ageing The aim of the thesis is not only to assess the sleep EEG but to also assess the waking EEG, as previously shown for an older age group, whereby theta activity in the waking EEG is related to both low frequency delta and to PFC performance This chapter will therefore establish whether these wake EEG associations are an effect of age or whether they are, like the delta Sleep EEG, specific to the PFC and found across different age groups.

The Chapter "Waking EEG and neuropsychological test performance in healthy, older people" (4) referred to the association between theta activity in the waking EEG and neuropsychological test performance, whilst also relating this activity to low frequency delta in the sleep EEG. The identification of theta activity (7-8Hz) is interesting since it was suspected that this activity might be that of the kappa rhythm, now more commonly referred to as 'frontal theta'. Theta activity, such as this, has been shown to be evoked during cognitive tasks (e g. Ramos et al., 1993; Smith et al., 1999) increasing with task complexity (McEvoy et al , 2001). Although this chapter used older participants, this was considered necessary given the findings from the sleep EEG and PFC performance of older people. However, given that this sleep EEG-PFC performance link has been shown in younger adults as well, it is thought necessary to explore the waking EEG and its associations with regard to a younger population

Attention has recently turned to the waking EEG, especially in relation to task performance, with many of these studies utilising younger participants Çiçek & Nalçaci (2001) found that activity 8 6-10 2Hz was indicative of performance on the WCST due to an underlying commonality since the wake period used for analysis was separate to task performance. Hoptman & Davidson (1998) also found that alpha activity was related to performance on the Tower of London and verbal fluency task. However, their correlations were low ($r < 0.35$), considerably lower that those found for the older group in Chapter 4. However, the extent to

which this is due to the different ages is not known since Hoptman & Davidson used younger participants. This chapter aims to address this issue to establish, firstly if associations are present, and secondly, if these are stronger than those of Hoptman & Davidson's findings.

The wake period used in the current chapter will consist of both a laboratory based wake EEG protocol and also a period taken after "lights out" but before sleep onset. Most wake EEG recordings have taken place during a controlled laboratory set-up However, the waking EEG can be problematic as shown in Chapter 4, namely due to artefact when utilising a laboratory based setting for these recordings A forgotten period in sleep research would appear to be the period preceding sleep onset prior to drowsiness, which is considered an optimum opportunity to record clean, relaxed wakefulness, where stimuli affecting the EEG are minimum. This period was shown to be a clean, reliable measure of waking EEG and will be further investigated in this chapter, albeit it with a younger age group

The sleep EEG exhibits both state-specific and frequency-specific topographical variations in the activity along the anterior-posterior axis (See Chapters 3+4) supporting the debate of sleep as a localised process These regional changes are also apparent in the wake-sleep transition whereby it is thought that the frontal areas of the brain fall asleep first (Wright et al., 1995, De Gennaro et al , 2001a) suggesting an urgency of sleep in this area possibly for recovery. De Gennaro et al. (2001b) investigated the antero-posterior shifts of spectral power during the wake-sleep transition, concluding that lower frequencies (<7Hz) were more prominent in frontal areas during sleep onset.

Ehlers et al. (1998) used the sleep onset period as a marker of waking EEG in younger (20-29yrs) and older (30-40yrs) subjects in an attempt to study the frequency changes and possible relations to the sleep EEG within this pre-sleep onset period The authors found that delta, theta, alpha and beta prior to sleep onset were significantly related to sleep EEG during the night for the same bands (e g. delta Vs delta; theta Vs theta etc.). This suggests the EEG prior to sleep onset is a strong indictor of the spectral properties of sleep Therefore, given that the

sleep EEG and performance on the NVPT were linked in chapter 5, can one expect the wake EEG to be associated with NVPT if the spectral properties of the EEG over the sleep/wake cycle are consistent? Ehlers et al. and previous findings reported in this thesis would suggest so

Finelli et al. (2000) found that daytime theta (5-8Hz) was related to nighttime SWA (0 5-4.5Hz), concluding daytime theta was a secondary marker of sleep propensity Of course, the theta referred to is probably that of sleepiness, especially given the wide band of 5-8Hz and the sleep deprivation conditions, however, the study does indicate a similar underlying process for delta and theta. The studies referring to frontal theta as a manifestation of thinking, are normally referring to theta that is higher in frequency For instance, Jensen et al (2002) refers to the frontal theta as 7-8.5Hz which was reflective of performance, and Çiçek & Naçaçi (2001) who refer to thinking EEG as low alpha (8.6-10.2Hz). The findings from chapter 4 would indicate activity 7-8Hz is the frequency of interest in relation to the sleep EEG, the extent to which this is referred to as theta or alpha would differ amongst researchers. However, this activity would seem important in the study of the wake EEG

6.1.1 Aims

The work described in this thesis has shown that low frequency delta during sleep is related to PFC performance in both older and younger people, suggesting that the EEG may be a marker of performance, specifically localised to the left frontal regions Research into the waking EEG has extended these associations in a healthy older age group, concluding that theta activity (7-8Hz) is associated with both PFC performances and also low frequency delta. Given these findings from Chapter 4, that activity 7-8Hz, proposed to be evoked by thinking (whether contrived or putative) is associated with the sleep EEG, it is thought that the theta generated prior to sleep onset is that of 'thinking' and thus explains why this may be related to night-time delta. The aim of this chapter is to investigate the wake EEG further with a younger age group to assess whether associations between wake EEG and performance and also wake EEG and the sleep EEG are consistent across different age groups.

Research Questions

- Is wake EEG during the daytime related to neuropsychological test performance in younger people?
- Is wake EEG prior to sleep onset related to neuropsychological test performance in younger people?
- Is the wake EEG identified to reflect PFC performance 7-8Hz?
- Are the two periods of wake EEG similar in distribution?
- Is wake EEG associated to low frequency delta sleep?
- Are these relationships localised?
- Is there a difference in the wake EEG due to age?

6.2 METHODOLOGY

Twelve participants (6 male; 6 female) with an age range of 19-23years (mean 21.12years, SD: 0 10years) took part in the study. All were normal healthy sleepers who undertook two nights of sleep EEG, a battery of neuropsychological tests and a daytime waking EEG recording

The Neuropsychological Tests in use for this chapter for this age range were:

- The Tower of London
- The Verbal Fluency Task
- Temporal Memory
- Reaction Time and IQ (Non-Cortically Specific).

EEG analysis began with a specific interest in the theta range 4-8Hz produced frontally. EEG power spectra was calculated in 5 second epochs, and power within each 1Hz frequency bin was expressed as a percentage of the full waking range 3-15Hz in order to standardise the data Wake EEG was analysed to assess the association with both neuropsychological test performance and low frequency delta during sleep at night Data was carefully selected to ensure only artefact free epochs were used

Although associations were investigated for all four quadrants, there was a focus on the frontal regions, specifically the left side.

Consistent with the methodology in Chapter 4, the two selected periods for analysis were a daytime waking EEG recording and a period after "lights out" but preceding drowsiness/sleep onset.

6.2.1 Experiment 1

Waking EEG was recorded during a time of optimal alertness (late morning) and subjects were asked to undergo a series of 'thinking' scenarios under controlled conditions in the laboratory.

All eyes closed conditions were spectrally analysed: Power spectra were calculated for 5-second epochs for the first 60seconds of each condition (verbal fluency only first 30seconds analysed, as verb generation dries up after this time – Harrison & Horne, 1997). This comprised twelve continuous artefact free epochs. Any data that failed to show the first six epochs to be artefact free were not analysed. Therefore, number of participants varied for each condition.

See Chapter 2 for full procedures: Neuropsychological Testing and Waking EEG Recordings.

6.2.2 Experiment 2

The selection of EEG was the 5-10minutes following "lights out", and was required to be a minimum of 12 epochs (1minute) of clean EEG. The absence of eye rolling was considered imperative since this affects the EEG from the fronto-polar channels, and also, it was important in the study to control for drowsiness in the assessment of theta.

See Chapter 2 for full procedures: Neuropsychological Testing and Sleep EEG Recordings since the wake EEG selection was made using the Sleep Recording montage, protocol etc.

Statistical Analysis

All statistical analyses are concerned with assessing the relationship between an independent variable (Wake EEG) and the dependent variables (neuropsychological test performance and low frequency delta EEG). Therefore, Pearson r correlation coefficients will be determined, with the use of partial correlation coefficients, if and when applicable. Any analysis concerning differences, such as female/male test scores will use the (un)related t-test or the One-Way ANOVA for multiple variables. The significance level is set at 0 05 unless otherwise stated.

In order to compare groups and/or databases for distribution, "box and whisker" plots will be used. The box plot consists of a lower "hinge" (25th percentile) and an upper "hinge" (75th Percentile), the centre of these being the median value. The "whiskers" of the plot represent the "fence" range of values, these fall within 1.5 times the value between the appropriate hinge and the median. Any values falling outside of this range are represented by a marker (*) and are termed "outliers".

6.3 RESULTS – Experiment 1

6.3.1 Participant Characteristics

All participants fulfilled the criteria as set out in chapter 2, with the sample being matched for sex, and within each age range, male and female subjects were matched for age. This can be seen in table 6 1.

Table 6.1: Characteristics of Participants, for young and older adults.

Ss	Age	ESS	TST (hrs)	Ss	Age	ESS	TST (hrs)
FEMALE				MALE			
1	21 4	2	8 66	3	22	9	7.52
2	20 3	9	7 46	4	22	8	8.36
5	19.7	10	9 04	7	22 1	2	8.51
6	21 1	8	9.11	9	20.9	3	7.38
8	21 7	9	7.59	10	21.7	4	8.29
10	21 7	4	8 46	12	21 6	5	8 43
Mean	**20.98**	**7.00**	**8.64**	**Mean**	**21.72**	**5.17**	**8.36**
SD	**0.82**	**3.22**	**0.62**	**SD**	**0.44**	**2.79**	**0.49**

6.3.2 Daytime Sleepiness Scores

The mean hourly values for the Karolinska Sleepiness Scale over 3 days showed a normal distribution of sleepiness, and also demonstrated the waking EEG was taken at a time of maximal alertness.

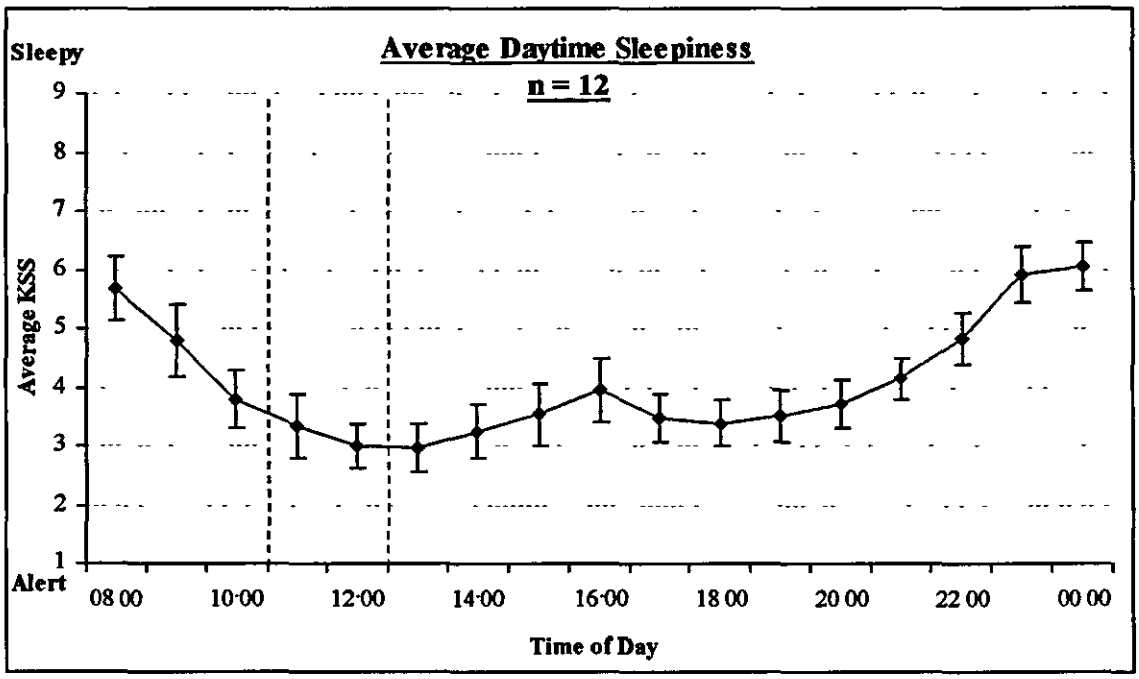


Figure 6.1: The Fluctuation in daytime sleepiness, as measured by the KSS. Average values over 3 days, inclusive of standard error. Dotted lines indicate the period used for daytime 'alert' measurements.

6.3.3 Sleepiness During the Trial

Once again, as the focus is on theta activity (4-8Hz), it is important to control for sleepiness by ensuring the theta activity taken is during a time of alertness. Therefore, throughout the trial, between each condition, participants were required to rate their feelings of sleepiness using the KSS, a known sensitive measure of subjective sleepiness. At a given point of 7 the trial was aborted given the finding that this is associated with physiological signs of sleepiness (Åkerstedt & Gillberg, 1990). The average rating of sleepiness throughout the trial is shown in Figure 6.2.

Although sleepiness increased over the duration of the session, average reports remained below a KSS of 6 ("Some signs of sleepiness"). As the experimenter recorded, and assessed, the on-line EEG recording, a secondary measure also ensured that no signs of EEG measured sleepiness was evident (i e eye rolling). No subject showed signs of sleepiness through the EEG, apart from one excluded subject during the final condition

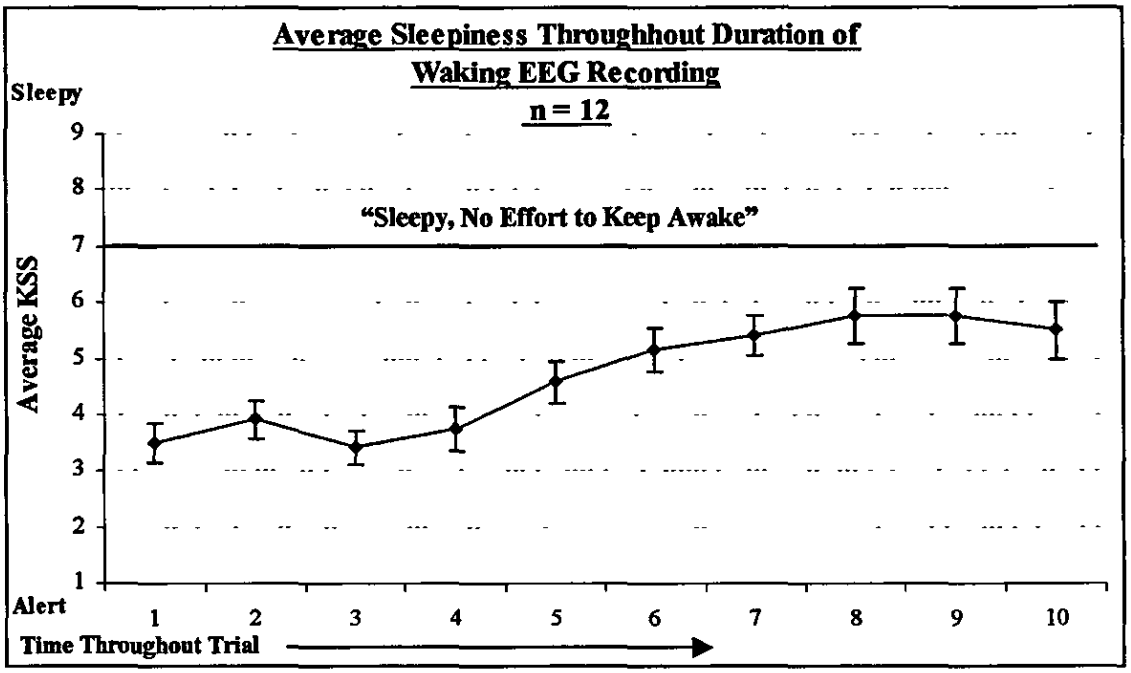


Figure 6.2: The fluctuation of sleepiness throughout the waking EEG recording session for both younger and older groups. Average KKS and Standard Error are shown.

6.3.4 Analysis of the Wake EEG

As with the older group the eyes open conditions were not analysed due to this portion of the EEG being prone to noise with frequent bursts of artefact due to eye blinking (0.2Hz) and eye movements (ranging from 0.6-2.5Hz) Although the band-pass filter would remove this artefact, the eyes open was still avoided as the eye movements interfered with the frontal channels throughout.

All eyes closed conditions were spectrally analysed: The first 12 continuous epochs of clean EEG for each condition were analysed (6 continuous for verbal fluency) Any data that failed to show the first twelve/six epochs artefact free were not analysed. Therefore, number of participants varied for each condition. This is

shown in table 6.2. As seen in this table, no condition had a 100% success rate (i e. n = 12)for data collection.

Table 6.2: Number of Participants displaying clean artefact EEG for the first twelve (six) continuous 5-second epochs. Total number of analysed epochs is also indicated.

	n =	no. epochs =
Eyes Closed	11	132
Verbal Fluency[1]	10	204
Journey	9	108
Yesterday	6	72
Experiment	6	72
Song	8	96
Thinking (See Below)	12	144

The three thinking conditions (journey, yesterday, experiment) had reduced sample sizes due to noise in the EEG Similarly to the older group (Chapter 4), it was thought these could be combined to form one condition thus increasing the number of participants. The distribution of EEG for the three conditions was similar as shown in Figure 6.3.

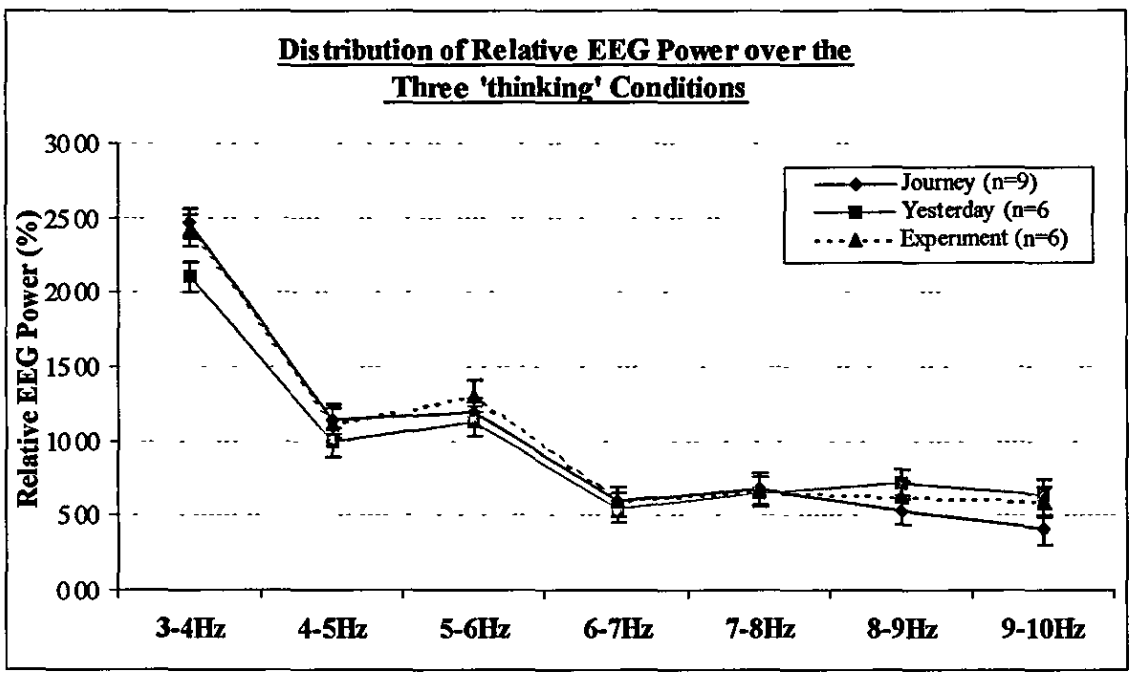


Figure 6.3: Distribution of data to show the similarity of the three 'thinking' conditions.

[1] This is not a performance measure, and is distinct from the verbal fluency task measures reported – This condition is merely to encourage 'active' thinking.

As can be seen, the distribution is equal as the conditions are very similar All quadrants demonstrated that the three thinking conditions were equally distributed. Therefore, these three conditions were analysed the same as the older group: A minute taken from each (if clean) and expressed as one condition. This increased the number of participants to 12, and the epochs analysed to 144 (See table 6 2).

6.3.5 Wake EEG Versus Neuropsychological Test Performance

Mean task performance did not differ between male and female participants These results are listed in Table 6.3. An Independent Samples t-test confirmed that males and females, within groups, did not differ ($t < 1.16$ [d f 10] $p > 0.1$). However, for reaction time, females were significantly slower than their male counterparts ($t = 2.798$ [d f 10] $p = 0\ 019$), which is attributed to an outlier

Table 6.3: Mean Task Performance for Young and Older Groups: A Comparison of Sex

		NVPT	VERBAL FLUENCY	TEMPORAL MEMORY	RT	IQ
Male $n = 6$	*Mean*	**16.49**	**8.75**	**1.55**	**247.20**	**125.83**
	Stdev	*5 60*	*1 65*	*1.15*	*23.86*	*13 57*
Female $n = 6$	*Mean*	**19.53**	**7.86**	**1.85**	**280.16**	**118.83**
	Stdev	*4.40*	*2 95*	*0 94*	*23 86*	*5 98*

The EEG for each condition was assessed independently to the NVPT, as there were seven correlations for each condition, the accepted level of significance was 1% to minimise the possibility of a type I error. Preliminary analyses will be carried out on the left channel since it is thought any interesting associations will be evident here due to previous findings throughout this thesis.

Eyes Closed

NVPT was not associated with relative power within any frequency band, in the left frontal channel ($r < 0\ 30$ [d f. 10] $p > 0.1$)

Verbal Fluency

NVPT was not associated with relative power within any frequency band, in the left frontal channel ($r < 0.55$ [d.f. 9] $p > 0.1$). The strongest associations were in the delta range, but these proved insignificant.

Song

Once again, NVPT was not associated with relative power within any frequency band, in the left frontal channel ($r < 0.48$ [d.f. 7] $p > 0.1$).

Thinking

NVPT was not associated with relative power within any frequency band, in the left frontal channel for a given significance level of 1% However, there was an association between 7-8Hz activity and NVPT for the left frontal channel for young adults (See Figure 6.4) that was significant at the 5% level ($r = -0.60$ [d.f. 11] $p = 0.03$). The relationship was not evident for the any other channel ($r < 0.35$, $p > 0.1$).

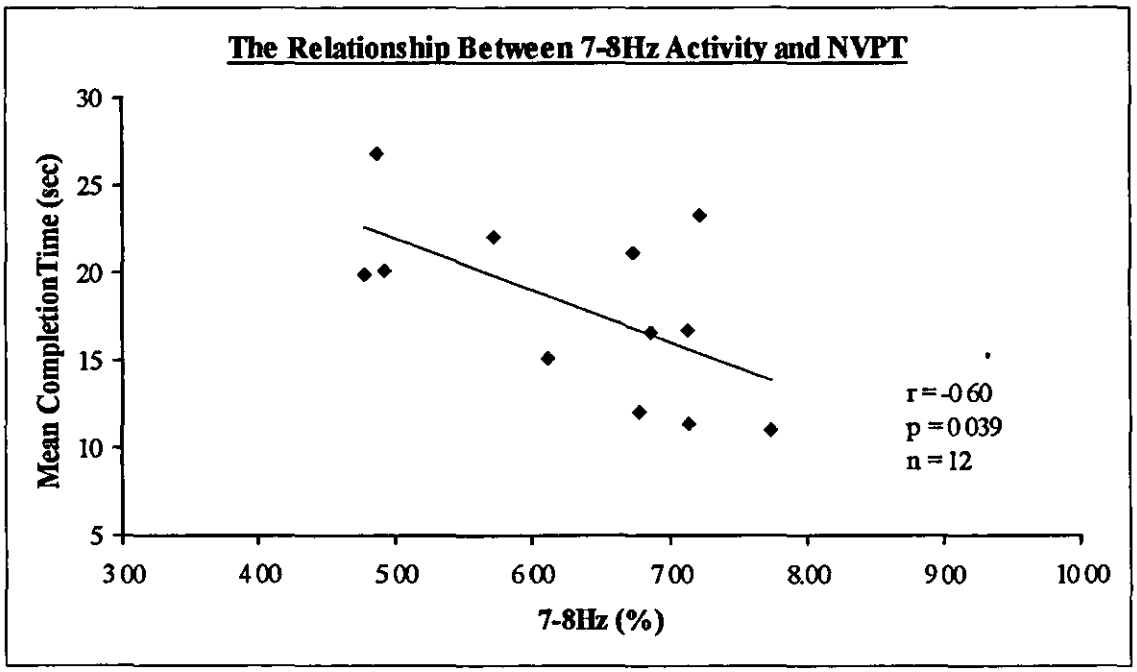


Figure 6.4: The relationship between 7-8Hz activity in the left frontal region and mean completion time on the NVPT for young adults.

There was a trend between verbal fluency and 7-8Hz activity in the left frontal channel but this was not found to be significant (See Figure 6 5). The right frontal and left parietal were both insignificant ($r < 0.51$, $p > 0.05$). However, there was a

relationship with the right parietal region (r = 0 68 [d f. 11] p = 0.014), which could possibly be a random effect.

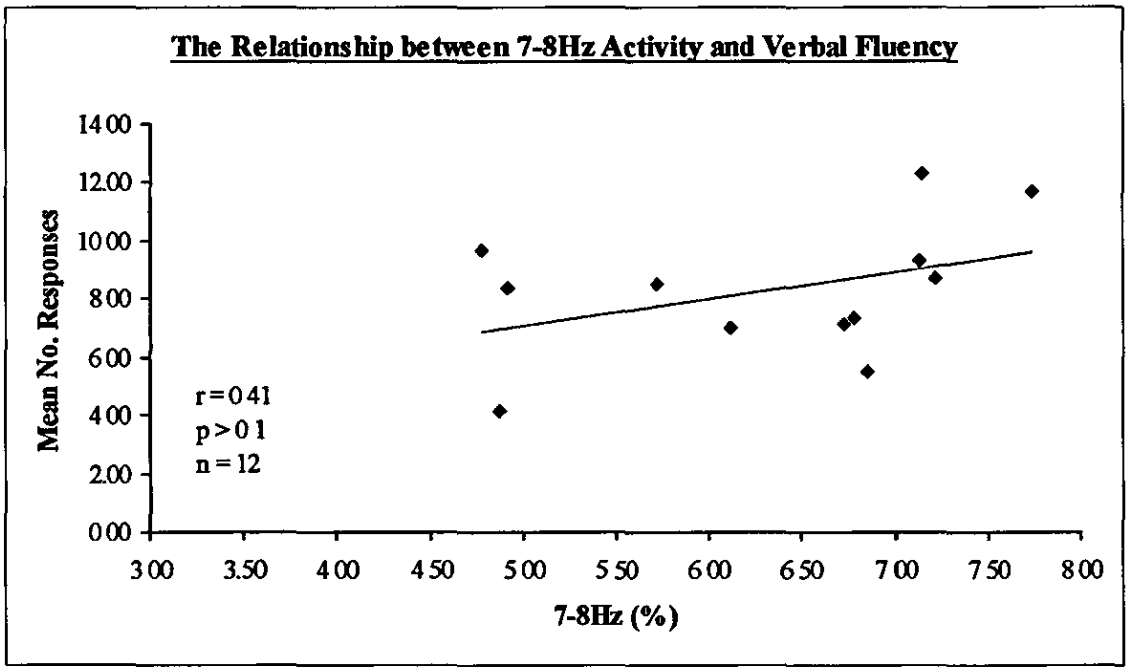


Figure 6.5: The relationship between 7-8Hz Activity in the left frontal derivation and mean number of responses on the Verbal Fluency Task.

6.3.6 Wake EEG Versus Low Frequency Delta

It was found that putative recovery sleep (2-2.5Hz – See chapter 5), was associated with relative power in the 7-8Hz range during the thinking condition (r = 0.84 [d f. 11] p = 0.001) This was not evident for the eyes closed, song condition (r <0 35, d f. 10] p > 0 1), nor verbal fluency (r < 0 57 [d f. 9] p > 0 05). It is noted that the strongest correlation for verbal fluency (r = 0.57, p = 0 08) was for the 7-8Hz range, which may, or may not, have been significant with more subjects, since this analysis was only with 10 subjects

These results indicate that increased 7-8Hz activity (contrived thinking) during the daytime was associated with an increase in low frequency delta at night for a younger group. This finding was not significant for the right frontal (r = -0 40 [d.f.11] p > 0.1) nor the posterior regions (r < 0.25 [d.f. 11] p > 0.4). The unique relationship between recovery sleep and daytime 7-8Hz activity in the left frontal region for younger adults is shown in figure 6 6. Given the findings presented in

Chapter 4, regarding trait sleepiness as cause, it was not given any credit with the older group Due to the similarities here, in regard to wake EEG distribution etc. it was not deemed to be problematic here, especially with a younger age group (as sleepiness is unlikely to increase over a minutes duration).

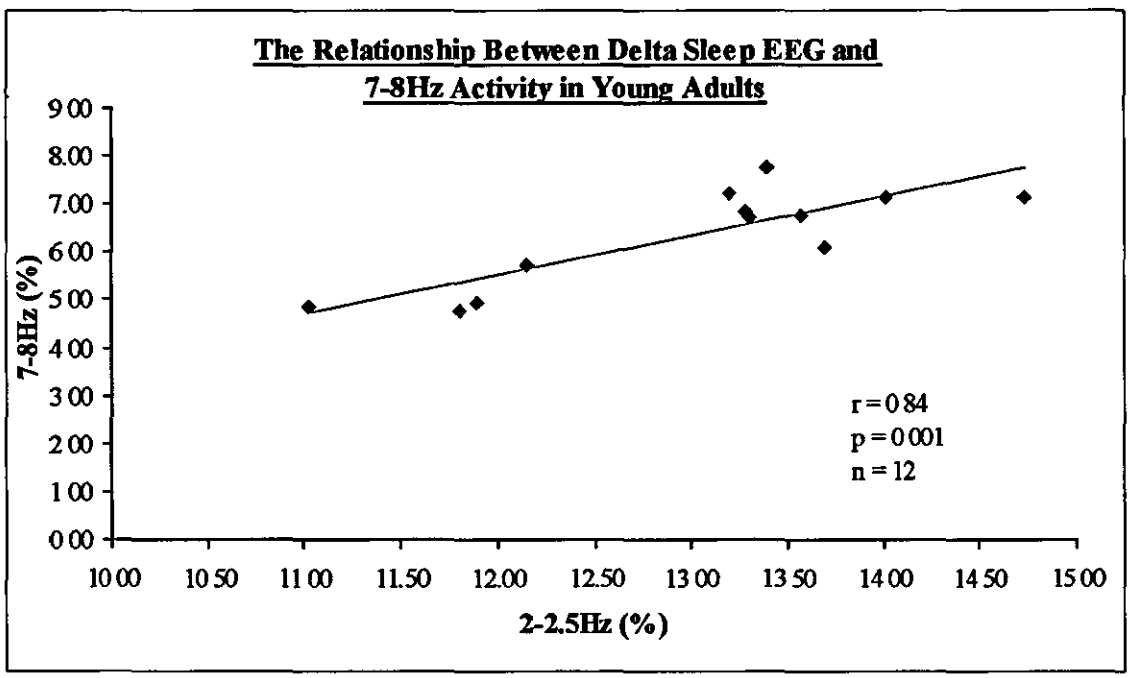


Figure 6.6: The relationship between relative EEG power in the low frequency range during sleep, and relative power within the 7-8Hz range during an alert thinking exercise in young adults. This relationship is unique to the left frontal region.

6.4 RESULTS – Experiment 2

Although the waking EEG taken during the daytime revealed interesting associations between 7-8Hz activity with both performance and proposed recovery sleep, Experiment 2 sought to assess the efficiency of the pre-sleep period given the findings in Chapter 4 (Wake EEG in an older age group) and also given that the daytime EEG was prone to noise resulting in reduced sample sizes for conditions

Once again, all the participants' information is the same as that presented in Experiment 1, the only change being to the Independent Variable, the Wake EEG period. This was a period of clean EEG after "lights out" but preceding any signs of drowsiness

6.4.1 Sample Information

The sample of the time taken varied between participants but a criteria of a minimum of 12 clean epochs (1 minute) was adhered to for all participants The mean sample taken for the group and time before sleep onset can be seen in Table 6 4.

Table 6.4: EEG Sample Information for a younger age group (19-23y)

		Sample Taken		Time to Sleep Onset	
		Mins	Epochs	Mins	Epochs
Young	*Mean*	3 01	36 17	15 49	185 92
	St. Dev.	1 52	18 25	9 44	113 4

6.4.2 Pre-Sleep 7-8Hz Activity – Relation to the Wake EEG

For the four frequency bins, all (bar 4-5Hz) demonstrated high correlations to daytime EEG ($r > 0.87$ [d f 11] $p < 0\ 05$) Therefore, as 7-8Hz was reflective of 'thinking' in chapter 4 and in Experiment 1, it will be analysed here as a similar concept. Once again, analyses will start with the left frontal derivation (Fp_1-F_3) since this is integral to the thesis, moving onto other quadrants as and when necessary.

The stability of 7-8Hz across waking states (Daytime Versus Pre-Sleep Theta 7-8Hz) was compared for all four quadrants· It was found that the two activities were related for the left frontal ($r = 0.69$ [d f. 11] $p = 0\ 012$) and the right parietal ($r = 0.96$ [d f. 10] $p < 0.0005$), but not for the right frontal nor left parietal ($r < 0.15$, $p > 0\ 5$) The relationship between the two activities can be seen in figure 6 7.

This graphs shows that the relative amount of power within 7-8Hz (as a function of 3-15Hz) during alert 'thinking' daytime levels is similar to that produced in the sleep period It may indicate that when participants put the light out at night, they 'think' similarly to the experimental conditions since there must be an underlying commonality as the recordings took place on days separate from each other.

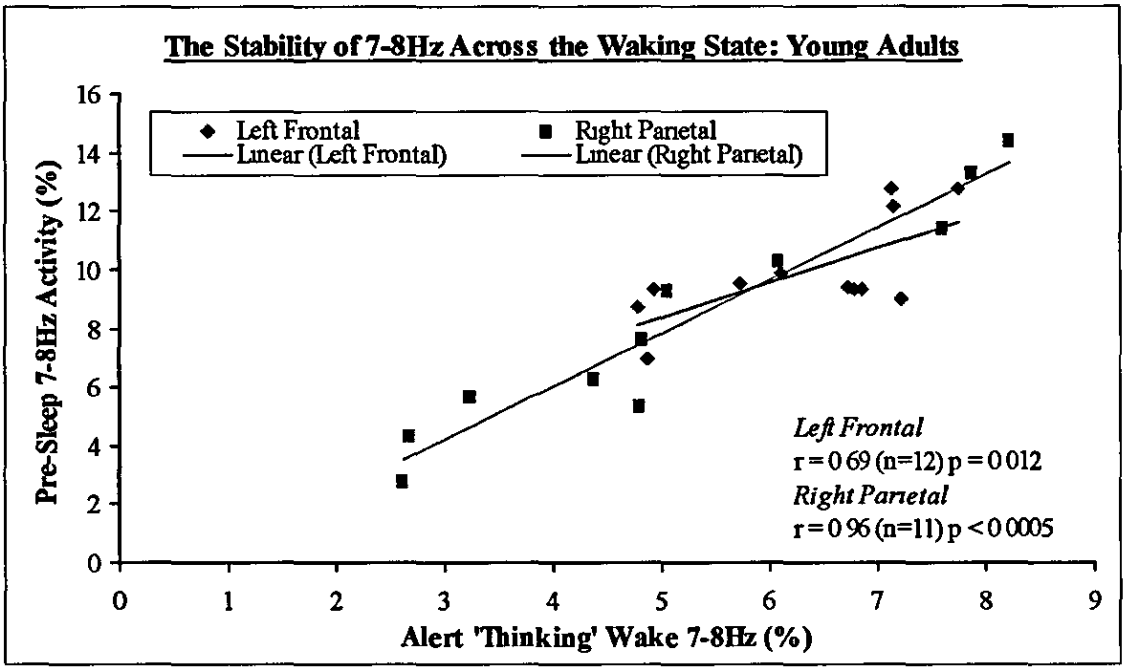


Figure 6.7: The stability of 7-8Hz activity across the waking state for the left frontal and right parietal regions in young adults.

6.4.3 Pre-Sleep 7-8Hz Activity– Relation to Delta Sleep

As Ehlers et al. (1998) demonstrated activity at sleep onset to be related to sleep, an analysis was performed to see if this was the case with the current data. It was found that pre-sleep 7-8Hz[2] activity was significantly associated with relative low frequency delta during sleep in younger people ($r = 0.76$ [d.f. 11] $p = 0.002$) for the left frontal derivation.

The relationship between left frontal pre-sleep 7-8Hz activity and low frequency delta during sleep is shown in Figure 6.8. As can be seen, increased amounts of 7-8Hz activity prior to sleep onset was associated with an increased amount of relative low frequency delta during sleep.

This relationship was only evident for the left frontal region as all other quadrants were insignificantly related to low frequency delta ($r < 0.30$, $p > 0.1$).

[2] It was found that 6-7Hz was also related (r=0 66, p = 0 01) but this was expected due to the overlap from the EEG and was not significant once 7-8Hz was partialled out (r < 0.2, P > 0 5).

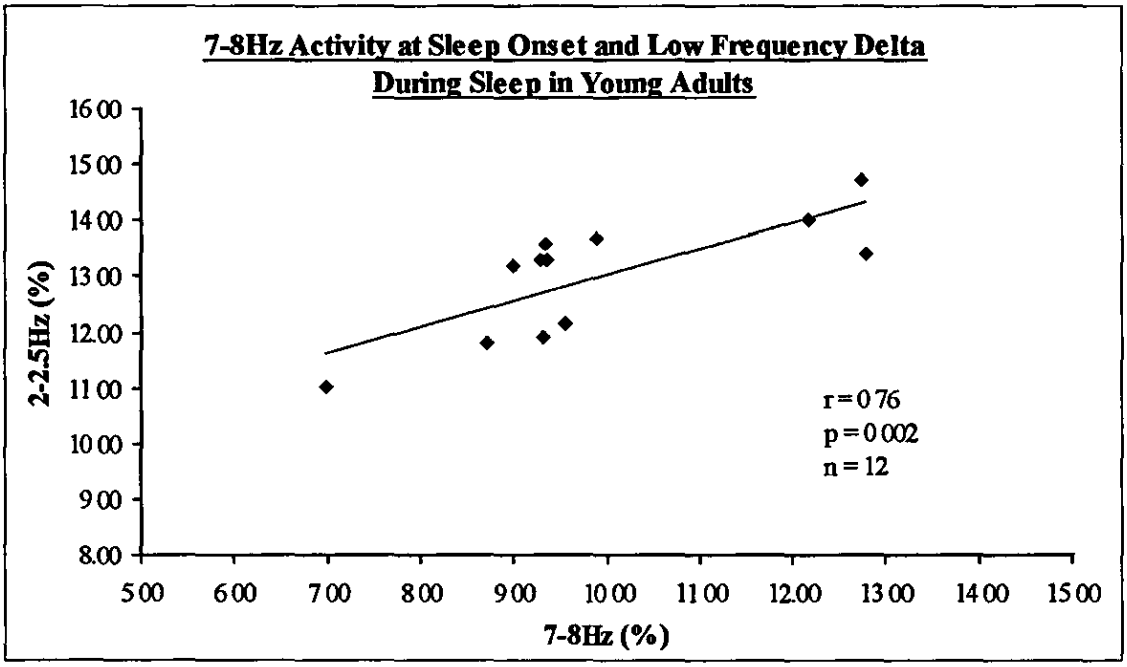


Figure 6.8: The relationship between left frontal relative pre-sleep 7-8Hz activity and relative power in low frequency delta (2-2.5Hz) during the first NREM period

6.4.4 7-8Hz Activity – An Issue of Impending Sleepiness

Although the relationship between low frequency delta and theta activity might be expected given the homeostatic properties of the sleep-wake cycle, it was shown in Chapter 4 that 7-8Hz activity was not indicative of a sleepy EEG; therefore a similar analysis was carried out on this younger subject population to ensure that 7-8Hz activity was not simply a factor of increased sleepiness at the settling down/pre-sleep period. Therefore, a spectral analysis over the range 3-11Hz was carried out for two separate samples: (i) The pre-sleep period discussed – Three minutes after lights out when the EMG becomes relaxed indicating 'settling down' but prior to any signs of drowsiness (e.g. eye rolling); (ii) Three minutes of artefact free EEG immediately before the onset of stage 1 sleep (Rechtschaffen & Kales, 1968). The comparison of power within each frequency bin is evident in figure 6.9. As with the older group, sleepiness is associated with the lower theta (3-6Hz) range, not 7-8Hz, as this is increased at immediately prior to sleep onset, whereby activities above 6Hz are generally similar for both conditions.

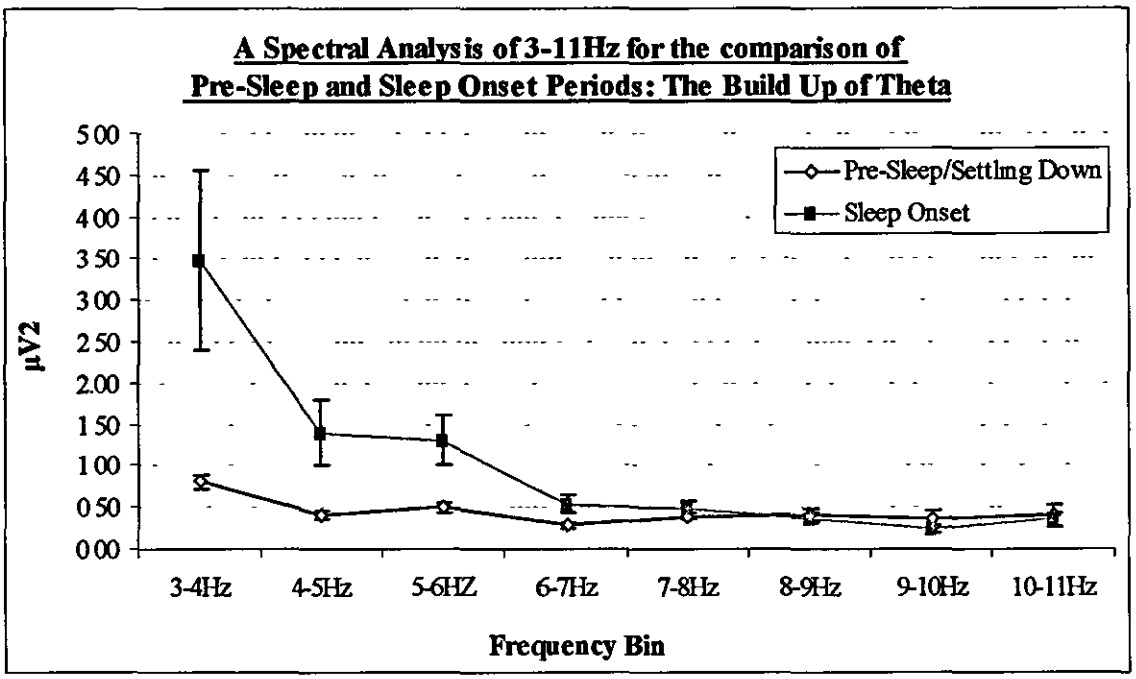


Figure 6.9: Spectral analyses of 3-11Hz power for two conditions: A clean period of EEG taken after lights out but prior to drowsiness and a period of clean EEG taken immediately before sleep onset.

6.4.5 Pre-Sleep 7-8Hz Activity Vs Neuropsychological Test Performance

Mean test performance is shown in Table 6 3 and is the same as that described in Experiment 1.

NVPT

It was found that relative power 7-8Hz in the left frontal region was significantly related to performance on the NVPT ($r = -0.77$ [d.f.11] $p = 0.002$). This can be seen in Figure 6.10. Once again, this relationship was unique to the left frontal channel with neither the right frontal ($r = -0.43$, $p > 0.1$), nor either parietal channel ($r < 0.31$, $p > 0.3$) demonstrating a relationship.

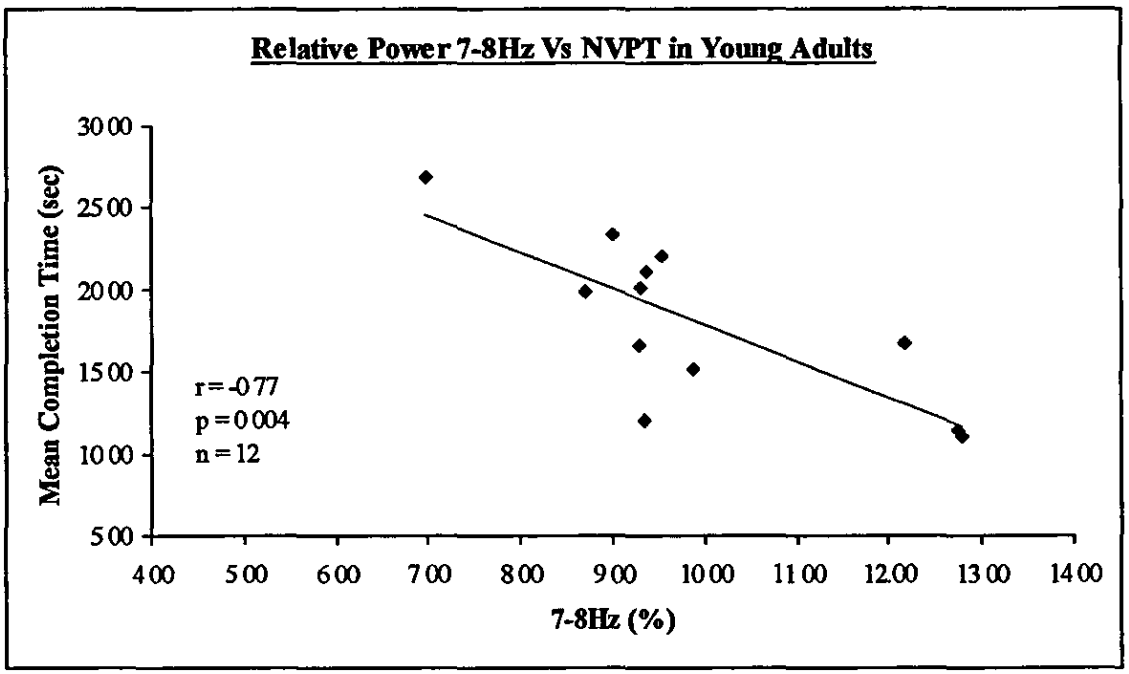


Figure 6.10: The relationship between left frontal relative power 7-8Hz prior to sleep onset and mean completion time on the NVPT in young adults.

Verbal Fluency

The relationship between 7-8Hz activity and Verbal Fluency (r = 0.77 [d f.11] p = 0.003) is shown in Figure 6.11. This shows that increased 7-8Hz activity at sleep onset is associated with better performance on the verbal fluency task.

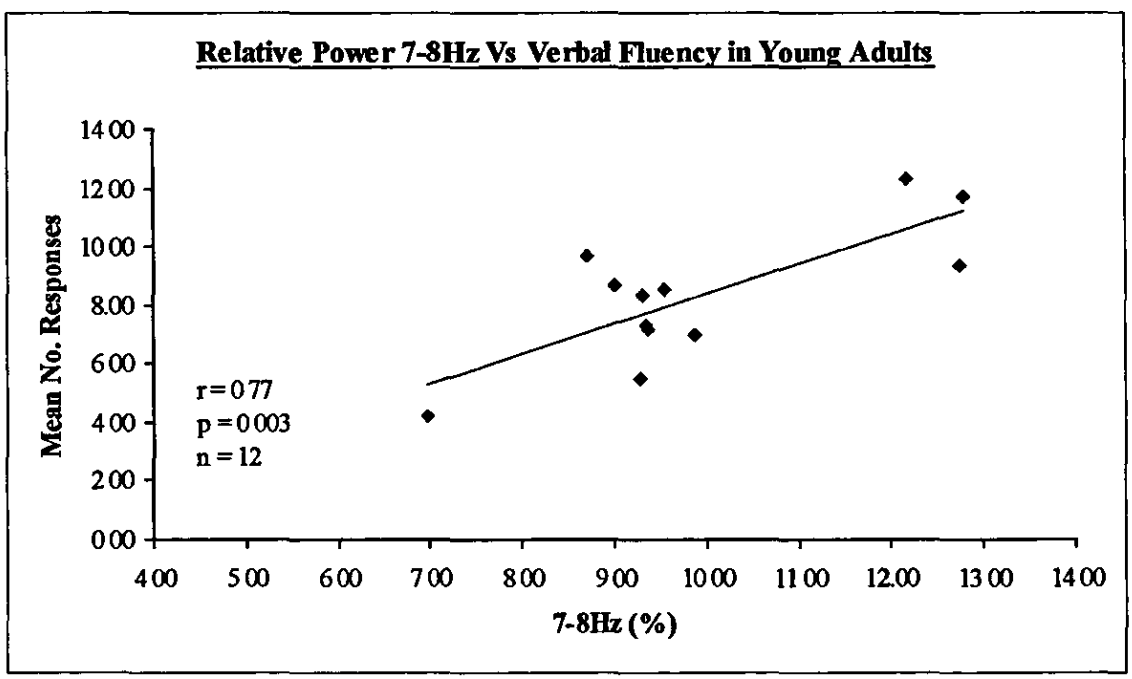


Figure 6.11: The relationship between relative power 7-8Hz, from the left frontal derivation prior to sleep onset, and mean number of generated responses on the verbal fluency task in young adults.

However, there is caution with this dataset since there appears three groups of data with the middle group showing a negative trend. A box plot of the data shows the distribution of this data (See Figure 6.12). The lower and higher points for the 7-8Hz data are not considered outliers (1.5times the median point) and the verbal fluency data also shows no outliers.

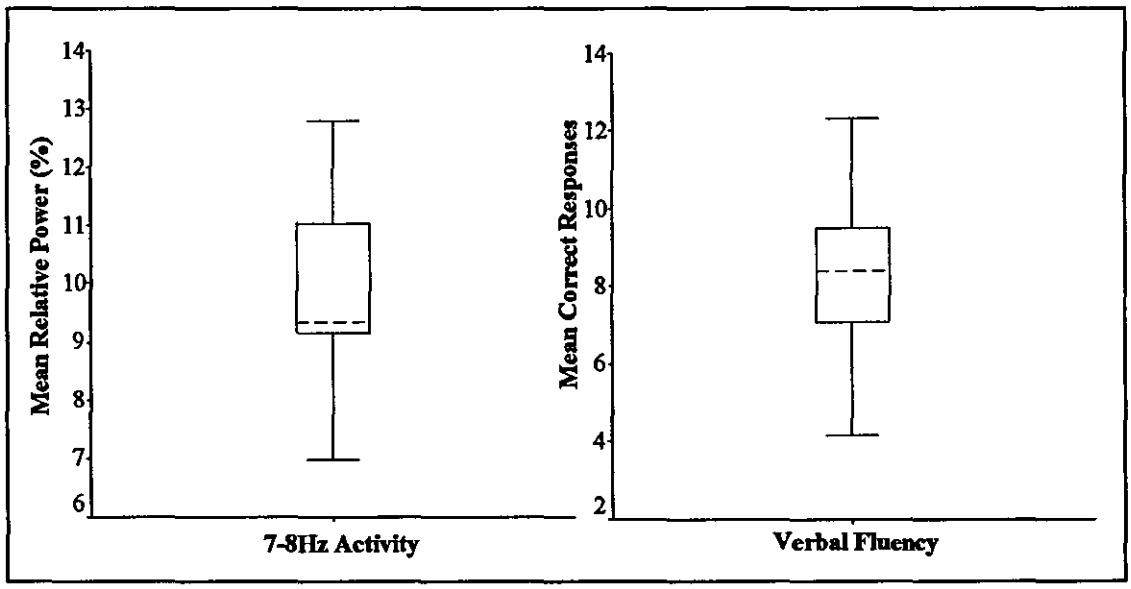


Figure 6.12: Box and Whisker Plot Showing the Distribution of Data for 7-8Hz Activity and Verbal Fluency Data. As seen no outliers are present in this dataset.

As a secondary measure, leverage values were computed for both sets of data. The verbal fluency data showed three high values (0 23; 0.24; 0.25) and the 7-8Hz activity showed two points of high leverage (0 27; 0 29) Leverage has a value of p/N[3] with an estimate of <0 2 being safe, 0.2-0 5 being viewed as risky and >0.5 to be avoided. However, when $p > 6$ and $(N - p) > 12$ (as in this case) then $3p/N$ is normally a cut-off Therefore, the cut-off point for leverage is 0.25 thus removing two of these extreme points. The removal of these values renders the correlation insignificant ($r = 0\ 58$ [d f. 9] $p = 0.07$), whilst still containing a further two points of high leverage. Therefore, the relationship between 7-8Hz activity and verbal fluency should be viewed with caution

[3] p = number of estimated parameters (including constant) N = Number of values

This relationship between 7-8Hz activity and verbal fluency is not evident for the right frontal channel (r = 0 27 p > 0.4) However, an interesting find concerns the parietal channels as there is a trend between verbal fluency and 7-8Hz activity in the left parietal (r = 0 51, p = 0.08) and a significant relationship with the right parietal channel (0.58, p = 0.046). The relationship for the right parietal channel is shown in Figure 6 13

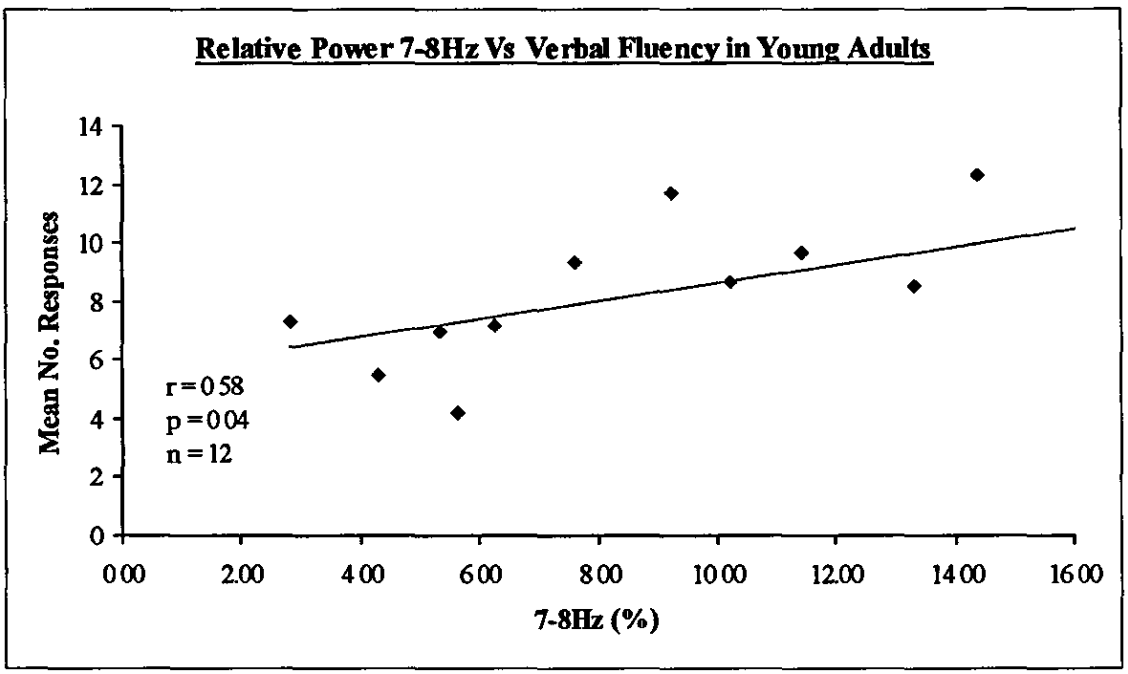


Figure 6.13: The relationship between relative power 7-8Hz in the right parietal channel and performance on the verbal fluency task.

The relationship between verbal fluency and the right parietal area is interesting. It is thought that the relationship may be due to a high intra-hemispheric correlation of the EEG, however, a cross-correlation reveals that the left PFC and right parietal are not correlated (r = 0.19, p > 0.5). Also, the correlation between verbal fluency and 7-8Hz activity in the left PFC whilst controlling for the right parietal, increases to 0.83 (p = 0.001) [from 0.77], and by correlating 7-8Hz activity from the right parietal and verbal fluency, whilst controlling for the left PFC, increases the correlation to r = 0.71 (p = 0 015) [from 0.58].

Given these partial correlations, it appears that 7-8Hz activity in the left frontal and right parietal together explain more variance in the verbal fluency data than when alone. Therefore, to investigate this further a forward stepwise regression

was carried out. The regression model shows that relative 7-8Hz activity in the left PFC and right parietal region account for 80% of the variance in the verbal fluency data. A relationship between the two independent variables is not evident given the high tolerance values between the two (0.96) indicating a correlation of approximately 0 20 (tolerance $= 1 - r^2$).

Other Neuropsychological Test Performance

Pre-Sleep 7-8Hz activity was not related to temporal memory ($r < 0.48$ [d.f.11] $p > 0.1$), IQ ($r<0.54$ [d f 11] $p > 0$ 05) nor reaction time ($r < 0$ 3 [d f.11] $p > 0$ 4) for any quadrant(s).

6.5 RESULTS – A Comparison of Age

The data presented in this chapter was compared against that presented in Chapter 4 (Wake EEG and Neuropsychological Test Performance in Healthy Older People).

6.5.1 Neuropsychological Test Performance

Table 6.5 shows the difference in means for test performance that was undertaken for both age groups

Table 6.5: The Difference in Mean Test Performance for Younger and Older Groups.

		NVPT	VERBAL FLUENCY	RT	IQ
Young (19-23y)	*Mean*	**18.01**	**8.31**	**263.68**	**122.33**
	Stdev	*5 00*	*2 30*	*20 05*	*9.78*
Older (61-75y)	*Mean*	**25.47**	**8.10**	**323.50**	**100.33**
	Stdev	*9.45*	*1.85*	*33 84*	*9 04*

An independent t-test assessing any possible age differences in the data confirmed that young people performed better on the NVPT ($t = 2.268$ [d f 22] $p = 0.03$), had faster reaction times ($t = 4$ 851 [d.f.22] $p = 0$ 0005), had a higher IQ ($t = 5$ 058 [d f 22] $p = 0$ 0005), but did not significantly differ on verbal fluency ($t = 0$ 460 [d f.18] $p > 0.1$)

6.5.2 Experiment 1 – Wake EEG: Daytime 7-8Hz Activity

The effect of age on 7-8Hz activity was assessed for each of the conditions It was found that the younger group displayed more 7-8Hz activity during the eyes closed condition (t = 2.9 [d.f. 21] p = 0.008) Neither the verbal fluency nor song condition displayed any significant difference between the two age groups (t < 1 2 [d.f.18] p > 0 1) However, the older group displayed significantly more 7-8Hz activity for both the left frontal (t = 4.86 [d f21] p < 0 001) and the right frontal channels (t = 2.87 [d f.21] p = 0 008) during the thinking condition However, there was no significant differences between age groups for the parietal channels (t < 1 6 [d f21] p > 0.1).

A comparison of percentages is shown in Table 6 6

Table 6.6: Relative Power in the 7-8Hz range for the left frontal region – A Comparison of Age

		EYES CLOSED	VERBAL FLUENCY	SONG	THINKING
YOUNG	*Mean*	**8.46***	**7.45**	**7.43**	**6.51**
	St Dev	2.31	1.71	2.12	1 66
	n =	*11*	*10*	*8*	*12*
OLDER	*Mean*	**6.33**	**7.76**	**9.00**	**8.20***
	St Dev	1 03	1.90	3 27	1.22
	n =	*12*	*12*	*12*	*12*

* = Significantly higher at the 1% level

6.5.3 Experiment 2 – Wake EEG Pre-Sleep 7-8Hz Activity

Sample Times

A comparison between sample times was undertaken between younger and older groups An unrelated t-test confirmed that the younger group had a significantly shorter sample period (t = 2.631 [d f. 30] p = 0 01) and also the time between the sample and sleep onset was shorter (t = 1 887 [d.f. 30] p = 0 03). The shorter sample period is expected given the shorter sleep onset latency for the younger age group

7-8Hz Activity Differences

An age comparison of mean relative power 7-8Hz after "lights out" but prior to sleep onset/drowsiness between young and older age groups was carried out. A One-Way ANOVA confirms that there is no significant difference in mean values for either young adults ($F = 2.470$ [d.f. 3,44] $p = 0.07$) or older groups ($F = 0.848$ [d f. 3, 44] $p = 0.47$) across the quadrants There was no significant difference in the percentage of 7-8Hz activity between young and older adult groups for the left frontal ($t = -0.135$ [d f. 22] $p > 0.5$), the right frontal ($t = -1.693$ [d f.22] $p > 0.1$);nor the right parietal ($t = -1.533$ [d f 22] $p > 0.1$) yet there as a significant difference in age for the left parietal ($t = -3.699$ [d f 22] $p = 0.001$) However, as discussed below this analysis should be approached with caution.

Comparison of Percentage Data

Due to the percentage basis of data analysis (for Experiment 1 and 2) a comparison between age groups is difficult since it would only compare on a distribution basis. Also, the amount of total power within the full range (4-8Hz) would affect the resulting percentage data This is confirmed with a spectral analysis of baseline, relaxed alert wakefulness (eyes closed) using the Fast Fourier Transform (FFT) method.

The FFT enabled the comparison of the peak frequency and mean power density within the theta range (4-7Hz) and the alpha range (8-11Hz) It was found that there was no significant difference between ages for the peak frequency in the theta range ($t=0.85$, [d f 20] $p>0.1$), but for alpha, the peak frequency was significantly higher for the younger group ($t = 3.85$, [d f 20] $p = 0.001$) indicating the well-known slowing of the EEG with age. This can be seen in Figure 6.14.

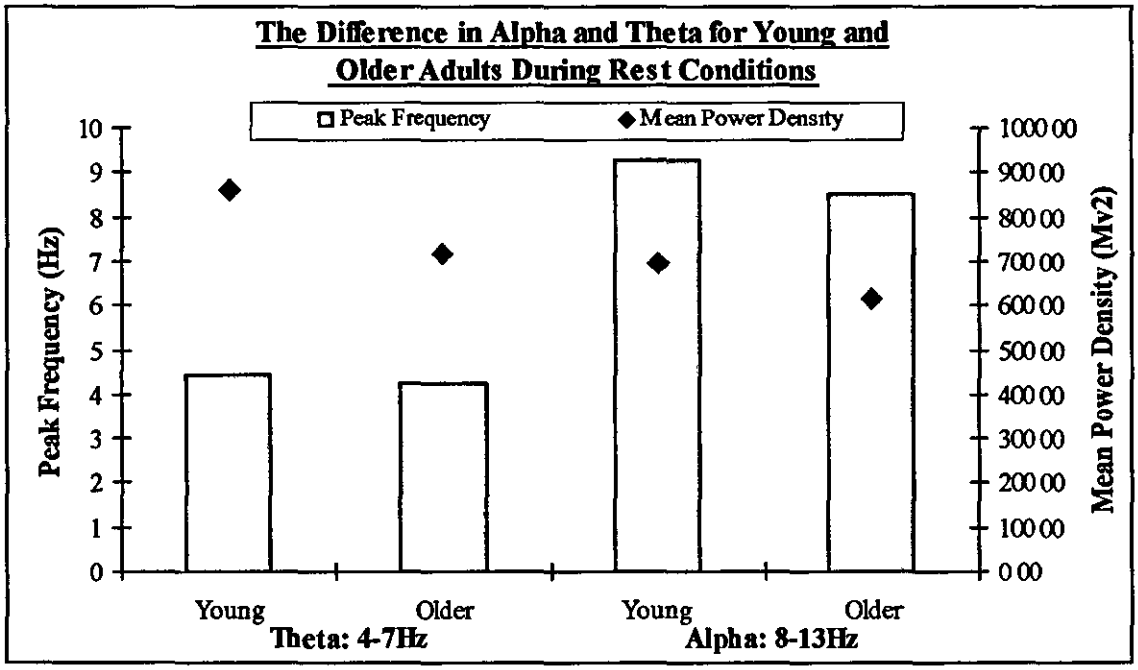


Figure 6.14: The Difference in the spectral properties of the alpha and theta range: An Age Comparison. The bar chart and left hand axis shows the peak frequency[4] and the markers and right hand axis indicates the mean power density[5].

It is evident from the graph that the younger group have a higher peak frequency in the 8-11Hz range, but not the 4-7Hz. Mean power density would indicate that the younger group have increased power density in both the theta and alpha range, although this was insignificant for both the theta ($t = 0\,98$ [d.f.20] $p > 0.3$) and alpha range ($t = 1.12$ [d.f. 20] $p > 0.2$)

6.6 DISCUSSION

It was found that activity 7-8Hz, during both daytime waking recordings and pre-sleep recordings, was related to delta sleep at night and also neuropsychological test performance. The two wake conditions were highly related possibly due to the similarity in thinking characteristics during the two conditions, albeit only putative, and so it is thought that increased 'thinking', evident in higher 7-8Hz levels, is associated with greater delta sleep at night and also better performance on tasks oriented towards the PFC. Once again, the associations found were unique to the left frontal region supporting a localised function of sleep in terms of cerebral recovery.

[4] Peak Frequency – Point of highest power in the frequency band (4-7Hz or 8-13Hz)
[5] Mean Power Density – Mean power of the full frequency band (4-7Hz or 8-13Hz)

6.6.1 7-8Hz Activity – Sleepiness Versus Thinking

Due to a focus on the theta/low alpha range (4-8Hz) it was imperative to account for any issue of sleepiness since this would not only affect the recording in terms of activity produced, but eye rolling associated with drowsiness would cause artefact on the EEG. Therefore, Experiment 1 controlled for this by prompting a KSS rating approximately every 3minutes during the trial, aborting if and when the reading was ever given above 7 (Sleepy, but no effort to keep awake) since this level is associated with physiological signs of sleepiness (Åkerstedt & Gillberg, 1990). For Experiment 2 it was ensured that all recordings were taken before any signs of drowsiness from the EEG and/or EOG, this period was just after "lights out" but preceded these signs of drowsiness It was expected that this criteria would cause a reduced sample length for the younger age group since it was thought they would have shorter sleep onset latencies. This was found to be the case with the younger group showing significantly shorter sample periods due to the issue of a quicker impending sleepiness.

Nevertheless, 7-8Hz activity was not thought to reflect sleepiness since a comparison of the pre-sleep period, with a period closer to sleep onset (and thus more characteristic of sleepiness), indicated that activities lower than 6Hz were higher closer to sleep onset whereas those above 6Hz showed no great increase with high levels of sleepiness Therefore, lower theta frequencies were associated with sleepiness, as supported by Cajochen et al. (1999)

As with the findings from Chapter 4, the specified frequency bin was 7-8Hz. This is considered interesting because:

1) It has been implicated in studies involving thinking process (e g Jensen et al , 2002)
2) It is argued to show homeostatic sleep propensity in the waking EEG (e g Finelli et al., 2001).
3) It may be what is known as the 'kappa' rhythm
4) It falls on the boundary between the theta range and the alpha range

The first three points will be discussed thoroughly later on, however, the latter point is of interest here. Rechtschaffen & Kales (1968) argue that the theta range

encompasses frequencies 4 5-7 5Hz with some researchers using 7Hz as the cut-off (e g. Cajochen et al , 1999) and the alpha range as 8-13Hz Therefore, 7-8Hz falls between these and could be regarded as high theta activity or low alpha activity. As frequencies in the lower end of the theta range are normally indicative of sleepiness(e g Cajochen et al., 1999) then it is argued that 7-8Hz may not reflect sleepiness and may actually be regarded, by some, as alpha activity. Nevertheless, sleepiness was controlled to ensure this was not problematic.

6.6.2 7-8Hz Activity Versus Night-Time Delta Sleep

A strong relationship was found between daytime 7-8Hz activity during a 'thinking' condition and night-time delta activity that was thought to reflect recovery sleep (See Chapter 5) This relationship was also found for pre-sleep 7-8Hz activity with night-time delta activity. Both relationships are expected given that Chapter 4 found a strong relationship between daytime and pre-sleep 7-8Hz activity with night-time delta in healthy older people. Once again, these relationship were specific to the left frontal region.

The finding that these relationships between wake EEG and delta EEG are consistent in both age groups, but not across different quadrants supports the argument that the associations between EEG and PFC performance are PFC-specific *not* age-specific. The idea that associations between the EEG and performance are unique to (left) frontal areas and not a consequence of age (i e. reduced delta, reduced PFC function) has also been demonstrated in Chapter 5 where the relationship between the Sleep EEG and PFC performance was also PFC-Specific and not age-specific.

As the wake EEG is only of interest during the 'thinking' conditions, and not eyes closed for instance, it is thought that the 'thinking' aspect is important. Therefore, 7-8Hz activity may be reflective of increased 'putative' thinking as proposed by researchers in the field of cognitive neurophysiology (e g. Jensen & Tesche, 2002; Kahana et al., 2001). The finding in this thesis between the wake and sleep EEG therefore supports a localised function of sleep since enhanced thinking (7-8Hz) is associated with higher levels of recovery delta localised to a region that works

hardest during the day, that is the (left) PFC. This supports the findings of Clark et al., (1998) who found that daytime rCBF was related to delta sleep at night, and that this relationship was stronger in the left PFC

The relationship between 7-8Hz activity and SWA also supports the findings of Finelli et al. (2000) as they proposed that EEG markers of sleep homeostasis in the wake and sleep EEG are similar. Furthermore, the authors describe how the increase in theta and SWA was exhibited most over the frontal areas. They ascribe this to a common underlying process between the two activities Given the finding that SWA was related to performance, it is argued that activity 7-8Hz might also be related to performance as these two activities share an underlying process as shown by Finelli et al. and also in the current study.

6.6.3 7-8Hz Activity Versus Neuropsychological Test Performance

Daytime wake EEG activity (7-8Hz) was related to performance on the NVPT, whilst a trend was also evident with the verbal fluency task Once again, this relationship was specific to activity from the left frontal region (bar the right parietal – discussed below) and to tasks that activated the left PFC during completion (NVPT – Morris et al , 1993; Verbal Fluency – Frith et al., 1991). The activity 7-8Hz from the pre-sleep period also indicated a relationship with performance on the NVPT and Verbal Fluency. Therefore, similar to the findings in regard to an older population, enhanced thinking (7-8Hz activity) is not only associated with higher levels of recovery sleep in the left PFC, but is also indicative of performance on tasks known to rely on the left PFC. This suggests, firstly, that sleep serves a localised function enabling a possible use of the EEG in assessing PFC performance, and secondly, given that the sleep and wake EEG may have an underlying commonality, the wake EEG may also be used in the association to PFC performance.

The relationship between 7-8Hz activity and neuropsychological test performance would support the findings of Hoptman & Davidson (1998). As stated in the introduction, these authors reported low correlations between wake EEG and the Tower of London, the correlations reported in this study were much higher

possibly due to the portion of EEG being during quiet, relaxed wakefulness after "lights out". The findings in this also replicate those of Çiçek & Nalçaci (2001) who found that resting EEG (8.6-10.2Hz) was related to performance on the WCST, a task known to activate frontal regions (e g. Rezai et al , 1993) Although these authors specify 8 6-10.2Hz it was argued in a previous chapter whether this activity was similar to the 7-8Hz activity located here, and that they are, in fact, both 'kappa' activity which is proposed to be 1Hz slower than alpha (around 7-12Hz) and is a result of increased thinking The authors found this relationship only for low alpha and not for high alpha (10.9-12.5Hz), which would support this idea. Although the kappa rhythm was not given much recognition, frontal theta was often referred to in the studies relating cognition and neurophysiology. Ishihara & Yoshii (1971) found that frontal theta increased during task performance, with the greatest increase during the Digit Symbol Substitution Task (DSST) which, incidentally or otherwise, was the only task they used that was predisposed towards activation of the frontal regions. Therefore, if conscious thinking generates more frontal theta/kappa activity, than eyes closed conditions for instance, then surely one would expect to find an association between activity in this region with delta sleep at night, and thus PFC performance, given the fact that the daytime PFC and night-time PFC show strong relations (e.g. Clark et al., 1998; Braun et al , 1997).

As aforementioned there was a finding between right parietal activity and performance on the verbal fluency task. Although this is possibly a random effect given the correlational nature of the study, findings by McEvoy et al (2001) may support this finding. They found that younger (mean 22y) older adults (mean 69y) differed in the topography of theta activity produced as a function of task complexity They propose that the younger participants utilise posterior sites as task complexity increases whereas the older group relied on the controlled and effortful frontal networks, which were showing signs of age-related decrements thus affecting performance *and* activity produced The finding that activity in the right parietal is related to verbal fluency performance here may therefore be accounted for by the idea that younger participants recruit other areas during times of thinking and/or task completion However, as pointed out this could be a

random effect and any relation to previous studies is done with care and merely at an observational level

6.6.4 A Comparison of Age

The aim of the study was to assess associations between neuropsychological test performance and the wake EEG, and was therefore not a study of ageing. The study of younger participants is merely to investigate these associations further. Therefore, the comparison of younger and older adults here is not to make assumptions based on the ageing cerebrum, but is to merely assess the differences between the associations found in different age groups of people Where possible age effects are investigated (i e. neuropsychological test performance) this is done to show the normality of the older group in terms of healthy ageing

Neuropsychological Test Performance

Although the sample of older participants were considered healthy and possibly elite, they did show age-related impairments on performance measures which supports previous studies indicated in brackets: NVPT (e g. Andres & Van der Linden, 2000); Reaction Time (e g. Wilkinson & Allison, 1989); and IQ. It is argued that IQ may demonstrate ageing effects for two possible reasons. Firstly, the task does rely on the frontal areas of the cerebrum as the task requires novel, goal directed behaviour and sustained attention. Secondly, the task employed (CCCF) is based on time, and it is thought the older group may have merely completed less categories due to a time constraint as opposed to an actual age-related reduction of fluid intelligence. This is further supported by the fact older adults were significantly slower on a task of speed, the reaction time task An effect of age was not found for the verbal fluency task which is surprising given previous findings that an age-effect is apparent (e g. Corey-Bloom et al , 1996). A possible reason for the lack of age-effect for the verbal fluency maybe attributed to the fact that the older group were split to include only those with post 16years education, and furthermore the verbal fluency task used the verb-to-noun generation task, of which the older group were seemingly more familiar with the concept and meaning of verbs/nouns than the younger group.

7-8Hz Activity

Daytime Wake EEG

The older participant group displayed more relative power 7-8Hz, during daytime alert recordings, than did the younger group for the frontal channels only, and during only the contrived thinking conditions This age difference was not evident during the pre-sleep period, apart from the left parietal region. There are possible reasons for this, such as that presented by McEvoy et al. (2001) who argue that younger adults rely more on posterior regions for general thinking whereby older participants rely on the more effortful frontal regions

It is difficult to make assumptions based on this data given that it is relative, and therefore one can only compare in terms of distribution. However, a resting FFT was computed during 'eyes closed' alert wakefulness and it was found that there was no difference in peak frequency for the theta range with age, but for the alpha range (8-13Hz) the younger group had a significantly higher peak frequency indicating the well-known phenomenon that the EEG slows with increasing age.

7-8Hz Activity Versus Sleep EEG and PFC Performance

There was a relationship between PFC performance and daytime 7-8Hz for the younger group was not evident in the older group. The lack of finding for the older group was attributed to a problem of artefact; although this was also problematic for the younger group, the signal may have been stronger for the younger group (they have higher mean power densities in the theta and alpha range) and thus associations were found.

The relationship between pre-sleep 7-8Hz activity and PFC performance was found for both groups as expected, thus showing that the associations between the wake EEG (7-8Hz) and PFC performance is consistent across different age groups

The inter-relationships between daytime 7-8Hz activity, pre-sleep 7-8Hz activity and delta sleep EEG were found for both age groups, thus showing that the EEG has underlying properties over the wake-night cycle in younger and older people Therefore, the inter-relation of these three variables is due to an underlying factor

that is common to the EEG as opposed to an age factor (i.e. reduction in delta for instance).

6.7 CONCLUSIONS

Summary

Experiment 1

1) Theta during the trial was thought to be reflective of increased thinking and not sleepiness because·
   a) KSS scores showed the recording was during a time of maximal alertness.
   b) Tasks were of short duration and were interesting and novel.
   c) KSS and EEG/EOG throughout the trial remained alert, and if not, the trial was aborted.
2) The frequency of interest was specified as relative power 7-8Hz as this was associated with PFC performance and the sleep EEG whereas other bands (4-7Hz) were not.
3) Daytime 7-8Hz activity was strongly related to delta activity at night indicating that contrived thinking during the day is associated with an increase in recovery sleep at night (low frequency delta) which would support functional imaging studies Once again, this is unique to the left PFC.
4) There was a relationship between daytime 7-8Hz activity and NVPT supporting findings that this activity is reflective of thinking processes and linked to task performance This was unique to the left PFC.
5) There was a trend of an association between daytime 7-8Hz and performance on the verbal fluency but this was not significant due to the small sample size (n=10). This trend was only evident in the left PFC.
6) Criticism lies in the methodology in that the EEG was prone to noise, and participants numbers were only kept maximal due to the integration of similar categories. No category had a 100% data collection record.

Experiment 2

7) Theta during the trial was thought to be reflective of increased thinking and not sleepiness because·
   a) Recordings were taken immediately after "lights out" once the participants has settled down and prior to drowsiness

b) No physiological signs of sleep were evident on the EEG/EOG - e g Eye rolling, slowing of the alpha rhythm.

c) A comparison of the pre-sleep period used with a period closer to sleep onset (reflecting peak sleepiness levels) indicated that activities below 6Hz were closely associated with sleepiness, and not those above 6Hz

8) Activity of interest was once again shown to be 7-8Hz Pre-Sleep 7-8Hz was strongly related to daytime 7-8Hz, and was argued to be due to thinking after lights out.

9) Pre-Sleep 7-8Hz was related to delta activity during the night. This relationship was unique to the left PFC.

10) Pre-Sleep 7-8Hz activity was associated with PFC performance in that increased activity was associated with better performance. This relationship was again unique to the PFC.

11) The 7-8Hz activity, during both daytime and pre-sleep recordings has been suspected to be reflective of thinking activity ('kappa' or 'frontal theta')

12) As Findings were found across both young and older participants (See chapter 4), the relationships found for the younger group show that these associations between wake EEG and performance/sleep EEG are consistent across age groups and are PFC-specific, not age-specific.

Conclusion

It was shown that wake EEG (7-8Hz) was related to both low frequency delta and PFC performance that was specific to the left PFC in a younger adult population. It has previously been shown that low frequency delta in the sleep EEG is related to PFC performance in older and younger groups due to a PFC-specific underlying commonality between the two indices However, the wake EEG was further analysed with an older population and not only did it demonstrate that the wake EEG was related to low frequency delta during sleep, it also was associated to PFC performance. This chapter shows how this inter-relation between low frequency delta, PFC performance and the wake EEG is not just found in older groups but is consistent in a younger population further supporting an underlying common factor between these three factors.

CHAPTER 7

GENERAL DISCUSSION

7.1 Prelude to the Experimental Studies Undertaken

Previous work had shown that the PFC was more vulnerable to sleep loss (c f. Horne, 1993) and the effects of healthy ageing (e g. West, 1996) possibly due to increased CMR during the day (Braun et al , 1997, Maquet et al , 1990). The decreased amount of CMR during the SWS period in the PFC (Maquet, 2000) and the increased amount of delta sleep in the same region (e g. Landolt et al., 1996) indicate that the PFC is a focus for recovery during the night Recent attention has turned towards low frequency delta as this is thought to be generated by the cortex (Steriade et al , 1993a-c) and was thought to be a true reflection of recovery sleep since it was frontally dominant (e.g. Werth et al., 1996, 1997). Nevertheless, even though PFC-delta sleep links were strong, no one had assessed the relationship between PFC performance and delta sleep. The majority of sleep and performance research has focussed on sleep/sleep disturbance with regard to behavioural measures of sleepiness (See Pilcher & Huffcutt, 1996) Studies that had looked at the EEG in an effort to assess performance either focussed on non-cortically specific areas (e g. central derivations) or non-cortically specific tasks (e g Bliwise, 1989; Crenshaw & Edinger, 1999, Edinger et al 2000).

In regard to the wake EEG, delta sleep (0.5-4.5Hz) has recently been shown to be positively correlated with accumulated daytime theta (5-8HZ) activity (Finelli et al., 2000), although this association was not localised Given the findings regarding low frequency delta, the thesis aimed to establish whether· (i) there were more specific links between night-time delta and daytime theta, (ii) whether any such association was localised to the left frontal region, and (iii) whether theta was linked to daytime PFC performance due to a similar underlying function/action in addition to the fact that daytime theta had already been linked to cognitive processes and performance (e.g. Kahana et al , 2001). Once again, a focus on the PFC was deemed necessary given the literature discussed above.

Therefore, research aims for this thesis were formed based on prior literature and ideas presented. The research aims were thus:

Research Aims

- Is the Sleep EEG related to neuropsychological test performance?
- Is this relationship specific to the PFC?
- Is low frequency delta a focus for this relationship?
- Is this relationship localised, supporting a localised function of sleep?
- Is delta activity in the Sleep EEG linked to theta activity in the wake EEG?
- Is theta activity linked to PFC performance
- Is this relationship localised?
- Are these relationships between wake EEG, Sleep EEG and PFC Performance links found for younger and older people alike?

7.2 Overview of Findings

Focussing on low frequency delta, it was investigated if this activity was related to PFC performance in healthy, older people since they show a reduction in both delta activity and PFC performance and it was thought any association might be enhanced. The relationship between the two indices was evident, and given the findings of Finelli et al. (2001) attention moved to the waking EEG to see if these associations were unique to the sleep period or were evident over the sleep-wake cycle Once again, associations between PFC performance and activity in the PFC during wakefulness were apparent.

It was then questioned whether these associations were due to an underlying effect of age, i e. reduced metabolism in the PFC (Martin et al., 1991), and thus unique to an older sample group, or whether these findings were unique to the PFC and thus found across older and younger people alike Findings confirmed that these associations were specific to the PFC and not a product of ageing, albeit the relationship was enhanced in an older group. The wake EEG and sleep EEG were highly inter-related supporting Finelli et al. (2001), with the current study showing this to be further related to PFC performance, possibly given the localised function of sleep (delta activity) and in turn, its association to the wake EEG. Therefore, the thesis not only demonstrated links between the wake EEG and neuropsychological test performance, it built on the delta-theta link proposed by

Finelli et al., by showing the relationship to be both frequency specific and topographically specific

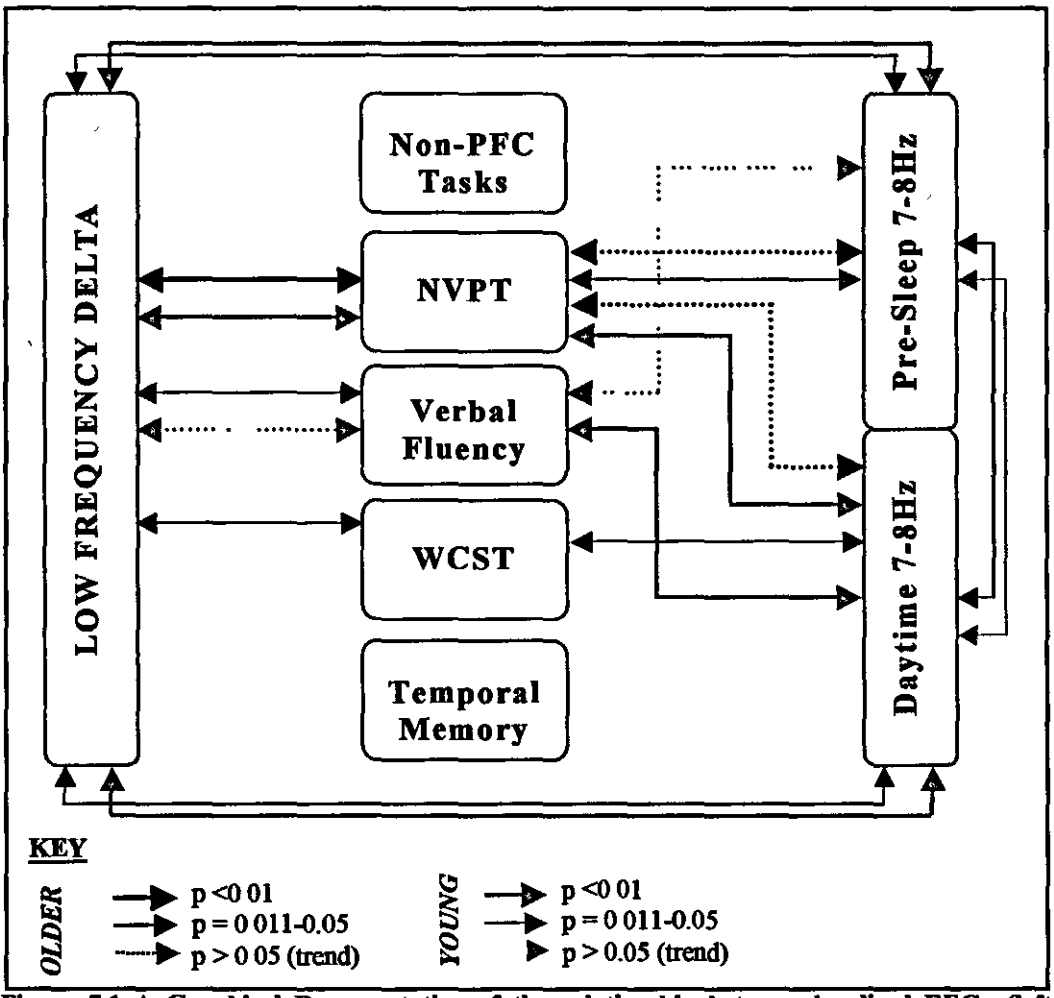


Figure 7.1 A Graphical Representation of the relationship between localised EEG (left frontal) and Neuropsychological test performance.

These findings between the sleep EEG, the wake EEG and neuropsychological test performance, for both age groups, are graphically depicted in Figure 7.1 as seen above. To refer back to the initial research aims, these questions can now be answered given the findings presented in this thesis:

- Is the Sleep EEG related to neuropsychological test performance?

  Yes, Low Frequency Delta was associated with better performance.

- Is this relationship specific to the PFC?

  Yes, both EEG and activity and task activation were PFC Specific

- Is Delta Activity in the Sleep EEG linked to Theta activity in the wake EEG?

  Yes, Strong associations were found between the sleep and wake EEG
- Is theta activity linked to PFC performance

  Yes, 7-8Hz was linked to PFC performance and sleep EEG. It was questioned what this activity was since it fell on the boundary theta/alpha boundary and was therefore suspected as 'kappa'
- Is this relationship localised?

  Yes, Once again, both activity and task activation were specific to the PFC.
- Are these relationships between wake EEG, Sleep EEG and PFC Performance links found for younger and older people alike?

  Yes, Associations were consistent for both younger and older adults, suggesting these associations to be PFC Specific and NOT at the behest of age.

7.3 Methodological Considerations

Although the use of the EEG is not as specific as functional imaging methods, this work has demonstrated that the EEG can be used to assess PFC performance However, in studying the relation between EEG and task performance, there are several methodological factors that should be considered, with respects to both the EEG and neuropsychological tests.

7.3.1 The Effectiveness of the Sleep EEG

Ambulatory Recordings

On reflection, the use of ambulatory sleep EEG recordings was considered more suitable than laboratory based recordings. It was thought that participants, particularly the older participants, would find sleeping away from home uncomfortable and may have become slightly apprehensive. The only concern with ambulatory data collection was a possible loss of an electrode throughout the night, which would result in a complete loss of data for that channel for the whole

night. However, out of the seventy-eight nights, each with eight channels of EEG (16 electrodes), only one electrode was lost (younger group, subject 11, O_2-P_4). Therefore, a loss of data due to an ambulatory recording method was a mere 0.08%.

The presence of a night effect is questioned by researchers; research indicates that sleep in the home is less prone to this effect (Johns & Doré, 1978) and that the first night effect does not exist at all, as opposed to general sleep measures, such as SOL (Kupfer et al., 1974; Coates et al., 1979, Browman & Cartwright, 1980, Kadar & Griffin, 0983). The reliability of EEG recordings was considered high due to high night-to-night stability reported both in the literature (Larsen et al., 1995, Tan et al , 2000) and in the older group in the sleep study (Chapter 3) reported here. As the older group were considered more vulnerable to any adaptation effects, a third night was carried out for 1 in 4 participants in the older group, this demonstrated that the second night used for analysis was representative of normal sleep. A night-to-night stability measure was not carried out on the younger age group as these show even stronger night-to-night stability in delta sleep EEG on non-consecutive nights suggesting that the EEG is trait like (Tan et al , 2003).

Selection of the EEG Period

The EEG measurements used were considered both effective and reliable Although the waking EEG and sleep EEG provided an association to PFC task performance, the sleep EEG was considered less problematic in terms of artefact The first NREM period used, not only contained the most delta activity, but was also less disturbed, specifically for the older age group as the latter part of the night became more disrupted as shown by Bliwise (1997)

The criteria of the selection of the NREM period differed amongst researchers although guidelines set by Rechtschaffen & Kales (1968) are normally adhered to. This method however, has become less popular in recent times, especially with the study of the elderly, whereby considerations of reduced amplitude are essential (Dijk et al., 1989). The data was therefore standardised to the REM period, so the NREM period was reflected as an increase in power from baseline levels (REM) –

REM being used as opposed to wakefulness as this was less affected by artefact. Chapter 2 (general methodologies) presented the graphical representation of the identification of the first NREM period using Rechtschaffen & Kales' technique and the standardised technique (See figure 2.14). It showed that the identification period used was similar but that the standardisation period started slightly later, thus included stages 2,3 and 4, whilst avoiding stage 1 and any possible eye movement associated with this. This work therefore recommends the use of the standardised procedure in identifying the first NREM period

Low Frequency Delta

The use of low frequency delta was a focus for this work given its putative enhanced recovery properties for frontal regions (e.g. Werth et al., 1996, 1997) and the fact that this is generated by the cortex (e g Steriade et al., 1996). However, the study of low frequency delta, that is activity <1Hz, should be approached with care, given the possibility for the inclusion of artefact. The power band analysis used here took frequencies only above 0.5Hz, and therefore all frequencies less than this was filtered out by this method With frequencies around this mark, the major consideration is artefact from eye movements, which are slow in nature (0 2-0 3Hz). It is thought that waves in duration of 1 second (0.5Hz) are not affected by eye movement artefact during the first NREM period since the standardisation method does not include stage 1 sleep.

The use of frequency analysis to determine the selection of bands is effective, however, it may lead to some distortion. For instance, the frequency band 0 5-1Hz is a much larger bandwidth than 1.5-2Hz when considering the waves on a period-analysis basis even though they are both 0.5Hz bins The band 0 5-1Hz contains waves 1-2 seconds, whereas the 1 5-2Hz bin only contains 0.5-0 67 seconds; therefore, the width of the 0 5-1Hz band in terms of time is 1 second whereas the width of 1.5-2Hz in terms of time is only 0.17second The wider bandwidth will therefore have more waves included and a larger possibility of containing a frequency of 'interest'. Given that the use of 0.5-1Hz data was used for the older study, a secondary analysis split this frequency range into smaller bins to attempt to address this problem. As expected, frequencies within this seemingly small range waxed and waned, and the association to PFC performance appeared around

the 0 7Hz mark, which incidentally or otherwise, is the peak frequency of the cortically-generated low frequency delta (Achermann et al., 2001)

As the older group revealed interesting associations with 0.6-0.7 Hz activity, it was questioned whether the younger group may have had associations between PFC performance and lower frequency delta, for instance around the 0.3Hz signal. However, analysis did not go beyond 0.5Hz due to a possible inclusion of artefact This point demonstrates the difference in the delta rhythm, and the large bandwidths studied when carrying out a frequency analysis. It also highlights that when studying the delta rhythm, the bandwidth is so large in terms of time, it is more likely to find interesting associations and therefore, the use of specific and much smaller bandwidths (e.g. 0 5Hz) is recommended.

7.3.2 The Effectiveness of the Wake EEG

The use of the waking EEG, in relation to performance, has much more support from previous literature than the sleep EEG, however, this thesis shows the sleep EEG to be more effective and also adds to the sleep as a localised process debate The waking EEG was taken during alert wakefulness and also between lights out and drowsiness It was found that the period of waking EEG in the pre-sleep condition was more effective as it was less prone to artefact; however, caution was taken to avoid any drowsiness in the EEG during this period.

The study of the EEG and its effectiveness in assessing performance has gained much recognition in recent times Gevins would appear a pioneer in the work of promoting the EEG in 'assessing neurocognitive functions' (e g Gevins, 1998, Gevins et al., 1999). Previous literature that supports the EEG as a tool for assessing neuropsychological test performance has focussed on the waking EEG, with particular reference to the theta rhythm (e g Jensen & Tesche, 2002, McEvoy et al., 2001; Smith et al., 1999). The test-retest reliability of the waking EEG, taken during rest and task, has been shown to be highly reliable (rest - r = 0.70, Task – r = 0.90: McEvoy et al , 2000) Gevins et al. (1999) argues for the use of EEG over fMRI methods highlighting the advantages of the EEG as:

- The ability to monitor everyday activities in the real world

- Its compactness and simplicity
- A Low cost, portable monitor for clinical assessment
- The ambulatory nature reducing interference

Given this background literature it would appear the EEG is an effective tool for assessing neurocognitive performance; the work in this thesis draws on previous findings whilst taking a step forward in localising the process Perhaps the strongest support for the findings in this thesis, with regards to the waking EEG, come from Çiçek & Nalçaci (2001). These authors report that activity 8.6-10 2Hz during rest conditions, in the left PFC, correlated to better performance on the WCST. This supports findings for both the younger and older subjects participants in this thesis although the thesis used multiple 'frontal' tasks, and also the use of two different age ranges.

Although the sleep EEG revealed stronger and possibly more robust associations with neuropsychological test performance (possibly due to less noise in the EEG), the wake EEG associations presented here were stronger those presented by Hoptman & Davidson (1998). They found that the alpha rhythm (8-15Hz) was related to performance, specifically from the left frontal derivations with the verbal fluency task The findings from the current work show the correlations of Hoptman & Davidson's work to be low ($r^2 < 0.12$) as current findings all had higher correlation coefficients ($r^2 > 0.42$) Therefore, it is argued that the current study had higher correlations given cleaner recordings since Hoptman & Davidson did specify artefact as a problem.

The use of the second period of wake EEG (the pre-sleep period) was considered interesting since the relationship between the pre-sleep activity and low frequency delta is stronger than that found for the daytime EEG and low frequency delta; Not only is the activity taken in the pre-sleep period artefact free, it is free from any stimuli, thus any thinking is internally generated. A follow up telephone interview was carried out with a selection of participants to find out what they thought about after turning the lights out. All those interviewed gave answers, no one reporting not thinking at all Answers included:

- Visually thinking of grandchildren, family etc.

- Visually thinking of what done during the day
- Visually think of what doing tomorrow
- Think of falling asleep – focus on body extremities
- Visually think of happy scenario/role play in mind

From a neuropsychological perspective, it is thought that these thought processes described above would implicate the left frontal region as this region is implicated in most aspects of memory (Nyberg et al , 2003) and self relevant thought (Kelley et al , 2002) However, the extent to which 7-8Hz activity is reflective of these behaviours remains to be established. Nevertheless, 7-8Hz activity specific to this region and during putative thinking (memory and self-thought) that is linked to the left frontal area, is associated with night-time recovery sleep, possibly due to enhanced waking thinking.

Although it was raised whether findings in the wake EEG (7-8Hz) were due to trait-sleepiness, as opposed to trait-EEG characteristics, the finding was quickly dismissed since.

- Delta is proposed to reflect recovery (e g Werth et al , 1996)
- Delta activity has high stability over non-consecutive nights, in both young and older people, indicating a trait in the EEG (Tan et al , 2003)
- PFC performance is not affected by sleepiness, caffeine or reward (See Harrison et al., 2000)
- The daytime wake EEG was during high levels of alertness.
- A partialling out of trait sleepiness only increased correlations between wake and sleep EEG
- A time on task analysis revealed no effects (expected given the short duration – 1minute).
- Pre-Sleep periods were short, prior to eye rolling, and spectral analysis revealed no difference in power density during maximal sleepiness (i e sleep onset) for activities >6Hz

7.3.3 EEG Analysis

The expression of the relative power was used to remove any variance in the data due to confounding variable such as age and sex (See Carrier et al., 2001 for review). This was considered effective in that it did remove such variance as the data was essentially standardised within participants, within derivations This also removed the problem of calibration as long as the impedance and inter-electrode distance was consistent (Nevertheless calibration was carried out for validity reasons – See Chapter 2) The use of percentages also gives an indication of value for the layperson. Most EEG literature refers to amplitude and frequency, which for people outside the field of sleep research can be arbitrary, whereas the layperson reading this thesis is able to understand the difference in relative power between locations and participants due to the percentage value used.

7.3.4 Evaluation of Tasks

The selection of tasks used here was based on the extent to which the task relied on the PFC, through studies based on functional imaging and/or sleep loss Tasks that were thought not to reflect PFC integrity to such an extent were also given as part of the test battery. Of course no task is wholly PFC specific, but tasks selected did 'predominately' activate the specified area(s). Verbal Fluency is perhaps the most consistently used task for identification of frontal lobe impairment due to its high reliability of frontal activation (Poline et al , 1996). The verbal fluency was considered an effective task that was simple and straightforward to administer. The short duration of the task kept participants interested and thus boredom effects were minimal. The verbal fluency task showed associations to the sleep EEG for both age groups, with the wake EEG data revealing no strong associations. The lack of finding between verbal fluency and waking EEG was attributed to a reduced sample size. An apparent finding with the verbal fluency was the educational factor; as the young group were all similarly educated this was not problematic but for the older group sixteen participants had received further and/or higher education (i.e. beyond 16years), and were therefore treated separately In regard to the waking EEG, only eight out of the twelve subjects had received post-16years education and so no trend was apparent for these eight

participants. Although the educational factor was not problematic for the younger group they did show variance in their ability to understand verbs/nouns given the different backgrounds studied at pre-degree level

Through the studies described in this thesis, the NVPT has been the most appropriate task for assessing the relationship between EEG and PFC performance. The NVPT is highly specific to the left PFC (Ward et al, 1996, Morris et al., 1993), it is short, novel and interesting, and more importantly it has advantages over the verbal fluency in that it is culture and education free. The use of the NVPT through sleep loss is minimal, which when considering the executive function involved, i e. planning, and the extent to which this task has been used to pinpoint frontal lobe damage (e.g. Shallice, 1982), this is surprising. The verbal fluency was considered a good task to utilise, but care was taken to ensure all participants fully understood the requirements of the task and they could distinguish between a noun and a verb, the NVPT, on the other hand, was much easier and the practice session ensured that all participants fully understood the task. No data was lost during the task, and no participants expressed a lack of understanding. The strong relationship between NVPT and the EEG was attributed to the reliance of the NVPT on the PFC, and the lack of external variance caused by confounding factors (i.e. comprehension)

The WCST has also been consistently used in the assessment of PFC damage, although the extent to which this causes left (e.g Rezai et al, 1993) or bilateral (e g. Mentzel et al, 1998, Nagahama et al., 1996) activations remains to be in debate causing some researchers to question the validity of this test (e g Barcelo, 2000; Chase-Carmicheal et al., 1999; Anderson et al., 1991). However, the sleep EEG and wake EEG was shown to be effective at showing an association to PFC performance as measured using the WCST. In this thesis the WCST was adapted so that it was short and novel like the other tasks, and so the 64-card version was utilised. The WCST was only used for older adults, as they generally demonstrate impairment on this task (Daum et al., 1996). It was thought that the WCST was too simple for the younger age group as confirmed through a pilot study, therefore, for the younger participants the WCST was replaced with a task of Temporal Memory.

The temporal memory did not reveal any associations to the EEG, as did non-PFC specific tasks. It is thought that the temporal memory task was easy, and perhaps more study on the activation of temporal memory is needed Nevertheless, this task has been show to be affected by sleep loss due to its reliance on the PFC (e g. Harrison & Horne, 2000a; Harrison et al., 2000), although it was not considered specific enough to relate to changes in the wake and sleep EEG here.

The associations between sleep EEG in the left frontal region and neuropsychological test performance was strongest with the NVPT, followed by the verbal fluency and finally the WCST for the older age group (NVPT still the strongest for the younger age group). Incidentally, or otherwise, the NVPT and Verbal Fluency are shown to rely more heavily on the left PFC than the WCST, which is thought to be bilateral (e g Nagahama et al, 1996) Non-PFC tasks showed no associations to the sleep EEG, further suggesting the relationship to be specific to PFC performance.

7.4 Clarifying the Assumption of Ageing

Most studies assessing the sleep EEG have been focussed on younger adults, the use of older adults has been sparse. However, given the extent to which low frequency delta in the PFC (Landolt & Borbély, 2001) and that PFC performance is reduced in older people (West 1996), it was thought that this age group might reveal associations between these two indices. This was found to be the case. Although, this might be considered an age effect, due to reasons presented above, similar findings were presented for a younger age group. As seen, the younger group showed strong associations with the NVPT but not the other tasks. This is possibly due to temporal memory[1] being a poorer marker of PFC performance, and some of the younger participants having trouble identifying verbs from nouns on the verbal fluency task. However, the findings from the younger group are an integral part of the conclusions from the previous study on older people, since it shows that the relationship between sleep EEG and performance is due to an underlying commonality between the waking and sleeping PFC, and that these

[1] This task substituted the WCST for the younger group, since the WCST was thought to be too simplistic for this age group and therefore a possibility of ceiling effects

links between EEG and neuropsychological test performance were topographically specific and not age specific (albeit that the association is exacerbated in an older age group).

Nevertheless, the relationship between low frequency delta and PFC performance in the older group is thought to have greater functional significance since ageing is associated with both a reduction of delta power during sleep (e g. Benson et al , 1997) and also there is a decrease in PFC volume (e g Cowell et al,. 1994) The cause and effect of the association between performance and delta sleep cannot be attributed, neither can the idea that both may be due to an underlying biological cause, such as reduced PFC volume (Cowell et al , 1994) or a reduction in the number of synapses (e g Gibson, 1983, Masliah et al , 1993). If an underlying biological cause is the reason for this relationship between EEG and performance, this would be evident across both age ranges, possibly exemplified in the older age range. By establishing what causes a reduction of low frequency delta with age, may give insight into the direction of associations between EEG and performance found here, in respect to both older and younger adults This study would require the use of functional imaging techniques running concurrently with an overnight EEG study which was beyond the scope of this work.

Although the two age groups had similar association, the two delta frequencies identified and explored for the two age groups were different, possibly expected given the slowing of the EEG with age Although it is impossible to compare the two frequencies identified for recovery sleep, the thesis was able to make comments on the associations they show to neuropsychological test performance The frequency of interest for the older grouper is slower than that found for the younger group, although both are suggestive of being an enhanced form of 'recovery' for the cerebrum given that they are both (left) frontally dominant and both are associated with better performance on tasks known to activate the (left) PFC. If both frequencies are of similar function, it is plausible that the frequency of interest for the older group is slower than that of the younger group, given that the sleep EEG slows as one ages (Bliwise, 1993) There is also a similarity in that both frequencies display an inverse relationship between high and low delta frequencies, which would support the work of Achermann & Borbély (1997) and

Benoit et al. (2000) for example. Therefore, although the two frequencies are different in terms of characteristics (frequency), they are not considered functionally distinct

The relation of the proposed 'recovery' delta to neuropsychological test performance was stronger in the older group, in regard to individual task correlation and also the number of tasks demonstrating associations. The intra-task relation is considered stronger given that more participants took place, and also that there was more variance on tasks due a wider range of ability – this was considered due to the age range being wider and variance as a function of age being present The verbal fluency also accounted for education in the older group, whereas the younger group were analysed together since they were all of university-standard education However, it soon became apparent that background knowledge on this task is a large variable, and the extent to which the younger group understood the difference between verbs and nouns was raised. Also, the WCST did not show any results for a pilot study on a younger group, as all four subjects demonstrated a ceiling effect thus withdrawing the tasks from use. Therefore, the younger group are likely to perform optimally on these tasks, whereas older people will show decrements and thus any associations to PFC activity is enhanced.

7.5 Future Work

7.5.1 A Focus Towards Ageing

This thesis was not a study of ageing that aimed to compare and contrast different age groups making assumptions on the rate of change through age; it merely used older people to investigate possible relationships between two indices of EEG and performance and younger people to investigate whether these effects were age-specific or PFC-specific The applicability of work contained within this thesis not only contributes to the literature on the relationship between EEG and performance, but also to the localised function of sleep debate. Although the work described makes headway into the association between EEG and performance, further work might reflect more on the effects of ageing. In an immediate sense,

future work might focus on two aspects· Firstly, the inclusion of a middle age range (35-50 years for instance), and secondly, the study of lower frequency delta (<0 5Hz) in the younger age group to determine whether any associations lie below this cut-off point

An interesting perspective, regarding future ageing work in this area, may evolve from the recent imaging work conducted by Drummond and Colleagues. As Drummond et al. (2000) point out, the sleep deprived PFC makes an apparent compensatory effort to overcome its decrements, and not only this, it also recruits other areas for help. The extent to which this is true for the healthy ageing group, that is whether the brain makes compensatory effort, is questioned Surely one would expect that with the reduction in delta activity, one would become less able to perform tasks of a PFC nature, whether due to a loss of recovery sleep or whether due to the same underlying cause. This thesis was unable to make any assumptions based on this, but functional imaging of recruitment areas during PFC tasks, and its subsequent relation to delta sleep, might prove successful over different age ranges.

A limitation with the current work is the correlational nature in that performance measures and recordings were on separate days and thus any causality is difficult to determine. Of course, correlation was most apt for the study given the investigation into relationships, however, future work might focus on the research into *what* causes the relationship It is thought that a study aimed to determine *why* low frequency delta is associated with a reduction in PFC performance would make headway into growing literature on low frequency delta Although the current study gives a neurophysiological basis for PFC performance given the use of low frequency delta (as produced by the cortex), a study showing a relationship between low frequency delta and PFC volume/synaptic density would provide overwhelming evidence for such a neurophysiological relation. However, the conductance of such a study would require expensive imaging techniques and a longitudinal study.

A possible logical progression of research may entail a study investigating the extent to which increased low frequency delta (if possible) in older people might

result in increased PFC performance. An initial study would need to assess whether low frequency delta could be enhanced with either exercise or increased novel stimuli similar to the findings for SWS (e g. Horne & Moore, 1985; Horne & Minard, 1985) before this can be determined. However, if a study was to assess the effect of increasing low frequency delta and its effect on PFC performance, this would require the comparison of PFC performance at pre- and post-experimental intervention (i.e. method of increasing delta levels), with the novelty associated with the task, and thus a major PFC component, being lost on the second presentation. Therefore, it is proposed that the repeatability of PFC tasks should also be investigated and the extent to which they a) demonstrate learning effects and b) retain their PFC focus

7.5.2 A Focus Towards Applied Research

Most research assessing PFC function utilises the expensive functional imaging tools due to their increased sensitivity over EEG methods However, this study supports the work of Gevins (See above) who is arguing for the use of EEG in assessing neurocognitive functions. The EEG is beneficial in terms of cost, applicability, its ambulatory nature, and its relatively small interference. Therefore, it is argued that more study is needed to further validate the EEG as an assessment of neurocognitive function, which is not just localised to the PFC, but a possible association between other regions and different tasks.

The extent to which the EEG may be reflective of those who may be more adversely affected by sleep loss is also questioned. As shown in this thesis, the sleep EEG is predictive of PFC test performance due a common underlying cause, therefore, are those people who have large amounts of low frequency delta more affected by sleep loss as they lose more recovery sleep? Or, are they more able to cope with sleep loss given that the PFC is more advanced and/or used to hard work reflected in higher delta levels? A study by Webb & Levy (1982) found that older adults who performed better on various tasks (non-PFC specific) were more impaired under sleep loss conditions. This study is an old study, but coupled with the findings from this thesis, it may provide an interesting perspective, and real-world application if one could predict, from a biological marker such as the EEG, the extent to which one could cope with sleep loss

7.6 Conclusions

Findings from this thesis found that low frequency delta, that was dominant in frontal regions (specifically the left), showed associations to performance on tasks known to rely on the integration of the PFC:

1) Older adults – Low frequency delta (0.5-1Hz) was associated with better performance on the WCST, the NVPT and the Verbal fluency task.
    a The relationship was not only apparent in the left frontal regions, but all three tasks demonstrated trend or significant associations with low frequency delta from the right frontal region. No parietal region demonstrated any associations
2) Young adults – Low frequency delta (2-2.5hz) was associated with better performance on the NVPT and verbal fluency
    a. The relationship only being apparent in the left frontal region and only with the tasks that relied on the left frontal cortex.

It was concluded that low frequency delta was associated with PFC performance, possibly reflecting an underlying commonality between the two variables, providing support for a frequency-specific and localised function of sleep, particularly as low frequency delta is thought to be generated directly by the cortex.

Although the waking EEG had been used in the assessment of performance (albeit only limited to one task), the waking EEG, sleep EEG and PFC performance had never been compared. Therefore, the thesis undertook two waking EEG recordings: One daytime recording and one pre-sleep recording, and found:

<u>Daytime – Contrived Thinking</u>

1) Older Adults – No Significant associations were found, but a trend that 7-8Hz activity during a 'thinking' condition was associated with better performance on the NVPT.

   a This was also localised to the left frontal region and specific to 7-8Hz

2) Young adults – 7-8Hz activity during a contrived 'thinking' condition was associated with better performance on the NVPT.
   a. This was localised to the left frontal region and specific to 7-8Hz
3) Waking EEG was problematic as artefact reduced the number of samples taken, resulting in the combination of conditions to produce over all 'thinking' condition, therefore, a second period was analysed: The Pre-Sleep Period.

Pre-Sleep – Putative Thinking

1) Older Adults – 7-8Hz activity in the left frontal region was associated with:
   a 7-8Hz activity generated during a contrived 'thinking' condition in the alert waking EEG.
   b Increased low frequency delta during the first NREM period
   c Increased performance on the WCST and NVPT (albeit the WCST only a trend)
2) Young Adults – 7-8Hz activity in the left frontal regions prior to sleep onset was associated with:
   a. 7-8Hz activity generated during a 'contrived thinking' condition in the alert waking EEG
   b. Increased low frequency delta during the first NREM period
   c Increased performance on the Verbal Fluency and NVPT
3) The 7-8Hz activity identified during this pre-sleep period was not thought to reflect sleepiness, since a spectral analysis of 3-11Hz revealed that increasing sleepiness was associated with theta in the lower range (4-6Hz) and not >6Hz.

The waking EEG findings show that the wake EEG is associated with neuropsychological test performance and delta sleep EEG However, in regard to the association to delta sleep, these associations were shown to be both frequency specific (7-8Hz and low frequency delta) and topographically specific (to the left frontal region).

The thesis demonstrated for younger and older participants, that the sleep and wake EEG was associated with performance on tasks known to rely on the integration of the PFC. It was shown that in those people who exhibit more low frequency delta during sleep, and more high frequency theta during putative 'thinking' wakefulness perform better on PFC orientated tasks. The relationship between the sleep and wake EEG demonstrated that activity during 'thinking' conditions is reflected by putative recovery sleep providing further evidence for a localised function of sleep in the (left) PFC. The inter-relation between the sleep EEG, wake EEG and PFC performance is apparent through the investigation described in this thesis, however, the cause and effect of these variables remains, for now, unknown

CHAPTER 8

REFERENCES

Achermann, P. & Borbély, A A. (1997) Low frequency (<1Hz) oscillations in the human sleep electroencephalogram *Neuroscience*, 81(1): 213-222.

Achermann, P , Finelli, L.A. & Borbély, A A (2000) Unihemispheric enhancement of frontal delta power after sleep deprivation. *Sleep*, 23, (Suppl 2) A19.

Achermann, P., Finelli, L A. & Borbély, A.A. (2001). Unihemispheric enhancement of delta power in human frontal sleep EEG by prolonged wakefulness. *Brain Research*, 913· 220-223.

Adam, K. (1980). Sleep as a restorative process and a theory to explain why. Progress in *Brain Research*, 53: 289-306.

Åkerstedt, T. & Gillberg, M. (1990). Subjective and Objective sleepiness in the active individual. *International Journal of Neuroscience*, 52: 29-37.

Anderson, S.W., Damasio, H , Jones, R.D. & Tranel, D (1991) Wisconsin card sorting test performance as a measure of frontal lobe damage. *Journal of Clinical and Experimental Neuropsychology: Official Journal of the Neuropsychological Society*, 13(6) 909-922.

Andres, P & Van der Linden, M (2000). Age-related differences in supervisory attentional system functions *The journals of Gerontology. Series B, Psychological sciences and social sciences*, 55 (6)· P373-P380.

Barcelo, F. (2001) Does the Wisconsin card sorting task measure prefrontal function? *The Spanish Journal of Psychology*, 4(1)· 79-100.

Bard, E.G., Sotillo, C., Anderson, A H , Thompsom, H.S. & Taylor, M.M. (1996) The DCIEM map task corpus: Spontaneous dialogue under SD and drug treatment *Speech Communication*, 20: 71-84.

Bechara, A , Damasio, A.R , Damasio, H. & Anderson, S W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50: 7-15.

Bechara, A , Damasio, H , Tranel, D & Anderson, S W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *The Journal Of Neuroscience*, 18(1) 428-443.

Belyavin, A. & Wright, N A. (1987) Changes in electrical activity of the brain with vigilance. *Electroencephalography and Clinical Neurophysiology*, 66· 137-144.

Benoit, O , Daurat, A. & Prado, J (2000). Slow (0.7-2Hz) and fast (2-4Hz) delta components are differently correlated to theta, alpha and beta frequency bands during NREM sleep. *Clinical Neurophysiology*, 111: 2103-2106.

Benoit, O , Foret, J., Bouard, G., Merle, B., Landau, J. & Marc, M E. (1980). Habitual sleep length and patterns of recovery sleep after 24 hour and 36 hour sleep deprivation. *Electroencephalography and Clinical Neurophysiology*, 50. 477-485.

Benson, K L., Lim, K O , Pffefferbaum, A. & Zarcone, V P. (1997) Sleep architecture and age. Influence of brain morphology . *Sleep Research*, 26. 153.

Bes, F., Schulz, H., Navelet, Y. & Salzarulo, P. (1991). The distribution of slow-wave sleep across the night: A comparison for infants, children, and adults *Sleep*, 14(1): 5-12.

Binks, P.G., Waters, W F. & Hurry, M. (1999). Short-term total sleep deprivations does not selectively impair higher cortical functioning. *Sleep*, 22(3): 328-334.

Bliwise, D.L. (1989) Neuropsychological function and sleep *Clinics in Geriatric Medicine*, 5(2): 381-394.

Bliwise, D.L. (1993). Sleep in normal aging and dementia. *Sleep*, 16(1). 40-81.

Bliwise, D L (1997). Normal Aging: In Kryger, M H. (Ed) *Principles and practice of sleep medicine*. 4th Edition (pp. 26-35) W.B Saunders Company, Philadelphia.

Bliwise, D.L. & Bergmann, B M. (1987). Individual differences in stages 3 + 4 sleep *Psychophysiology*, 24(1): 35-40.

Bloom, P A. & Fischler, I. (1980). Completion norms for 329 sentence contexts. *Memory & Cognition*, 8(6): 631-642.

Bonnet, M H. & Arand, D.L. (1994). Impact of naps and caffeine on extended performance. *Physiology and Behaviour*, 56(1): 103-109.

Bonnet, M H. & Arand, D L. (1994b). The Use of prophylactic naps and caffeine to maintain performance during sustained continuous operations. *Ergonomics*, 37(6) 1009-1020.

Borbély, A.A (1982). A two-process model of sleep regulation *Human Neurobiology*, 1: 205-210.

Borbély, A A., Baumann, F., Brandeis, D., Strauch, I., & Lehmann, D. (1981). Sleep deprivation Effect on sleep stages and EEG power density in man. *Electroencephalography and Clinical Neurophysiology*, 51(5): 483-495

Bouma, H. & Baghuis, L C. (1971). Hippus of the pupil. Periods of slow oscillations of unknown origin. *Vision Research*, 11(11): 1344-1351

Braun, A R., Balkin, T J., Wesensten, N J., Carson, R.E., Varga, M. Baldwin, P , Selbie, S. Belenky, G. & Herscovitch, P. (1997). Regional Cerebral Blood Flow Throughout the Sleep-Wake Cycle. *Brain*, 120. 1173-1197.

Brenner, R.P , Ulrish, R.F. & Reynolds, C.F. III (1995). EEG spectral findings in healthy, elderly men and women-sex differences. *Electroencephalography and Clinical Neurophysiology*, 94: 1-5.

Browman, C P. & Cartwright, R.D. (1980). The first-night effect on sleep and dreams *Biological Psychiatry*, 15(5). 809-812.

Buchsbaum, M S , Gillin, J C., Wu, J , Hazlett, E., Sicotte, N., Dupont, R.M. & Bunney, W E Jr. (1989) Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography. *Life Sciences*, 45(15). 1349-1356.

Butters, M A., Kaszniak, A.W , Glisky, E L , Eslinger, P.J. & Schacter, D.L. (1994). Recency discrimination deficits in frontal lobe patients. *Neuropsychology*, 8(3): 343-353

Cajochen, C , Brunner, D P., Kräuchi, K , Graw, P. & Wirz-Justice, A. (1995). Power density in theta/alpha frequencies of the waking EEG progressively increases during sustained wakefulness. *Sleep*, 18(10) 890-894.

Cajochen, C , Foy, R. & Dijk, D-J. (1999). Frontal predominance of relative increase in sleep delta and theta EEG activity after sleep loss in humans. *Sleep Research online*, 2(3) 65-69.

Cajochen, C., Knoblauch, V., Krauchi, K., Renz, C. & Wirz-Justice, A (2001). Dynamics of frontal EEG activity, sleepiness and body temperature under high and low sleep pressure. *Neuroreport*, 12(10) 2277-2281

Cantor-Graae, E., Warkentin, S., Franzén, G. & Risberg, J. (1993). Frontal lobe challenge: A comparison of activation procedures during rCBF measurements in normal subjects *Neuropsychiatry, neuropsychology, and Behavioural neurology*, 6(2) 83-92

Carrier, J., Land, S , Buysse, D J , Kupfer, D J. & Monk, T H. (2001) The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20-60 years old) *Psychophysiology*, 38: 232-242

Carskadon, M A. & Dement, W C. (1985). Sleep loss in elderly volunteers *Sleep*, 8(3) 207-221.

Cattell, R.B. (1963). Theory of Fluid and Chrystallised Intelligence. A Critical Experiment. *Journal Of Educational Psychology*, 54: 1-22.

Chapman, R.M., Armington, J.C. & Bragdon, H R. (1962). A quantitative survey of kappa and alpha EEG activity. *Electroencephalography and Clinical Neurophysiology*, 14: 858-868

Chase-Carmicheal, C.A., Ris, M D , Weber, A.M. & Schefft, B K. (1999). Neurological validity of the Wisconsin card sorting test with a paediatric population *The Clinical Neuropsychologist*, 13(4): 405-413.

Çiçek, M. & Nalçaci, E. (2001) Interhemispheric asymmetry of EEG alpha activity at rest and during the Wisconsin Card Sorting Test· relations with performance *Biological Psychology*, 58(1): 75-88.

Clark, C., Dupont, R., Lehr, P., Yeung, D., Halpern, S , Golshan, S. & Gillin, J C (1998) Is there a relationship between delta sleep at night and afternoon cerebral blood flow, assessed by HMPAO-SPECT in depressed patients and normal control subjects? Preliminary data. *Psychiatry Research. Neuroimaging Section*, 84: 89-99.

Coates, T.J , Rosekind, M.R., Strossen, R J., Thoresen, C E and Kirmil-Gray, K. (1979) Sleep recordings in the laboratory and home: A comparative analysis *Psychophysiology*, 16(4): 339-346

Coffey, C E , Lucke, J.F., Saxton, J A , Ratcliffe, G., Unitas, L J., Billig, B & Bryan, N. (1998). Sex differences in brain aging. *Archives of Neurology*, 55: 169-179.

Corey-Bloom, J., Wiederholt, W.C., Edelstein, S , Salmon, D P., Cahn, D. & Barrett-Connor, E. (1996). Cognitive and functional status of the oldest old *Journal of the American Geriatrics Society*, 44: 671-674.

Corsi-Cabrera, M., Solís-Ortiz, S. & Guevara, M.A. (1997). Stability of EEG inter- and intrahemispheric correlation in women. *Electroencephalography and Clinical Neurophysiology*, 102: 248-255.

Cowell, P.E., Turetsky, B I., Gur, R.C., Grossman, R.I , Shtasel, D.L & Gur, R.E. (1994) Sex differences in aging of the human frontal and temporal lobes. *The Journal of Neuroscience*, 14(8) 4748-4755

Craik, F I. (1990). Relations between source amnesia and frontal lobe functioning in older adults. *Psychology and Aging*, 5(1)· 148-151.

Crenshaw, M.C. & Edinger, J D. (1999). Slow-wave sleep and waking cognitive performance among older adults with and without insomnia complaints. *Physiology and behaviour*, 66(3): 485-492.

Dagher, A , Owen, A.M , Boecker, H & Brooks, D J. (1999). Mapping the network for planning· A correlational PET activation study with the Tower of London task. *Brain*, 122 (Pt 10) 1973-1987.

Daum, I , Gräber, S., Schugens, M M., Mayes, A & Birbaumer, N (1996). Memory dysfunction of the frontal type in normal aging. *Neuroreport*, 7 (15-17): 2625-2628.

De Gennaro, L., Ferrara, M. & Bertini, M. (2001a). The boundary between wakefulness and sleep· Quantitative electroencephalographic changes during the sleep onset period *Neuroscience*, 107(1): 1-11.

De Gennaro, L , Ferrara, M , Curcio, G. & Cristiani, R. (2001b). Antero-posterior EEG changes during the wakefulness-sleep transition. *Clinical Neurophysiology*, 112: 1901-1911.

Dement, W (1972) *Some Must watch while some must sleep*. Norton & Company. New York

Dement, W C., Miles, L E. & Carskadon, M A. (1982) "White paper " on sleep and aging *Journal of the American geriatric Society*, 30(1): 25-50.

Dement, W.C., Richardson, G , Prinz, P., Carskadon, M., Kripke, D. & Czeisler, C. (1985). Changes of sleep and wakefulness with age: In Finch, C. (Ed) *Handbook on the Biology of Aging*, (pp 692-717). Van Nostrand, New York.

Dijk, D-J, Brunner, D.P. & Borbély, A.A. (1990). Time course of EEG power density during long sleep in humans. *American Journal of Physiology*, 258 (3, Pt 2): R650-651.

Dijk, D-J., Beersma, D.G M. & Bloem, G M. (1989) Sex differences in the sleep EEG of young adults: Visual scoring and spectra analysis. *Sleep*, 12(6): 500-507.

Dijk, D-J , Hayes, B. & Czeisler, C.A. (1993). Dynamics of electroencephalographic sleep spindles and slow wave activity in men: Effect of sleep deprivation. *Brain Research*, 626 190-199.

Dinges, D. F. & Kribbs, N.B. (1991). Performing while sleepy. Effects of experimentally induced sleepiness: In Monk, T H. (Ed) *Sleep, sleepiness and performance* (pp 97-128). John Wiley, Winchester, UK.

Drummond, S P.A , Brown, G G , Gillin, J.C , Stricker, J L., Wong, E C. & Buxton, R.B. (2000) Altered brain response to verbal learning following sleep deprivation *Nature*, 403: 655-657.

Duffy, F.H , McAnulty, G B. & Albert, M.S. (1993). The pattern of age-realted differences in electrophysiological activity of healthy males and females. *Neurobiology of Aging*, 14(1): 73-84

Duncan, J. (1995). Attention, intelligence, and the frontal lobes : In Gazzaniga, M.S. (Ed) *The Cognitive Neurosciences*, (pp 721-733). MIT Press, Cambridge

Duncan, J., Burgess, P. Emslie, H (1995) Fluid intelligence after frontal lobe lesions. *Neuropsychologia*, 33(3): 261-268.

Duncan, J. & Owen, A M. (2000). Common regions of human frontal lobe recruited by diverse cognitive demands. *Trends in Neuroscience*, 23(10): 475-483.

Duncan, J , Seitz, R.J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., Newell, F N & Emslie, H (2000). A neural basis for general intelligence. *Science*, 289 457-460.

Dustman, R.E., Ruhling, R.O , Russell, E M., Shearer, D E , Bonekat, H.W , Shigeoka, J.W , Wood, J.S. & Bradford, D.C. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiology of Aging*, 5(1): 35-42.

Dustman, R.E., Shearer, D E. & Emmerson, R.Y. (1993) EEG and event-related potentials in normal aging *Progress in Neurobiology*, 41(3): 369-401.

Edinger, J D., Glenn, D.M , Bastian, L A & Marsh, G.R. (2000). Slow-wave sleep and waking cognitive performance II. Findings among middle-aged adults with and without insomnia complaints. *Physiology and behaviour*, 70(1-2) 127-134.

Ehlers, C L & Kupfer, D J. (1989) Effects of age on delta and REM sleep parameters. *Electroencephalography and Clinical Neurophysiology*, 72: 118-125.

Ehlers, C L & Kupfer, D J. (1997) Slow-wave sleep. Do young men and women age differently? *Journal of Sleep Research*, 6(3) 211-215

Ehlers, C.L , Kupfer, D J , Buysse, D J , Cluss, P.A , Mlewald, J M., Bisson, E.F & Grochocinski, V.J. (1998). The Pittsburgh study of normal sleep in young adults· Focus on the relationship between waking and sleeping EEG spectral patterns. *Electroencephalography and Clinical Neurophysiology*, 106: 199-205.

Engleman, H M , Kingshott, R.N , Martin, S E. & Douglas, N.J (2000) Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). *Sleep*, 23(Suppl 4) S102-S108.

Fabiani, M. & Friedman, D (1997). Dissociations between memory for temporal order and recognition memory in aging. *Neuropsychologia*, 35(2) 129-141.

Feinberg, I. (1974). Changes in sleep cycle patterns with age *Journal of Psychiatric Research*, 10 283-306

Feinberg, I. (1989). Effects of Maturation and Ageing on Slow Wave Sleep in Man: Implications for Neurobiology: In Wauquier, A , Dugovic, C. & Radulovacki, M. (Eds). *Slow Wave Sleep· Physiological, Pathophysiological and Functional Aspects*. (pp 31-48). Raven Press, New York.

Feinberg, I., Fein, G., Floyd, T.C. & Aminoff, M J. (1983). Delta (0 5-3Hz) waveforms during sleep in young and elderly normal subjects In Chase, M H. & Weitzman, E D. (Eds). *Sleep Disorders· Basic and Clinical Research*, (pp 449-462). SP Medical and Scientific Books. New York.

Feinberg, I , Floyd, T C. & March, J D. (1991). Acute deprivation of the terminal 3.5hours of sleep does not increase delta (0-3Hz) electroencephalograms in recovery sleep. *Sleep*, 14· 316-319.

Ferrara, M , De Gennaro, L. Curcio, G., Cristiani, R., Corvasce, C. & Bertini, M. (2002) Regional difference of the human sleep electroencephalogram in response to selective slow-wave sleep deprivation. *Cerebral Cortex*, 12(7)· 737-748.

Fey, E T. (1951) The performance of young schizophrenics and young normals on the Wisconsin Card Sorting Task. *Journal of Consulting Psychology*, 15: 311-319.

Finelli, L A., Baumann, H., Borbély, A A & Achermann, P. (2000). Dual electroencephalogram markers of human sleep homeostasis· correlation between theta activity in waking and slow-wave activity in sleep. *Neuroscience*, 101(3). 523-529.

Finelli, L A., Achermann, P. & Borbély, A.A. (2001). Individual 'fingerprints' in human sleep EEG topography. Neuropsychopharmacology, 25 (S5)· S57-S62.

Fristoe, N.M , Salthouse, T A. & Woodard, J.L. (1997) Examination of age-related deficits on the Wisconsin card sorting test *Neuropsychology*, 11(3): 428-436

Friston, K.J , Frith, C D., Liddle, P.F. & Frackowiak, R S J. (1991). Investigating a network of word generation with positron emission tomography. *Proceedings of the Royal Society of London. Series B· Biological Sciences*, 244: 101-106.

Frith, C.D., Friston, K J., Little, P.F. & Frackowiak, R.S (1991). A PET study of word finding. *Neuropsychologia*, 29(12) 1137-1148

Fuster, J.M. (1989). *The Prefrontal Cortex: Anatomy, physiology, and neuropsychology of the frontal lobe.* Raven Press, New York

Geinisman, Y , Detoledo-Morrell, F. & Heller, R E. (1995) Hippocampal markers of age-related memory dysfunction: Behavioural, electrophysiological and morphological perspectives *Progress in Neurobiology*, 45(3)· 223-252.

Gevins, A S (1979a) EEG patterns during 'cognitive' tasks. II. Analysis of controlled tasks. *Electroencephalography and Clinical neurophysiology*, 47: 704-710

Gevins, A.S. (1979b). Electroencephalogram correlates of higher cortical functions *Science*, 203· 665-668.

Gevins, A. (1998). The future of electroencephalography in assessing neurocognitive functioning. *Electroencephalography and Clinical Neurophysiology*, 106: 165-172

Gevins, A, Smith, M E., McEvoy, L K, Leong, H & Le, J. (1999). Electroencephalographic imaging of higher brain function. *Philosophical Transactions of the Royal Society of London. Series B· Biological Sciences*, 354: 1125-1134.

Gibson, P.H. (1983) EM study of the numbers of cortical synapses in the brains of ageing people and people with Alzheimer-type dementia. *Acta Neuropathology*, 62(1-2)· 127-133

Gillberg, M & Åkerstedt, T. (1994). Sleep restriction and SWS-suppression: Effects of daytime alertness and night-time recovery. *Journal of Sleep Research*, 3(3): 144-151.

Goldberg, T E., Weinberger, D R., Berman, K.F., Pliskin, N.H. & Podd, M H (1987). Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin card sorting task. *Archives of General Psychiatry*, 44(11): 1008-1014.

Grant, D A & Berg, E.A. (1948) A behavioural analysis of degree of reinforcement and ease of shifting to a new response in a Weigl-Type card sorting task. *Journal of Experimental Psychology*, 38: 404-411.

Grant, D A., Jones, O R & Tallantis, B. (1949). The relative difficulty of number, form, and colour concepts of a Weigl-Type problem *Journal Of Experimental Psychology*, 39: 552-557.

Gulevich, G., Dement, W , Johnson, L. (1966) Psychiatric and EEG observations of a case of prolonged (264hours) wakefulness *Archives of General Psychiatry*, 15· 29-35.

Gundel, A. & Wilson, G.F. (1992). Topographical changes in the ongoing EEG related to the difficulty of mental tasks. *Brain Topography*, 5(1) 17-25.

Harrison, Y. & Horne, J A. (1997) Sleep deprivation affects speech *Sleep*, 20(10) 871-877.

Harrison, Y. & Horne, J.A. (1998). Sleep loss impairs short and novel language tasks having a prefrontal focus. *Journal of Sleep Research*, 7: 95-100.

Harrison, Y & Horne, J A. (1999). One night of sleep loss impairs innovative thinking and flexible decision making *Organizational Behaviour and Human Decision Processes*, 78. 128-145.

Harrison, Y & Horne, J A. (2000a) Sleep loss and temporal memory. *Quarterly Journal of Experimental Psychology*, 53(1): 271-279.

Harrison, Y. & Horne, J A (2000b) The impact of sleep deprivation on decision making: A review. *Journal of Experimental Psychology: Applied*, 6(3) 236-249.

Harrison, Y , Horne, J.A , Rothwell, A. (2000) Prefrontal neuropyschological effects of sleep deprivation in young adults - a model for healthy aging? *Sleep*, 23(8): 1067-1073.

Hayward, L.B., Eyland, E A., Hewitt, H., Pond, C D. & Saunders, N A. (1992). Neuropsychological functioning and sleep patterns in the elderly. *The Medical Journal of Australia*, 157(1)· 51-52.

Heaton, R.K. (1981) *A manual for the Wisconsin Card Sorting Task.* Psychological Assessment Resources, Inc. Florida, USA.

Hofle, N , Paus, T., Reutens, D , Fiset, P., Gotman, J., Evans, A.C. & Jones, B.E. (1997). Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. *The Journal of Neuroscience*, 17(12) 4800-4808.

Hoptman, M J. & Davidson, R.J. (1998). Baseline EEG asymmetries and performance on neuropsychological tasks. *Neuropsychologia*, 36(12): 1343-1353

Hori, T , Hayashi, M. & Morikawa, T. (1994) Topographical EEG changes and the hypnagogic experience In· Ogilvie, R D. & Harsh, J R. (Eds). *Sleep Onset· Normal and Abnormal Processes*, (pp 237-253) American Psychological Association, Washington DC

Horne, J.A. (1983). Sleep Function, with particular reference to sleep deprivation. *Annals of Clinical Research*, 17: 199-208

Horne, J A (1985). Mammalian sleep function, with special reference to man. In Mayes, *Sleep mechanisms and functions* Van Nostrand, London

Horne, J A. (1988a) *Why we sleep. The functions of sleep in humans and other mammals.* Oxford University Press

Horne, J.A (1988b) Sleep loss and "Divergent" thinking ability. *Sleep*, 11(6): 528-536

Horne, J.A. (1992a). Human slow wave sleep. A review and appraisal of recent findings, with implications for sleep functions, and psychiatric illness. *Experientia*, 48: 941-954.

Horne, J.A. (1992b) Human slow-wave sleep and the cerebral cortex. *Journal of Sleep Research*, 1: 122-124.

Horne, J.A. (1993). Human sleep, sleep loss and behaviour: Implications for the prefrontal cortex and psychiatric disorder. *British Journal of Psychiatry*, 162: 413-419.

Horne, J.A & Walmsley, B. (1976). Daytime visual load and the effects upon human sleep. *Psychophysiology*, 13(2) 115-120.

Horne, J.A. & Staff, L H E. (1983). Exercise and sleep: Body heating effects. *Sleep*, 6(1). 36-46

Horne, J.A. & Minard, A. (1985). Sleep and sleepiness following a behaviourally 'active' day. *Ergonomics*, 28(3) : 567-575.

Horne, J.A. & Moore, V.J. (1985). Sleep EEG effects of exercise with and without additional body cooling. *Electroencephalography and Clinical Neurophysiology*, 60: 33-38.

Horne, J.A. & Pettitt, A N. (1985). High incentive effects on vigilance performance during 72 hours' total sleep deprivation, *Acta Psychologica*, 25: 123-139.

Horne, J.A , Pankhurst, F.L , Reyner, L.A , Hume, K. & Diamond, I.D. (1994). A field study of sleep disturbance Effects of aircraft noise and other factors on 5,742 nights of actimetrically monitored sleep in a large subject sample. *Sleep*, 17(2): 146-59.

Horne, J.A & Reyner, L.A. (1996). Counteracting driver sleepiness: Effects of napping, caffeine and placebo. *Psychophysiology*, 33· 306-309.

Ishihara, T. & Yoshii, N. (1971). Multivariate analytical study of EEG and mental activity in juvenille delinquents *Electroencephalography and Clinical Neurophysiology*, 33: 71-80.

Jensen, O. & Tesche, C D. (2002). Frontal theta activity in human increases with memory load in a working memory task. *European Journal of Neuroscience*, 15(8)· 1395-1399.

Jobert, M , Escola, H , Poiseau, E. & Gaillard, P. (1994) Automatic analysis of sleep using two parameters based on principal component analysis of electroencephalography spectral data. *Biological Cybernetics*, 71(3): 197-207

Johns, M.W. (1991). A new method for measuring daytime sleepiness· The Epworth Sleepiness Scale *Sleep*, 14(6). 540-546.

Johns, M.W. & Doré, C. (1978). Sleep at home and in the sleep laboratory: Disturbance by recording procedures. *Ergonomics*, 21(5): 325-330.

Johnson, L.C. & Macleod, W L. (1973). Sleep and awake behaviour during gradual sleep reduction. *Perceptual and Motor Skills*, 36: 87-97.

Kader, G A. & Griffin, P.T. (1983). Reevaluation of the phenomena of the first night effect *Sleep*, 6(1). 67-71.

Kahana, M J , Seelig, D & Madsen, J R. (2001). Theta returns. *Current Opinions in Neurobiology*, 11(6): 739-744.

Kales, A , Tan, T-L , Kollar, E J., Naitoh, P., Preston, T.A & Malmstrom, E J. (1970) Sleep patterns following 205hours of sleep deprivation. *Psychomatic Medicine*, 32. 189-200.

Kelley, W M., Macrae, C N , Wyland, C.L , Caglar, S., Inati, S. & Heatherton, T.F (2002). Finding the Self: An event-related fMRI study. *Journal of Cognitive Neuroscience.* 14(5): 785-794.

Kennedy, J.L , Gottsdanker, R.M , Armington J C. & Gray, F.E. (1949). The kappa rhythm and problem-solving behaviour. *Electroencephalography and Clinical Neurophysiology,* 1: 516.

Kolb, B & Wishaw, I.Q. (1985). *Fundamentals of Human Neuropsychology* Second Edition. Freeman, New York.

Kupfer, D.J , Weiss, B.L , Detre, T P , Foster, F G (1974). First night effect revisited: A clinical note. *The Journal of Nervous and Mental Disease,* 159(3) 205-209.

Landolt, H P. & Borbély, A A. (2001). Age-dependent changes in sleep EEG topography. *Clinical Neurophysiology,* 112: 369-377.

Landolt, H P , Dijk, D-J., Achermann, P. & Borbély, A.A. (1996). Effect of age on the sleep EEG Slow wave activity and spindle frequency activity in young and middle-aged men. *Brain Research,* 738(2): 205-212.

Lanquart, J.P., Kerkhofs, M , Stanus, E., Mendlewicz, J. & Linkowski, P. (1996). Sleep EEG analysis by linear prediction. Frequency changes of slow-wave activity within NREM and REM sleep episodes in healthy men *Neuropsychobiology,* 34(1): 1-8.

Larsen, L H , Moe, K E., Vitiello, M.V. & Prinz, P N. (1995a). Age trends in the sleep EEG of healthy older men and women. *Journal of Sleep Research,* 4: 160-172

Larsen, L.H , Moe, K.E , Vitiello, M.V. & Prinz, P.N. (1995b). A note on the night-to-night stability of stages 3 + 4 sleep in healthy older adults: A comparison of visual and spectral evaluations of stages 3 + 4 sleep. *Sleep,* 18(1): 7-10.

Lazeron, R H C , Rombouts, S.A R.B., Machielsen, W.C.M , Scheltens, P., Witter, M P , Uylings, H B M. & Barkhof, F. (2000) Visualising brain activation during planning: The Towr of London Test adapted for functional MR imaging. *AJNR American Journal of Neuroradiology,* 21: 1407-1414.

Loranger, A W. & Misiak, H. (1960) The performance of aged females on five non-language tests of intellectual functions. *Journal of Clinical Psychology*, 16: 189-191.

Lowe, C. & Rabbitt, P. (1991). Cognitive models of ageing and frontal lobe deficits: In Lowe, P. (Ed). *Methodology of frontal and executive function* (pp 39-59). Psychology Press.

Luria, A R. (1973) *The Working Brain*. Basic Books, New York

McCarthy, G , Blamire, A.M., Rothman, D.L., Gruetter, R. & Schulman, R.G. (1993) Echo-planar magnetic resonance imaging studies of frontal cortex activation during word generation in humans. *Proceedings of the National Academy of Science of the United States of America*, 90(11): 4952-4956.

McEvoy, L K., Smith, M.E. & Gevins, A. (2000). Test-retest reliability of cognitive EEG. *Clinical Neurophysiology*, 111(3): 457-463.

McEvoy, L K., Pellouchoud, E , Smith, M E & Gevins, A (2001). Neurophysiological signals of working memory in normal aging. *Brain Research. Cognitive Brain Research*, 11(3): 363-376.

Mathew, R J. (1989) Hyperfrontality of regional cerebral blood flow distribution in normals during resting wakefulness: fact or artifact? *Biological Psychiatry*, 26(7) 717-724

Maquet, P. (1999). Brain mechanisms of sleep. Contribution of neuroimaging techniques *Journal of Psychopharmacology*, 13(4 suppl 1): S25-S28.

Maquet, P. (2000). Functional Neuroimaging of Normal Human Sleep in Positron Emission Tomography *Journal of Sleep Research*, 9(3) 207-231.

Maquet, P , Degueldre, C., Delfiore, G , Aerts, J , Péters, J-M , Luxen, A. & Franck, G. (1997). Functional neuroanatomy of human slow wave sleep. *The Journal of Neuroscience*, 17(8) 2807-2812.

Maquet, P , Dive, D , Salmon, E , Sadzot, B., Franco, G , Poirrier, R., von Frenckell, R. & Franck, G. (1990). Cerebral glucose utilization during sleep-wake cycle in man

determined by positron emission tomography and [18F]2-fluro-2-deoxy-D-glucose method. *Brain Research*, 513(1) 134-143

Martin, A J., Friston, K J., Colebatch, J.G. & Frackowiak, R.S (1991). Decreases in regional cerebral blood flow with normal aging. *Journal of Cerebral Blood Flow and Metabolism*, 11(4): 684-689

Masliah, E , Mallory, M., Hansen, L , DeTeresa, R. & Terry, R.D. (1993). Quantitative synaptic alterations in the human neocortex during normal aging. *Neurology*, 43(1): 192-197.

Mentzel, H.J., Gaser, C., Volz, H.P., Rzanny, R., Häger, F , Sauer, F. & Kaiser, W.A. (1998). Cognitive stimulation with the Wisconsin card sorting test Functional MR Imaging at 1.5T. *Radiology*, 207(2): 399-404.

Milner, B (1963). Effects of different brain lesions on card sorting. *Archives of Neurology*, 9· 90-100.

Milner, B. (1995) Aspects of human frontal lobe function. *Advances in Neurology*, 66: 67-81.

Milner, B & Petrides, M. (1984) Behavioural effects of frontal lobe lesions in man *Trends in Neuroscience*, 7: 717-724.

Milner, B , Petrides, M. & Smith, M L. (1985). Frontal lobes and the temporal organization of memory. *Human Neurobiology*, 4 137-142.

Milner, B , Corsi, P. & Leonard, G. (1991) Frontal-lobe contributions to recency judgements. *Neuropsychologia*, 29(6) 601-618.

Morikawa, T., Hayashi, M. & Hori, T. (1997). Auto power and coherence analysis of delta-theta band EEG during the waking-sleeping transition. *Electroencephalography and Clinical Neurophysiology*, 103: 633-641.

Morris, G O., Williams, H.L. & Lubin, A. (1960). Misperception and disorientation during sleep. *Archives of General Psychiatry*, 2: 247-254.

Morris, R.G., Ahmed, S , Syed, G M. & Toone, B.K. (1993) Neural correlates of planning ability: Frontal lobe activity during the Tower of London test. *Neuropsychologia*, 31(12): 1367-1378

Moscovitch, M. & Winocur, G. (1995) Frontal lobe, memory and aging. *Annals of the New York Academy of Science*, 769: 119-150

Mourtazaev, M.S., Kemp, B., Zwinderman, A H Z. & Kamphuisen, H A C. (1995). Age and gender affect different characteristics of slow waves in the sleep EEG *Sleep*, 18(7): 557-564.

Mundy-Castle, A.C. (1957). The Electroencephalogram and mental activity *Electroencephalography and Clinical Neurophysiology*, 9. 643-655.

Naëgelé, B , Thouvard, V., Pépin, J-L , Lévy, P., Bonnet, C., Perret, J E., Pellat, J. & Feuerstein, C. (1995) Deficits of cognitive executive functions in patients with sleep apnea syndrome. *Sleep*, 18(1): 43-52

Nagahama, Y., Fukuyama, H., Yamauchi, H., Matsuzaki, S , konishi, J., Shibasaki, H. & Kimura, J. (1996). Cerebral activation during performance of a card sorting test. *Brain*, 119(Pt. 5): 1667-75.

Nathaniel-James, D.A , Fletcher, P. & Frith, C.D. (1997). The functional anatomy of verbal initiation and suppression using the Hayling test. *Neuropsychologia*, 35(4) 559-566.

Naylor, E., Penev, P.D , Orbeta, L , Janssen, I , Ortiz, R , Colechia, E.F., Keng, M., Finkel, S. & Zee, P.C. (2000). Daily social and physical activity increases slow-wave sleep and daytime neuropsychological performance in the elderly *Sleep*, 23(1): 87-95.

Nyberg, L , Marklund, P., Persson, J., Cabeza, R., Forkstam, C , Petersson, K.M & Ingvar, M. (2003). Common prefrontal activations during working memory, episodic memory, and semantic memory. *Neuropsychologia*, 41(3) 371-377.

Oldfield, R.C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia*, 9 97-113

Parkin, A.J. (1997). Normal age-related memory loss and its relation to frontal lobe dysfunction: In Rabbitt, P. (Ed) *Methodology of Frontal and Executive Functions*, (pp 177-190). Psychological Press

Parkin, A J & Walter, B.M. (1991). Aging, short-term memory, and frontal dysfunction. *Psychobiology*, 19(2): 175-179.

Parkin, A J. & Lawrence, A. (1994). A dissociation in the relation between memory tasks and frontal lobe tests in the normal elderly *Neuropsychologia*, 32(12) 1523-1532.

Parkin, A J , Hunkin, N M & Walter, B M. (1995). Relationships between normal aging, frontal lobe function and memory for temporal and spatial information. *Neuropsychology*, 9(3): 304-312

Petersen, S E., Fox, P.T , Posner, M.I , Mintun, M. & Raichle, M E. (1988). Positron emission tomography studies of the cortical anatomy of single-word processing. *Nature*, 331(6157) 585-589

Phelps, E.A., Hyder, F , Blamire, A M. & Schulman, R.G (1997). fMRI of the prefrontal cortex during overt verbal fluency *Neuroreport*, 8(2): 561-565.

Pilcher, J J. & Huffcutt, A I. (1996). Effects of sleep deprivation on performance: A meta-analysis Sleep, 19(4) 318-326.

Polich, J. (1997). EEG and ERP assessment of normal aging. *Electroencephalography and Clinical Neurophysiology*, 104(3): 244-256

Poline, J-B , Vandenberghe, R., Holmes, A.P., Friston, K.J. & Frackowiak, R.S J. (1996) Reproducibility of PET activations studies: Lessons from a multi-centre European experiment *Neuroimage*, 4 34-54

Ramos, J , Corsi-Cabrera, M., Guevara, M A. & Arce, C. (1993). EEG activity during cognitive performance in women. *International Journal of Neuroscience*, 69(1-4), 185-195.

Randazzo, A C., Muehlbach, M J., Schweitzer, P.K. & Walsh, J.K. (1998). Cognitive function following acute sleep restriction in children ages 10-14. *Sleep*, 21(8): 861-868.

Raz, N , Briggs, S D., Marks, W. & Acker, J D (1999). Age-related deficits in generation and manipulation of mental images· II. The role of the dorsolateral prefrontal cortex. *Psychology and Aging*, 14(3) 436-444.

Rechtschaffen, A. & Kales, A. (1968). *A manual of standardised terminology. Techniques and scoring system for sleep stages of human subjects*. UCLA Brain Information Services, Los Angeles.

Reynolds, C.F. III, Kupfer, D J., Taska, L S , Hoch, C.C., Sewitch, D.E. & Spiker, D G. (1985). Sleep of healthy seniors: A revisit. *Sleep*, 8(1). 20-29.

Rezai, K., Andreasen, N C. & Alliger, R. (1993). The Neuropsychology of the Prefrontal Cortex. *Archives of Neurology*, 50: 636-642.

Robinson, A.L., Heaton, R K., Lehman, R.A. & Stilson, D.W. (1980) The utility of the Wisconsin Card Sorting Test in detecting and localising frontal lobe lesions *Journal of Consulting and Clinical Psychology*, 48 605-614.

Ross, J J (1965) Neurological findings after prolonged sleep deprivation *Archives of Neurology*, 12: 399-403.

Roubicek, J. (1977) The electroencephalogram in the middle-aged and the elderly. *Journal of the American Geriatric Society*, 25(4). 145-152.

Schacter, D L (1976) The hypnagogic state: A review of the literature. *Psychological Bulletin*, 83(3): 452-481.

Schacter, D L , Savage, C.R., Alpert, N M , Rauch, S L. & Albert, M.S. (1996). The role of the hippocampus and frontal cortex in age-related memory changes: a PET study *Neuroreport*, 7(6) 1165-1169.

Sekimoto, M , Kato, M., Kajimura, N., Watanabe, T , Takahashi, K & Okuma, T. (2000) Asymmetric interhemispheric delta waves during all-night sleep in humans. *Clinical Neurophysiology*, 111(5): 924-928.

Sewitch, D E , Weitzman, E.D., Czeisler, C.A. & Trencher, B. (1978). Alpha frequency waves (kappa rhythm) during stages 3-4 sleep in normal man *Sleep Research*, 7: 47.

Shallice, T. (1982). Specific impairments of planning *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 298 199-209.

Shimamura, A P. (1995) Memory and frontal lobe function: In Gazzaniga, M S. (Ed) *The Cognitive Neurosciences* (pp 803-813) MIT Press, Cambridge.

Smith, M E., McEvoy, L.K. & Gevins, A (1999). Neurophysiological indices of strategy development and skill acquisition. *Brain Research: Cognitive Brain Research*, 7(3): 389-404

Spiegel, R., Koberle, S. & Alen, S.R. (1986). Significance of slow wave sleep: Considerations form a clinical viewpoint. *Sleep*, 9: 66-79.

Steriade, M. & Amzica, F. (1998). Coalescence of sleep rhythms and their chronology in corticothalamic networks *Sleep research Online*, 1(1). 1-10.

Steriade, M , Contreras, D., Curro Dossi, R. & Nunez, A. (1993a) The slow (<1Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation interacting thalamic and neocortical networks. Jo*urnal of Neuroscience*, 13(8): 3284-3299.

Steriade, M., Nunez, A & Amzica, F (1993b). A novel slow (<1Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components *Journal of Neuroscience*, 13 (8): 3252-3265.

Steriade, M., Nunez, A. & Amzica, F. (1993c) Intracellular analysis of relations between the slow (<1Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *Journal of Neuroscience*, 13(8): 3266-3283.

Stern, R.M , Ray, W J. & Quigley, K S. (2001). *Psychophysiological recording*. 2nd Edition. Oxford University Press.

Stickgold, R., Whidbee, D., Schirmer, B , Patel, V. & Hobson, J.A (2000). Visual discrimination task improvement: A multi-step process occurring during sleep. *Journal of Cognitive Neuroscience*, 12(2) 246-254

Stuss, D T. & Benson, D F. (1986). *The Frontal Lobes* Raven Press, New York

Suetsugi, M., Mizuki, Y., Ushijimi, I. & Watanabe, Y (2002). A Qualitative and quantitative analysis of rhythmic activities during a mental task and sleep spindles. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 26(4): 619-629.

Tallon-Baudry, C & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Science*, 3(4): 151-162.

Tan, X, Campbell, I G, & Feinberg, I. (2003) Internight reliability and benchmark values for computer analyses of non-rapid eye movement (NREM) and REM EEG in normal young adult and elderly subjects. *Clinical Neurophysiology*, 114(2) 395-396.

Tan, X, Campbell, I G, Palagini, L. & Feinberg, I. (2000). High internight reliability of computer-measured NREM delta, sigma, and beta: biological implications *Biological Psychiatry*, 48(10): 1010-1019.

Tanaka, H, Hayashi, M. & Hori, T. (1997). Topographical characteristics and principal component structure of the hypnagogic EEG. *Sleep*, 20(7): 523-534.

Tarter, R E. (1973) An analysis of cognitive deficits in chronic alcoholics *Journal of Abnormal Psychology*, 77: 71-75

Taylor, S.R. & Driver, H S. (1995). Is sleep affected by physical exercise and fitness? *Critical Reviews in Physical and Rehabilitation Medicine*, 7(2). 131-145.

Teece, J J. (1972) Contingent negative variation (CNV) and psychological processes in man *Psychological Bulletin*, 77: 73-108.

Thomas, M., Balkin, T., Sing, H, Wesensteu, N. & Belenky, G. (1998). PET imaging studies of sleep deprivation and sleep: Implications for behaviour and sleep function *Journal of Sleep Research*, 7(Suppl 2): 274

Thomas, M, Sing, H, Belenky, G, Holcomb, H, Mayberg, H., Dannals, R., Wagner, H Jr, Thorne, D, Popp, K., Rowland, L., Welsh, A, Balwinski, S. & Redmond, D (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I Effects of 24h of sleep deprivation on waking human regional brain activity *Journal of Sleep Research*, 9(4): 335-352.

Timofeev, I. & Steriade, M (1996). Low-frequency rhythms in the thalamus of intact-cortex and decorticated cats *Journal of Neurophysiology*, 76(6) 4152-4168.

Torsvall, L. & Åkerstedt, T. (1987) Sleepiness on the job: Continuously measured EEG changes in train drivers. *Electroencephalography and Clinical Neurophysiology*, 66(6): 502-511.

Trachsel, L., Dijk, D.J., Brunner, D P., Klene, C. & Borbély, A.A. (1990). Effect of zopiclone and midasolam on sleep and EEG spectra in a phase-advance sleep schedule. Neuropsychopharmacology, 3(1) 11-18.

Tucker, D.M., Dawson, S.L., Roth, D L. & Penland, J G. (1985). Regional changes in EEG power and coherence during cognition: Intensive study of two individuals *Behavioural Neuroscience*, 99(3): 564-577.

Ukai, K., Tsuchiyta, K. & Ishikawa, S. (1997). Induced pupillary hippus following near vision: increased occurrence in visual display unit workers. *Ergonomics*, 40(11): 1201-1211

Vogel, W, Broverman, D.M. & Klaiber, E L. (1968). EEG and mental abilities. *Electroencephalography and Clinical Neurophysiology*, 24: 166-175.

Volz, H-P., Gaser, C, Häger, F., Rzanny, R., Mentzel, H-J., Kreitschmann-Andermahr, I, Kaiser, W.A. & Sauer, H. (1997). Brain activation during cognitive stimulation with the Wisconsin card sorting test - A functional MRI study on healthy volunteers and schizophrenics. *Psychiatry Research: Neuroimaging Section*, 75: 145-157.

Ward, P B., Schall, U, bender, S., Lagopoulos, J. & Little, C. (1999). Functional magnetic resonance imaging investigation of brain activity during performance on the Tower of London. *Psychophysiology*, 36(51). S123.

Webb, W.B. & Agnew, H.A. (1970) Sleep stage characteristics of long and short sleepers. *Science*, 168 146-147

Webb, W B. & Agnew, H W. Jr. (1971). Stage 4 sleep· Influence of time course variables. *Science*, 174(16)· 1354-1356

Webb, W B. & Campbell, S S. (1979). The first night effect revisited with age as a variable *Waking and Sleeping*, 3: 319-324.

Webb, W B. & Dreblow, L M (1982) A modified method for scoring slow wave sleep in older subjects *Sleep*, 5: 195-199

Webb, W.B. & Levy, M C. (1982). Age, sleep deprivation, and performance. *Psychophysiology*, 19(3). 272-276

Werth, E, Achermann, P. & Borbély, A A. (1996). Brain topography of the human sleep EEG: Anterior-posterior shifts of spectral power. *Neuroreport*, 8(1): 123-127.

Werth, E., Achermann, P. & Borbély, A.A. (1997). Fronto-occipital EEG power gradients in human sleep. *Journal of Sleep Research*, 6: 102-112

West, R.L. (1996). An application to prefrontal cortex function theory to cognitive aging *Psychological Bulletin*, 120(2): 272-292.

Wilkinson, R.T. & Allison, S. (1989). Age and simple reaction time: decade differences for 5,325 subjects. *Journal of Gerontology*, 44 (2). P29-P35.

Wilkinson, R.T. & Mullaney, D. (1976). Electroencephalogram recording of sleep in the home *Postgraduate Medical Journal*, 52(7) 92-96.

Wimmer, F., Hoffman, R.F., Bonato, R.A. & Moffitt, A.R. (1992) The effect of sleep deprivation on divergent thinking and attention processes. *Journal of Sleep Research*, 1: 223-230.

Woodruff, D.S & Kramer, D.A. (1979) EEG alpha slowing, refractory period, and reaction time in aging. *Experimental Aging Research*, 5(4): 279-292.

Wright, K.P. Jr., Badia, P. & Wauquier, A. (1995). Topographical and temporal patters of brain activity during the transition from wakefulness to sleep *Sleep*, 18(10) 880-889

Ylikoski, R., Ylikoski, A , Keskivaara, P , Tilvis, R., Sulkava, R. & Erkinjuntti, T. (1999). Heterogeneity of cognitive profiles in aging: Successful aging, normal aging, and

individuals at risk for cognitive decline. *European Journal Of Neurology*, 6(6) 645-652.

Zepelin, H. (1983). Normal age related change in sleep. In Chase, M H. & Weitzman, E D. (Eds). Sleep *Disorders: Basic and Clinical Research*. (pp 431-444). SP Medical and Scientific Books New York

APPENDICES

Appendix 1

SLEEP RESEARCH CENTRE
Consent Form: CONFIDENTIAL

Consent of Subject to be included in Research Trial:

I.....,

Consent to taking part in a series of psychological tests, inclusive of a simultaneous EEG recording, within the sleep research laboratory. An explanation of the nature and purpose of the procedure has been given to me by..... ....

I understand that I may withdraw from the experiment at any time, and that I am under no obligation to give reasons for such withdrawal. Upon withdrawal, I understand that I may request any data already collected to be discarded from the study.

I understand that any information about myself that I have given will be treated as confidential by the experimenter.

Signed: .....

Date: .....

Signature of Experimenter: .....

http //humsci lboro ac uk/sleep
Tel 01509 223005
E-Mail c Anderson@lboro ac uk

Appendix 2

SLEEP RESEARCH CENTRE
Screening Questionnaire: CONFIDENTIAL

Interview Date.....	Ss No:..... ....
Name:	Sex: .....
Address:	Age/DoB:..... .....
.. ..	Phone No:.....
.....	Occupation.....

Outcome/Participation.....
....
....

GENERAL QUESTIONS

1) Do you consider yourself to be a "nervous" person?

Yes	1
Sometimes	2
No	3
Don't Know	0

2) Do you consider yourself to be a "worrier"?

Yes	1
Sometimes	2
No	3
Don't Know	0

3) Have any events in the last 6months caused you particular concern or anxiety?

Yes	1
No	3
Don't Know	0

4) How many cups of tea/coffee do you usually drink in a day?

None	1
1-2	2
3-4	3
5-6	4
Over 6	5
Don't Know	0

5) Do you smoke?

Yes	1
Sometimes	2
No	3
Don't Know	0

5a) If yes, How many cigarettes per day?

1-5	1
5 or more	2
Don't Know	0

HEALTH QUESTIONS

6) In general would you say your health is:

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't Know	0

7) Compared to a year ago, how would you rate your health in general now?

Much better than a year ago	1
Somewhat better than a year ago	2
About the same	3
Somewhat worse than a year ago	4
Much worse than a year ago	5
Don't Know	0

8) During the past 8 weeks, have you had any problems with work or other daily activities as a result of your physical/emotional health?

Yes	1
No	3
Don't Know	0

9) Have you ever experienced any of the following medical conditions, and if so when?

No = 1 **Yes in the past = 2**
Yes, sometimes = 3 **Yes, at present = 4**
Don't know = 0

(a)	Asthma	.....	(b)	Hay fever	. . ..
(c)	Eczema	.....	(d)	Allergies	... .
(e)	Thyroid Problems	. ...	(f)	Undue anxiety	.....
(g)	Sleepwalking	. .....	(h)	Loud snoring	....
(I)	Nightmares	. .....	(j)	Bruxism	.. . ..
(k)	Difficulty reading/writing	.	(l)	Arthritis/Rheumatism	..... .
(m)	Depression	. .....	(n)	Heart problems	. . .. ..
(o)	Stomach problems	. .....	(p)	Waking up with a jolt	.....
(q)	Waking up excessively early	.. . . ..	(r)	Difficulty falling asleep	....
(s)	Stress/anxiety at home/work	. . ..	(t)	Epilepsy	.....
(u)	Migraine	.....	(v)	Colour blindness	. ... ..
(w)	Hearing Problems	.... .			

10) Do you worry about your health?

Yes	1
Sometimes	2
No	3
Don't Know	0

10a) If yes, in what way?

....
....

11) Do you regularly task pills or medicines from the chemist or by prescription?

Yes	1
No	3
Don't Know	0

If so can you tell me what they are?

....
....

SLEEP QUESTIONS

12) What time do you normally go to bed? .. . .

13) What time do you normally get up? ....

14) How long does it normally take you to fall asleep?

0-5 minutes	1
5-10 Minutes	2
10-20 Minutes	3
20-30 Minutes	4
Over 30 Minutes	5
Don't know	0

15) Do you ever miss a night's sleep or have much sleep than usual?

No	1
Yes, sometimes	2
Yes, regularly	3
Don't know	0

15a) If yes, can you tell me what is the reason for this?

.. ..
....

16) How would you describe your level of wakefulness in the hour before you go to bed?

Very Alert	1
Fairly Alert	2
Neither Sleepy nor Alert	3
Sleepy but not fighting sleep	4
Very sleepy, effort to stay awake.	5
Don't know	0

17) How much does your quality of sleep vary from one night to the next?

Very much	1
Moderately	2
Slightly	3
Not at All	4
Don't Know	0

18) How often do you lie awake worrying at night?

Every night	1
Several nights/week	2
Several times/month	3
Once a month or less	4
Never	5
Don't know	0

19) How many times do you wake , on average, a night?

Never	1
Hardly Ever	2
Once or Twice	3
Once a month	4
Never	5
Don't know	0

19a) If volunteer wakes up:
How long does it take you to get back to sleep again?

Less than 10 minutes	1
10 – 30 Minutes	2
30 – 60 Minutes	3
Over 60 Minutes	4
Don't know	0

19b) What usually causes you to wake up?

Awake spontaneously	1
Nerves, tension, worry	2
Need to go to the toilet	3
Shortness of breath/coughing	4
Pain in the chest	5
Pain in the stomach	6
Pain in the legs	7
Twitching/Kicking of legs	
Noise	8
Dreams or nightmares	9
Don't know	0
Other	10

20) How easy do you find getting up on the morning?

Very easy	1
Fairly Easy	2
Okay	3
Fairly Difficult	4
Very Difficult	5
Don't know	0

21) How refreshed do you feel after waking?

Very refreshed	1
Refreshed	2
Neither refreshed nor tired	3
Tired	4
Very Tired	5
Don't know	0

22) How would you describe your general level of wakefulness 15 minutes after getting up in the morning?

Very Alert	1
Fairly Alert	2
Neither Sleepy nor Alert	3
Sleepy but not fighting sleep	4
Very sleepy, effort to stay awake	5
Don't know	0

23) Do you ever have difficulty staying awake during the day?

Yes every day	1
Yes, several times a week	2
Yes, several times a month	3
Yes, once a month	4
Never	5
Don't know	0

23a) If yes, At about what time does this sleepiness usually start?

....
. ...

23b) How long does this sleepiness usually last for?

5-10 minutes	1
10-20 minutes	2
20-30 minutes	3
30-60 minutes	4
Over 60 minutes	5
Don't know	0

24) Is there usually a good reason for this sleepiness?

Yes	1
No	3
Don't Know	0

24a) If yes, can you explain the reason to me?

....
. . . .

25) Do you ever nap during the day?

Yes	1
No	3
Don't Know	0

25a) If yes, how often on average?

Every Day	1
2-3 Times per week	2
Once per week	3
Once per month	0
Don't know	

26) Do you ever experience 'poor sleep'?

Yes	1
Sometimes	2
No	3
Don't know	0

26a) If yes, what constitutes this 'poor sleep' Code as many as applicable

I moved a lot during the night	1
I took a long time to fall asleep	2
My dreams made me anxious	3
I had an headache on waking	4
I woke up a great deal	5
I had many dreams	6
I felt dizzy on waking	7
I was aware of thinking all night	8
I felt tired when I awoke	9
Parts of me ached when I awoke	10
I slept shorter than usual	11
Don't know	0
Other (Code & Write)	12

27) If you had a poor nights sleep, does it affect:

How you feel	1
How you perform	2
Both of these	3
Neither of these	4
Don't know	0

33a) If you had a poor night's sleep, when do you feel the consequences?

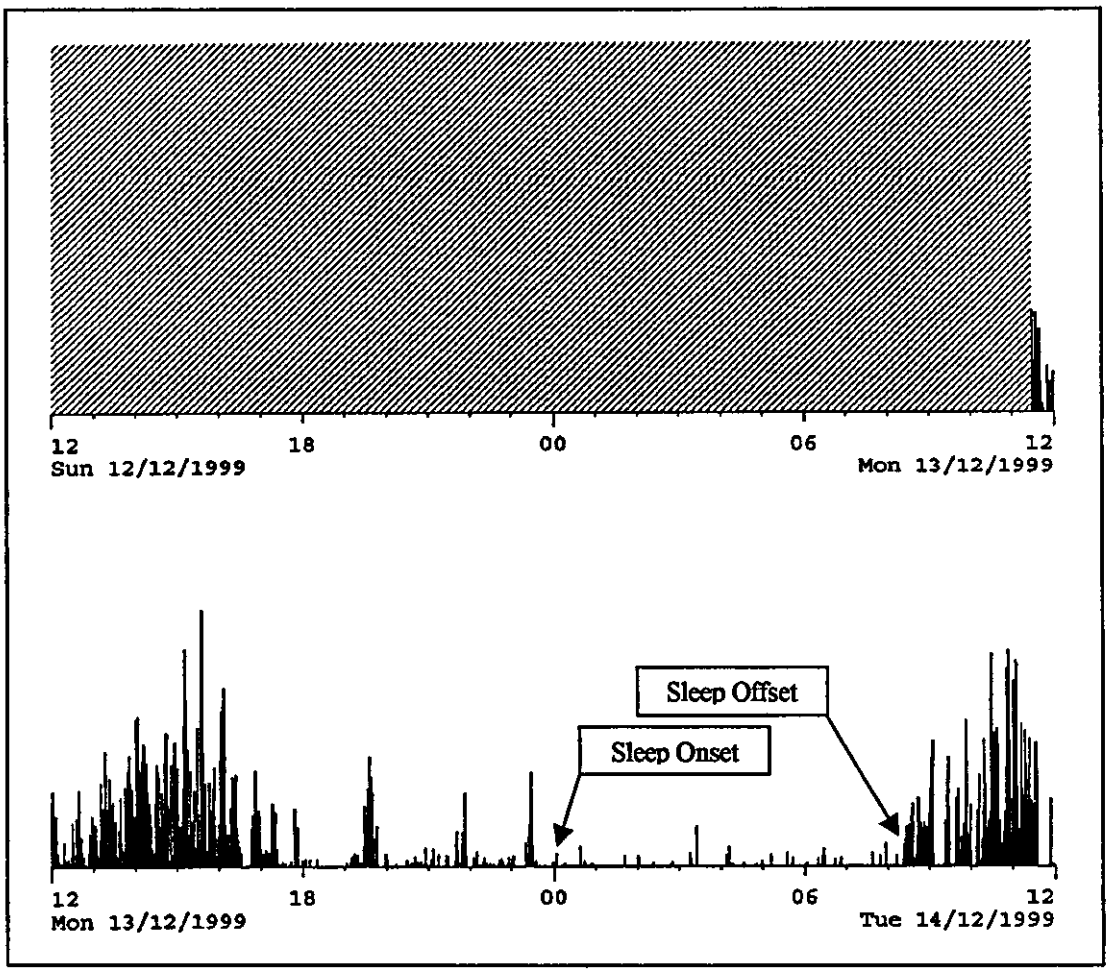
The next day	1
The day after	2
Both of these days	3
Neither of these days	4

THANK YOU, THAT IS THE END OF THE QUESTIONNAIRE

http //humsci lboro ac uk/sleep
Tel. 01509 223005
E-Mail c Anderson@lboro ac uk

Appendix 3

Example of Actigraph – Used for Sleep Onset/Offset and Sleep Disturbance Screen



Subject: rr4
Sex: Male
Age: 68.1 years
Sleep Onset: 23.35h
Sleep Offset: 08.20h

Appendix 4

SLEEP RESEARCH CENTRE
Daytime Sleepiness: CONFIDENTIAL

The Karolinska Sleepiness Scale shows how you rate how sleepy you are feeling at a given time. Please rate your feeling of sleepiness every hour that you are awake for 3 days. Please write in what time you went to sleep and what time you awoke. Thank You

The number you put in the box should correspond to the following rating guide:

The Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990)

1. Extremely Alert
2. Very Alert
3. Alert
4. Rather Alert
5. Neither Alert nor sleepy
6. Some signs of Sleepiness
7. Sleepy, but no effort to keep awake
8. Sleepy, some effort to keep awake
9. Very Sleepy, great effort to keep awake, fighting sleep

Day 1		*Day 2*		*Day 3*	
Time	**KSS**	**Time**	**KSS**	**Time**	**KSS**
07 00		07.00		07:00	
08 00		08 00		08:00	
09 00		09 00		09:00	
10.00		10.00		10 00	
11:00		11:00		11:00	
12:00		12:00		12.00	
13:00		13:00		13 00	
14:00		14:00		14.00	
15:00		15:00		15 00	
16.00		16:00		16:00	
17 00		17.00		17:00	
18 00		18 00		18:00	
19 00		19 00		19.00	
20 00		20 00		20 00	
21:00		21:00		21·00	
22.00		22:00		22 00	
23:00		23:00		23 00	
00:00		00:00		00 00	
01:00		01:00		01 00	

Loughborough Sleep Research Centre

http //humsci lboro ac uk/sleep
Tel 01509 223005
E-Mail c Anderson@lboro ac uk

Appendix 5

SLEEP RESEARCH CENTRE

Sleep Diary: CONFIDENTIAL

Subject Number: ....Date: .....

Fill in the details or tick as appropriate.

BEDTIME LOG

I got into bed at .... I turned the light out at ....

MORNING LOG

I woke up at . ..... this morning. I got out of bed at ....

15 minutes after waking I felt:		**Last night I slept:**		**Compared to normal, my sleep was:**	
a) Very refreshed	☐	a) Extremely Well	☐	a) Much Better	☐
b) Refreshed	☐	b) Very Well	☐	b) Somewhat Better	☐
c) Neither	☐	c) Fairly Well	☐	c) About the Same	☐
d) Tired	☐	d) Rather Badly	☐	d) Somewhat Worse	☐
e) Very tired	☐	e) Extremely Badly	☐	e) Much Worse	☐

NIGHT DIARY

During the night my partner slept in. *(delete as appropriate)*

the same bed as me / a different bed to me

As far as I can remember it took me ..... minutes to fall asleep
As far as I can remember I woke up ..... times last night.

Please note the details of any awakenings you can remember in the table below.

Time	**Length of Awakening (minutes)**	**Reason for Awakening**
.. ..	....	....
. ...	.. ..	.. ..
.....	....	....

Loughborough Sleep Research Centre

http //humsci lboro ac uk/sleep
Tel 01509 223005
E-Mail c Anderson@lboro ac uk

Appendix 6

Wisconsin Card Sorting Test: Score Sheet

WISCONSIN CARD SORTING TEST
SCORING AND RECORDING FORM

Robert Heaton, Ph.D.

NAME ______________________ AGE ________ SEX ________

EDUCATION ______________________ OCCUPATION ______________________

BEHAVIOR DURING TESTING ______________________

ADDITIONAL COMMENTS ______________________

Trials C, F, N, C, F, N,

C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O	C F N O	C F N O	C F N O	C F N O	C F N O
C F N O	C F N O					

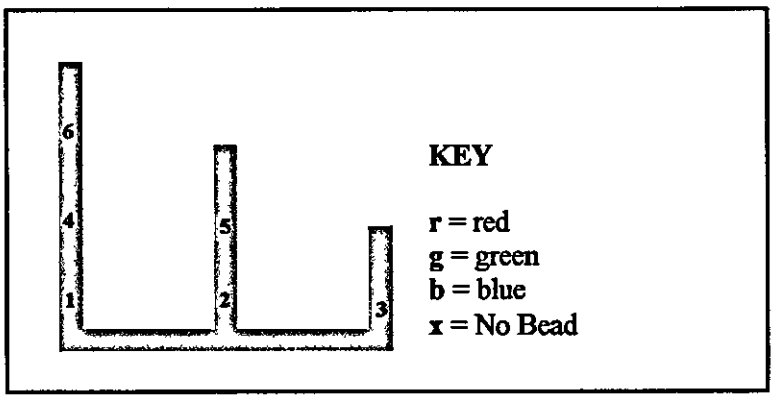
CORRECT ________ ERRORS ________ PERSEVERATIVE RESPONSES ________

NONPERSEVERATIVE ERRORS ________ PERSEVERATIVE ERRORS ________ CATEGORIES ________

FORM #307-SF

Appendix 7

Tower of London Configurations Used



Beads can be placed in locations 1-6, the table below shows the configurations used for the Tower of London (NVPT) based on the key above.

	Location						
Pattern	**1**	**2**	**3**	**4**	**5**	**6**	**No. Moves**
Standard Configuration	g	b	x	r	x	x	-
Practice 1	x	b	g	x	r	x	2
Practice 2	r	b	x	x	g	x	3
Target Pattern							
Problem 1	x	b	r	x	g	x	2
Problem 2	g	r	b	x	x	x	2
Problem 3	g	r	x	b	x	x	3
Problem 4	g	r	x	x	b	x	3
Problem 5	r	b	x	g	x	x	4
Problem 6	b	r	x	x	g	x	4
Problem 7	r	x	g	b	x	x	4
Problem 8	x	r	g	x	b	x	4
Problem 9	r	x	x	g	x	b	5
Problem 10	r	x	x	b	x	g	5
Problem 11	b	r	x	g	x	x	5
Problem 12	b	r	g	x	x	x	5

Appendix 8

Temporal Memory Score Sheet

Please fill in your details

Ss No.	
Sex:	
Age:	

All Data is Treated Confidentially & Anonymously

	Yes/No	*If Yes which list?*	List A	List B		Yes/No	*If Yes which list?*	List A	List B
No 1					No 25				
2					26				
3					27				
4					28				
5					29				
6					30				
7					31				
8					32				
9					33				
10					34				
11					35				
12					36				
13					37				
14					38				
15					39				
16					40				
17					41				
18					42				
19					43				
20					44				
21					45				
22					46				
23					47				
24					48				

Appendix 9

SLEEP RESEARCH CENTRE
Wake EEG Comment Form

Subject Number _____ **Date** _____
Time _____

PART A - Visual Instruction

	KSS	Time	From	To	Comments
KSS 1					
Eyes Open		3mins			
KSS 2					
NVPT 1		*SP*			
NVPT 2		*SP*			
NVPT 3		*SP*			
NVPT 4		*SP*			
NVPT 5		*SP*			
NVPT 6		*SP*			
KSS 3					
Object Location		1min			
KSS 4					

PART B – Auditory Instruction

	KSS		From	To	Comments
T1 - Eyes Closed		3mins			
KSS 5					
T2 - Verbal Fluency					
Book		1min			
School		1min			
Car		1min			
Picture		1min			
Holiday		1min			
KSS 6					
T3 - Journey		2mins			
KSS 7					
T4 - Song		2mins			
KSS 8					
T5 - Yesterday		3mins			
KSS 9					
T6 - Experiment		3mins			
KSS 10					