Cognitive, Neuroanatomical and Neuroendocrine Effects of Long-Term Rotating Shift Work in a Nursing Sample

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DECLARATION

I, Alexia Pavlis, declare that the Doctor of Psychology (Clinical Neuropsychology) thesis entitled "Cognitive, Neuroanatomical and Neuroendocrine Effects of Long-Term Rotating Shift Work in a Nursing Sample" is no more than 40,000 words in length, exclusive of tables, figures, appendices, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

Signature: Date:

Submitted with emendations: July 2007

DEDICATION

This thesis is dedicated to the memory of my brother Yani Anthony Pavlis: music boffin, science lover, brain.

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LIST OF ABBREVIATIONS

ACTH	adrenocorticotropic hormone
BOLD	blood oxygen level dependent
Cho	choline
Cr	creatine
CRH	corticotropin releasing hormone
CVLT	California Verbal Learning Test
DSM-IV	Diagnostic & Statistical Manual of Mental Disorders 4th edition
EEG	electroencephalogram
ESS	Epworth Sleepiness Scale
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
GC	glucocorticoid
HPA	hypothalamic-pituitary-adrenal
KSS	Karolinska Sleepiness Scale
mI	myo-Inositol
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAA	N-acetyl-aspartate
NPMD	non-psychotic major depression
PET	positron emission tomography
PMD	psychotic major depression
POMS	Profile of Mood States
PTSD	posttraumatic stress disorder
RAVLT	Rey Auditory Verbal Learning Test
ROI	region of interest
TSH	thyroid stimulating hormone
VBM	voxel-based morphometry
WAIS-III	Wechsler Adult Intelligence Scale 3rd edition
WMS-III	Wechsler Memory Scale 3rd edition
WMS-R	Wechsler Memory Scale Revised

ABSTRACT

Sleep disruption, like that experienced by long-term rotating shift workers, is a physiological stressor which causes a variety of adverse physical, psychological and cognitive symptoms. Some cognitive symptoms are thought to be mediated by the direct effect of stress hormones on the hippocampus. Regardless of its source, stress provokes endocrine responses in the body that affect the hypothalamic-pituitary-adrenal (HPA) axis. Whereas acute activation of the HPA axis adaptively activates the body's stress response by increasing cortisol production, prolonged or repeated activation is detrimental to health due to dysregulation of the HPA axis. Cortisol affects the hippocampus, which has a high concentration of glucocorticoid receptors and plays a prominent role in the down-regulation of the HPA axis. Overstimulation of glucocortioid receptors can cause hippocampal atrophy and related cognitive deficits. Research has found that air crew with inadequate recovery time between outbound, transmeridian long-haul flights showed performance decrements on cognitive tasks, reduced hippocampal volumes and increased cortisol levels. The current study aimed to investigate whether work-related sleep disruption caused similar effects among rotating shift-workers from outside the flight industry. Twelve long-term female rotating shift-workers (nurses) and 17 day working female control participants (nurses and others) participated in the study. Analyses of the sleep health, cognitive (memory, attention, visual-spatial skills), endocrine (salivary cortisol), magnetic resonance imaging (MRI) and spectroscopy (MRS) data of these participants showed few differences between groups in cognitive performance, volumetric MRI or MRS. Shift workers reported less sleep over a fortnight, higher levels of fatigue and lower levels of vigor compared to controls. Cortisol rhythm changes including earlier morning rise and peak attenuation were apparent in shift workers. The results are interpreted in terms of age differences between the groups and the existence of a "healthy worker" effect in the shift workers.

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INTRODUCTION

In humans and other mammals, adrenal steroid secretion via the hypothalamic pituitary adrenal (HPA) axis increases in response to stress. Acute increases in circulating glucocorticoids (GCs), such as cortisol in humans and corticosterone in other animals such as rats, act as a physiological marker of stress. GCs are produced by the adrenal cortex in response to both physical and psychological stressors. GCs serve to mobilise the organism in times of stress, providing the physical resources to "fight or flee" immediate danger. In the short term, such a response is obviously adaptive. However, in the longer term a prolonged stress response can be harmful to the organism, and may lead to the breakdown of the very systems that are adaptively stimulated during the acute stress response.

For the modern human, stressors have developed beyond the mere physical danger posed by predators of our evolutionary forebears. We are confronted daily by an array of potential physiological and psychological stressors that may provoke acute responses that mobilise energy or prime psychomotor responses. With the physiological resources activated by acute stress we are able to react to immediate stressors such as when we swerve evasively while driving, or when we successfully speak in public. However, some stressors are ongoing, and provoke chronic, prolonged activation of the HPA axis. Due to personal or social circumstances, some stressors such as adverse working conditions may be more difficult to overcome or control. The focus of this thesis is the effect of a work-related physiological stressor, namely sleep and circadian disruption, on HPA axis activity, the flow-on effects to the brain as a site of high concentrations of GC receptors, and finally the effects on cognitive functioning.

In the introductory section, sleep disruption, such as that caused by rotating shift work or frequent jet lag, will be defined as a physiological stressor with reference to its effects on the circadian rhythmicity of HPA axis hormones, particularly cortisol. The effects of elevated cortisol, both endogenously produced and exogenously administered, and HPA axis dysregulation, on

cognition and behaviour will be explored, as will the cognitive and behavioural effects of sleep disruption. The known effects of GCs on hippocampal structure and function will be described, and a case will be made that long-term rotating shift work (a chronic physiological stressor) causes dysregulation of the HPA axis. Potential alterations to hippocampal structure and function will also be explored.

1.1. Circadian rhythms

Human biological rhythms are endogenous, periodic cycles of biochemical, physiological and behavioural processes, constrained and influenced by exogenous sources of temporal information that serve to synchronise and regulate the various rhythms. Biological rhythms can be defined according to their frequency. Respiratory, cardiac, sleep-stage and electroencephalographic (EEG) rhythms with cycles much shorter than 24 hours, are known as ultradian rhythms. Those with frequencies of greater than 24 hours, such as the menstrual cycle in human women and hibernation patterns in some mammals, are known as infradian rhythms. Rhythms or cycles with periods of about 24 hours are known as circadian rhythms, and include the sleep-wake cycle and other activity or arousal rhythms, thermoregulation, eating and drinking, and endocrine rhythms (Moore-Ede, Sulzman, & Fuller, 1982). True circadian rhythms persist or free-run with a period close to, but not exactly, 24 hours under conditions of temporal isolation. This indicates that circadian rhythms are driven by an endogenous mechanism.

In terms of the timing and control of circadian rhythms, the primary source of exogenous temporal information, which acts as a phase regulator or *zeitgeber* (German; literally "time giver") is photoperiod. Photoperiod can be defined as the ratio of light to dark hours experienced by an organism. Depending upon latitude and the time of the year photoperiod can vary; humans experience between nine to fifteen hours of maintained light following a period of partial, increasing light (dawn), then a period of partial decreasing light at dusk followed by a period of darkness, which corresponds approximately to the usual

sleep-wake cycle (Moore-Ede et al., 1982). In terms of internal, endogenous circadian timekeeping, the hormone melatonin acts as an endogenous regulator of many other circadian rhythms, such as the sleep-wake cycle and thermoregulation (Cajochen, Kräuchi, & Wirz-Justice, 2003)

A number of other exogenous zeitgebers, such as social interactions and work commitments, may affect the influence of the light-dark cycle in synchronising rhythms in humans (Winget, DeRoshia, Markley, & Holley, 1984), leading to circadian desynchronisation. Work or social conditions that cause chronic disruptions to sleep, such as frequent jet lag or rotating shift-systems, can lead to the situation where some circadian rhythms (such as activity-rest cycles) are shifted in relation to other cycles, such as the natural light-dark cycle. This kind of discrepancy can lead to internal desynchronisation of circadian rhythms (Copinschi, Spiegel, Leproult, & Van Cauter, 2000). Desynchronisation refers to a loss of phase relationship between different circadian rhythms, which differ substantially in phase and amplitude over the 24-hour period. For example, growth hormone in the normal human system reaches its peak (acrophase) a few hours after sleep onset, coinciding with the trough (nadir) of the cortisol rhythm. Body temperature rises gradually over the morning as we wake up, reaching a peak in the afternoon and tapering off over the night and early morning hours (Moore-Ede et al., 1982). Melatonin shows a circadian rise in the evening after bedtime, reaching its acrophase over night before subsiding around 0700h and a return to quiescence (Copinschi et al., 2000).

1.1.1. Cortisol rhythm and stress

Cortisol is an adrenal glucocorticoid found in humans; its analogue in experimental animals such as rats is corticosterone. In humans it shows an episodic, pulsatile pattern of secretion of about six to nine discrete episodes over a 24-hour period, resulting in acute increases followed by an attenuation in concentration. Superimposed over this is a circadian rhythm that is strongly synchronised to the sleep-wake and light-dark cycles. Following a quiescent period overnight and during the early morning hours, cortisol begins to rise

about five hours before waking, peaking in the morning after waking-time. Levels gradually fall again during the daylight hours and reach the lowest concentrations about one hour after nocturnal sleep onset (Moore-Ede et al., 1982; Redwine, Hauger, Gillin, & Irwin, 2000). Although it is superficially synchronised to the sleep-wake cycle, the cortisol rhythm is influenced little by sleep availability and regularity, but is controlled by a circadian clock located in the suprachiasmic nuclei. The cortisol rhythm is viewed as a robust marker of overall circadian rhythmicity (Aschoff, 1979; Gronfier & Brandenberger, 1998).

In the adult human, the acrophase and nadir of the cortisol rhythm correspond to the rise and fall of arousal levels, such as waking up and falling asleep, over the 24-hour solar day. In addition to its circadian rhythmicity, cortisol output is acutely affected by stress. When human and other animals are confronted with physical or psychological stressors, extra glucocorticoids are produced by the adrenal glands and serve to mobilise energy, increase cardiovascular activity, heighten vigilance and speed of information processing and attenuate nonessential bodily functions such as growth, immune response, tissue repair and reproduction (Sapolsky, 2000a). In the short term, acute activation of the stress-response has clear adaptive value, causing activation of the sympathetic nervous system, and is known as the fight-or-flight response (Cannon, 1927). If constantly activated, the stress response can become maladaptive. For example, the mobilisation of the body's energy for action can result in myopathy and fatigue. Increased cardiovascular tone can lead to stress-induced hypertension. The suppression of nonessential functions such as reproduction and immune activity can lead to reduced fertility (amenorrhoea, impotence), and increased susceptibility to illness, respectively. While acute stress can cause temporary suppression of growth, chronic psychological and physiological stress in infancy and childhood can cause psychogenic dwarfism. In terms of stress effects on the central nervous system, acute stress can produce an increase in speed of mental processing and heightened vigilance; chronic stress can cause apoptosis due to over-activation of glucocorticoid-binding neurons (Sapolsky, 1992).

Differential effects of stress on the HPA axis are seen depending on the time of day the stressor is experienced. Plasma cortisol levels show the greatest elevation when humans are subjected to stressors during the nadir in the circadian rhythm of cortisol secretion, occurring at night just before sleep onset (Takebe, Setaishi, & Hirami, 1966). However, in terms of effects on functioning, psychological stressors experienced in the morning (0900h), when cortisol levels are still quite high, appear to have a greater effect on declarative memory than afternoon stressors, particularly on memory for emotionally-laden material (Maheu, Collicutt, Kornik, Moszkowski, & Lupien, 2005).

1.2. Sleep disruption as a stressor

Sleep disruption can be considered a physiological stressor with both physical and psychological consequences (McEwen, 2006). Constant or prolonged sleep disruption, resulting in repeated disturbance of synchronisation of the circadian system to the environment, is known to be detrimental to health and cause stress (Winget et al., 1984). Disruptions to the sleep-wake cycle, such as sleep deprivation, night shift work and jet lag following rapid transmeridian flight, cause transient internal desynchronisation of circadian rhythms (Winget et al., 1984). The effects of sleep disruption are well known to shift workers in many different occupations, as well as anyone who has suffered from jet lag following transmeridian flight. Sleep disruption has also been used punitively and as a 'soft' torture or coercion method due to its ability to provoke psychological reactions in those who are exposed to it chronically (Bloche & Marks, 2005; McCoy, 2006). Health consequences of circadian disruption include acute effects such as fatigue, difficulty initiating or maintaining sleep and irritability. The effects of chronic disruption to the sleep wake cycle can manifest as increased risk of cardiovascular (Knutsson, Hallquist, Reuterwall, Theorell, & Akerstedt, 1999; Taylor & Pocock, 1972), gastrointestinal and psychological illnesses (Costa, 1997). There is also evidence of an increased incidence of industrial and workplace accidents and injuries due to work-related sleep disruption (Åkerstedt, Fredlund, Gillberg, & Jansson, 2002; Costa, 1996; Ohayon, Lemoine, Arnaud-Briant, & Dreyfus, 2002). In the following section

the effects of acute and chronic sleep-deprivation, jet lag and different shift work schedules on cortisol level and other physiological, psychological and cognitive measures will be discussed.

1.2.1. Sleep deprivation

Although cortisol has been characterised as a hormone that is influenced little by sleep and is under the endogenous regulation of a circadian biological clock (Gronfier & Brandenberger, 1998), sleep deprivation appears to have some, albeit variable, effects on the cortisol rhythm. In some studies normal participants displayed a reduction of cortisol levels following acute sleep deprivation (Åkerstedt, Palmblad, de la Torre, Marana, & Gillberg, 1980; Vgontzas et al., 1999), although acute total sleep deprivation in normal males did not affect cortisol in a study by Heiser and colleagues (2000). Dysregulation of the cortisol rhythm has been reported by others. For example, Goh, Tong, Lin, Low and Lee (2001) found an atypical cortisol peak at 1330h in military personnel deprived of one night's sleep, compared to a normal sleep group, There were no significant group differences in total cortisol levels over 24 hours.

Accumulated sleep debt has also been shown to phase delay and shorten the cortisol quiescent period as well as raising afternoon and early evening cortisol concentrations (Spiegel, Leproult, & Van Cauter, 1999) in young adult males following six days of shortened sleep (four hours). An increase in daytime cortisol after one night's sleep deprivation was found by Chapotot and colleagues (2001) in their study of 12 healthy men. In a comparison of normal nocturnal sleep (2300h to 0800h), partial sleep deprivation (enforced wakefulness until 0400h followed by sleep from 0400h to 0800h) and total sleep deprivation (32 hours continuous wakefulness), evening cortisol levels were significantly elevated after both forms of sleep deprivation (Leproult, Copinschi, Buxton, & Van Cauter, 1997). The authors suggested that continued sleep loss could facilitate the development of glucocorticoid-related cognitive deficits such as impairments in hippocampal-dependent memory function.

1.2.1.1.Cognitive and psychiatric effects of sleep deprivation

It has long been acknowledged that sleep deprivation impairs numerous cognitive abilities (Patrick & Gilbert, 1896). One night of total sleep deprivation can affect reaction times and task accuracy to the same extent as having a blood alcohol concentration of .05% (Falleti, Maruff, Collie, Darby, & McStephen, 2003). Significant deficits have been reported in logical reasoning (Blagrove, Alexander, & Horne, 1995), vigilance (Blagrove et al., 1995; Caldwell, Caldwell, Brown, & Smith, 2004; Orton & Gruzelier, 1989), sustained attention, attentional switching and short-term auditory attention span (Frey, Badia, & Wright, 2004), executive functions (Harrison & Horne, 1998; Nilsson et al., 2005), inhibition of prepotent responses (Chuah, Venkatraman, Dinges, & Chee, 2006), temporal memory for visual stimuli (Harrison & Horne, 2000) and verbal memory (Deary & Tait, 1987). Some studies have sought evidence of more functional, work related, deficits by testing participants on tasks designed to simulate work conditions. The performance of fighter pilots on computerised cockpit simulation tasks assessing reaction time and vigilance and on a flight simulator was shown to deteriorate significantly during 37 hours sleep deprivation (Caldwell et al., 2004). However, Deary and Tait (1987) reported no significant differences between sleep deprived, sleep reduced and normal sleep conditions when medical interns were required to read pathology reports and diagnose arrhythmias on echocardiograms.

Sleep loss also affects effort and motivation to complete tasks. Reductions in persistence and vigour as measured by speed of task completion and work rates related to sleep deprivation have been reported by a number of researchers (Blagrove et al., 1995; Chmiel, Totterdell, & Folkard, 1995). Although sleep deprived participants' performance can be improved with rewards (Horne & Pettitt, 1985) and feedback (Steyvers & Gailard, 1993), these effects appear to be short-lived (Horne & Pettitt, 1985) as fatigue overcomes transient improvements in effort. More recently, Engle-Friedman and colleagues (2003), in a study of the effects of one night of sleep loss on undergraduate students (n = 58), showed that sleep deprivation lead to the selection of tasks that were less demanding when participants were able to choose the task difficulty level. This

preference for easier tasks was not in response to performance failures, but appeared to be rather a decision to take the path of least resistance when cognitive resources were stretched by fatigue. Some researchers have suggested that it is this aspect of sleep deprivation, the inability to summon or sustain the required effort, that affects task performance, rather than impairments in specific cognitive abilities due to the physiological effects of sleep loss (Meddis, 1982).

Sleep deprivation affects mood. Self-reports of mood after sleep deprivation of up to 72 hours showed a gradual deterioration in subjective mood state. This was positively correlated with duration of sleep deprivation in a study of 12 normal participants (Mikulincer, Babkoff, Caspy, & Sing, 1989). Fighter pilots subjected to up to 37 hours sleep deprivation showed increased self-reported depression-dejection and confusion-bewilderment ratings on the Profile of Mood States over the period of sleep loss (Caldwell et al., 2004). Shorter periods of sleep (1.5 hours vs. 5 to 7 hours) were shown to lead to reductions in vigour and motivation ('deactivated' mood on the Nowlis Mood Adjective Checklist) in medical interns (Deary & Tait, 1987). Similarly, on-call work periods resulting in disrupted sleep patterns in general practitioners have been shown to cause increases in reported anxiety and depression (Nicol & Botterill, 2004).

1.2.1.2. Brain effects of sleep deprivation

Sleep deprivation appears to have an effect on neurophysiological processes, as measured by electroencephalography (EEG), magnetic resonance spectroscopy (MRS) and functional imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Slowed event related potentials (ERPs) and attenuated ERP amplitudes on EEG have been reported following sleep deprivation (Cajochen, Jewett, & Dijk, 2003; Smith, McEvoy, & Gevins, 2002). EEG power in the delta, theta and gamma frequency bands (associated with increased effort in concentration and

vigilance) in frontal cerebral areas has been shown to increase following one night's sleep deprivation (Chapotot et al., 2001).

MRS studies have shown widespread effects of sleep deprivation on brain metabolite levels. Murck et al. (2002) reported an increase in GABA, glutamate and glutamine in the medio-dorsal pontine and pontomesencephalic region compared to baseline measurements following 24 hours total sleep deprivation. In study that also incorporated fMRI to identify brain areas active during a word generation task, Urrila and colleagues (2004) reported a diminished lactate response in the left frontal lobe following 40 hours total sleep deprivation, indicative of a lowered brain energy metabolism. The reduction in lactate was associated with poorer performance on the word generation task only in older participants (older group with a mean age of 63 years compared to the young group, mean age 21 years).

Functional PET and MRI studies of brain activity during cognitive tasks (particularly working memory tasks) after sleep deprivation have shown equivocal results. However, decreases in fronto-parietal activity have been most consistently reported (Chee et al., 2006). Thomas and colleagues (2000) demonstrated that 24 hours sleep deprivation caused a significant decrease from baseline measurements in brain glucose metabolism (as measured by PET) indicating decreases in brain activity, particularly in attention- and alertness-mediating bilateral prefrontal-posterior parietal-thalamic networks.

A series of studies by Drummond and colleagues (1999; 2000; 2001; 2004) reported the effects of 35 hours total sleep deprivation on brain dynamics (fMRI) during verbal learning, serial subtraction, arithmetic and divided attention tasks. They found greater cerebral blood oxygen level dependent (BOLD) responses bilaterally in the prefrontal cortex and parietal lobes during the verbal learning, serial subtraction and divided attention tasks following sleep deprivation. During the completion of the arithmetic task after sleep deprivation there was a reduction in number of areas activated, compared to performance after a normal night of sleep (Drummond & Brown, 2001). Chee and colleagues (2006) reported reduced BOLD responses in the left prefrontal,

bilateral superior parietal and left thalamic regions following 24 to 25 hours total sleep deprivation.

These studies, along with other research showing alterations in prefrontal cortex dynamics following sleep deprivation (Mu et al., 2005; Strangman, Thompson, Strauss, Marshburn, & Sutton, 2005; Stricker, Brown, Wetherell, & Drummond, 2006; Wu et al., 1991), are consistent with behavioural studies showing deficits in attention and higher-order cognitive processes known to be mediated by the frontal lobes and various frontal reciprocal connections to other brain regions, which are activated during tasks requiring integrated executive functioning (Nilsson et al., 2005). However, there is also great interindividual variability in these findings, suggesting that there are subsets of people who are either more resistant or more vulnerable to the effects of sleep deprivation on brain functioning and cognitive performance. It may be possible to identify such differences by looking at rested-state fMRI, and thus predict which people will cope well in occupations that are likely to involve sleep disruption (Caldwell et al., 2005; Chuah et al., 2006).

1.2.2. Jet lag

A large body of research from the 1960s and 1970s (see Winget, DeRoshia, Markley and Holley (1984) for a review) has shown that international flight involving the crossing of several time zones results in internal desynchronisation (loss of phase relations) from external zeitgebers (mainly the light-dark cycle) at the destination, as well as desynchronisation between the body's numerous physiological rhythms. The symptoms caused by these two types of desynchronisation are known to most international flyers as "jet lag".

Re-entrainment of the circadian sleep-wake rhythm to new local time usually takes somewhere from five to ten days (Wever, 1979). However, the rate of re-entrainment of individual circadian rhythms varies and full re-entrainment of the circadian system probably takes much longer (Wever, 1979). Loss of phase relations between the different rhythms is responsible for the physiological and psychological symptoms experienced during jet lag (Deacon & Arendt, 1996),

which include difficulties initiating and maintaining sleep, gastrointestinal upsets, daytime somnolence, fatigue and impaired cognitive functioning (Moore-Ede et al., 1982; Wright et al., 1983).

Severity of jet lag symptoms and time taken to recover depend upon the number of time zones crossed, direction of flight and the strength of zeitgeber signal at the destination (Moore-Ede et al., 1982). Resynchronisation of the psychomotor performance rhythm after eastward flight over six time zones, which causes an abrupt phase advance of the sleep-wake cycle, can take up to 18 days, whereas resynchronisation after a similar westbound flight (causing a phase delay) takes only up to eight days (K. E. Klein & Wegmann, 1979). Long haul travellers who remain in hotel rooms or succumb to sleep and meals at destination-inappropriate times take longer to adjust than those who are quickly exposed to environmental zeitgebers at the destination (Moore-Ede et al., 1982).

Abrupt phase advances of the sleep-wake cycle, such as those that occur in eastward jet lag, can cause marked disruption to endocrine rhythms. A phase advance of eight hours, mimicking a eastward long haul flight, causes disruption of the cortisol quiescent period, even without any sleep disruption (Caufriez et al., 2002). In a study of male travellers after one westward transmeridian flight, Désir and colleagues (1981) reported temporal disorganisation of the cortisol rhythm which took 11 days to fully adapt to the new time zone, although there was no overall increase in cortisol secretion. Eastward flight was shown to exert a more lengthy effect. Recovery of the cortisol quiescent period after a flight from Brussels to Chicago took up to three weeks (Désir et al., 1983). Adjusting to phase delays in the sleep wake cycle is more rapid in most people because the free-running circadian rhythm is longer than 24 hours in most individuals, and a phase delay can therefore be "absorbed" by the system.

There is a misconception that frequent air travel reduces the effects of jet lag (Criglington, 1998). However, a 1998 survey of New Zealand flight attendants who completed a jet lag symptoms questionnaire reported that these workers experienced rates of jet lag symptoms (tiredness, sleep disruption, reduced energy and motivation, disorientation, respiratory illness) similar to the general

flying public, suggesting that frequency of transmeridian flight does not ameliorate the effects of time-zone desynchronisation (Criglington, 1998).

It is difficult to gauge the long-term effects repeated episodes of rapid international flight and subsequent jet lag have on human health. For this reason, and possibly due to the economic self-interests of the travel industry, little attention has been focused on the effects of frequent international travel. Earlier studies involving the simulation of repeated transatlantic flights using blowflies as subjects found that lifespan was significantly (20%) reduced (Aschoff, Saint-Paul, & Wever, 1977). Similarly, Halberg, Nelson and Cadotte (1977) found mice subjected to repeated weekly 180° reversals of the light-dark cycle showed a 6% decrease in longevity. Translated into human terms this might mean a four to five year shortening of life-span for people who are subjected to constantly changing time zones or shift-work schedules. The question of whether these results can be directly translated to humans currently remains unanswered.

1.2.2.1.Cognitive and psychiatric effects of jet lag

Cognitive and neuroanatomical effects of chronic jet lag have been reported by Cho and colleagues (Cho, 2001; Cho, Ennaceur, Cole, & Kook Suh, 2000). They hypothesised that chronic disturbance of the circadian system resulting from repeated exposure to jet lag leads to significantly elevated cortisol levels and related cognitive and neuroanatomical deficits. In an initial study focussing on cortisol levels and memory functioning, Cho et al. (2000) compared average daily cortisol secretion and working memory performance (visual delayed-match-to-sample tasks) of female flight attendants (n = 28) who made weekly transmeridian flights with ground crew (n=10) who rarely made transmeridian flights. It was hypothesised that the chronic jetlag experienced by flight attendants would lead to elevated cortisol levels and cognitive deficits related to circadian rhythm disruption. Flight attendants had significantly higher salivary cortisol levels than ground crew over a typical working day involving transmeridian flight. Although the two groups did not differ overall on working

memory performance, flight attendants with longer working histories (>3 years on weekly transmeridian flights) made significantly fewer correct responses than did ground crew. Flight attendants, but not ground crew, showed a significant correlation (r = -.78) between cortisol level and correct responses on the working memory task, indicating that cortisol elevation was associated with poorer memory performance.

A further study by Cho (2001) compared temporal lobe volume (MRI scans corrected for head size), responses to an experimental visual spatial cognitive task and cortisol levels between two groups (each group n = 10) of international long-haul female flight attendants. One group had less than five days between outbound transmeridian flights, while the other group had more than 14 days between outbound flights. The total flight time exposure of the two groups was approximately the same (controlling for the low level hypoxia inherent in the working environment) and both groups had been in the industry for five years. Cho (2001) found that the short recovery group had significantly reduced right temporal lobe volume, made more errors and were significantly slower on the visual-spatial task. The correlation (r = -.78) between right temporal volume and salivary cortisol levels was significant only for the short recovery group. This indicates a strong negative association between chronic elevation of cortisol levels and right temporal lobe atrophy. Importantly, these results also showed that longer periods between outbound flights may circumvent the temporal lobe atrophy associated with chronic jet lag induced stress.

Circadian dysregulation and sleep disruption due to acute jet lag have been linked to the precipitation or relapse of mental illness (Jauhar & Weller, 1982; Katz, Knobler, Laibel, Strauss, & Durst, 2002; Oyewumi, 1998; D. M. Young, 1995). In a study of 30 travellers to Honolulu who presented with acute psychiatric disturbance within 10 days of a flight involving at least a two-hour time-zone change, Young (1995) reported that departure preceded acute illness onset for 18 patients (60%). Westbound patients were more likely to have developed depressive illness than eastbound patients, providing support for the phase-advance hypothesis of depression (Wehr & Wirz-Justice, 1982; Wirz-Justice, 2000). Eastward flight from Canada to Lebanon was seen to precipitate

a relapse of psychotic symptoms in a patient previously stabilised on clozapine (Oyewumi, 1998). Katz and colleagues (2002) reported a prospective study of 152 long-distance travellers admitted to an Israeli hospital with psychiatric disturbances (psychotic or affective disorders) occurring within seven days of a long (greater than seven hours) east-west flight. After controlling for other factors such as demographic, religious or diagnostic background, the results indicated a connection between the relapse of existing psychotic or affective disorders and jet lag after long flights. Although it could not be decided whether the effect was due to circadian dysregulation or sleep deprivation, this study, and the others cited, highlight the possible increased vulnerability to, and the additional effects of, jet lag in people with mental illness.

1.2.3. Shift work

Shift work, particularly night work, causes disruption of circadian rhythms and social and family life, which can negatively affect performance, efficiency, health and social relations (Costa, 1997). The adverse effects may be manifested in the short-term as sleep disturbances (Marquié & Foret, 1999; Menezes, Pires, Benedito-Silva, & Tufik, 2004), psychosomatic illnesses, work-errors and accidents at work or while travelling to and from work (Åkerstedt, 1990). Longer-term, there is increased risk of gastrointestinal, psychoneurotic and cardiovascular diseases (Portela, Rotenberg, & Waissmann, 2004), and women may be more vulnerable in relation to reproductive function and family duties (Costa, 1997). High inter-individual variability is recorded in both short-term and long-term adjustment, with tolerance linked to individual factors as well as to work organisation (shift schedules) and social conditions.

Sleep disturbances due to shift work are included as a subtype (Shift Work Type) in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association, 2000) under the category “Circadian Rhythm Sleep Disorder”. The essential features of this disorder are chronic difficulties in initiating and maintaining sleep, excessive somnolence, and other chronic related phenomena (Karacan, Williams, &

Moore, 1989). These difficulties arise due to conflict between the endogenously timed sleep-wake cycle and patterns of sleep and wakefulness required by work shifts. Recent Australian statistics report that 14% of the Australian workforce works shifts, and of those, 46% are required to work rotating shifts (Australian Bureau of Statistics, 2003). In general, about 65-75% of shift-workers complain about sleep disturbances (Åkerstedt & Torsvall, 1981). Both fixed and rotating night shift workers have been shown to have significantly shorter average sleep over 24 hours than fixed daytime workers, and a higher level of DSM-IV sleep disorder diagnoses (Ohayon et al., 2002). It has been estimated that up to ten percent of rotating and night shift workers experience shift work related sleep disorder, a rate greater than that seen in day workers (Drake, Roehrs, Richardson, Walsh, & Roth, 2004). However, the presentation of shift-workers at sleep clinics is rare (Regestein & Monk, 1991).

There is acknowledgement that the health of shift workers is not as bad as might be expected. This is most likely due to the fact that shift workers may represent a self-selected group of workers (Knutsson & Åkerstedt, 1992). That is, workers who are not able to tolerate shift work probably leave the industry after a couple of years. Motohashi (1992) in his small study of seven male ambulance personnel on a rotating shift schedule reported that workers with shorter shift work histories had higher levels of intolerance for shift work (persistent fatigue, sleep problems and gastrointestinal disturbance). Poor tolerance of shift work can lead to the "shiftworker syndrome", consisting of digestive, cardiovascular and psychological disorders. This was observed by Bourdouxhe et al. (1999) in their study of Canadian oil-refinery workers who had worked a rotating shift for up to 20 years. Like Knuttson and Åkerstedt (1992), they also reported a "healthy worker effect" in older workers who appeared well adapted to the shift-work environment, as compared to former workers of a comparable age.

Sleepiness and fatigue appear to be the most serious problem in shift work with respect to individual tolerance and safety issues. Åkerstedt, Kecklund, Gillberg and Bjorvatn (1998) summarised their research group's findings using the Karolinska Sleepiness Scale (KSS) to characterise shift workers under various

conditions. In the workers they studied, the morning shift (0600-1400h) was characterised by high sleepiness, falling to lower levels of sleepiness by early afternoon. Afternoon shift (1400-2200h) was characterised by low sleepiness increasing towards the end of the shift. Night shift was characterised by sleepiness increasing from low to high levels in the early morning (associated with sleep intrusions in EEG and pathologically short sleep latencies). During days off, day workers levels of self-reported sleepiness were significantly lower than those of shift workers, suggesting that the shift workers were never as alert as day workers. Negative effects on sleepiness were caused by displacing work hours to the circadian trough, by extending the duration of time awake, and by curtailing sleep. In this study, adjustment of the circadian sleepiness rhythm did not usually occur during a sequence of night shifts.

Such evidence suggests that night workers rarely become re-entrained to sleeping during the day, instead merely "staying up late" to work the night shift (Folkard, 1990). Folkard asserted that in occupations where safety is important, the creation of a "nocturnal subsociety" of workers, who essentially invert the normal diurnal pattern, may be the best way to ensure the health and safety of both the workers and those they work with.

1.2.3.1. Endocrine effects of shift work

Sleep disruption and reversal of the light dark (LD) cycle are known to cause dysregulation of glucocorticoid rhythms in humans and other animals. Early studies with rats showed that a 180° reversal of the LD cycle resulted in inversion of the plasma corticosterone rhythm (Krieger & Hauser, 1978). In humans it has been shown that five consecutive night shifts are enough to reverse the cortisol rhythm, although this does not happen in all workers (Hennig, Kieferdorf, Moritz, Huwe, & Netter, 1998; Roden, Koller, Pirich, Vierhapper, & Waldhauser, 1993). It has been suggested that "non-adapters" (those workers whose cortisol rhythms do not reverse after five or more consecutive night shifts) are self-selected out of night shift work due to their ongoing symptoms of circadian dysregulation, resulting in an over-

representation of "adapters" in groups of long-term shift workers (Hennig et al., 1998). Work satisfaction can be seen as one subjective measure of adaptation to shift schedule. Axelsson and colleagues (2003) compared satisfied (n=22) and dissatisfied (n=20) male rapidly rotating shift workers (night, afternoon, morning, day off for seven cycles followed by one week off) on various hormonal (testosterone, cortisol, prolactin) and sleep health measures. Blood samples were taken on the morning shift between 0700h and 0900h during the first and last work cycles. Morning cortisol levels were seen to significantly decrease over the seven work cycles, but no effect was observed for satisfaction with work.

There are few studies that show rotating night shift work causes an increase in overall cortisol production. Rather, the literature suggests that shift work causes dysregulation of the cortisol rhythm including phase shifts, reduced amplitude and a truncated quiescent period compared to day work. An exception is a case study by Lac and Chamoux (2003) where extremely high levels of cortisol were seen at the end of a 40 hour rotating-shift work period punctuated by less than 11 hours sleep. However, other studies have suggested that cortisol is lower on a night shift. For example, a study of 19 Polish air traffic controllers reported that urinary cortisol excretion (sampled at 4-hourly intervals) was significantly lower during a 12-hour night shift (1900h to 0700h) compared to a 12-hour day shift (0700h to 1900h) or a 24-hour shift (nap times not reported), with highest cortisol concentrations associated with the day shift. However, the study failed to report phase comparisons of the cortisol rhythm, making it difficult to conclude that shift work did not have an effect on rhythm dynamics (Zuzewicz, Kwarecki, & Waterhouse, 2000).

Internal dissociation of the circadian cortisol rhythm and phase shifts have been reported in a number of studies. Long term, fulltime night work (4-5 consecutive nights per week for at least 2 years) was shown to disrupt the cortisol rhythm in 11 male shift-workers , but not 11 male day workers (Weibel, Spiegel, Follenius, Ehrhart, & Brandenberger, 1996). The expected 8-hour phase delay (to waking time) of the cortisol acrophase was seen in the shift work group, and mean 24-hour cortisol levels (plasma sampled at 10-minute

intervals) did not differ between the two groups. However, internal dissociation of circadian markers of the cortisol rhythm were seen in all shift workers; in eight shift workers an additional cortisol peak interrupted the quiescent period at 0645h, around the time of the day workers' acrophase. For three shift workers, no quiescent period was apparent, despite a shift of the acrophase to the afternoon. These results suggest poor circadian adaptation to the reversed sleep wake cycle despite the length of shift work career. Motohashi (1992) reported an overall phase advance of the cortisol rhythm in seven male ambulance personnel working a rotating shift pattern consisting of day shift (0800h – 1700h) and a 24-hour shift, with one to two days off following a 24-hour shift. However, there were large inter-individual differences both in length of shift work history and in terms of tolerance of the rotating shift schedule. This, as well as the small sample size and unusual 24-hour shift, makes it difficult to draw firm conclusions about the effects of the rotating shift schedules overall.

Other studies have shown a dysregulation of circadian markers of the cortisol rhythm, but no phase shift, in shift workers compared to control day workers. Touitou and colleagues (1990) measured plasma cortisol two-hourly from 2400h to 0800h in four male rotating shift workers (rapid rotating shift system; duration about 10 years) and six age matched controls who spent 24 hours in a sleep laboratory with lights on between 0700 and 2300h. Significantly higher cortisol levels were observed in the night workers during the quiescent period, but with lower amplitude overall, compared to the controls. No phase shifts were observed, but one participant showed an abnormal peak at 0400h. Leese and colleagues (1996) studied the effects of night work on pituitary adrenal response to corticotropin-releasing hormone (CRH) in 10 rotating night shift workers (eight females; five night shifts followed by two days off, followed by five day shifts). Following five shifts of night work and five shifts of day work, participants provided blood samples before and 10, 30, 60, 90 and 120 minutes after injection of ovine CRH. Basal plasma cortisol levels were shown to be significantly lower following five consecutive night shifts compared to day shifts. However, increases from baseline following CRH injection were higher following a block of night shifts than following days. Their study showed that

the pituitary adrenal response to CRH was disrupted after five days of night shift. Similarly to Touitou and colleagues' (1990) study, no phase shifts were apparent.

Experimental manipulations of sleep mimicking shift work have also resulted in disruptions of the cortisol rhythm. Goichot et al. (1998) found that the amplitude and phase of the cortisol rhythm was unchanged compared to baseline after one night's sleep deprivation. However, two night's sleep shift, similar to the sleep pattern of night shift workers (daytime sleep between 0700h and 1500h) resulted in a cortisol phase shift with a delayed onset of the quiescent period. The night time melatonin and afternoon thyroid stimulating hormone (TSH) surges were also both delayed by about two hours, and amplitude of the TSH rhythm was attenuated.

Different shift systems appear to cause differential effects to the cortisol rhythm. In a study by Lac and Chamoux (2004), eight fast clockwise rotating shift workers (3 days work, 2 days rest) and eight slow clockwise rotating shiftworkers (7 days work, 5 days rest) were compared to 16 day working controls. Rotating shift work schedules were shown to induce changes in the cortisol profile compared to controls over all shifts. The 7/5 schedule resulted in a phase advance of the acrophase (0500h vs. 0700h in both other groups) and an earlier rise in cortisol level during the morning shift. During the evening shift the 3/2 schedule resulted in a (non-significant) flattening of the curve compared the controls. The night shift acrophase was lower for both shift schedules compared to controls. Notably, the 7/5 shift schedule produced in increased cortisol secretion compared to the 3/2 schedule during the night shift. Cortisol levels during days of rest were not reported.

In contrast to the general trend for cortisol rhythm dysregulation reported in the literature, Roden and colleagues (1993) reported no differences in plasma cortisol rhythm characteristics (acrophase, amplitude, average secretion and phase relationship with melatonin) between seven male controls and nine long-term, fulltime male night shift workers with high levels of work satisfaction (5-6 consecutive nights per week for at least a year) who were tested after their last night shift.

1.2.3.2. Cognitive, performance and psychiatric effects of shift work

Despite the large body of literature attesting to the significant deleterious health effects of sleep disruptions due to shift work there is little research that has systematically investigated the cognitive effects of shift work. Much of the available literature reports on subjective measures of mental fatigue (Tepas et al., 2004) and decreased alertness (Cavallo, Jaskiewicz, & Ris, 2002), and objective measures of reduced work performance, increased errors (Browne, 1949; Hildebrandt, Rohmert, & Rutenfranz, 1974) and increased workplace accidents (Åkerstedt, 1990; Bjerner, Holm, & Swensson, 1955; Folkard & Tucker, 2003; Muecke, 2005). Few report the effects of shift work on cognitive test performance (Rouch, Wild, Ansiau, & Marquié, 2005).

The effects of shift work on memory and speed of processing have been reported by some researchers. Meijman, van der Meer and van Dormolen (1993) compared performance on a delayed match-to-sample memory task in 20 night shift workers on either slow (eight workers: seven day, seven afternoon and seven night shifts) or medium (12 workers: four day, four afternoon and four night shifts) rotating shift systems who had just finished a series of night shifts, with eight control workers on the medium rotating system who had just finished a series of days and afternoons. Baseline measurements were obtained from all workers on the third day off following a period of afternoon shifts. Tasks were administered again to the night workers 32 hours after a series of night shifts, and to the control workers 17 to 25 hours following the last day or afternoon shift. No differences between groups on baseline performance were apparent, but there were significant differences in reaction time and accuracy on the memory task between the night groups and the day group in the recovery phase. Interestingly there were no significant differences in performance between the two different night shift groups, suggesting that duration of night shift is less important in affecting cognitive performance than length of recovery period following the last night shift.

In a large cross-sectional cohort study (N = 3237; males 51.3%) of workers aged 32, 42, 52 and 62 years, Rouch and colleagues (2005) showed that shift

work experience in males was associated with lower speed of cognitive processing on the WAIS Digit Symbol Substitution test and a letter cancellation task. Longer duration of shift work experience (10 to 20 years vs. 1 to 4 years, adjusted for age and education level) was associated with poorer performance on a verbal measure of immediate recall memory. For both men and women, memory scores were higher for those who had ceased shift work for at least four years compared to those who were currently working shifts. This suggests that the detrimental effects of shift work on cognition are ameliorated with a return to day-only work. However, cohort effects are inherent in such a cross-sectional design. Therefore, longitudinal studies of shift workers' cognitive abilities would provide more robust evidence for these findings.

Performance on a visual memory span test deteriorated by 18.5% over the course of a night shift in a study examining neuropsychological performance in twelve medical interns who worked four consecutive night shifts (Rollinson et al., 2003). However, as this study failed to report cognitive performance over the course of a day shift as a comparison, it is difficult to discount the effects of general work fatigue, unrelated to shift type, on the interns' visual memory performance. A study which did make this comparison is that of Smith-Coggins and colleagues (1994), who showed that physicians' performance on simulated work tasks (intubation of a mannequin and mock patient triage) deteriorated over a night shift as compared to day shift, where performance remained accurate. A study of 16 emergency room residents' performance on a test of hypothesis testing and decision-making showed that scores were reduced following five consecutive night shifts compared to performance after three day shifts (Dula, Dula, Hamrick, & Wood, 2001).

Electroencephalographic (EEG) correlates of attention, such as the P300 waveform, are affected by rotating night shift work (Yasukouchi, Wada, Urasaki, & Yokota, 1995). P300 is an event related potential (ERP) which provides an electrophysiological measure of attentional resources (Coull, 1998; Muller-Gass & Campbell, 2002) and speed of cognitive processing in humans (Verleger, 1997). This positive waveform appears about 300ms after the detection of a target stimulus, and can be elicited using an auditory oddball task

(Picton, 1992). Yasukouchi and colleagues (1995) investigated the effects of rotating night shift work and ageing on the P300 ERP by comparing young and older rotating shift workers (14 young female nurses, mean age 24.9 years; 3 older female nurses, mean age 39.0 years; and 12 "elderly" male security guards, mean age 62.8 years) and age-matched controls (young group: n = 12, 50% female, mean age 25.1 years; old group: n = 10, 50% female, mean age 63.4 years). Attentional resources (as measured by P300 amplitude) following a night shift showed a trend towards reduction for the younger nurses and elderly security guards, but were significantly reduced in the older nurse group compared to those measured after a holiday. Speed of mental processing (as measured by P300 latency) following a night shift was significantly reduced only for the elderly security guards. Although these results are somewhat confounded by the low numbers in the older nurse group, the mixture of occupations which perhaps do not involve the same levels of stress, and by the comparison of males and females, they suggest that long-term rotating night shift work (the older nurse group) may lead to a physiologically measurable reduction of attentional resources if sufficient recovery time is not available following a night shift. The increased latency results in the elderly security guard group speak more to the effects of normal ageing on speed of mental processing, rather than to the effects of long-term night shift work.

In contrast to the general finding of cognitive impairment associated with shift work, Lamond and colleagues (2001) found that psychomotor vigilance performance increased in 15 young healthy adults across a week of simulated night work. However, the applicability of this finding to shift workers at large is problematic. It is not clear that long-term night workers, generally a self-selected group who cope well with chronic sleep disruption or shortened sleep duration, would show the same effects as non-shift workers subjected to simulated night shifts.

Adverse effects on mental state, particularly an increase in depressed mood, have been reported following rotating shift work, especially if there is an inadequate recovery period following a block of night shifts. One night of work followed by an inadequate recovery period (straight from night to day shift) has

been shown to cause significant negative changes in all mood scales of the Profile of Mood States compared to pre-night shift responses (Orton & Gruzelier, 1989).

Significantly higher levels of depressed mood have been reported in medical interns completing night-float rotation compared to day shift (Cavallo et al., 2002). Male shift workers on a rotating shift system including a 'back to back' (24-hour) shift and female shift workers rotating between morning and afternoon shifts had higher 'depression tendency" scores on a self-report measure than did matched day workers in a study by Kaneko and colleagues (2004).

Nurses working on irregular three-shift systems reported higher levels of stress and psychological symptoms such as anxiety, tension and depression than paper mill workers on regular shifts (Olsson, Kandolin, & Kauppinen-Toropainen, 1990). However, given the variety of stressors inherent in the different work environments, it is difficult to attribute this difference to shift work system alone. In contrast, Skipper, Jung and Coffey (1990) did not find a relationship between shift work and measures of depression in their study of 463 nurses, of whom 53.6% had worked rotating shifts for a mean of 48 months.

1.2.3.3. Night shift versus rotating shift work

Rotating shift-workers, who alternate between nights and other shifts, are perhaps even less likely than fulltime night workers to adapt to their shift schedules. Alternating without taking appropriate recovery periods between different shifts is more likely to result in poor adaptation and increased adverse outcomes (Brugere, Barrit, Butat, Cosset, & Volkoff, 1997). In recent years, improved occupational health and safety standards have led to greater regulation of rotating shifts schedules to ensure workers have more appropriate recovery times between different shifts (Kogi, 1998). However, in practice, many rotating shift workers, or those who work night shift only on a part time basis, use time off to attend to family duties, or complete other tasks that can only be done in the daytime such as banking or keeping medical appointments

or even work other jobs (Portela et al., 2004). Few use recovery periods to properly adapt to the alternate shift schedule. The need for appropriate recovery periods was highlighted by Totterdell and colleagues (Totterdell, Spelten, Smith, Barton, & Folkard, 1995), who showed that cognitive deficits accumulated after consecutive nights of shift work persisted into the first rest period after a block of nights. The authors asserted that "time was a healer" when it came to recovering from the effects of night shift. Åkerstedt and colleagues (2000) suggested that although two days recovery is usually sufficient after a week of work, three to four days are necessary following schedules resulting in severely disrupted circadian rhythmicity.

1.3. Corticosteroids, the hippocampus and cognition

Glucocorticoids (GCs) have important direct effects on the brain (McEwen, Weiss, & Schwartz, 1968). In both animals and humans, the hippocampus in particular has been recognised as a site with a high density of adrenal steroid receptors. Studies over the last 50 years have shown that heightened levels of GCs as a result of sustained stress, as well as long-term exogenous administration, can disrupt hippocampal neurogenesis, cause atrophy of dendritic processes and impair neuroplastic responses after neurological insult (Sapolsky, 2000a, 2001).

The hippocampus, in the medial aspect of the temporal lobe, along with the amygdala, is essential to the remembering of facts and the formation of declarative memory. The case of HM (Scoville & Milner, 1957), who underwent bilateral temporal lobectomy for treatment of intractable epilepsy, provided the first clear evidence of the role of the medial temporal lobes and hippocampus in particular for memory and new learning (Drachman & Arbit, 1966; Knott & Marslen-Wilson, 2001; Milner, 2005). The temporal lobes are sensitive to a variety of disease processes and neurological insults including herpes simplex encephalitis (Kennedy & Chaudhuri, 2002), focal epilepsies (Leritz, Grande, & Bauer, 2006) and hypoxia (Yonelinas et al., 2002). In addition, the hippocampus is a site of high metabolic activity, and as such is

vulnerable to local reductions in glucose availability, such as in diabetes (McEwen, Magarinos, & Reagan, 2002).

The hippocampus is linked to the HPA axis via a negative feedback loop, which contributes to the control of GC release. The stress response begins when the hypothalamus detects stress in the system either by afferent neural pathways (in the case of stressors such as pain) or directly (such as through the direct effect of hypoglycaemia on the hypothalamus), causing the release of corticotropin-releasing hormone (CRH). CRH acts upon the pituitary gland, stimulating secretion of adrenocorticotropic hormone (ACTH). ACTH then causes the release of GCs from the adrenal cortex, which are detectable in the bloodstream within minutes of the onset of stress (see Figure 1.01). GCs are then able to exert effects throughout the body due to the presence of GC receptors in various target organs (Sapolsky, 1992).

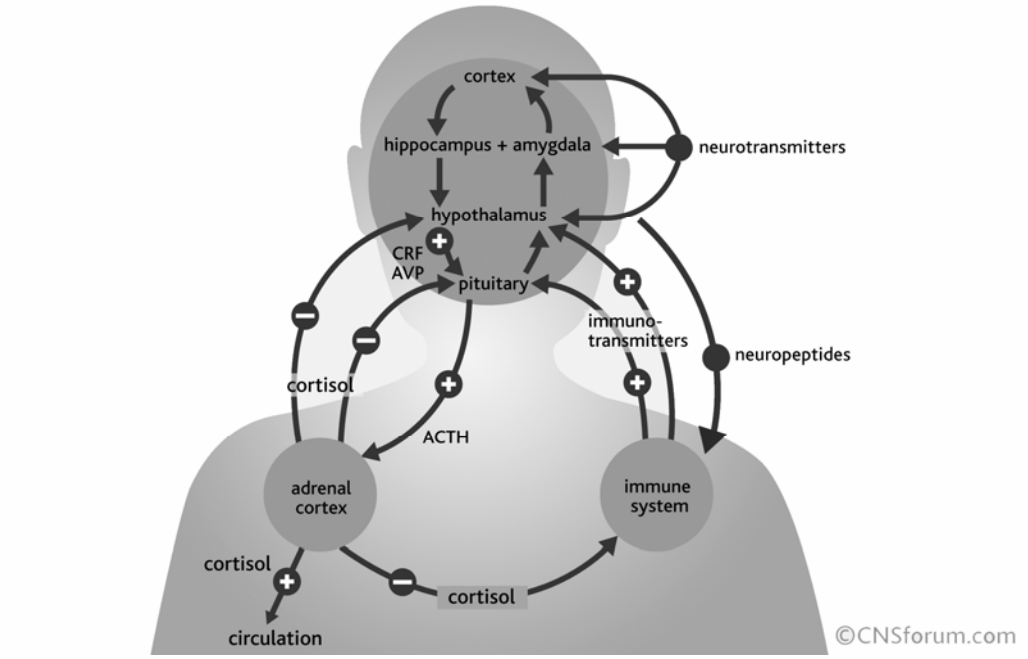

Figure 1.01. Stress causes the hypothalamus to release corticotropin releasing hormone (CRH) which stimulates the pituitary to produce adrenocorticotropic hormone (ACTH). ACTH causes the adrenal cortex to release cortisol into circulation, activating the sympathetic nervous system. Negative feedback to the pituitary via a loop incorporating the hippocampus and amygdala terminates the stress response.

"End-product" stimulation of GC receptors in the hippocampus (and possibly other brain regions to a lesser extent) causes negative feedback to the hypothalamus, rapidly terminating the release of CRH and therefore GCs downstream (Cullinan, Herman, Helmreich, & Watson, 1995). Data from hippocampal lesioning studies have shown that damage to the hippocampus can impair negative feedback, resulting in prolonged activation of the HPA axis. Chronic stress also appears to cause down-regulation of glucocorticoid receptors, impairing negative feedback and leading to over-activation of the HPA axis (Jameison & Dinan, 2001).

In humans, high levels of circulating corticosteriods, both exogenously delivered and endogenously produced, have been associated with cognitive impairments in normal subjects (Belanoff, Gross, Yager, & Schatzberg, 2001) and cognitive decline in older adults (Karlamangla, Singer, Chodosh, McEwen, & Seeman, 2005). It has been hypothesised that these cognitive deficits, particularly in hippocampus-dependent learning and memory, are due to hippocampal atrophy caused by significant elevations of circulating GCs (Lupien et al., 1998; Newcomer et al., 1999; Porter & Landfield, 1998).

Evidence of the effects of systemic and neurological diseases, as well as psychological disturbances that affect both HPA axis function and memory abilities, have reinforced understanding of both the vulnerability of the hippocampus to injury, and its importance in normal memory functioning (M. W. Brown & Aggleton, 2001; Nunn, Graydon, Polkey, & Morris, 1999; Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Squire, Amaral, & Press, 1990)

In the following sections the vulnerability of the hippocampus due to its role in the HPA axis will be explored. The effects of both endogenous and exogenous disruptions to the HPA axis on hippocampal functioning, cognition and psychological health will be reviewed.

1.3.1. Effects of exogenously administered corticosteroids

Therapeutic treatment with corticosteroids is common practice for a number of medical conditions including asthma, multiple sclerosis and rheumatoid arthritis, and may cause deleterious side-effects. As early as the 1950s, prior to the identification of adrenal steroid receptors in the brain, it was observed that treatment with glucocorticoids for a variety of medical complaints resulted in "thinking disturbances" (Rome & Braceland, 1952) with both cognitive and psychiatric manifestations (Quarton, Clark, Cobb, & Bauer, 1955). More recently, impairment of explicit and declarative memory related to therapeutic use of GCs has been reported (Barnes & Pederson, 1993; Keenan, Jacobson, Soleymani, & Newcomer, 1995). Brown and colleagues (E. S. Brown et al., 2004) reported reduced hippocampal volume, lowered hippocampal N-acetyl aspartate (NAA), creatine (Cr) and choline (Cho) ratios (NAA/Cho and NAA/(Cr+Cho)) and poorer cognitive performance on tests of verbal learning and delayed recall (RAVLT) and response inhibition (Stroop Color-Word) in 17 patients undergoing long-term treatment with prednisolone (> 6 months; mean duration of treatment 7.6 years) due to various medical conditions such as asthma and arthritis. Participants with comparable medical histories who were not undergoing corticosteroid treatment did not show such effects.

Controlled exogenous administration of GCs has been used experimentally to demonstrate the adverse effects of high levels of corticosteroids in humans. Acute administration of cortisone (25mg) to young men and women one hour prior to a delayed retention test significantly impaired recall on a list of unrelated words (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Roozendaal, Okuda, de Quervain, & McGaugh, 2006). Similar effects were seen in a study by Kuhlman, Kirschbaum and Wolf (2005), who reported that 30mg of hydrocortisone given to 16 healthy young women (mean age 26.56 years) four hours after initial learning impaired free recall of both neutral and negative emotionally-laden words, compared to placebo-treated controls, with a trend towards poorer recall of the negative words. Newcomer and colleagues (1999) reported significant reductions in participants' memory performance (WMS-R Logical Memory) after four days of hydrocortisone administration,

with a dose dependent effect on memory performance (lower memory performance with a higher dose). There were no differences between groups (160 mg/day vs. 40 mg/day vs. placebo) at baseline or after only one day's administration, suggesting a cumulative rather than an acute effect of GCs on memory performance. The effect was reversible, with memory performance rebounding to above baseline levels following a six-day washout. In contrast to studies reporting adverse affects on memory performance, Abercrombie and colleagues (2003) reported fewer commission errors in free recall of a word list after administration of 40mg of hydrocortisone, as well as fewer errors of commission in a picture recall task after 20mg, compared to placebo in a group of 90 healthy males.

The acute effect of exogenous GCs appears to be attenuated with repeated administration (E. S. Brown, Beard, Frol, & Rush, 2006). In a recent study with a placebo controlled cross-over design, Brown and colleagues showed that memory performance on the RAVLT decreased compared to baseline following three days exposure to 60mg prednisolone per day. Repeated administration of prednisolone following an 11-day washout period also resulted in reduced performance, however the effect was significantly smaller than that seen after the first administration. The authors suggested the development of tolerance or habituation to the effects of prednisolone with repeated exposures. However, this is inconsistent with the same group's findings (outlined above) that prolonged exposure to exogenous GCs results in measurable effects on hippocampal volume, metabolism and declarative memory performance (E. S. Brown et al., 2004).

The effect of corticosteroids on memory performance is thought to be dependent upon the time of day of administration, and on the timing of administration in relation to memory task. Administration of exogenous GCs to coincide with the morning peak is more likely to impair declarative memory performance than when it is administered in the afternoon (Fehm-Wolfsdorf, Reutter, Zenz, Born, & Fehm, 1993; Lupien et al., 2002; Maheu et al., 2005). A recent meta-analysis of 16 studies examining the effect of cortisol on human memory showed that cortisol administered before learning had little to no effect

on later information retrieval. If administered after learning and before retrieval, significant decreases in memory were likely (Het, Ramlow, & Wolf, 2005).

Blockade of cortisol production during sleep (particularly during the early morning) by administration of metyrapone has also been shown to affect memory. Metyrapone given to 16 healthy males after a verbal learning task (consisting of neutral and emotionally-laden words) was shown to affect consolidation of the neutral material only. Memory for neutral material was assumed to be related to hippocampal memory processes. In contrast, memory for emotionally-laden words (thought to be dependent on an intact amygdala) was not affected (Wagner, Degirmenci, Drosopoulos, Perras, & Born, 2005).

Animal studies have provided further evidence for the effects of GCs on memory functioning. Filipini, Gijsbers, Birmingham and Dubrovsky (1991) showed that administration of exogenous GCs to adrenalectomised rats resulted in impairment of long-term potentiation (LTP). LTP is an excitatory post-synaptic potential brought about by repeated stimulation, and is thought to mediate aspects of learning and memory. GCs have also been shown to affect performance on a spatial memory task (the Morris water maze) in adrenalectomised rats, restoring performance to pre-lesion levels (McCormick, McNamara, Kelsey, & Klecker, 1995). In intact rats, GCs have been demonstrated to exert a direct and deleterious effect on performance on spatial memory tasks (Catalani et al., 1993; Dachir, Kadar, Robinson, & Levy, 1993). McClay, Freeman and Zadina (1998) reported that corticosterone-treated rats were significantly impaired on their performance on the Morris water maze, the Barnes circular platform maze and the Radial Arm maze, making significantly more errors, taking longer and covering a greater distance (i.e. performing less economically) compared to control rats.

In summary, the administration of exogenous corticosteroids, either therapeutically or experimentally, is associated with reductions in memory performance. However, this effect may be attenuated with repeated administration. In humans, performance is modulated by the emotional salience of the material to be recalled, providing further evidence of the preferential effects of corticosteroids on the hippocampus.

1.3.2. Effects of endogenous HPA axis dysregulation

Experimental manipulation of endogenous GC production in humans and other animals provides further evidence for the effects of stress on GC production and consequent effects on the hippocampus and various cognitive functions. A series of studies by Bohnen and colleagues (1990; 1992; 1991) reported that increased cortisol reactivity during stress was related to poorer performance on attention and vigilance tasks. However, although stress is often related to reduced performance, it may not always affect performance on commonly used cognitive assessment tasks. For example, Hoffman and al'Absi (2004) induced psychological stress in 25 participants (mean age 24.8 years) with a public-speaking task. Salivary cortisol levels were significantly increased following the stressful task; however, performance on cognitive tests of memory and attention was not significantly affected by the acute mental stressor.

Experimental manipulation of endogenous GC levels in animals has been achieved by introduction of both physical and psychological stressors into the animal's environment. Forced swimming, painful stimuli, as well as food and water deprivation are common methods (Sutano & de Kloet, 1994) used to increase stress, and therefore levels of GCs. Rats exposed to six months of chronic stress (low levels of foot-shock resulting in sustained anxiety) showed heightened levels of GCs and accelerated hippocampal ageing measured electrophysiologically (Kerr, Campbell, Applegate, Brodish, & Landfield, 1991). The effects of psychological stressors on tree shrews have been examined by Fuchs and Flügge (1998), who housed dominant and subordinate tree shrews in close proximity to each other. The subordinate animals' level of stress was demonstrated physiologically by elevated levels of urinary GCs, and behaviourally by decreased locomotor activity and cessation of self-grooming.

Endogenous cortisol production across the lifespan in normal development and ageing has been associated with changes in hippocampal morphology and cognitive performance. Wiedenmayer and colleagues (2006) reported differential effects of cortisol on the hippocampus in normally developing healthy children aged seven to 12 years. Cortisol levels were positively correlated with the size of anterior areas of the hippocampus, but negatively

correlated with size of lateral areas. Subjective complaints of memory disturbance in older people (mean age 61.8 years) have also been shown to be associated with both higher basal cortisol and cortisol levels after administration of dexamethasone (Wolf et al., 2005). In aged adults (63 to 80 years) increases in basal cortisol levels over a five- to six-year period were associated with decreases in both hippocampal volumes and memory performance (Lupien et al., 1998). These findings highlight the vulnerability and sensitivity of hippocampal morphometry to changes in cortisol availability across the lifespan.

A variety of physical and psychiatric disorders are associated also with disruptions to the HPA axis. Cushing's Disease, depression and posttraumatic stress disorder (PTSD) represent "natural experiments" that provide further insights into the effects of HPA axis dysregulation. These will be discussed in the next sections.

1.3.2.1. Cushing's Disease

Hypercortisolaemia due to endogenous overproduction of cortisol is a symptom of Cushing's Disease and illustrates the effects of long-term heightened levels of cortisol on human cognitive performance. Dysfunction at any level of the HPA axis which increases corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) or cortisol synthesis can cause hypercortisolaemia, and as a consequence, Cushing's Disease. Overproduction of ACTH due to benign pituitary adenoma, or ectopic ACTH-producing tumour cause remote overstimulation of the adrenal glands and excess cortisol production. Other causes include adrenal adenoma and carcinoma, and adrenal hyperplasia, which disrupt the action of the adrenal gland directly.

Clinical features of the disease include systemic symptoms such as truncal obesity, "moon facies", diabetes mellitus, gonadal dysfunction, amenorrhea and hirsutism in woman, acne, hypertension, muscle weakness, skin atrophy/bruising, oedema, osteoporosis and immune suppression (Sapolsky, 2000a; Sonino & Fava, 2001). Adverse effects on central nervous system

(CNS) function are also possible, including mood disorders and effects on learning, memory and synaptic plasticity (Sapolsky, 2000a). Patients with Cushing's Disease and Cushing's syndrome (Cushingoid symptoms due to exogenous GCs) have been shown to have significant impairments in visual memory, non-verbal visual ideation and visual-spatial processing (Forget, Lacroix, Somma, & Cohen, 2000; Whelan, Schteingart, Starkman, & Smith, 1980) and verbal memory (Starkman, Giordani, Berent, Schork, & Schteingart, 2001) as compared to normal controls. Treatment of Cushing's Disease by surgical ablation of tumours or administration of the drug mitotane reduces circulating GC levels, and consequently improves memory and other cognitive deficits (Mauri et al., 1993; Schteingart, Tsao, McKenzie, Victoria, & Therrian, 1980).

The sustained decrease in cortisol levels seen after successful treatment of Cushing's syndrome appears to reverse cortisol-induced hippocampal atrophy (Starkman, Giordani, Gebarski, Berent, Schork & Schteingart, 1999). Starkman et al. reported hippocampal volume increased in 82% of patients (up to 10% increase in some individuals) after 7 to 25 months remission of Cushing's syndrome. In a further study investigating the functional gains after treatment, Starkman and colleagues (2003) reported that the increase in hippocampal volume was associated with improved performance on a selective reminding (word lists) task.

1.3.2.2. Depression

Depression is known to impact upon cognitive functioning. In addition, depressed mood has been associated with disruptions to the HPA axis (Sachar, 1967; Thakore, 1998), hippocampal neuronal damage (Lee, Ogle, & Sapolsky, 2002; Sapolsky, 2000b) and hippocampal irregularities in imaging studies (Sapolsky, 2000a). It has been suggested that disruptions to the normal functioning of the HPA axis underlie both the affective and cognitive symptoms of depression (Thakore, 1998; Wirz-Justice, 2000). Phase advance of the

cortisol rhythm in particular (early trough and hypersecretion) has been a consistent finding in neuroendocrine studies of depression (Wirz-Justice, 2000).

Sleep deprivation has been shown to cause rapid, although transient, mood improvements in people with major depression (Voderholzer et al., 2004). This improvement in mood is thought to be mediated by the effects of sleep deprivation on the HPA axis. Acute sleep deprivation can cause a transient decrease in cortisol secretion related to the initial post-sleep deprivation deep sleep phase (Ilias, Vgontzas, Provata, & Mastorakos, 2002). This reduces the high levels of cortisol seen in patients with depression, and is associated with improved mood. In addition, GC treatment (dexamethasone) has been found to improve mood in some depressed patients, adding credence to the claim that HPA axis dysregulation rather than GC overproduction is present in depression (Thakore, 1998).

Although deficits in cognitive function have been seen in all subtypes of major depression, the psychotic subtype appears to be associated with a greater degree of cognitive impairment, which in turn is correlated with cortisol elevations (Belanoff, Kalehzan, Sund, Fleming Ficek, & Schatzberg, 2001). In a study comparing patients with psychotic major depression (PMD) to those with non-psychotic major depression (NPMD) and healthy controls, Belanoff, Kalehzan et al. (2001) showed that participants with PMD made more commission errors on a verbal memory test compared to the other groups. PMD was also associated with elevations of cortisol, particularly in the afternoon. This study was replicated by Gomez and colleagues (Gomez et al., 2006), who reported greater cognitive impairment in patients with PMD compared to those with NPMD and healthy controls. The NPMD group also showed significantly poorer verbal memory performance compared to the controls. In addition, the PMD patients showed elevated overnight cortisol levels compared to the other groups, which was negatively correlated with psychomotor speed and verbal memory on a list-learning task (CVLT).

Findings of reduced hippocampal size in volumetric MRI studies of depressed patients aside, there is little evidence as yet that depression disrupts hippocampal neurogenesis or apoptosis in humans (Fossati, Radtchenko, &

Boyer, 2004). For example, in a post-mortem study of 15 patients who had major depressive disorder compared with 10 patients who had been treated with corticosteroids and 16 controls, Müller and colleagues (2001) reported no significant levels of hippocampal neuron loss or morphological evidence of apoptosis in either the depression or corticosteroid groups compared to controls. A reduction in neuronal size, or loss of support cells such as glia, may instead be responsible for the hippocampal atrophy seen on MRI.

1.3.2.3. Post-Traumatic Stress Disorder

In a minority of people, exposure to extreme emotional and psychological stressors, such as physical or sexual abuse or combat experience, causes post-traumatic stress disorder (PTSD). The behavioural, affective and cognitive manifestations of PTSD include excessive fear reactions, anxiety, dissociative states including flashbacks, and memory disruptions (Bremner, 2001). While early research focussed on identifying behavioural and affective symptoms, more recent studies exploring systemic effects have shown measurable physiological and neuroanatomical changes associated with PTSD. These changes are thought to mediate the cognitive, behavioural and affective symptoms seen in the disorder.

Survivors of trauma who go on to develop PTSD show HPA axis activity that differs significantly from that seen in the normal response to stress and trauma. While acute stress clearly causes spikes in HPA axis activity measurable as increased circulating cortisol, the prolonged stress of PTSD does not appear to cause chronic elevations of GCs (E. A. Young & Breslau, 2004). Perhaps unexpectedly, trauma survivors with chronic PTSD show lower basal levels of cortisol, enhanced negative feedback inhibition (Yehuda, 2001; Yehuda, Boisoneau, Lowry, & Giller, 1995) and a disrupted circadian cortisol rhythm compared to normal participants (Golier & Yehuda, 1998). PTSD sufferers appear to have higher numbers of glucocorticoid receptors, as well as an increased sensitivity to exogenously administered corticosteroids such as dexamethasone, which suppresses endogenous cortisol production (Yehuda,

2001). Yehuda (2001) further suggested that the hippocampal damage and cognitive dysfunction associated with PTSD may be due to the increased number and sensitivity of glucocorticoid receptors in the hippocampus, rather than increased circulating cortisol.

Significant volumetric MRI differences between the brains of participants with PTSD and those without have been shown by some researchers. There are reports of hippocampal atrophy of up to 25% volume loss in patients with a diagnosis of PTSD (Bremner, Krystal, Southwick, & Charney, 1995; Bremner et al., 1997; Gurvits et al., 1996; Lindauer et al., 2004; Stein, Koverola, Hanna, Torchia, & McClarty, 1997). However, these studies are equivocal on the issue of whether the volumetric changes are associated with cognitive deficits. Correlations between hippocampal atrophy and deficits in verbal memory were shown by Gurvits et al (1996) in their study of patients with combat-related PTSD. In contrast, female participants with sexual-abuse related PTSD and hippocampal atrophy did not show deficits in word-list learning compared to controls (Stein et al., 1997); nor did a similar participant group in Bremner and colleagues (1997) study. A later study (Bremner et al., 2003) using volumetric MRI, and positron emission tomography (PET) to measure hippocampal function, found both reduced hippocampal volumes and attenuated recruitment of the hippocampus during auditory-verbal declarative memory tasks in women with sexual-abuse related PTSD. However, significant previous (not current) psychiatric comorbidities were reported in the PTSD group, including major depressive disorder, panic disorder and substance abuse disorder. This suggests the findings may be due to multiple stressors beyond pure PTSD.

A well controlled study by Schuff and colleagues (2001) investigated the effects of combat-related PTSD on hippocampal NAA levels and volumes in 18 men with no history of substance abuse disorders in the previous 10 years or depressive disorders in the previous three months. Men with other previous psychiatric diagnoses were excluded from the study. Schuff and colleagues reported decreases in hippocampal NAA levels of 23% to 24% in the PTSD group compared to the controls, despite finding no difference in hippocampal volumes between the groups. A later study by the same group (Neylan et al.,

2003) reported a positive correlation between cortisol levels and hippocampal NAA. Neylan and colleagues suggested that reduced NAA may impact upon the role of the hippocampus in causing down-regulation of the HPA axis via its links to the hypothalamus.

In summary, these studies suggest that sustained, excessive endogenous increases in cortisol due to systemic illness or psychological disorders are associated with hippocampal atrophy and consequent memory impairment. There may be measurable metabolic disturbances, such as decreased NAA, indicative of hippocampal damage, even in the absence of hippocampal volume changes. Memory performance and hippocampal volume often recover after the return of normal cortisol levels. Susceptibility to such effects may be caused by additional risk factors, such as increased hippocampal glucocorticoid receptors.

1.4. Magnetic resonance brain imaging methods

Proton magnetic resonance imaging (MRI) is a technique that provides visual images of the brain in vivo based upon the resonance or spin of hydrogen atom nuclei (protons) exposed to electromagnetic frequencies. All body tissue has magnetic properties. When a magnetic field is applied to brain tissue the protons within hydrogen atoms become aligned. The application of a radio frequency pulse causes the protons to spin on their axes, generating an aligned, rotating magnetic field that produces a measurable electric current. When the radio frequency pulse is removed, the protons' axes return to the original, unaligned magnetic field. MRI images are built up by scanning "slices" through the brain that measure the relaxation rates of protons back to their original state (Kandel, Schwartz, & Jessell, 2000). The slices are comprised of three dimensional areas called voxels, each of which has a volume of about 3 mm^3 (Hornak, 2006). The data can be used to derive information about brain tissue volume, integrity and metabolite levels in the scanned regions. The following sections provide a brief overview of the MR methods utilised in the current study.

1.4.1. Volumetrics

MRI volumetry is the study of structural volumes observable on MRI images. Traditionally, specific changes in tissue structures using MRI volumetry provided clear and demonstrable measures of absolute reductions as well comparative changes, in the form of ratios. This technique has been widely employed in the investigation of epilepsy (Jutila et al., 2001; Kuzniecky et al., 1999; Van Paesschen, Connelly, Johnson, & Duncan, 1996), schizophrenia (Kalus et al., 2004; Molina et al., 2006), and dementias (Fukui & Kertesz, 2000; Kantarci & Jack, 2003; Wahlund, Julin, Johansson, & Scheltens, 2000). In studies of hippocampal sclerosis, asymmetries or ratios exceeding 15% (one structure smaller than another or a ratio of .85) are considered sufficient to be highly suggestive of structural abnormality (Van Paesschen et al., 1995), however other studies have demonstrated that volumetry is not infallible in its detection in the absence of bilateral pathology (Ho, Kuzniecky, Gilliam, Faught, & Morawetz, 1998). In the event of more widespread and diffuse changes that impact upon the absolute volume of the structure of interest, clarifying the total volume of the structure can provide valuable metrics in comparing not only asymmetries, but also whether those structures lie outside the normally distributed ranges of control populations or when comparing other effects of confounders such as gender (Kruggel, 2006).

Volumetry has traditionally been performed on the individual's MRI scans with little pre-processing. However, the broad range of variance in specific structures based on confounders such as age, sex, and even race (Blatter et al., 1995; Jernigan et al., 2001), has resulted in further volumetric analysis based upon "normalized" scans. Individual scans are transformed into a normalized space, prior to image processing, and then restored into original space to compare volumes and or ratios (Buckner et al., 2004).

1.4.2. Voxel based morphometry

Voxel Based Morphometry (VBM) is a method of assessing the distribution of various tissue classes, namely gray matter, white matter as well as cerebrospinal

fluid on MRI scans (Ashburner & Friston, 2000). Based upon a mathematical analysis approach called Random Gaussian Theory, it has been implemented as an algorithm within Statistical Parametric Mapping (or SPM), which was originally developed as a tool for analyzing Positron Emission Tomography (PET) scans. The main benefit of this approach is that it is able to integrate tissue class distributions for individuals in a normalized head space, and then provide a statistical measure of the probability of the tissue class on a voxel-by-voxel basis throughout the whole MRI volume of the head. In order to assess differences in relative tissue class probabilities, it requires multiple subjects per group, making it a powerful research tool, but limiting its value as a diagnostic tool for individual scans (Ashburner & Friston, 2000).

1.4.3. T2 relaxometry

T2 relaxometry is a MR technique based on measuring the energy dissipation of excited protons from the radio frequency pulse to their surrounding environment. T2 relaxometry provides a measure of the level of disorganized neuronal density, as in the case of hippocampal sclerosis whereby reduction in neuronal cell density and increased gliosis is represented as an increased T2 signal (Jackson & Connelly, 1999). Decreases in T2 relaxation times are associated with brain maturation throughout childhood and into mid-adulthood (Ding et al., 2004), while increases are associated with normal ageing (Suzuki, Sakai, & Jara, 2006). The technique permits comparisons of bilaterally represented structures in determining their similarity or dissimilarity depending upon the pathological process involved. T2 relaxometry thus provides an objective measure compared with a trained observer visually describing relative differences in signal intensity, particularly when higher field strength (greater than 1.5T) scanners are used (Briellmann et al., 2003).

1.4.4. Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a non-invasive methodology that provides in vivo measures of brain metabolism (Urrila et al., 2004). It measures differences in resonance frequencies among nuclei present in particular positions within molecules or compounds (Constantinidis, 2000; Di Costanzo et al., 2003). It allows not only the detection of particular nuclei, but also a measure of relative concentrations in a circumscribed region. MRS is represented as spectral frequency graph with individual nuclei within compounds represented by a simple or complex peak centred at a specific frequency. This allows each compound to be represented by a unique "signature peak", and provides information of the local distribution of metabolites. Many nuclei have been investigated for MRS, namely 31P, 23Na, 39K, 13C and 19F. Proton (1H-MRS) spectra are most commonly studied, as it is possible to obtain higher resolution spectra from smaller regions of interest compared to earlier studies using other nuclei (Barker, 2005). 1H-MRS is therefore well suited to examine brain metabolism in small areas of the brain such as the hippocampus. Typical compounds relating to the distribution of specific spectral peaks from 1H-MRS are N-acetyl amino acids (NAA); Choline (Cho); Creatine (Cr); myo-Inositol; and Glutamate/Glutamine (Glx).

Compounds investigated for neuronal structure include the NAA and Cho group. The NAA group (uniquely present in adult CNS neurons) includes N-acetyl-aspartate and N-acetyl-glutamate and is used as marker of neuronal density (Ross & Sachdev, 2004). The Choline spectra (including compounds such as choline, phosphocholine and glycerophosphocholine) are indicated as a marker to general cellular density. Reductions in NAA are associated with conditions involving neuronal loss, as in hippocampal sclerosis (Namer et al., 1999; Woermann et al., 1999), while increases in Cho peaks represent a breakdown of cellular membrane integrity from active demyelinating processes (Barker, 2005; Ross & Sachdev, 2004). Increased levels of myo-Inositol and choline have also been reported to be correlated with gliosis, such as seen in some cases of temporal lobe epilepsy (Briellmann, Wellard, & Jackson, 2005; Wellard, Briellmann, Prichard, Syngeniotis, & Jackson, 2003).

Specific indicators for energy metabolism are represented by the creatine (Cr) peak and include such metabolites as creatine, phosphocreatine and glycerophosphocreatine (Barker, 2005). Cr levels are commonly used as a baseline or reference signal (Ross & Sachdev, 2004) for comparing levels of other metabolite peaks in the form of a ratio (Barker, 2005). Recent evidence has suggested that Cr levels do vary, and are associated with some rare disease processes (Ross & Sachdev, 2004).

1.5. Rationale for the current study

Constant sleep disruption, like that experienced by rotating shift workers who have inadequate recovery time between shifts, is a physiological stressor. Stress provokes a number of endocrine responses in the body, particularly affecting the hypothalamic-pituitary-adrenal (HPA) axis. Acute stress induces an immediate and adaptive increase in glucocorticoid production, preparing the organism to deal with the stressor. However, prolonged stress leads to chronic dysregulation of the HPA axis, most likely mediated by impaired negative feedback from glucocorticoid (GC) receptors located in target tissue throughout the body. GCs have a particular affinity with the hippocampus, which contains high levels of GC receptors. Chronic stimulation of GC receptors leads to impaired down-regulation of the HPA axis, and potentially to atrophy of the hippocampus.

The hippocampus is known to be involved in declarative and associative memory formation in humans, and spatial memory in animals. Converging evidence from a number of different fields suggests that long-term rotating night shift workers such as nurses suffer shift-work induced circadian rhythm disorder. This condition is chronic and the symptoms are similar to those observed in international aircrew jet lag. Therefore, it is likely that shift workers may be subject to chronic dysregulation of the HPA axis or elevations of cortisol, and the concomitant deleterious effects on brain morphology and function that have been demonstrated by Cho (2001) in aircrew.

1.5.1. Aims and hypotheses

The present study aimed to explore the relationship between circadian sleep-wake cycle disruptions, HPA axis dysregulation and temporal lobe atrophy in participants with shift-work related sleep-disruption. A further aim was to examine whether deficits experienced by long-term shift workers are comparable to those in other professions with circadian sleep-wake cycle disruption, such as aircrew who are denied sufficient recovery time between long haul flights.

In terms of cognitive outcomes, it was hypothesised that rotating shift workers would show poorer performance compared to control participants on tasks assessing memory, a cognitive domain dependent upon intact hippocampal and temporal lobe functioning. In addition, it was hypothesised that shift workers' performance on tasks assessing attention and concentration would be poorer than control participants, perhaps reflecting the effects of fatigue on recruitment of cognitive resources.

It was hypothesised that the cortisol rhythm in shift workers would show signs of dysregulation such as phase shift and loss of normal circadian phase markers like a defined acrophase, compared to the rhythm seen in control participants. It was further hypothesised that alterations to the cortisol rhythm in shift workers would be associated with any deficits seen in the cognitive measures.

For the MR measures, it was hypothesised that shift workers would have smaller hippocampal and temporal lobe volumes compared to shift workers, as well as reduced T2 relaxation times (a measures of neuronal integrity). It was further hypothesised that brain volumes and integrity would be positively associated with cognitive performance and negatively associated with cortisol levels.

With reference to the spectroscopy measures, it was hypothesised that shift workers would show reduced levels of NAA group metabolites (indicators of reduced neuronal density), and increased levels of choline group metabolites (indicative of a breakdown in cell membranes) compared to controls. It was also hypothesised that changes in brain metabolite spectra would be associated

with reduced hippocampal and temporal lobe volumes and poorer cognitive performance, and associated with increased cortisol levels.

METHOD

2.1. Participants

The participants were 12 female rotating night shift workers and 17 female permanent day shift workers (control participants). All rotating night shift workers were nurses, recruited from public hospitals in Melbourne through either direct contact with nurse unit managers or advertisements placed in professional journals and hospital newsletters (see Appendix 1). Permanent day shift workers were mainly nurses recruited in the same fashion as the rotating night shift workers. Additional control participants were recruited via convenience sampling. Participants were excluded on the basis of any of the following: severe sleep-related breathing disorders; recent extremely stressful events such as the death of spouse; medical implants contraindicated for MRI scanning; medications that may affect cognitive function; history of brain injury; chronic medical, neurological or psychiatric conditions; and inability to give informed consent. Participants taking the contraceptive pill were included. As far as possible, participants were matched on the basis of: (1) age; (2) educational level; (3) years of employment; (4) hours worked per week; and (5) type of work performed.

2.1.1. Rotating night shift workers

Rotating shift workers were required to have worked their current shift for at least three years. The rotating shift included at least one switch between night shift and another shift on a weekly or fortnightly basis, with no more than 72 hours recovery time between the last night shift and the next rostered shift. Participants who worked only nights on a part-time basis but had family responsibilities on their non-working days were permitted to participate.

2.1.2. Permanent day workers (control participants)

Permanent day workers were required to have never worked full-time night shifts or a rotating shift including nights as part of their regular work schedule.

They were allowed to have worked occasional night shifts, but should not have worked nights in the six weeks preceding their participation in the study.

2.2. Apparatus

2.2.1. Screening tools and sleep log

The Sleep Health Questionnaire (see Appendix 3A) was constructed for the current study and consisted of demographic questions, questions about work and medical history relevant to the exclusion and inclusion criteria, and included the Apnea Prediction Index (Maislin et al., 1995) and the Epworth Sleepiness Scale (Johns, 1991). Participants also completed a two-week sleep log constructed for the purposes of the current study (see Appendix 3B) and the Profile of Mood States (McNair, Lorr, & Droppleman, 1971).

Maislin Apnea Prediction Index (Maislin et al., 1995)

The Maislin Apnea Prediction Index is a self-report rating scale consisting of three questions about sleep disordered breathing and 10 questions about other symptoms of excessive daytime sleepiness. Participants are asked to consider whether during the last month they have experienced, or have been told that they experienced, symptoms of sleep apnoea. Responses are recorded on a 6-point scale (0 = never, 1 = rarely/less than once a week, 2 = 1-2 times a week, 3 = 3-4 times a week, 4 = 5-7 times a week, 5 = don't know). Questions rated 1 to 4 are scored.

Test-retest correlations (retest after 2 weeks) for the Maislin Apnea Prediction Index are high (r = .92). Measures of the predictive ability of the Index (endorsement of apnoea items compared to clinical diagnosis of sleep apnoea) showed that the prevalence of clinically diagnosable sleep apnoea ranged predictive model sample (n = 321) from 20% of patients with an Index value of <1, to 74% of patients with an Index value of 4 (having highly endorsed all sleep apnoea items) (Maislin et al., 1995).

Epworth Sleepiness Scale (Johns, 1991)

The Epworth Sleepiness Scale is an eight item self-report ratings scale which measures self-perceived likelihood of falling asleep or dozing in various daily situations, such as while watching television, while a passenger in a car or while sitting in a cinema. Participants respond to items on a 4-point scale (0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing). Scores of above 16 are considered indicative of a probable sleep-related disorder. The scale is used as a screen for excessive daytime somnolence and symptom identification in disorders such as insomnia, sleep apnoea and narcolepsy.

Profile of Mood States (McNair et al., 1971)

The Profile of Mood States (POMS) is self-report rating scale consisting of 65 5-point items (adjectives describing mood), which assess six mood factors (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigour, Fatigue and Confusion-Bewilderment). It also provides a Total Mood Disturbance score when all factor scores are summed (with Vigour negatively weighted). It is used as a measure of mood state changes in psychiatric outpatients and in both clinical and normal research populations. Participants are required to respond to items with reference to how they have been feeling in the past week including the day of test completion. Participants circle the number that best represents their recent mood state (0 = Not at all; 1 = A little; 2 = Moderately; 3 = Quite a bit; 4 = Extremely). Test-retest reliabilities in the normative sample of 100 psychiatric patients show reliability estimates of .65 to .74 over a median period of 20 days (range 3 to 110) covering intake to therapy commencement. Given that the POMS is designed to measure, among other things, mood change over time, test-retest scores are perhaps not the best measures of its reliability. Internal consistency of the POMS is high, with indices of .87 and above for all six factors.

Standard scores for all six mood factors and the Total Mood Disturbance score were analysed in the current study.

2.2.2. Cognitive test battery

The cognitive test battery consisted of the following tests:

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III): subtests Vocabulary, Arithmetic, Digit Span and Block Design (Wechsler, 1997a).

The WAIS-III is a widely used and comprehensively researched cognitive assessment instrument used to assess general intellectual functioning in adolescents and adults aged 16 to 89 years. It provides a measure of global ability (the full-scale IQ (FSIQ) score) based on the aggregate of specific abilities (broadly divided in verbal and non-verbal, or performance, abilities) measured by the various core subtests (Lezak, Howieson, & Loring, 2004). All subtests require the participant to complete test items of increasing difficulty, and subtests are discontinued after a requisite number of (usually) consecutive item failures.

The *Vocabulary* subtest is a 36-item test of receptive word knowledge requiring the participant to define a list of words presented verbally and in written form. It is considered a strong indicator of general intellectual ability (correlation of r = .80 with FSIQ), and has a high reliability coefficient of r_{xx} = .93.

Arithmetic (20 items) measures mental reasoning and arithmetic ability and requires participants to solve verbally presented arithmetic problems. The subtest correlates highly with FSIQ (r = .72) and has a reliability coefficient of r_{xx} = .88.

The *Digit Span* subtest provides measures of both span of immediate verbal recall (*Digits Forward*) and of working memory (*Digits Backward*) (Lezak et al., 2004). For Digits Forward, the participant is required to repeat back to the examiner progressively longer sequences (from two to eight digits) of verbally presented digits. For Digits Backward, the participant is required to repeat back the digit sequences in the reverse order. Overall the Digit Span subtest has a reliability of r_{xx} = .91, and a moderate correlation with FSIQ of r = .52.

Block Design is a 2-dimensional block construction task of 14 items, assessing visuo-spatial and visuo-constructional abilities. The participant is required to make replicas of the block designs modelled by the examiner (easy items) or presented in a stimulus booklet (increasingly more difficult items), using two, four or nine blocks. Each block is identical, having two red sides, two white sides and two diagonally divided half-red half-white sides (Lezak et al., 2004). Block Design is a reliable subtest (r_{xx} = .86), and correlates moderately with FSIQ (r = .66).

Wechsler Memory Scale – Third Edition (WMS-III): Faces I & II and Word Lists I & II (Wechsler, 1997b)

The WMS-III is a comprehensive battery of tests assessing memory for visual and auditory information in adolescents and adults aged 16 to 89 years. It provides a measure of general memory ability (the General Memory index), as well as measures of immediate and delayed visual and auditory memory, immediate memory, delayed auditory recognition and working memory, based on scores on the Primary Subtests. Optional subtests provide additional information about specific areas of memory functioning.

Faces (I & II) is a test of visual recognition of faces. A memory set of photographs of 24 different faces (an ethnically diverse mixture of Caucasian, African-American, Hispanic and Asian faces representative of the US population) is presented to participants at the rate of one face per two seconds. Participants are then required to immediately pick out the memory set from a larger set of 48 faces, by indicating with a 'yes' or 'no' whether they had seen each face in the previously presented memory set (Faces I). A delayed recognition trial (Faces II) of the 48 reordered faces is conducted after 25-35 minutes.

Raw scores of Faces I and II were converted to age-scaled scores for the purposes of analysis in the present study.

Word Lists (I & II) assesses verbal learning and memory over repeated trials. Participants are read a list of 12 words and asked to recall the words in any order. The list is then read a further three times, with participants responding

after each trial. A new (distractor) list is then read and participants recall those words. Then participants are required to freely recall the words from the first list without cues. After a period of 25-35 minutes a delayed recall trial is administered, and a 24-item recognition trial may also be given.

In the present study age-scaled scores for Word List I Total Recall score and Word Lists 2 Delayed recall were used in all data analyses.

Austin Maze (Milner, 1965; Tucker, Kinsella, Gawith, & Harrison, 1987; Walsh, 1978)

The Austin Maze is an electric push-button maze based on Milner's (1965) Spatial Maze Learning Test. It is considered to be a measure of visual-spatial ability, and procedural and visual-spatial memory (Crowe et al., 1999). In the basic administration of the test, the participant is required to learn the path through the maze using a trial and error approach, following rules restricting direction of movement (no diagonal moves) and response to errors (if an error, indicated by a red light and a buzzer, is made the participant must return to the last correct button position and then continue), until reaching the criterion of two errorless trials. In the current study, administration was limited to 10 trials, as previous research (Bowden et al., 1992) shows a high correlation between errors to criterion and errors over 10 trials in both normal (r = .89) and clinical populations (r = .94).

Raw scores for total errors over 10 trials and total time taken over 10 trials (seconds) were used in the all data analyses.

d2 Test – Concentration Endurance Test 7th Edition (Brickencamp, 1981).

The d2 Test is designed to assess sustained attention and visual scanning ability (Spreen & Strauss, 1998). It is a timed letter cancellation task consisting of 14 lines each with 47 letters (d or p). Participants are required to identify and mark as many targets (the letter 'd' with two quotation marks (") either both above or below it, or one (') above and one below) per line as possible, with a time limit of 20 seconds per line. Test-retest reliabilities are high over both short (5-hour interval, range from r = .89 to r = .92) and long periods (12 months, r = .92).

Brickencamp's original factor analytic studies with normal participants showed high loading on an attentional factor, and low correlations with WAIS subtests, suggesting that the d2 is measuring abilities distinct from those measured by conventional intelligence tests (Brickencamp, 1981).

Raw scores for total items correct and total errors were used in data analyses.

2.2.3. Salivary cortisol collection and analysis

Salivary cortisol measurement, an accurate, reliable and non-invasive method of establishing free cortisol levels within the human system (Laudat et al., 1988) was utilised in the present study.

Night-shift participants were provided with 12 plastic saliva collection tubes with screw tops, for collection of saliva at four-hourly intervals over two 24-hour periods. One 24-hour period took place over a night shift, and the other over the first day shift or day off following the completion of the night-shift work period. Collection tubes were marked with the participants' identification code (SW*n*), shift cycle ("day" or "night") and time of collection in 24-hour time (0300; 0700; 1100; 1500; 1900; or 2300).

Day worker (control) participants were provided with six plastic saliva collection tubes with screw tops for collection of saliva at four-hourly intervals over one 24-hour period corresponding with a work day. Collection tubes were marked with the participants' identification code (C*n*), shift cycle ("day") and time of collection in 24-hour time (0300; 0700; 1100; 1500; 1900; or 2300). All participants were provided with typed instructions for saliva collection and a collection time checklist (see Appendix 4).

Radioimmunoassay (RIA) for cortisol (Orion Diagnostica SPECTRIA Cortisol RIA test) was performed by Analytical Reference Laboratories, St Kilda Road, Melbourne. The SPECTRIA Cortisol test is based on the competitive RIA principle, where a known amount of labelled cortisol and an unknown amount of unlabelled cortisol in the saliva sample compete for a limited number of

binding sites of (polyclonal rabbit anticortisol) antibodies on the inside of a specially coated test tube. After the unbound antigen is washed away, the amount of labelled cortisol in the tube is inversely related to the amount of cortisol in the saliva sample (Orion Diagnostica, 2005).

After defrosting and centrifuging, each sample was transferred into test tubes coated with the cortisol-binding antibodies (150µl of sample and 150µl of buffered 2000n/mol lyophilised cortisol calibrator per tube). Cortisol tracer (500µl of NaN_3) was added to all tubes, which were then mixed briefly on a vortex mixer.

The tubes were then covered with paraffin film and incubated in a 37°C water bath for 30 minutes. After decanting onto absorbent paper, the tubes were then each washed with 1ml of distilled water, decanted again and left standing upside down to drain for at least five minutes.

Each tube was then counted using a gamma counter for at least one minute or until 10,000 counts per tube were accumulated.

2.2.4. Magnetic resonance imaging and spectroscopy

Magnetic resonance imaging (T1-volumetric and T2-relaxometry studies) and magnetic resonance spectroscopy were carried out at the Brain Research Institute (BRI), Austin Health, Melbourne, using a 3-Tesla GE LX Horizon scanner (Milwaukee, WI).

2.2.4.1. Volumetrics

A fast spoiled gradient recalled echo at steady state (FSPGR) sequence (TR/TE 8.9/1.9, flip angle 20, matrix size 256x256 and a field of view (FOV) of 25 x 18.75cm) with contiguous coronal slices of 1.5mm thickness was used for volumetric studies. Analysis was done using a manual segmentation method. An automated technique known as voxel based morphometry (VBM) was used to assess any potential volume differences throughout the whole brain.

The volumes of the hippocampus, the temporal lobe and the whole brain were measured by tracing the outline of the anatomical border of the region. Using the convention established in previous research at the Brain Research Institute, the hippocampus was defined posteriorly with reference to the MR slice which showed the fornix most clearly, and the outline was delineated on every slice (Briellman, Berkovic, & Jackson, 2000). Segmentation of the temporal lobe was commenced in the same slice as the hippocampus, and delineated in every second slice (O'Donoghue et al., 2005). Whole brain volumes were measured by delineating every tenth slice. The ImageJ software program (Rasband, 2006) was used for volumetric analyses.

Hippocampal (HCV) and temporal lobe (TLV) volumes were corrected for whole brain (intracranial) volume (ICV) using the covariance method (Free et al., 1995), according to the following equation:

$$Volume_{corrected} = Volume_{measured} - gradient \times (ICV_{measured} - ICV_{mean})$$

where gradient is the slope of the regression line (calculated using linear regression analysis) of control HCV or TLV versus ICV (Van Paesschen, Connelly, King, Jackson, & Duncan, 1997).

For the VBM analysis, images were spatially normalised, transferred into standard space and smoothed. Whole brain differences between the two groups were assessed on a voxel-wise basis using Statistical Parametric Mapping (SPM), to generate a map of any localised grey matter changes between the two groups (Good et al., 2001).

2.2.4.2. T2 relaxometry

Multi echo T2 weighted MR scans were acquired in the coronal plane (TR 5000ms, 8 echoes per location with TE between 28ms and 231 ms, matrix 256 x 128, FOV 24 cm, 20 slices, 6 mm thick with 1.5 mm spacing, 1 NEX). T2 maps were generated using the acquired T2-weighted images by fitting a single exponential to the signal intensity values on a voxel-wise basis. The T2

relaxometry analysis was carried out using the software package iBrain® (Abbott & Jackson, 2001). Analysis included a region of interest (ROI) approach and a voxel-based approach (VB-relaxometry, VBR). For the ROI analysis T2-relaxation time was measured by placing a circular region of interest over the head of the left and right hippocampi. The VBR analysis assessed group differences on a voxel basis using SPM.

2.2.4.3. Magnetic resonance spectroscopy

Bilateral hippocampal single voxel magnetic resonance proton spectra (MRS) of creatine (Cr), myo-Inositol (mI), choline-group (Cho) and N-acetyl-aspartate group (NAA) metabolites were acquired with a standard short-point echo resolved spectroscopy (PRESS) sequence. Isotropic 3 cm^3 spectra were acquired with the following parameters: echo time (TE) 30 ms, relaxation delay (TR) 3 sec, and represent the sum of 64 transients.

MRS data for each region of interest (ROI) were analysed using the program LCModel v. 6.1 (Provencher, 1993, 2006). Absolute concentrations of metabolite spectra for Cr, mI, Cho and NAA were expressed as millimoles per litre.

2.3. Procedure

After initial telephone or email contact, which included basic screening questions regarding exclusion criteria, the participants were provided with a detailed information sheet outlining the study and an informed consent form (see Appendix 2). If the participant agreed to participate in the study, a date and time for cognitive assessment was made, and the Profile of Mood States and Sleep Health Questionnaire were mailed to the participant to be completed by the first meeting. At the first meeting, sleep health questionnaires were reviewed to screen for sleep disorder, and if no sleep pathology was apparent, cognitive assessment was completed.

The saliva collection schedule and two-week sleep log were then explained to the participant, and a second date was then made for brain MRI and collection of the completed sleep log and saliva samples. Where possible, saliva collection was completed during the two weeks of sleep-logging, and the MRI was completed at the end of the two week period. The POMS and Sleep Health Questionnaire were only administered at commencement of participation.

Cognitive assessment of shift workers was performed at least 24 hours after the end of the last night shift. In order to minimise the effect of menstrual cycle fluctuations on cortisol levels, all participants were instructed, where possible, to collect saliva samples seven to ten days after the end of the last menstrual period. This was to minimise the potential effects of including women taking the contraceptive pill. Cortisol levels and stress reactivity at the follicular stage of the menstrual cycle have been shown to be closest to that of women taking the contraceptive pill (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999).

2.4. Analysis

Data analysis in the current study was limited by the low number of participants whose data was suitable for retention, and the violation of the assumption of normal distribution by some variables required for the use of parametric statistics. The Shapiro-Wilk Test (for small sample sizes) was used to test the normality of data distribution (see Appendix 5). In addition, there were unequal numbers of participants in each group. For these reasons, where appropriate, non-parametric statistical analyses were performed.

Simple comparisons of the two groups (which, despite attempts to match them, differed significantly on a number of demographic variables; see section 3.1) were conducted using independent samples t-tests for normally distributed variables, and the Kolmogorov-Smirnov Z test for those that were not normally distributed. The Kolmogorov-Smirnov Z test was chosen over other possible non-parametric comparative tests such as the Mann-Whitney U or Wilcoxon's test due to *n* for each group being less than 25. When comparing shift workers'

cortisol levels between a day and a night shift, paired samples t-tests were used for normally distributed variables, and the Wilcoxon Signed Ranks test was used for variables that were not normally distributed. For all analyses, missing cases were excluded on a test-by-test basis. Effect sizes for all comparisons were calculated using Pearson's *r*.

Correlational analysis of the two groups was conducted using Kendall's *tau*. Significant differences in correlations between the two groups were examined using Fisher's r-to-z transformation. Where possible, values were converted into categorical data and Chi-square likelihood ratios were used to determine the likelihood of participants having cognitive or neuroanatomical deficits as a result of their work schedule. Cramer's *V* statistic was used as a measure of effect size for Chi-square analyses.

RESULTS

3.1. Demographic characteristics of the participants

Twelve female rotating shift workers (mean age 36.58 years; SD 7.77 years) and 17 female day-shift working control participants (mean age 30.59 years; SD 6.33 years) participated in the study. Kolmogorov-Smirnov Z tests showed that the rotating shift workers were significantly older $D(12,27) = 0.57$, $p = .01$, had spent more years in total in the workforce $t(27) = 2.41$, $p < .05$, and had worked longer in their current occupation $D(12,27) = 0.66$, $p = .01$, than control participants. The groups did not differ on height, weight or education level (all $p > .05$; see Table 3.01).

Table 3.01: Independent samples t-tests and Kolmogorov-Smirnov Z tests for differences between demographic characteristics of shift workers and control participants

	Shift workers (n=12)		Control participants (n=17)					
	M	*SD*	*M*	*SD*	*t*	*D*	*p*	*r*
Age	36.58	7.77	30.59	6.33	-	0.57	.01	.28
Years in work force	16.33	6.20	10.24	7.03	2.41	-	.02	.42
Years in current job	11.46	6.56	3.82	5.55	-	0.66	.001	.32
Height (cm)#	162.90	4.82	164.13	7.63	-0.45	-	.67	.09
Weight (kg)**	61.26	4.59	67.69	10.06	-1.97	-	.06	.43
Education (years)	15.42	0.67	15.41	1.23	-	0.29	.21	.14
Sleep over 24 hrs*	6.61	0.83	7.47	0.64	-2.97	-	.01	.52
Epworth Sleepiness Scale*	8.73	3.38	5.07	2.99	2.92	-	.01	.51

* = shift workers n = 11, controls n = 15; ** = shift workers n = 11, controls n = 16;
# = shift workers n = 10, controls n = 16

Sleep health variables were analysed using independent samples t-tests (see Table 3.01). On average, shift-workers had higher scores on the Epworth Sleepiness Scale than did control participants; this difference was significant $t(24) = 2.92$, $p = .01$, with a large effect size $r = .51$. Over a two-week period, shift-workers had on average significantly fewer hours daily sleep than did control participants, $t(24) = 2.97$, $p = .01$. A large effect size of $r = .52$ was found.

3.2. Differences between groups

3.2.1. Cognitive variables

Independent samples t-tests and Kolmogorov-Smirnov Z tests, where appropriate, were used to compare shift workers and control participants on cognitive measures. There were no significant differences between groups on the Austin Maze (time taken), the d2 test (concentration and errors), the WMS-III Faces and Word List subtests or the WAIS-III Block Design, Vocabulary and Arithmetic subtests (all $p > .05$ with low effect sizes; see Table 3.02). On average shift workers made more errors on the Austin Maze. This difference approached significance, $t(26) = 1.95$, $p = .06$, and had a medium effect size, $r = .35$. For WAIS-III Digit Span backwards, on average shift-workers recited fewer digits backwards than control participants. Although this difference was not significant $t(26) = 1.67$, $p > .05$, there was a medium effect size, $r = .31$. For the WAIS-III Digit Span total score, on average shift-workers scores were lower than control participants, a difference which approached significance, and there was a medium effect size $t(26) = 1.93$, $p = .06$, $r = .36$.

Table 3.02: Independent samples t-test and Kolmogorov-Smirnov Z test results for differences between shift workers and control participants on cognitive variables

	Shift workers (n=12)		Control participants (n=17)					
	M	*SD*	*M*	*SD*	*t*	*D*	*p*	*r*
Austin Maze Time*	482.00	163.23	455.47	147.38	-	0.23	.79	.11
Austin Maze Errors*	165.73	65.37	118.76	60.97	1.95	-	.06	.35
Test d2 Concentration	165.58	52.40	168.94	43.12	-0.19	-	.86	.04
Test d2 Errors	20.83	19.26	17.06	14.52	0.60	-	.55	.12
WMS-III Faces 1	11.42	2.57	10.88	2.72	-	0.27	.47	.13
WMS-III Faces 2	11.42	2.31	11.65	2.37	-0.26	-	.80	.05
WMS-III Word List 1	12.83	1.90	12.41	2.85	0.45	-	.66	.09
WMS-III Word List 2	12.33	2.46	12.24	2.54	0.10	-	.92	.02
WAIS-III Block Design	11.58	2.68	12.35	3.08	-0.70	-	.49	.13
WAIS-III Arithmetic	11.17	2.21	11.94	2.77	-0.80	-	.43	.16
WAIS-III Vocabulary	11.75	2.22	12.76	2.97	-1.00	-	.33	.19
WAIS-III Digits Forward**	9.50	1.38	10.50	2.03	-	0.21	.60	.10
WAIS-III Digits Back**	6.92	1.51	8.06	1.98	-1.67	-	.11	.31
WAIS-III Digit Span SS**	9.50	1.38	10.88	2.36	-1.93	-	.06	.36

* = shift workers n = 11, controls n = 17; ** = shift workers n = 12, controls n = 16

3.2.2. Psychological (Profile of Mood States) variables

Table 3.03 shows the results of independent t-tests and Kolmogorov-Smirnov Z tests used to compare shift workers' and control participants' scores on the various subscales of the Profile of Mood States (POMS). There were no significant differences between the groups for the Total Mood Score, or the Tension-Anxiety and Anger-Hostility subscales (all $p > .05$, effect sizes $< .1$). On average control participants had higher Depression-Dejection and Confusion-Bewilderment scores than shift workers. These differences were not significant (for both $p > .5$), and there were small effect sizes, $r = .13$ and $r = .11$ respectively. Shift workers had on average higher levels of Fatigue and lower levels of Vigor than control participants. These differences were not significant (for both, $p > .1$), and there were small to medium effect sizes, $r = .19$ and $r = .26$ respectively.

Table 3.03: Independent samples t-test and Kolmogorov-Smirnov Z test results for differences between shift workers and control participants on the Profile of Mood States

	Shift workers (n=11)		Control participants (n=17)					
	M	*SD*	*M*	*SD*	*t*	*D*	*p*	*r*
Total Mood Score	28.45	25.44	28.76	34.33	-0.03	-	0.98	0.01
Tension-Anxiety	7.09	5.38	8.41	7.31	-	0.46	0.90	0.09
Depression-Dejection	5.45	6.77	9.29	10.20	-	0.66	0.51	0.13
Anger-Hostility	8.09	5.11	9.12	5.88	0.44	-	0.64	0.09
Fatigue	11.45	4.68	9.29	6.18	0.19	-	0.33	0.19
Confusion-Bewilderment	7.82	4.79	8.12	6.00	-	0.57	0.74	0.11
Vigor	13.63	6.67	17.24	6.65	-1.39	-	0.17	0.26

3.2.3. Endocrine (cortisol) variables

Figure 3.01 shows mean cortisol values at six collection times over 24 hours for shift-workers on day shift and night shift, and control participants on day shift only. Visual inspection shows that control participants and shift workers on either day shift or night shift had broadly normal cortisol rhythms, with a falling off of cortisol level over the evening as the normal sleep time approached, and a late night or early morning quiescent period followed by a morning peak.

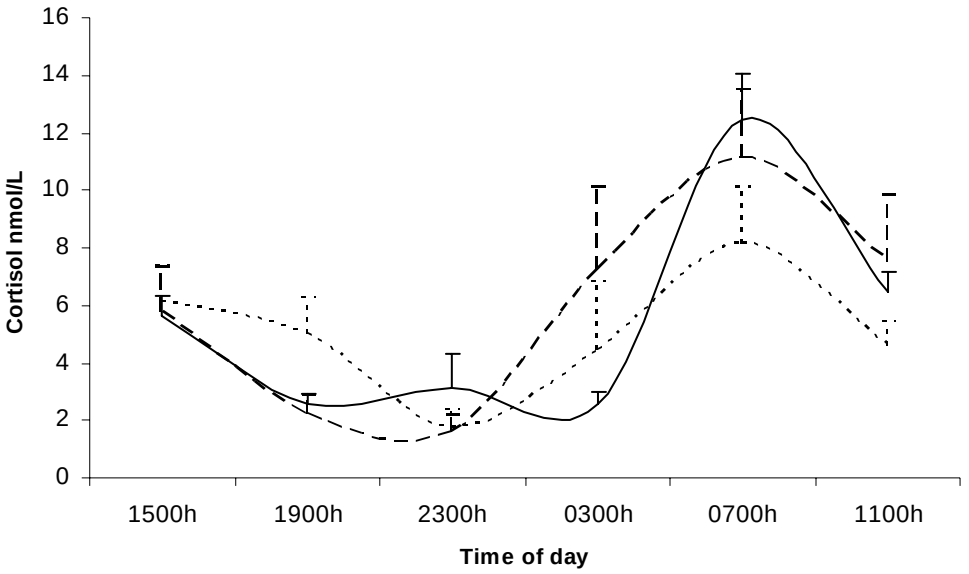

Figure 3.01. Mean cortisol levels (nmol/L) at the six sampling times over 24 hours for shift workers on day shift (dashed), shift workers on night shift (dotted) and control participants (solid). Errors bars represent the standard error of the mean.

3.2.3.1. Control day shift vs shift worker day shift cortisol

Figure 3.01 shows that a sinusoidal rhythm was apparent for both control participants and shift workers regardless of shift worked. For shift workers, the cortisol levels at the acrophase of the rhythm were higher for day shift than for night shift. Control participants and shift workers had similar levels of cortisol at 1500h and 1900h during a day shift. At 2300h, control participants showed an atypical rise compared to shift workers, whose levels appear to be following the normal waning into the quiescent period. At 0300h, shift workers showed an early rise in cortisol level compared to control participants, who still appeared to be in the overnight quiescent period of the rhythm. By 0700h control cortisol levels had peaked, along with shift workers, while both groups showed a normal falling off of cortisol as the morning progressed (1100h).

Independent samples t-test did not reveal a significant difference between shift workers and control participants for mean 24-hour cortisol levels over a day shift, $t(25) = 0.22$, $p > .05$, $r = .04$, or for total 24 hour cortisol levels, $t(25) = 0.34$, $p > .05$, $r = .07$ (see Table 3.03). Shift workers did not have significantly higher day shift cortisol levels than control participants at any of the collection times over a 24-hour period (for all comparison, $p > .05$ with small effect sizes,

see Table 3.04). Although cortisol levels at 2300h did not significantly differ between shift workers and control participants, a medium effect size was found, $t(23) = 1.79$, $p > .05$, $r = .38$.

Table 3.04: Independent t-test and Kolmogorov-Smirnov Z test results for difference between cortisol levels of control participants and shift-workers on day shift

	Shift workers		Control participants					
Collection time	*M*	*SD*	*M*	*SD*	*t*	*D*	*p*	*r*
1500h day shift**	5.80	4.78	5.48	2.80	0.23	-	.83	.04
1900h day shift##	2.00	1.89	2.60	1.19	-0.89	-	.39	.23
2300h day shift#	1.44	1.42	3.76	4.81	-1.79	-	.09	.38
0300h day shift	7.22	8.54	2.59	1.69	-	0.44	.10	.21
0700h day shift*	11.70	6.27	12.86	6.46	-0.46	-	.65	.09
1100h day shift†	7.56	6.27	6.39	2.92	-	0.22	.73	.10
24h dayshift total*	34.10	13.57	32.52	10.51	0.34	-	.74	.07
24h dayshift mean*	6.03	2.27	5.84	2.01	0.22	-	.83	.04

* = shift workers n = 10, controls n = 17; ** = shift workers n = 10, controls n = 16;
# = shift workers n = 9, controls n = 16; ## = shift workers n = 10, controls n = 14;
† = shift workers n = 12, controls n = 17

3.2.3.2. Control day shift vs shift worker night shift cortisol

Figure 3.01 shows that on average, cortisol levels at 1500h and 1900h did not differ between control participants on day shift and shift workers on night shift. At 2300h, control participants showed a slight elevation compared to shift workers; however by 0300h shift workers on night shift had slightly higher cortisol. At 0700h, control participants showed a higher level. By 1100h both groups' cortisol had fallen off, although shift workers were lower on average.

Over a 24-hour period, there was not a significant difference between the mean, D (10,17) = .41, $p > .10$, $r = .20$, or total, $D(10,17) = .39$, $p > .10$, $r = .19$, cortisol levels of control participants on day shift and shift workers on night shift, (see Table 3.05). Cortisol levels did not differ significantly at 1500h $t(24) = 0.48$, $p = .64$, $r = .10$, nor at 1900h, $t(21) = 1.82$, $p = .10$, although there was a large effect size, $r = .52$. At 2300h, 0300h, 0700h and 1100h, control participants and shift workers did not differ in cortisol levels (all $p > .05$), and effect sizes were small.

Table 3.05: Independent samples t-test and Kolmogorov-Smirnov Z test results for differences between cortisol levels of shift-workers on night shift and control participants on day shift

	Shift workers		Control participants					
Collection time	*M*	*SD*	*M*	*SD*	*t*	*D*	*p*	*r*
1500h*	6.10	3.93	5.48	2.80	0.48	-	.64	.10
1900h#	5.00	3.84	2.60	1.19	1.82	-	.10	.52
2300h**	1.67	1.58	3.76	4.81	-	0.37	.20	.18
0300h*	4.10	6.76	2.59	1.69	-	0.24	.69	.12
0700h##	8.13	5.62	12.86	6.46	-	0.45	.11	.21
1100h##	4.63	2.33	6.39	2.92	-	0.38	.21	.19
24 hour total†	26.40	11.25	32.52	10.51	-	0.39	.18	.19
24 hour mean†	4.82	1.91	5.84	2.01	-	0.41	.17	.20

* = shift workers n = 10, controls n = 16; ** = shift workers n = 9, controls n = 16;
# = shift workers n = 9, controls n = 14; ## = shift workers n = 8, controls n = 17;
† = shift workers n =10, controls n = 17

3.2.3.3. Night shift vs day shift cortisol levels for shift workers

Figure 3.01 shows that on average, shift workers on a night shift had higher mid-evening (1900h) cortisol levels, a relatively slower morning rise of cortisol and a lower acrophase (0700h) compared to the rhythm seen on a day shift. Paired samples t-tests and the Wilcoxon Signed Ranks test were used to compare cortisol on a night shift versus on a day shift (see Table 3.06). On average, mean cortisol levels over 24 hours were higher during the day shift compared to the night shift. Although this difference was not significant, a large effect size was found: $t(9) = 1.91$, $p > .05$, $r = .54$. However, total cortisol over a day shift was significantly higher than that seen over a night shift, and the effect was large, $t(9) = 2.37$, $p < .05$, $r = .62$.

At 1500h, there was a negligible difference between day shift and night shift cortisol levels, $t(9) = 0.18$, $p > .50$, $r = .06$. At 1900h, although the difference between day shift cortisol and night shift cortisol was not significant $t(8) = 2.19$, $p > .05$, there was a large effect size, $r = .61$. There was no significant difference between day shift and night shift cortisol levels at 2300h, $t(7) = 0.16$, $p > .5$, $r = .06$.

Table 3.06: Paired samples t-test and Wilcoxon signed ranks test results for differences between shift workers' day shift and night shift salivary cortisol levels

	Shift workers							
	Day shift		Night shift					
Collection time	*M*	*SD*	*M*	*SD*	*t*	*T*	*p*	*r*
1500h (n = 10)	5.80	4.78	6.10	3.93	-0.18	-	.86	.06
1900h (n = 9)	2.00	1.89	5.00	3.84	-2.19	-	06	.61
2300h (n = 8)	1.44	1.42	1.67	1.58	-0.16	-	.88	.06
0300h (n = 9)	7.22	8.54	4.10	6.76	-	10.50	.19	-.34
0700h (n = 8)	11.70	6.27	8.13	5.62	1.01	-	.35	.36
1100h (n = 8)	7.56	6.27	4.63	2.33	1.27	-	.25	.43
24 hr total (n = 10)	34.10	13.57	26.40	11.25	2.37	-	.04	.62
24 hr mean (n = 10)	6.03	2.27	4.82	1.91	1.91	-	.09	.54

For the morning collection times (0300h, 0700h and 1100h), on average cortisol was higher during the day shift compared to night shift levels (see Figure 3.01). Although these differences were not significant, medium to large effect sizes were evident: at 0300h $T(9) = 10.50$, $p > .05$, $r = -.34$; at 0700h $t(7) = 1.01$, $p = .35$, $r = .36$; and at 1100h $t(7) = 1.27$, $p = .25$, $r = .43$.

3.2.3.4. Nocturnal cortisol levels

Nocturnal cortisol levels were calculated by summing 2300h and 0300h levels for shift workers on both day shift and night shift, and control participants on day shift (see Table 3.07).

Table 3.07: Kolmogorov-Smirov Z test and Wilcoxon Signed Ranks test results for differences between shift workers' and control participants' total (panel B) and mean (panel C) nocturnal cortisol (2300h+0300h)

	Total		Mean	
A: 2300h+0300h	M	SD	M	SD
Shift workers (SW) day	8.67	8.53	4.33	4.26
Shift workers (SW) night	3.67	2.12	3.95	6.77
Control participants (C) day	5.83	4.58	3.40	3.31
B: Total 2300h+0300h	*D*	*T*	*p*	*r*
SW day vs SW night	-	6.50	0.27	-0.32
SW day vs C day	0.25	-	0.27	0.10
C day vs SW night	0.22	-	0.96	0.11
C: Mean 2300h+0300h	*D*	*T*	*p*	*r*
SW day vs SW night	-	14.50	0.68	-0.12
SW day vs C day	0.21	-	0.68	0.12
C day vs SW night	0.15	-	0.76	0.07

The Wilcoxon Signed Ranks test and the Kolmogorov-Smirnov Z test were used to compare groups. Nocturnal cortisol did not significantly differ between shift workers on day shift and control participants on day shift for either mean, $D(9,16) = 0.25$, p (two-tailed) > .50, $r = .12$, or total levels, $D(9,14) = 0.21$, p (two-tailed) > .50, $r = .10$.

There were no significant differences between either mean, $T = 14.50$, p (two tailed) > .50, $r = -.11$, or total, $T = 6.50$, p (two tailed) > .10, $r = -.32$, nocturnal cortisol on a day shift and on a night shift for shift workers, although the difference for total nocturnal cortisol represented a medium effect size.

Nocturnal cortisol of Control participants on a day shift did not significantly differ from that of shift workers on a night shift for either mean, $D(10,17) = 0.15$, p (two-tailed) > .50, $r = .10$, or total levels, $D(9,15) = 0.22$, p (two-tailed) > .50, $r = .11$.

3.2.4. MRI volumetric variables

3.2.4.1. Hippocampal volumes

Table 3.08 shows the results for comparison of T1-volumetric MR measures. Total right hippocampal lobe volume in mm^3 did not differ between groups $t(24) = 0.09$, $p > .05$, $r = .02$, nor did total left hippocampal, $D(10, 16) = 0.33$, $p > .05$, $r = .16$.

Table 3.08: Independent samples t-test and Kolmogorov-Smirnov Z test results for differences between shift workers and control participants in mean volumetric T1 MRI values (mm^2), for the whole brain, and temporal lobes and hippocampi bilaterally

	Shift workers (n=10)		Control participants (n=16)					
	M	*SD*	*M*	*SD*	*t*	*D*	*p*	*r*
R hipp. TV	2673.70	210.70	2665.01	277.97	0.09	-	.93	.02
R hipp. % TIV	0.24	0.01	0.24	0.02	-	0.39	.24	.19
L hipp. TV	2538.88	279.49	2496.18	252.61	-	0.33	.43	.16
L hipp. % TIV	0.23	0.02	0.22	0.02	-	0.28	.65	.13
R temp. lobe TV	65726.83	7031.77	67624.11	5285.45	-0.78	-	.44	.16
R temp. lobe % TIV	5.85	0.52	6.09	0.39	-1.36	-	.19	.27
L temp. lobe TV	63279.22	6991.06	64499.93	7703.41	-0.41	-	.69	.08
L temp. lobe % TIV	5.63	0.54	5.80	0.58	-0.75	-	.46	.15
TIV	1123631.65	69118.60	1111698.22	77432.96	-	0.23	.84	.11

L = left; R = right; hipp = hippocampus; temp. lobe = temporal lobe; TIV = total intracranial volume; TV = total volume

When analysed as a percentage of intracranial volume, there was still no significant difference for either right, $D(10,16) = 0..39$, $p = .24$, $r = .19$, or left, $D(10,16) = 0.28$, $p > .05$, $r = .13$, hippocampal volume between groups.

3.2.4.2. Temporal lobe volumes

Total left temporal lobe volume in millimetres squared (mm^3) did not differ between groups, $t(24) = 0.41$, $p > .5$, $r = .08$, nor did total right temporal lobe volume $t(24) = 0.78$, $p > .5$, $r = .16$.

When analysed as a percentage of intracranial volume, there was no significant difference for left temporal lobe volume between groups, although a slightly larger effect size was apparent, $t(24) = 0.75$, $p > .1$, $r = .15$. For the right temporal lobe, correcting for intracranial volume did not result in a significant difference between groups; however the effect size was slightly increased, $t(24) = 1.36$, $p > .1$, $r = .27$.

3.2.4.3. Total intracranial volume

Overall, there was no significant difference between the total intracranial volumes of control participants and shift workers, $t(24) = 0.40$, $p > .5$, $r = .08$.

3.2.4.4. Ratios of right to left MRI variables

The relative sizes of right and left hippocampal and temporal lobe volumes of shift workers and control participants were calculated using the ratio of right/left total volumes. These values were then categorised as R > L, L > R or R = L, and analysed using Chi-square likelihood ratios (see Table 3.09). Cramer's *V* statistic is reported as an effect size.

There was no significant association between group membership (shift worker or control) and relative size of right versus left hippocampus, $\chi^2 (1) = 0.64$, $p > .05$, $V = .16$, and there was no significant association between group

membership and relative size of right versus left temporal lobe, χ^2 (2) = 0.66, p > .05 V = .16.

Table 3.09: Contingency table and Chi-square analysis of right-to-left hippocampal and temporal lobe volume ratios for shift workers and control participants

	Hippocampal volumes			
A.	R > L	L > R		Total
Shift workers	6	4		10
Control participants	12	4		16
Total	18	8		26
	χ^2	df	*p*	*V*
Likelihood ratio	0.64	1	.42	.16
	Temporal lobe volumes			
B.	R > L	L > R	R = L	Total
Shift workers	6	3	1	10
Control participants	10	3	3	16
Total	16	6	4	26
	χ^2	df	*p*	*V*
Likelihood ratio	0.66	2	.74	.16

3.2.5. T2 relaxometry

Independent t-tests were used to compare mean T2 relaxation times for left and right hippocampi between shift workers and control participants (see Table 3.10).

Table 3.10: Independent samples t-test results for differences between right and left hippocampal ROI T2 values for shift workers and control participants

	Shift workers (n=10)		Control participants (n=15)				
	M	*SD*	*M*	*SD*	*t*	*p*	*r*
Right hipp T2 ROI	89.12	3.50	93.09	4.25	-2.45	.02	.46
Left hipp T2 ROI	90.03	4.61	92.06	4.31	-1.12	.27	.23

Shift workers' right hippocampal T2 relaxation times were significantly lower than those of the control participants, $t(23) = 2.45$, $p < .05$, and the effect size was medium, $r = .46$. There was no significant difference between shift workers' and control participants' left hippocampal T2 relaxation times, $t(23) = 1.12$, $p > .10$, $r = .23$.

Table 3.11 shows the number of voxels in the voxel-based morphometry (VBM) and voxel-based relaxometry (VBR) analyses where there were significant differences between shift workers and control participants

Table 3.11: Number of significant voxel differences (control participants > shift workers) for voxel-based morphometry (VBM) and voxel-based relaxometry (VBR) analyses

	VBM	VBR
Total voxels	1828544	1331989
Significant voxels	21771	39377
Percentage significant	1.19	2.66

The VBM and VBR analyses of the whole brain did not indicate any significant regional differences in grey matter between shift workers and control participants. Although a number of voxels in the normalised MR images had *p* values less than .05, the large number of comparisons increased Type I error rates, meaning that significant values were likely to be false positives rather than real differences (see Table 3.11). This is an ongoing problem with voxel-based measurements.

3.2.6. MRS brain metabolite variables

Table 3.12 show the results for comparison of hippocampal metabolite levels between control participants and shift workers. There were no significant differences between the groups for any of the individual metabolites or metabolite ratios for either the left or the right hippocampus.

Table 3.12: Independent samples t-test and Kolmogorov-Smirnov Z test results for differences between control participants' and shift workers' left (panel A) and right (panel B) hippocampal MRS of brain metabolites

	Shift workers (n=10)		Control participants (n=15)					
A: Left MRS	*M*	*SD*	*M*	*SD*	*t*	*D*	*p*	*r*
Creatine (Cr)	5.17	0.50	5.27	0.86	-0.33	-	.75	.07
myo-Inositol (mI)	4.24	0.93	4.39	1.20	-0.35	-	.73	.07
mI/Cr	0.82	0.15	0.83	0.13	-0.20	-	.85	.04
GPC + PCh	1.74	0.16	1.74	0.25	-	0.33	.46	.16
GPC + PCh/Cr	0.36	0.07	0.33	0.04	-	0.33	.46	.16
NAA + NAAG	6.98	0.56	6.98	1.12	-0.01	-	.99	.00
NAA + NAAG/Cr	1.36	0.12	1.33	0.13	0.56	-	.58	.12

B: Right MRS	*M*	*SD*	*M*	*SD*	*t*	*D*	*p*	*r*
Creatine (Cr)	5.31	0.51	5.48	0.74	-0.65	-	.52	.13
myo-Inositol (mI)	5.01	1.17	4.52	0.90	1.18	-	.25	.24
mI/Cr	0.94	0.18	1.69	3.42	-	0.37	.34	.18
GPC + PCh	1.79	0.21	1.77	0.24	0.22	-	.83	.05
GPC + PCh/Cr	0.34	0.03	0.32	0.02	1.31	-	.20	.26
NAA + NAAG	6.91	0.66	7.07	0.71	-0.55	-	.59	.11
NAA + NAAG/Cr	1.31	0.13	1.30	0.15	0.14	-	.89	.03

GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate; NAAG = N-acetyl-aspartyl-glutamate

3.3. Correlational analyses

3.3.1. Cognitive performance and T1-volumetric MRI

Table 3.13 shows correlations (Kendall's *tau*) between T1-volumetric MRI variables and scores on the Austin Maze and Test d2 for both shift workers and control participants.

Table 3.13: Correlations (Kendall's *tau*) between T1-volumetric MRI and Austin Maze & Test d2 for shift workers and control participants

	Shift workers (n = 10)				Control participants (n = 16)			
	Austin Maze		test d2		Austin Maze		test d2	
	Time(s)	Errors	Correct	Errors	Time(s)	Errors	Correct	Errors
R hipp. TV	**.49***	**.45***	.04	-.23	-.03	-.18	**.37***	-.08
R hipp. % TIV	.27	.13	-.09	**-.55***	.18	.00	.15	.02
L hipp. TV	**.63***	**.67****	-.09	-.09	**-.40***	**-.38***	.22	.05
L hipp. % TIV	.31	.09	-.40	-.09	-.10	-.18	.07	.00
R temp. lobe TV	.02	.33	.24	.07	-.25	-.17	.02	-.03
R temp. lobe % TIV	-.16	.07	.42	-.20	.10	.08	-.20	.00
L temp. lobe TV	-.16	.24	-.02	.34	**-.42**	-.33	-.02	.07
L temp. lobe % TIV	-.29	.02	-.07	.16	-.17	-.18	-.20	.00
TIV	.27	**.58***	.27	.18	**-.59****	**-.37***	.12	-.07

* = significant at .05 ** = significant at .01

L = left; R = right; hipp = hippocampus; temp. lobe = temporal lobe; TIV = total intracranial volume; TV = total volume

For shift workers, time taken on the Austin Maze to complete 10 trials was positively correlated with total right hippocampal volume, $\tau = .49$, p (two-tailed) $< .05$, and total left hippocampal volume, $\tau = .63$, p (two-tailed) $< .05$. Total errors made on the Austin Maze over 10 trials were positively correlated with total right hippocampal volume, $\tau = .45$, p (two-tailed) $< .05$, total left hippocampal volume $\tau = .67$, p (two-tailed) $< .01$ and total intracranial volume τ

= .58, *p* (two-tailed) < .05. For the Test d2, shift workers showed a significant negative correlation between total errors made and right hippocampal percentage of intracranial volume τ = -.55, *p* (two-tailed) < .05.

For control participants, time taken on the Austin Maze was negatively correlated with total left hippocampal volume τ = -.40, *p* (two-tailed) < .05, total left temporal lobe volume τ = -.42, *p* (two-tailed) < .05 and total intracranial volume τ = -.59, *p* (two-tailed) < .01. Negative correlations were also found between Austin Maze total errors and total left hippocampal volume τ = -.38, *p* (two-tailed) < .05 and total intracranial volume τ = -.36, *p* (two-tailed) < .05. For the Test d2, control participants showed a significant positive correlation between total items correct and right hippocampal percentage of intracranial volume τ = .37, *p* (two-tailed) < .05.

Table 3.14 shows correlations between T1-volumetric MRI measures and WMS-III subtests for both shift workers and control participants. Total left hippocampal volume was negatively correlated with initial word list learning (WMS-III Word Lists 1) for shift workers, τ = -.53, *p* (two-tailed) < .05. For control participants there were no significant correlations between WMS-III variables and T1-volumetric MRI variables.

Table 3.14: Correlations (Kendall's *tau*) between T1-volumetric MRI and WMS-III subtests for shift workers and control participants

	Shift workers (n = 10)				Control participants (n = 16)			
	WMS-III Faces		WMS-III Word Lists		WMS-III Faces		WMS-III Word Lists	
	1	2	1	2	1	2	1	2
R hipp. TV	.03	.28	-.03	.17	.21	.15	.01	-.10
R hipp. % TIV	.23	.14	.13	.02	.08	.11	-.13	-.08
L hipp. TV	.28	.24	**-.53***	-.07	-.08	-.01	-.16	-.29
L hipp. % TIV	.18	-.19	-.43	-.31	-.05	.04	-.27	-.22
R temp. lobe TV	.03	.07	.10	-.05	.27	.13	.22	-.01
R temp. lobe % TIV	.18	.02	.20	-.05	.14	.06	.10	.10
L temp. lobe TV	-.43	-.26	.00	.47	.05	-.19	.08	-.17
L temp. lobe % TIV	-.38	-.21	.15	.24	-.06	-.22	-.01	-.11
TIV	-.13	.24	-.13	.17	.10	.13	.13	.03

* = significant at .05 ** = significant at .01

Table 3.15 shows correlations between T-1 volumetric MRI variables and performance on WAIS-III subtests for both shift workers (panel A) and control participants (panel B). Shift workers showed a negative correlation between Block Design scaled score and right hippocampal percentage of total intracranial volume, $\tau = -.73$, p (two-tailed) $< .05$. For control participants, Digit Span forward raw score was positively correlated with total volume of the right temporal lobe, $\tau = .42$, p (two-tailed) $< .05$ and with total intracranial volume $\tau = .42$, p (two-tailed) $< .05$. Digit Span backward raw score was positively correlated with total volume of the left temporal lobe $\tau = .46$, p (two-tailed) $< .05$ and with the left temporal lobe percentage of total intracranial volume, $\tau = .54$, p (two-tailed) $< .01$.Digit Span scaled score was positively correlated with total right temporal lobe volume, $\tau = .44$, p (two-tailed) $< .05$, and total left temporal lobe volume, $\tau = .50$, p (two-tailed) $< .05$.

Table 3.15: Correlations (Kendall's *tau*) between T1-volumetric MRI variables & WAIS-III subtests for shift workers (panel A) and control participants (panel B)

	WAIS-III subtest scaled scores					
A: Shift workers (n=10)	BDesign	Arithmetic	Vocab	DSpan F	DSpan B	DSpan
R hipp. TV	-.34	-.21	-.42	-.43	-.29	-.41
R hipp. % TIV	**-.73***	.30	-.49	-.54	.03	-.30
L hipp. TV	-.53	.22	-.59	-.55	-.09	-.41
L hipp. % TIV	.35	.12	.00	-.10	.09	.01
R temp. lobe TV	-.23	-.29	.03	.30	-.04	.12
R temp. lobe % TIV	-.25	.00	-.02	.27	.28	.26
L temp. lobe TV	-.28	.07	-.15	-.18	.01	-.20
L temp. lobe % TIV	.46	-.08	.29	-.14	-.37	-.28
TIV	.20	.16	.21	-.35	.25	.15
B: Control participants (n = 16)						
R hipp. TV	.12	.10	.08	.15	.11	.20
R hipp. % TIV	-.14	-.09	-.11	-.09	.01	-.04
L hipp. TV	.25	-.07	.16	.30	.26	.38
L hipp. % TIV	.04	-.24	-.09	-.13	.24	.10
R temp. lobe TV	.21	.16	.21	**.42***	.28	**.44***
R temp. lobe % TIV	-.05	-.10	-.06	.01	.26	.14
L temp. lobe TV	.37	-.03	.33	.32	**.46***	**.50***
L temp. lobe % TIV	.14	-.29	.13	.01	**.54****	.36
TIV	.39	.21	.25	**.42***	.15	.32

* = significant at .05 ** = significant at .01

BDesign = Block Design; Vocab = Vocabulary; DSpan F = Digit Span forwards raw score; DSpan B = Digit Span backwards raw score; DSpan = Digit Span.

Please note, with the exception of DSpan F and DSpan B, all WAIS-III analyses are based on scaled scores.

The correlation coefficients of the two groups for cognitive variables versus T1 MRI variables were compared using the Fisher r-to-z transformation (see Table 3.16 for significant values; full r-to-z transformations in Appendix 6A). Shift workers showed a significantly stronger correlation than did control participants between time taken on the Austin Maze and total volume of the left hippocampus, $z = 2.49$, p (two-tailed) $< .01$, and total intracranial volume, $z = 2.03$, p (two-tailed) $< .05$. Shift workers' correlations were also significantly stronger between Austin Maze errors and the total volume of the left hippocampus, $z = 2.61$, p (two-tailed) $< .01$, and total intracranial volume, $z = 2.25$, p (two-tailed) $< .05$.

Table 3.16: Significant Fisher's r-to-z-transformations for cognitive vs. MRI variable correlation coefficients for shift workers and control participants

	Shift workers (n=10)		Control participants (n =16)			
	r	z	r	z	z-test	p
Austin Maze time						
L hipp. TV	.63	0.74	-.40	-0.43	2.49	.01
TIV	.27	0.28	-.59	-0.68	2.03	.04
Austin Maze errors						
L hipp. TV	.67	0.82	-.38	-0.40	2.61	.01
TIV	.58	0.67	-.37	-0.38	2.25	.02
WAIS-III BDesign						
L hipp. TV	-.68	-0.84	.25	0.25	-2.33	.02
WAIS-III Vocab						
L hipp. TV	-.75	-0.98	.16	0.16	-2.44	.01
WAIS-III DSpan F						
R hipp. TV	-.73	-0.93	.15	0.15	-2.27	.02

BDesign = Block Design; Vocab = Vocabulary; DSpan F = Digit Span forwards raw score

Shift workers also had a significantly stronger relationship between total volume of the left hippocampus and WAIS-III Block Design, $z = -2.33$, $p < .05$, and WAIS-II Vocabulary, $z = -2.44$, $p = .01$. Total volume of the right temporal lobe was more significantly more strongly associated with WAIS-III Digit Span forward for shift workers compared to control participants, $z = -2.27$, $p < .05$.

3.3.2. Cognitive performance and brain metabolites (MRS)

Table 3.17 shows correlations between left hippocampal (panel A) and right hippocampal (panel B) brain metabolites as measured by magnetic resonance spectroscopy and Austin Maze and Test d2 performance for both shift workers and control participants. Shift workers showed a significant correlation between errors made on the Austin Maze and left hippocampal ratio of myo-Inositol (mI) to creatine (Cr), $\tau = .51$, p (two-tailed) $< .05$. Number of items correct on the Test d2 was positively correlated with left hippocampal creatine, $\tau = .56$, p (two-tailed) $< .05$. Total errors on the Test d2 were positively correlated with left hippocampal N-acetyl aspartate plus N-acetyl-aspartyl-glutamate (NAA+NAAG) levels, $\tau = -.57$, p (two-tailed) $< .05$.

Table 3.17: Correlations (Kendall's *tau*) between MRS and the Austin Maze and Test d2 for shift workers and control participants

	Shift workers (n = 10)				Control participants (n = 15)			
	Austin Maze		test d2		Austin Maze		test d2	
A: Left hippocampus	Time(s)	Errors	Correct	Errors	Time(s)	Errors	Correct	Errors
Creatine (Cr)	-.29	.02	**.56***	-.16	.21	.20	-.10	-.07
myo-Inositol (mI)	.16	.38	.20	-.07	-.06	.05	-.23	-.07
mI/Cr	.29	**.51***	-.02	-.11	-.15	-.09	-.21	-.07
GPC + PCh	.16	.29	.02	.16	.17	.09	.02	-.20
GPC + PCh/Cr	.38	.07	-.29	.16	-.08	-.22	.21	-.03
NAA + NAAG	-.20	-.07	.20	**-.57***	**.40***	.20	-.10	-.11
NAA + NAAG/Cr	.24	.02	-.07	-.43	.33	.10	.19	.09
B: Right hippocampus								
Creatine (Cr)	-.42	-.20	.33	-.25	-.02	-.03	-.13	-.01
myo-Inositol (mI)	-.24	.07	.16	-.02	-.08	.03	-.33	-.03
mI/Cr	-.11	.02	.02	.02	-.19	.03	-.36	.03
GPC + PCh	-.29	-.07	.38	-.25	-.23	-.16	-.15	-.03
GPC + PCh/Cr	.24	.11	.11	-.20	-.31	-.26	.06	.28
NAA + NAAG	-.33	-.38	.42	-.30	.27	.03	.00	-.13
NAA + NAAG/Cr	-.07	-.29	-.02	-.07	.25	-.03	**.48***	-.20

* = significant at .05 ** = significant at .01

GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate; NAAG = N-acetyl-aspartyl-glutamate

For control participants, time taken on the Austin Maze was positively correlated with left hippocampal NAA+NAAG, $\tau = .40$, p (two-tailed) $< .05$.

Total items correct on the Test d2 showed a significant positive correlation with NAA+NAAG/Cr, $\tau = .48$, p (two-tailed) $< .05$.

Table 3.18: Correlations (Kendall's *tau*) between MRS and WMS-III variables for shift workers and control participants

	Shift workers (n = 10)				Control participants (n = 15)			
	WMS-III Faces		WMS-III Word Lists		WMS-III Faces		WMS-III Word Lists	
A: Left hippocampus	1	2	1	2	1	2	1	2
Creatine (Cr)	-.08	-.12	.25	-.05	-.02	.05	.24	.20
myo-Inositol (mI)	-.08	-.40	.00	.05	.12	.07	.32	.34
mI/Cr	.08	-.16	-.10	.05	.19	-.07	.12	.20
GPC + PCh	-.48	-.26	.05	.52	.25	.17	.08	.24
GPC + PCh/Cr	-.13	-.07	.00	.19	.25	.05	-.18	-.06
NAA + NAAG	.23	.12	.35	-.38	.17	.17	.22	.30
NAA + NAAG/Cr	.28	.40	.15	-.19	.08	.05	.00	-.04
B: Right hippocampus								
Creatine (Cr)	.03	.02	**.55***	-.09	-.02	.03	-.28	-.22
myo-Inositol (mI)	**-.53***	**-.58***	.25	.19	.15	.17	.02	.02
mI/Cr	**-.53***	**-.72****	.20	.14	.06	.07	.26	.14
GPC + PCh	-.38	-.44	.50	.05	-.06	-.07	-.34	-.14
GPC + PCh/Cr	-.28	-.49	-.10	.09	-.15	-.34	-.04	.06
NAA + NAAG	.08	.02	.40	.14	.37	0.33	-.04	.06
NAA + NAAG/Cr	-.18	-.02	.00	.19	.31	0.23	.26	.12

* = significant at .05 ** = significant at .01

GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate; NAAG = N-acetyl-aspartyl-glutamate

For shift workers, there were no significant correlations between left hippocampal metabolites and performance on WMS-III subtests (see Table 3.18). Immediate recognition of faces (WMS-III Faces 1) showed a significant negative correlation with right hippocampal mI, $\tau = -.53$, p (two-tailed) $< .05$, and mI/Cr, $\tau = -.53$, p (two-tailed) $< .05$. Delayed recognition (WMS-III Faces 2) also showed a negative correlation with right hippocampal mI, $\tau = -.58$, p (two-tailed) $< .05$, and mI/Cr, $\tau = -.72$, p (two-tailed) $< .01$. Shift workers also showed a significant positive correlation between right hippocampal creatine and word list learning (WMS-III Word List 1), $\tau = .55$, p (two-tailed) $< .05$. There were no significant correlations for control participants between MRS and WMS-III variables.

Correlations between WAIS-III subtests and left and right hippocampal metabolite levels for shift workers can be found in Table 3.19. A significant negative correlation was found between overall Digit Span scaled score and left mI/Cr, τ = -.52, *p* (two-tailed) < .05, and a significant positive correlation was found between Block Design and right NAA+NAAG, τ = .53, *p* (two-tailed) < .05.

Table 3.19: Correlations (Kendall's *tau*) between left (panel A) and right (panel B) MRS and WAIS-III subtests for shift workers (n = 10)

	WAIS-III subtest scaled scores					
A: Left hippocampus	BDesign	Arithmetic	Vocabulary	DSpan F	DSpan B	DSpan
Creatine (Cr)	.24	-.44	-.12	.20	-.36	-.24
myo-Inositol (mI)	-.10	-.13	-.40	-.20	-.41	-.38
mI/Cr	-.24	.08	-.49	-.45	-.36	**-.52***
GPC + PCh	-.24	-.08	-.02	-.40	-.17	-.24
GPC + PCh/Cr	-.34	.13	.12	-.40	-.07	-.14
NAA + NAAG	.15	-.08	-.16	.00	-.36	-.33
NAA + NAAG/Cr	-.24	.49	-.12	-.30	-.17	-.28
B: Right hippocampus						
Creatine (Cr)	.48	-.13	.21	.10	-.31	-.14
myo-Inositol (mI)	.34	-.13	.16	.05	-.41	-.14
mI/Cr	.24	-.13	.02	.05	-.36	-.09
GPC + PCh	.34	-.23	.12	.10	-.50	-.19
GPC + PCh/Cr	-.24	-.18	-.21	-.05	-.12	-.14
NAA + NAAG	**.53***	.08	.44	.20	.07	.14
NAA + NAAG/Cr	.05	.03	.21	.10	.21	.24

* = significant at .05 ** = significant at .01

GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate; NAAG = N-acetyl-aspartyl-glutamate

BDesign = Block Design; DSpan F = Digit Span forwards raw score; DSpan B = Digit Span backwards raw score; DSpan = Digit Span.

Please note, with the exception of DSpan F and DSpan B, all WAIS-III analyses are based on scaled scores.

Control participants showed a significant positive correlation between Digit Span backward and the glycerophosphocholine/phosphocholine (GPC/PCh) ratio τ = .44, *p* (two-tailed) < .05 (see table 3.20).

Table 3.20: Correlations (Kendall's *tau*) between left (panel A) and right (panel B) MRS and WAIS-III subtests for control participants (n = 15)

	WAIS-III subtests					
A: L hippocampus	BDesign	Arithmetic	Vocabulary	DSpan F	DSpan B	DSpan
Creatine (Cr)	-.12	-.09	.01	-.37	.08	-.03
myo-Inositol (mI)	-.02	.01	-.05	-.18	.11	-.01
mI/Cr	.02	-.13	-.03	-.15	.18	.03
GPC + PCh	.08	-.01	-.05	-.39	.04	-.10
GPC + PCh/Cr	.32	.13	.15	.04	.06	.03
NAA + NAAG	-.10	-.09	-.25	-.37	-.08	-.27
NAA + NAAG/Cr	-.08	.05	-.09	-.06	-.11	-.10
B: R hippocampus						
Creatine (Cr)	.04	-.03	-.01	-.01	.39	.27
myo-Inositol (mI)	.08	-.07	-.11	-.13	.20	.10
mI/Cr	.04	-.03	-.07	-.04	.16	.10
GPC + PCh	.06	-.03	.05	.15	**.44***	.34
GPC + PCh/Cr	.10	.01	.21	.18	.21	.15
NAA + NAAG	.20	-.07	-.13	-.32	.06	-.06
NAA + NAAG/Cr	.20	.17	.09	-.15	-.20	-.13

* = significant at .05 ** = significant at .01

GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate; NAAG = N-acetyl-aspartyl-glutamate

BDesign = Block Design; DSpan F = Digit Span forwards raw score; DSpan B = Digit Span backwards raw score; DSpan = Digit Span.

Please note, with the exception of DSpan F and DSpan B, all WAIS-III analyses are based on scaled scores.

The correlation coefficients of the two groups for cognitive variables versus MRS variables were compared using the Fisher r-to-z transformation (see full r-to-z transformations in Appendix 6B). Shift workers and control participants did not differ in strength of association between cognitive variables and left hippocampal metabolites. Shift workers showed significantly stronger strength of association between right hippocampal mI/Cr and WMS-III Faces 2, $z = -2.07$, $p < .05$. There were no other significant differences between shift workers and control participants for correlations between right hippocampal metabolites and cognitive variables.

3.3.3. Cognitive performance and cortisol levels

Correlations between the cortisol levels and the Austin Maze and Test d2 for shift workers and control participants are shown in Table 3.21. Shift workers'

day shift cortisol level at 0300h was significantly correlated with time taken on the Austin Maze, $\tau = .57$, p (two-tailed) $< .05$. Errors on the Test d2 were negatively correlated with night shift cortisol levels at 0300h, $\tau = -.58$, p (two-tailed) $< .05$, with total cortisol over 24 hours including a night shift, $\tau = -.74$, p (two-tailed) $< .01$ and with mean cortisol over 24 hours including a night shift, $\tau = -.80$, p (two-tailed) $< .01$.

For control participants, cortisol levels at 0300h were negatively correlated with errors made on the Test d2, $\tau = -.38$, p (two-tailed) $< .05$.

Table 3.21: Correlations (Kendall's *tau*) between cortisol levels and Austin Maze & Test d2 for shift workers on day shift and night shift, and control participants on day shift

	Shift workers				Control participants			
	Austin Maze		test d2		Austin Maze		test d2	
Day shift	Time (s)	Errors	Correct	Errors	Time (s)	Errors	Correct	Errors
1500h	-.08	-.03	.07	-.12	-.22	-.07	.31	**-.38***
1900h	-.24	-.29	.09	.19	-.01	.13	-.07	-.09
2300h	-.03	.33	.39	.09	-.11	.05	.02	.04
0300h	**.57***	.33	.21	-.15	.10	-.07	.04	.05
0700h	.20	.25	-.13	-.14	-.12	.03	.14	.15
1100h	-.25	-.25	-.20	-.11	-.17	-.17	.05	.28
total dayshift	.11	.06	.11	-.39	-.16	-.04	.13	.10
mean dayshift	.11	.06	-.02	-.25	-.08	.05	.04	.11
Night Shift								
1500h	.33	-.06	-.09	-.46				
1900h	-.15	.15	.09	.28				
2300h	-.11	-.11	.27	.03				
0300h	.00	-.18	.45	**-.58***				
0700h	-.04	-.11	.04	-.38				
1100h	.44	.07	-.22	-.11				
total night shift	.03	-.03	.27	**-.74****				
mean night shift	.00	-.06	.38	**-.80****				

* = significant at .05

** = significant at .01

Note: : *n*s for both groups varied between cells; please see Appendices 6C & 6D for all *n*s

Shift workers showed a significant negative correlation between delayed word recall (WMS-III Word Lists 2) and cortisol level at 1100h on a day shift, $\tau = -.75$, p (two-tailed) $< .01$ (see Table 3.22). Control participants showed significant negative correlations between immediate recall of faces (WMS-III Faces 1) and cortisol at 1900h, $\tau = -.45$, p (two-tailed) $< .05$, and between initial word list learning (WMS-III Word Lists 1) and cortisol at 0300h, $\tau = -.40$, p (two-tailed) $< .05$. Their performance on WMS-III Word Lists 2 showed a

significant negative correlation with mean 24h cortisol on a dayshift, $\tau = -.43$, p (two-tailed) < .05.

Table 3.22: Correlations (Kendall's *tau*) between cortisol levels and WMS-III subtests for shift workers on day shift and night shift, and control participants on day shift

	Shift workers				Control participants			
	WMS-III Faces		WMS-III Word Lists		WMS-III Faces		WMS-III Word Lists	
Day shift	1	2	1	2	1	2	1	2
1500h	-.15	.05	.12	.46	-.22	-.05	.11	-.05
1900h	-.08	-.12	.03	-.28	**-.45***	-.04	-.10	.10
2300h	-.47	.03	.20	.19	-.31	-.23	-.11	-.30
0300h	27	-.03	-.13	-.29	-.04	-.18	**-.40***	-.33
0700h	.15	.12	-.02	-.34	-.17	-.06	-.01	-.32
1100h	-.15	-.29	.36	**-.75****	-.13	-.32	.11	-.11
total dayshift	.19	-.14	.15	-.26	-.27	-.10	-.03	-.34
mean dayshift	.24	.00	.10	-.41	-.28	-.17	-.12	**-.43***
Night Shift								
1500h	.22	-.07	.12	.05				
1900h	.20	.13	-.29	-.35				
2300h	.20	.09	-.03	-.23				
0300h	.20	.09	-.03	-.23				
0700h	-.37	-.11	.43	.47				
1100h	-.08	-.31	.08	-.04				
total night shift	.22	.07	.34	.10				
mean night shift	.19	-.09	.29	.07				

* = significant at .05

** = significant at .01

Note: *n*s for both groups varied between cells; please see Appendices 6C & 6D for all *n*s

There were no significant correlations between cortisol on either the day or night shift with any of the measures on the WAIS-III for shift workers (see Appendix 7 for correlation matrix). In contrast, for control participants there were significant positive correlations between cortisol levels at 1500h and Arithmetic, $\tau = .54$, p (two-tailed) < .01, Vocabulary $\tau = .47$, p (two-tailed) < .05, and Digit Span forward, $\tau = .45$, p (two-tailed) < .05. In addition there was a positive correlation between Vocabulary and cortisol at 1100h, $\tau = .42$, p (two-tailed) < .05 (see Table 3.23).

The correlation coefficients of the two groups for cognitive variables versus dayshift cortisol variables were compared using the Fisher r-to-z transformation (see Appendix 6C for all r-to-z transformations). Shift workers and control participants did not significantly differ in strength of association between any of the cognitive and dayshift cortisol variables.

Table 3.23: Correlations (Kendall's *tau*) between cortisol levels and WAIS-III subtests for control participants

	WAIS-III subtests (see Appendix 6C for *n*s for all cells)					
Day shift	BDesign	Arithmetic	Vocabulary	DSpan F	DSpan B	DSpan
1500h	.04	**.54****	**.47***	**.45***	-.05	.19
1900h	-.30	.06	-.17	.05	-.33	-.31
2300h	-.29	.05	.02	.35	-.01	.12
0300h	.01	-.11	.05	-.24	.04	-.10
0700h	.04	.25	.20	.38	.14	.31
1100h	.16	.10	**.42***	.08	.32	.29
total dayshift	.07	.20	.27	.34	.14	.29
mean dayshift	-.08	.07	.22	.38	.08	.23

* = significant at .05 ** = significant at .01

BDesign = Block Design; DSpan F = Digit Span forwards raw score; DSpan B = Digit Span backwards raw score; DSpan = Digit Span.

Please note, with the exception of DSpan F and DSpan B, all WAIS-III analyses are based on scaled scores.

Fisher's r-to-z transformations were also performed on the correlation coefficients for shift-workers day- and night-shift cortisol and cognitive variables. None of the night shift cortisol correlations with cognitive variables differed significantly with correlations between day shift cortisol and cognitive variables (see Appendix 6D for r-to-z transformations).

3.3.4. Cortisol levels and Profile of Mood States variables

Correlations between cortisol levels and the subscales of the Profile of Mood States (POMS) for shift workers on both day shift and night shift are shown in Table 3.24. Shift workers showed significant positive correlations between cortisol levels at 1900h on a day shift and scores on the Tension-Anxiety, τ = .58, p (two-tailed) < .05, and Depression-Dejection, τ = .66, p (two-tailed) < .05, subscales of the POMS. The Depression-Dejection subscale also showed a significant positive correlation with cortisol levels at 2300h, τ = .71, p (two-tailed) < .05, and a significant negative correlation with levels at 0700h, τ = -.62, p (two-tailed) < .05, on a night shift. Cortisol levels at 1900h on a night shift showed a significant positive correlation with Anger-Hostility, τ = .67, p (two-tailed) < .05. Total Score on the POMS showed a significant negative correlation with cortisol at 0700h on a night shift, τ = -.59, p (two-tailed) < .05.

Table 3.24: Correlations (Kendall's *tau*) between cortisol levels and Profile of Mood States subscales for shift workers

	Profile of Mood States						
Day shift	Total Score	Tension Anxiety	Depression Dejection	Anger Hostility	Fatigue	Confusion Bewilderment	Vigor
1500h	0.11	-0.09	0.03	0.40	0.29	0.29	-0.17
1900h	0.51	**0.58***	**0.66***	0.21	-0.09	0.24	-0.45
2300h	-0.24	-0.18	-0.19	-0.43	-0.30	-0.36	-0.06
0300h	-0.12	0.03	-0.06	-0.36	0.12	-0.30	0.03
0700h	0.23	0.14	0.09	0.17	0.40	0.34	-0.34
1100h	0.30	0.49	0.34	-0.11	-0.11	0.25	-0.52
total dayshift	0.20	0.29	0.24	0.14	0.37	0.31	-0.42
mean dayshift	0.20	0.29	0.24	0.14	0.37	0.31	-0.42
Night Shift							
1500h	-0.03	0.06	0.00	-0.08	0.31	0.14	-0.08
1900h	0.35	0.20	0.41	**0.67***	0.12	0.35	-0.20
2300h	0.54	0.58	**0.71***	0.42	0.38	0.38	-0.62
0300h	-0.31	-0.06	-0.13	-0.34	0.22	-0.31	0.15
0700h	**-0.59***	-0.37	**-0.62***	-0.37	-0.11	-0.22	0.00
1100h	-0.11	0.00	-0.15	-0.37	0.00	-0.15	-0.19
total night shift	-0.17	-0.03	-0.09	0.00	0.51	0.06	-0.06
mean night shift	-0.25	0.00	-0.12	0.03	0.37	0.08	-0.08

* = significant at .05 ** = significant at .01

Correlations between cortisol levels and the subscales of the POMS for control participants are shown in Table 3.25. Control participants showed a significant positive correlation between Total Score on the POMS and mean cortisol produced over a day shift, $\tau = .37$, p (two-tailed) $< .05$. Cortisol levels at 1100h showed a significant negative correlation with the POMS Vigor subscale, $\tau = -.51$, p (two-tailed) $< .01$.

Table 3.25: Correlations (Kendall's *tau*) between cortisol levels and Profile of Mood States subscales for control participants

	Profile of Mood States						
Day shift	Total Score	Tension Anxiety	Depression Dejection	Anger Hostility	Fatigue	Confusion Bewilderment	Vigor
1500h	-0.04	-0.12	-0.14	-0.06	-0.04	0.01	-0.04
1900h	0.14	0.19	0.19	-0.01	-0.02	0.08	0.18
2300h	0.22	-0.01	0.04	0.38	0.27	0.18	0.02
0300h	0.20	-0.09	0.25	0.06	0.29	0.09	-0.13
0700h	0.20	0.03	-0.08	0.05	0.23	0.23	-0.14
1100h	0.24	0.07	0.16	-0.02	0.19	0.13	**-0.51****
total dayshift	0.29	0.06	0.02	0.08	0.31	0.32	-0.24
mean dayshift	**0.37***	0.10	0.05	0.18	0.34	0.34	-0.25

* = significant at .05 ** = significant at .01

Fisher's r-to-z transformation was used to compare correlations coefficients between cortisol levels and POMS Total Score and subscales for both shift workers and control participants. There were no differences in strength of association between these variables between shift workers and control participants. Shift workers showed a trend towards greater strength of association between cortisol levels at 2300h on a dayshift and POMS Anger-Hostility subscales compared to controls, z = -1.74, p (two-tailed) = .08 (for all r-to-z transformations, see Appendix 6E).

3.3.5. Cortisol levels and volumetric MRI

Correlations between cortisol levels and T1-voloumetric MRI measures for shift workers and control participants are shown in Table 3.26. Shift workers' total intracranial volume was significantly correlated with cortisol levels at 2300h during a day shift, $\tau = .69$, p (two-tailed) $< .05$. Right hippocampal percentage of intracranial volume was significantly correlated with shift workers' night shift cortisol levels at 1500h, $\tau = .56$, p (two-tailed) $< .05$, and with total and mean 24 hour cortisol output over a night shift, $\tau = .59$ and .56 respectively, p (two-tailed) $< .05$. Control participants showed significant negative correlations between cortisol levels at 1900h and total volume of right and left temporal lobes, both $\tau = -.46$, p (two-tailed) $< .05$.

Table 3.26: Correlations (Kendall's *tau*) between cortisol levels and T1-volumetric MRI measures for shift workers on a day shift (panel A), on a night shift (panel B) and control participants on a day shift (panel C)

	Shift workers							
A: Day shift	1500h	1900h	2300h	0300h	0700h	1100h	24h total	24h mean
R hipp. TV	.37	-.30	.45	.15	.31	-.18	.22	.22
R hipp. % TIV	.48	-.35	-.15	.09	.48	.04	.44	.44
L hipp. TV	-.08	-.29	.15	.27	.31	-.25	.22	.22
L hipp. % TIV	-.31	-.41	-.45	.09	.25	.11	.17	.17
R temp. lobe TV	-.20	.12	.33	.15	.31	.11	.33	.33
R temp. lobe % TIV	-.25	.12	-.03	.03	.25	.18	.22	.22
L temp. lobe TV	.20	-.35	.33	-.39	.31	-.18	.00	.00
L temp. lobe % TIV	-.08	-.47	.03	-.45	.37	.11	.06	.06
TIV	.03	.00	**.69***	.15	-.03	-.33	-.11	-.11

B: Night shift	1500h	1900h	2300h	0300h	0700h	1100h	24h total	24h mean
R hipp. TV	.11	-.23	-.11	-.12	.25	.30	.14	.11
R hipp. % TIV	**.56***	-.31	-.11	.12	.47	.37	**.59***	**.56***
L hipp. TV	.00	.23	.11	-.30	-.25	.15	-.03	-.11
L hipp. % TIV	.39	-.15	-.34	-.18	-.04	.44	.03	-.06
R temp. lobe TV	-.22	.54	.42	.00	-.25	-.15	.08	.11
R temp. lobe % TIV	-.11	.46	.49	.37	-.18	-.37	.31	.44
L temp. lobe TV	-.44	.46	-.11	-.61	-.04	-.22	-.37	-.33
L temp. lobe % TIV	-.28	.23	-.34	-.43	.04	-.30	-.08	-.17
TIV	-.33	.15	.19	-.24	-.04	-.07	-.31	-.22
C: Day shift	Control participants							
R hipp. TV	-.08	-.27	.32	.16	.10	-.17	.06	.15
R hipp. % TIV	-.23	.00	.44	.22	-.02	-.21	-.03	.13
L hipp. TV	.00	-.22	.18	.04	.07	-.12	.14	.18
L hipp. % TIV	-.21	.00	.18	.22	-.07	-.14	.03	.12
R temp. lobe TV	.04	**-.46***	.04	-.34	-.03	-.02	-.19	-.07
R temp. lobe % TIV	-.17	-.24	-.08	-.26	-.20	-.09	-.34	-.22
L temp. lobe TV	.02	**-.46***	-.06	-.08	-.05	.17	.03	.03
L temp. lobe % TIV	-.19	-.32	-.10	-.10	-.14	.10	-.06	-.05
TIV	.17	-.11	.02	-.14	-.03	-.05	-.01	-.03

* = significant at .05 ** = significant at .01

L = left; R = right; hipp = hippocampus; TIV = total intracranial volume; TV = total volume; temp. lobe = temporal lobe

Note: *n*s for both groups varied between cells; please see Appendix 6F for all *n*s

Fisher's r-to-z transformation was used to compare correlations coefficients between cortisol levels and T1-volumetric MRI variables for both shift workers and control participants. Shift workers and control participants did not significantly differ in strength of association between any of the day-shift cortisol and MRI measures. For shift workers, correlation coefficients did not differ significantly when comparing day and night-shift cortisol correlations with MRI variables (for all r-to-z transformations, see Appendix 6F).

3.3.6. Cortisol levels and brain metabolites (MRS)

For shift workers (Table 3.27), cortisol levels at 1900h on a day shift were significantly correlated with left hippocampal mI/Cr, $\tau = -.59$, p (two-tailed) < .05. Left hippocampal mI/Cr was positively correlated with day shift cortisol at 0700h, $\tau = .54$, p (two-tailed) < .05. There was a significant correlation between night shift 1900h cortisol and left hippocampal GPC+PCh/Cr, $\tau = -.77$, p (two-

tailed) < .05. Cortisol at 1100h on a night shift was significantly correlated with left hippocampal GPC+PCh/Cr, τ = .82, *p* (two-tailed) < .01. There were no significant correlations between right hippocampal metabolite levels and cortisol on either the day or the night shift for shift workers (see Appendix 8 for correlation matrix).

Table 3.27: Correlations (Kendall's *tau*) between dayshift (panel A) and night shift (panel B) cortisol levels and left hippocampal MRS values for shift workers

	A: Day shift							
	1500h	1900h	2300h	0300h	0700h	1100h	24h total	24h mean
mI/Cr	-0.14	**-0.59***	0.03	-0.03	**0.54***	0.04	0.22	0.22
	B: Night shift							
GPC + PCh/Cr	0.50	**-0.77***	-0.26	0.06	0.33	**0.82****	0.08	-0.06

* = significant at .05 ** = significant at .01
mI = myo-Inositol; Cr = creatine; GPC = glycerophosphocholine; PCh = phosphocholine
Note: *n*s varied between cells; please see Appendix 6G for all *n*s

For control participants (Table 3.28), cortisol levels at 2300h were significantly correlated with left hippocampal Cr, τ = -.45, *p* (two-tailed) < .05, mI τ = -.52, *p* (two-tailed) < .05, GPC+PCh τ = -.75, *p* (two-tailed) < .01 and NAA+NAAG τ = -.49, *p* (two-tailed) < .05. Cortisol at 0700h was negatively correlated with left hippocampal mI/Cr, τ = -.42, *p* (two-tailed) < .05. Mean cortisol over 24 hours was negatively correlated with left hippocampal GPC+PCh, τ = -.43, *p* (two-tailed) < .05. Cortisol at 1900h was negatively correlated with left GPC+PCh, τ = -.55, *p* (two-tailed) < .05 and right hippocampal NAA+NAAG, τ = -.45, *p* (two-tailed) < .05. The complete correlation matrix can be found in Appendix 8.

Table 3.28: Correlations (Kendall's *tau*) between cortisol levels and left (panel A) and right (panel B) hippocampal MRS values for control participants

A: Left hippocampus	1500h	1900h	2300h	0300h	0700h	1100h	24h total	24h mean
Creatine (Cr)	-.03	-.03	**-.45***	-.18	-.03	.10	.02	-.20
myo-Inositol (mI)	-.01	-.06	**-.52***	-.14	-.24	.16	-.10	-.24
mI/Cr	-.10	.00	-.09	.00	**-.42***	-.06	-.23	-.22
GPC + PCh	-.12	**-.55***	**-.75****	.14	-.24	.04	-.19	**-.43***
GPC + PCh/Cr	.06	-.36	-.12	.25	-.13	-.02	-.11	-.20
NAA + NAAG	-.17	-.23	**-.49***	-.14	-.13	-.02	-.15	-.31
B: Right hippocampus								
NAA + NAAG	-.19	**-.45***	-.35	-.09	-.17	-.14	-.17	-.33

* = significant at .05 ** = significant at .01
mI = myo-Inositol; GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate; NAAG = N-acetyl-aspartyl-glutamate
Note: *n*s for both groups varied between cells; please see Appendix 6G for all *n*s

Correlations coefficients between cortisol levels and MRS brain metabolite variables for both shift workers and control participants were compared using Fisher's r-to-z transformation (see Table 3.29; Appendix 6G shows all r-to-z transformations). Shift workers and control participants differed significantly in strength of association between left hippocampal GPC+PCh and cortisol levels at 2300h during a day shift, $z = 2.87$, p (two-tailed) $< .001$. The difference between correlation coefficients for cortisol at 2300h on a day shift and left hippocampal creatine levels approached significance, $z = 1.77$, p (two-tailed) $> .05$. When comparing shift-workers' correlations between night shift and day shift, the difference between left GPC+PCh/Cr versus 1100h cortisol correlations approached significance, $z = 1.77$, p (two-tailed) $> .05$. There were no significant differences between correlations for the two groups for right hippocampal MRS versus cortisol variables, nor were there any significant differences between night shift and day shift cortisol correlations with MRS variables for shift workers.

Table 3.29: Significant and approaching significance Fisher's r-to-z-transformations for cortisol vs. left hippocampal brain metabolite spectra correlation coefficients for shift workers and control participants on a day shift (Panel A) and shift workers (SW) on a day shift and a night shift (panel B)

A.	Shift workers (n=9)		Control participants (n=14)			
	r	z	r	z	z-test	p
Left GPC+PCh						
cortisol 2300h	.45	0.48	-.75	-0.97	2.87	.00
Left Creatine						
cortisol 2300h	.39	-0.45	.41	-0.48	1.77	.08
B.	**SW Night shift (n=8)**		**SW Day shift (n=8)**			
Left GPC+PCh/Cr						
cortisol 1100h	.82	1.16	.04	0.04	1.77	.08

GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate

3.3.7. Volumetric MRI and brain metabolite (MRS) variables

Table 3.30 shows correlation coefficients for left hippocampal and temporal lobe T1-MRI measurements and left hippocampal brain metabolite (MRS) variables for shift workers and control participants. Shift workers showed a significant positive correlation between total volume of the left hippocampus

and left hippocampal mI, τ = .60, *p* (two-tailed) < .05. Control participants showed significant positive correlations between mI/Cr and total left hippocampal volume, τ = .39, *p* (two-tailed) < .05 and left hippocampal percentage of intracranial volume, τ = .45, *p* (two-tailed) < .05. They also showed significant negative correlations between NAA + NAAG/Cr and total left hippocampal volume, τ = -.41, *p* (two-tailed) < .05 and left hippocampal percentage of intracranial volume, τ = -.39, *p* (two-tailed) < .05.

Table 3.30: Correlations (Kendall's *tau*) between left hippocampal and temporal lobe volumes and left hippocampal MRS values for shift workers (panel A) and control participants (panel B)

	Shift workers (n = 10)			
A.	Left TL TV	Left TL % TIV	Left hipp. TV	Left hipp. % TIV
Creatine (Cr)	-.18	-.31	.33	.29
myo-Inositol (mI)	.22	.18	**.60***	.47
mI/Cr	.36	.40	.47	.42
GPC + PCh	.04	-.09	.33	.11
GPC + PCh/Cr	.09	.22	-.07	-.20
NAA + NAAG	.00	.04	-.02	.11
NAA + NAAG/Cr	.18	.22	-.29	-.16

	Control participants (n = 15)			
B.	Left TL TV	Left TL % TIV	Left hipp. TV	Left hipp. % TIV
Creatine (Cr)	-.18	.09	-.05	.28
myo-Inositol (mI)	.01	.09	.22	.31
mI/Cr	.18	.26	**.39***	**.45***
GPC + PCh	-.22	-.07	-.09	.09
GPC + PCh/Cr	.01	-.14	.07	-.14
NAA + NAAG	-.37	-.07	-.35	.01
NAA + NAAG/Cr	-.16	-.12	**-.41***	**-.39***

* = significant at .05 ** = significant at .01

GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate; NAAG = N-acetyl-aspartyl-glutamate

hipp = hippocampus; TL = temporal lobe; TV = total volume; TIV = total intracranial volume

For right hippocampal MRS and hippocampal and temporal lobe T1-MRI volumes (see Table 3.31), shift workers showed a significant positive correlation between right hippocampal percentage of total intracranial volume and Cr levels, τ = .64, *p* (two-tailed) < .01. They showed significant negative correlations between NAA + NAAG/Cr and total right hippocampal volume, τ = -.60, *p* (two-tailed) < .05 and right hippocampal percentage of intracranial volume, τ = -.51, *p* (two-tailed) < .05. Control participants showed significant negative correlations between total right temporal lobe volume and mI, τ = -.43,

p (two-tailed) < .05, and between right hippocampal percentage of total intracranial volume and mI/Cr, τ = -.41, *p* (two-tailed) < .05.

Table 3.31: Correlations (Kendall's *tau*) between right hippocampal and temporal lobe volumes and right hippocampal MRS values for shift workers and control participants

	Shift workers (n = 10)			
	Right TL TV	Right TL % TIV	Right hipp. TV	Right hipp. % TIV
Creatine (Cr)	-.27	-.22	.38	**.64****
myo-Inositol (mI)	-.13	-.27	.20	.29
mI/Cr	-.18	-.22	.07	.16
GPC + PCh	-.13	-.09	.07	.33
GPC + PCh/Cr	.13	.27	-.29	-.29
NAA + NAAG	-.09	.13	-.16	.11
NAA + NAAG/Cr	.09	.31	**-.60***	**-.51***
	Control participants (n = 15)			
	Right TL TV	Right TL % TIV	Right hipp. TV	Right hipp. % TIV
Creatine (Cr)	-.14	-.01	-.22	.16
myo-Inositol (mI)	**-.43***	-.33	-.09	.18
mI/Cr	-.35	**-.41***	-.01	.03
GPC + PCh	-.12	-.07	-.05	.14
GPC + PCh/Cr	.01	-.03	.05	-.20
NAA + NAAG	.03	-.03	.07	.37
NAA + NAAG/Cr	.31	.14	.31	.12

* = significant at .05 ** = significant at .01

GPC = glycerophosphocholine; PCh = phosphocholine; NAA = N-acetyl-aspartate; NAAG = N-acetyl-aspartyl-glutamate

hipp = hippocampus; TL = temporal lobe; TV = total volume; TIV = total intracranial volume

Fisher's r-to-z transformation was used to compare correlation coefficients between shift workers and control participants. Shift workers had a significantly stronger association than control participants between total volume of the right hippocampus and right NAA + NAAG/Cr, *z* = -2.13, *p* < .05. There were no other significant differences between shift workers and control participants for any T1-MRI versus MRS correlations (see Appendix 6H for full r-to-z transformations).

3.3.8. T2-relaxometric MRI and other variables

Kendall's *tau* correlation coefficient was used to examine the relationships between T2 MRI measures and other variables. Table 3.32 shows correlations between right and left hippocampal T2 measures and cognitive variables for both shift workers and control participants. Shift workers showed a strong positive correlation between right hippocampal T2 values and time taken on the Austin Maze, τ = .56, *p* (two-tailed) < .05. Significant negative correlations

were found between right hippocampal T2 and WMS-III Word List 1, τ = .-57, *p* (two-tailed) < .05, and WAIS-III Block Design, τ = .68, *p* (two-tailed) < .01. Left hippocampal T2 values had a significant negative correlation with WMS-III Word List 2, τ = .58, *p* (two-tailed) < .05. Control participants showed a significant positive correlation between left hippocampal T2 values and total errors on the d2 Test, τ = .46, *p* (two-tailed) < .05.

Fisher's r-to-z transformation was used to compare correlation coefficients between shift workers and control participants. The difference between shift workers' and control participants' correlation coefficients for WMS-III Word List 2 and left hippocampal T2 values approached significance, *z* = -1.79, *p* = .07. There were no significant differences between shift workers and control participants for any T2-MRI versus cognitive measures correlations (see Appendix 6I for full r-to-z transformations).

Table 3.32: Correlations (Kendall's *tau*) between right and left hippocampal T2 MRI values and cognitive measures for shift workers and control participants

	Right hippocampal T2		Left hippocampal T2	
	SW	C	SW	C
Austin Maze time	**0.56***	0.07	0.09	-0.30
Austin Maze errors	0.42	0.08	-0.13	-0.04
d2 Concentration	0.07	-0.38	-0.22	-0.18
d2 Total Errors	0.30	**0.46***	0.05	0.06
WMS-III Faces 1	0.28	-0.07	0.25	0.01
WMS-III Faces 2	0.40	-0.06	0.19	0.16
WMS-III Word list 1	**-0.57***	0.09	-0.18	0.07
WMS-III Word list 2	-0.09	0.27	**-0.58***	0.23
WAIS-III Vocab	-0.35	-0.14	-0.14	-0.10
WAIS-III BDesign	**-0.68****	-0.11	-0.46	0.09
WAIS-III Arithmetic	-0.03	-0.14	-0.26	0.12
WAIS-III DSpan F	-0.20	-0.17	0.20	0.07
WAIS-III DSpan B	0.12	0.11	0.14	-0.02
WAIS-III DSpan	-0.05	-0.07	0.17	0.02

* = significant at .05 ** = significant at .01

SW = shift workers, C = control participants

BDesign = Block Design; Vocab = Vocabulary; DSpan F = Digit Span forwards raw score; DSpan B = Digit Span backwards raw score; DSpan = Digit Span

Note: *n*s for both groups varied between cells; please see Appendix 6I for all *n*s

Table 3.33 shows correlations between right and left hippocampal T2 values and cortisol measures for both shift workers and control participants. There were no significant correlations between these variables for either shift workers or control participants. Analysis with Fisher's r-to-z transformation did not

reveal any significant differences in strength of association of these variables between shift workers and control participants (see Appendix 6J for full r-to-z transformations).

Table 3.33: Correlations (Kendall's *tau*) between right and left hippocampal T2 MRI values and cortisol levels for shift workers and control participants

	Right hippocampal T2		Left hippocampal T2	
Day shift	SW	C	SW	C
1500h	-0.03	-0.16	0.00	0.04
1900h	0.18	0.18	0.54	0.21
2300h	0.09	-0.15	-0.18	-0.20
0300h	0.27	-0.24	0.18	-0.31
0700h	0.03	0.12	0.06	-0.06
1100h	-0.25	0.09	0.22	-0.13
total dayshift	0.06	0.03	0.25	-0.01
mean dayshift	0.06	0.00	0.25	-0.15
Night shift				
1500h	0.06	-	0.20	-
1900h	0.15	-	-0.08	-
2300h	0.34	-	0.42	-
0300h	-0.18	-	0.03	-
0700h	-0.33	-	-0.33	-
1100h	0.15	-	0.11	-
total night shift	-0.20	-	-0.06	-
mean night shift	-0.28	-	-0.14	-

* = significant at .05 ** = significant at .01
SW = shift workers, C = control participants

Note: *n*s for both groups varied between cells; please see Appendix 6J for all *n*s

3.3.9. MR and Profile of Mood States variables

Table 3.34 shows correlations between MRI volumetric and relaxometry variables and POMS Total Score and subscale scores for both shift workers and control participants. For shift workers there were no significant correlations between these variables. Control participants showed a significant positive correlation between the POMS Vigor subscale and right hippocampal T2 relaxation times, $\tau = .39$, p (two-tailed) $< .05$.

Analysis with Fisher's r-to-z transformation did not reveal any significant differences in strength of association between POMS and MR variables between shift workers and control participants. There was a trend towards a significant difference when comparing the shift workers' and control participants' correlations between POMS Depression-Dejection subscale and

the total volume of the right temporal lobe, z = 1.71, p (two-tailed) = .09 (see Appendix 6K for full r-to-z transformations).

Table 3.34: Correlations (Kendall's *tau*) between brain volumes, right and left hippocampal T2 MRI values and POMS Total Score and subscales for shift workers and control participants

	Profile of Mood States						
Shift workers	Total Score	Tension Anxiety	Depression Dejection	Anger Hostility	Fatigue	Confusion Bewilderment	Vigor
R hipp. TV	-0.30	-0.23	-0.29	-0.20	-0.02	-0.32	0.05
R hipp. % TIV	-0.20	-0.14	-0.29	-0.07	0.20	0.00	0.00
L hipp. TV	-0.16	-0.18	-0.19	-0.02	0.20	-0.28	0.09
L hipp. % TIV	-0.16	-0.14	-0.24	-0.16	-0.16	0.00	0.14
R temp. lobe TV	0.31	0.34	0.41	0.18	0.40	0.07	-0.30
L temp. lobe TV	0.13	-0.16	-0.02	0.31	0.04	0.25	-0.07
L temp. lobe % TIV	0.04	-0.20	-0.12	0.22	0.04	0.30	0.07
TIV	-0.07	-0.09	-0.05	-0.16	0.02	-0.32	0.05
ROI T2 R hipp	0.22	0.11	0.26	0.00	0.13	-0.07	-0.07
ROI T2 L hipp	0.34	0.48	0.36	-0.02	-0.02	0.09	-0.32
Control participants							
R hipp. TV	0.21	0.04	0.03	0.31	-0.03	0.16	-0.09
R hipp. % TIV	0.28	0.19	0.17	0.27	0.03	0.23	-0.14
L hipp. TV	0.11	-0.13	-0.05	0.22	0.07	0.20	0.00
L hipp. % TIV	0.19	-0.01	0.17	0.12	0.21	0.37	0.03
R temp. lobe TV	-0.14	0.04	-0.35	-0.03	-0.21	-0.23	-0.14
R temp. lobe % TIV	-0.21	0.11	-0.14	-0.26	-0.16	-0.23	0.10
L temp. lobe TV	-0.04	-0.03	-0.21	-0.14	0.07	-0.04	-0.22
L temp. lobe % TIV	-0.09	0.08	-0.07	-0.27	0.12	0.01	-0.09
TIV	0.06	0.04	-0.07	0.07	-0.14	-0.15	-0.14
ROI T2 R hipp	-0.07	0.25	-0.13	-0.28	-0.15	-0.29	-0.10
ROI T2 L hipp	-0.22	-0.25	-0.17	-0.28	0.03	-0.09	**0.39***

* = significant at .05 ** = significant at .01

L = left; R = right; hipp = hippocampus; temp. lobe = temporal lobe; TIV = total intracranial volume; TV = total volume; ROI = region of interest

DISCUSSION

Stress, regardless of its source, provokes a number of endocrine responses in the body, particularly affecting the hypothalamic-pituitary-adrenal (HPA) axis. Acute activation of the HPA axis induces an immediate, adaptive increase in cortisol production that primes the sympathetic nervous system in order to deal with the stressor. Prolonged activation leads to chronic dysregulation of the HPA axis. Constant sleep disruption, like that experienced by long-term rotating shift workers, particularly those who have inadequate recovery time between shifts, is a physiological stressor. Research by Cho and colleagues (2001; 2000) reported that air crew with inadequate recovery time between outbound, transmeridian long-haul flights showed performance decrements on cognitive tasks, reduced hippocampal volumes and increased cortisol levels.

The current study attempted to extend these findings by exploring the effects of sleep disruption caused by work schedule in a group of rotating shift-workers (nurses), to determine whether the effects reported by Cho and colleagues (2001; 2000) occurred in shift-workers from other occupations, or whether they were specific to the flight industry. Overall, few significant differences were found between the two groups of workers studied.

An unfortunate consequence of the difficulty in recruiting participants for this study was the difference in ages between the shift workers and control participants. However, given the effects of age on many of the variables studied, particularly the MR measures, it is surprising that so few differences were found between the groups. One might expect that the combination of older average age and shift-work would be more likely to result in significant differences. There are a number of possible explanations for the absence of differences, despite the significant age discrepancy between the groups. It is possible that the rotating shift workers in the current study were a group of adapters who could cope well with the circadian disruption inherent in their work schedule. Hennig and colleagues (1998) reported a subgroup of night workers whose cortisol rhythms did not display the expected reversal following five consecutive night shifts; the shift workers in the current study overall

displayed a phase advance of cortisol during the night shift, suggesting that they are able to adapt. Possibly due to this adaptation to circadian disruption, they did not display the adverse effects reported by Cho and colleagues (2001; 2000).

Although Cho (2001) attempted to control for the low level hypoxia inherent in an aircraft work environment by matching short recovery time/long haul flight and long recovery time/short haul aircrew for total flight time, there are a number of other factors that may have contributed to the differences found between the groups. It is possible that controlling for total flight time is not enough. A long haul flight may be more damaging and aircrew may incur greater hypoxia than they would if undertaking numerous short hops with the same total time in the air. Evidence from obstructive sleep apnoea (OSA) studies suggest that more severe OSA with greater hypoxia is associated with increased MR abnormalities and cognitive impairment (Alchanatis et al., 2004; Bartlett et al., 2004). The deficits seen in long haul aircrew in Cho and colleagues' studies may have been due to the combined effects of chronic low level hypoxia, sleep disruption and increased cortisol, rather than only increased cortisol due to circadian and sleep disruption.

The following discussion addresses the results of the current study with specific reference to previous research and the hypotheses investigated. The results of group comparisons and correlations within groups will be discussed initially. The impact of using Fisher's r-to-z transformation to compare the two groups' correlations will then be discussed with reference to the work of Cho and colleagues (2001; 2000).

4.1. Cognitive performance

Previous research has demonstrated that rotating shift workers and other workers who experience sleep disruption or deprivation show measurable cognitive deficits (Cho et al., 2000; Harrison & Horne, 2000; Meijman et al., 1993). In the current study it was hypothesised that long-term, rotating, shift workers would show poorer performance on measures of attention and memory than control day working participants.

The current study did not reveal significant differences between shift workers' and control participants' performance on the cognitive measures administered. However, there were some differences that approached significance and had medium effect sizes. Shift workers made relatively more errors than control participants on the Austin Maze, a measure of visual-spatial ability and procedural and visual memory (Crowe et al., 1999). This is consistent with the work of Meijman and colleagues (1993), who reported greater errors on a delayed-match-to-sample task in night workers compared to day workers. Although the difference was not significant, shift workers in the current study made relatively more errors on the test d2, consistent with the poorer performance on a letter cancellation task by long-term shift workers reported by Rouch et al. (2005).

Shift workers in the current study took relatively longer to complete 10 trials on the Austin Maze. This is consistent with previous research reporting reduced work rates and longer task completion times in sleep deprived participants (Blagrove et al., 1995; Chmiel et al., 1995), reinforcing the potential effects of fatigue in the performance of shift workers. In addition, shift workers in the current study showed relatively poorer performance on all WAIS-III Digit span measures (tests of short term auditory attention and auditory-verbal working memory), with medium effect sizes seen for Digits Back and the overall scaled score. This is consistent with the performance of long-haul air crew with short recovery times between outbound flights reported by Cho (2001), who showed performance decrements on delayed-match-to-sample tasks measuring visual-spatial memory and working memory abilities.

The non-significant differences seen in the current study may be due to test choice, rather than a true absence of difference between the groups. The clinical tests utilised in the current study may not be sensitive enough (compared to the experimental measures used by Cho and colleagues) to detect the subtle deficits experienced by the shift workers. However, the absence of significant differences when using clinical tests is important too. Clinical measures are the tests that will be administered to the few shift workers who do report cognitive difficulties and who are seen by a clinical neuropsychologist. Testing with these

instruments may not reveal clinically significant changes in functioning when performance is compared to normative data. Despite such results, subtle but functionally important deficits may still be present, but may be overlooked. Workers' concerns about cognitive difficulties may be disregarded or minimised.

4.2. Cortisol levels

Changes to the circadian rhythmicity of cortisol production due to sleep disruption and shift work is widely reported within the literature, although there is some inconsistency in the findings (Lac & Chamoux, 2004; Spiegel et al., 1999; Weibel et al., 1996). In the current study it was hypothesised that shift workers would show cortisol rhythm disruptions compared to control day working participants. In addition, it was hypothesised that shift workers' cortisol rhythm on a day shift would differ from that observed on a night shift.

When comparing the overall cortisol rhythm of shift workers on day shift with that of control participants, shift workers showed an advance of termination of the quiescent period, with higher cortisol than day workers at 0300h. This alteration to rhythm profile is consistent with that reported by Weibel and colleagues (1996) in a study of male fulltime night workers. However, the magnitude of the advance was somewhat smaller. This is likely to be due to the shorter run of night shifts (in the context of a rotating shift system) that the shift workers in the current study completed, suggesting a dose-dependent relationship between number of nights worked and phase shift.

Shift workers on a day shift did not have significantly higher overall cortisol levels over 24 hours compared to the control participants, a finding that supports some previous studies examining night shift workers (Touitou et al., 1990; Weibel et al., 1996). This finding is inconsistent with that of Cho et al. (2000) who showed that female flight attendants on weekly transmeridian flights had significantly higher total cortisol output over 24 hours than airport ground crew. The difference between Cho's two groups, and between Cho's flight attendants and the shift workers in the current study, may be due to the

acute effects of flight (a physiological stressor) rather than jet lag associated with frequent transmeridian flight.

Shift workers' cortisol levels on a night shift did not differ overall from those of control participants on a day shift. However, there appeared to be some attenuation of the rhythm overall, and there was an atypical peak at 1900h with a large effect size compared to control participants. The flattening of the rhythm is consistent with the observations of Lac and Chamoux (2004). Their fast rotating group showed a non-significant flattening of the rhythm compared to controls, as well as a lower acrophase. The amplitude of the shift workers' cortisol rhythm on night shift in the current study was also lower on average than that of the control participants.

In the current study, shift workers' total 24-hour cortisol levels were higher during a day shift compared to during a night shift, and were similar to the results reported by Zuzewicz and colleagues (2000) in their study of air traffic controllers. Overall the cortisol rhythm of shift workers on the night shift in the current study was flattened, with an attenuated acrophase compared to the rhythm seen for shift workers on a day shift. As described above, these findings are consistent with previous research that has reported flattening of the cortisol rhythm during a night shift (Lac & Chamoux, 2004). These between- and within-subject comparisons show that the shift workers' circadian cortisol rhythmicity is dysregulated compared to day working control participants, and more so on a night shift compared to a day shift.

The effect of shift work on cortisol production over the normal quiescent period (2300h – 0300h) was also investigated in the current study. Shift workers' cortisol levels during the quiescent period on either a day shift or a night shift did not differ significantly from those of the control participants. This is in contrast to previous research by Touitou and colleagues (1990) who reported higher overall cortisol levels during the normal quiescent period, but lower overall rhythm amplitude following night shifts when comparing night workers with controls. When comparing shift workers' quiescent period cortisol between day shift and night shift, a larger difference with a medium effect size was found. On average shift workers' quiescent period cortisol levels were

higher during a day shift, due to the advance of the end of quiescent period (0300h). Although this result does not fit neatly with specific previous research, it does fit with the broader findings of cortisol rhythm dysregulation following long-term shift work reported in the literature (Lac & Chamoux, 2004; Touitou et al., 1990; Weibel et al., 1996).

4.3. Magnetic resonance imaging and spectroscopy

There is little research that investigates the effects of shift work or sleep disruption on the volume and function of particular brain regions (Cho, 2001; Cho et al., 2000), and as such hypotheses in the current study were driven mainly by theoretical considerations about the potency of sleep disruption as an HPA axis stressor and consequent effects on the brain.

In terms of brain volumes, it was hypothesised that shift workers, due to increased levels of cortisol, would have smaller temporal lobe and hippocampal volumes than control participants. This was not the case; there were no significant differences between shift workers' and control participants' hippocampal, temporal lobe or total intracranial volumes. Nor were there any differences between the volumes of left and right structures for either of the groups. This is not consistent with the findings of Cho (2001), who reported significantly smaller right temporal lobes in a group of flight attendants with short recovery times between outbound transmeridian flights compared to flight attendants who enjoyed longer recovery periods.

MR relaxometry and spectroscopy (MRS) were also utilised in the current study. These methods provide information about cellular integrity and neuronal density, which can be affected prior to the appearance of structural changes measurable with volumetric imaging. Consistent with the hypothesis for volumetric changes outlined above, it was hypothesised that shift workers would show signs of reduced neuronal density and cellular integrity on MR relaxometry and spectroscopy when compared with control participants. This hypothesis was not supported for differences in brain metabolites measured by MRS. There were no significant differences between shift workers and controls

for any of the individual metabolites or metabolite ratios reported, and effect sizes were small.

For the hippocampal T2 relaxometry region-of-interest (ROI) measures, it was also hypothesised that shift workers would show increased relaxation times compared to control participants. This hypothesis was not supported. In fact, shift workers showed significantly lower right hippocampal T2 relaxation times compared to control participants. It is possible that this finding is due to the significant age difference between the two groups. T2 relaxation times are known to reduce with increased age in adulthood (Suzuki et al., 2006), so it is possible that this significant difference, in the opposite direction to that hypothesised, represents an age effect. Due to the statistical constraints in the current study, it is difficult to fractionate out the effects of age from the effects of work schedule and cortisol rhythm disruptions on T2 relaxation times.

The absence of differences in the current study compared to the results of Cho and colleagues (2001; 2000) may be due to the different participant groups used. Cho's samples of women were younger (aged 22 to 28) and had worked in the industry only up to five years. The shift work participants in the current study were significantly older and had worked in their current shifts for longer periods of time. They may represent that self-selected group of workers who cope well with shift work and sleep disruption, whereas Cho's participants were essentially "early-career" flight attendants. The group may have included a high proportion of poor adapters (Hennig et al., 1998) who had not yet self-selected out of the industry.

4.4. Relationships between variables

4.4.1. Cognitive performance and MR imaging

Based on the work of Cho and colleagues (2001; 2000), as well as the more extensive research literature examining the relationship between brain atrophy and cognitive dysfunction, it was hypothesised that brain volumes would be positively associated with performance on the cognitive tasks administered. That is, larger brain volumes would be associated with better task performance,

and lower volumes with poorer task performance. This was indeed the case for the control participants on some of the cognitive measures. Larger total intracranial volumes were associated with faster and more accurate performance on the Austin Maze. Larger right temporal lobes were associated with faster times on the Austin Maze and better performance on digits backwards and total WAIS-III Digit Span scores. Better digit span performance was also associated with bigger right temporal lobes. Large left hippocampal volumes were positively correlated with faster and more accurate Austin Maze performance, and larger right hippocampal volumes were associated with more items correct on the d2 task. There were no significant positive correlations between hippocampal volumes and performance on the memory tasks. Theoretically, a relationship between these variables is more likely given the pre-eminent role of the hippocampus in explicit memory encoding (Cohen et al., 1999; Deweer, Pillon, Pochon, & Dubois, 2001).

In contrast, shift workers showed a number of negative correlations between task performance and brain volumes. The correlations for the Austin Maze in particular were in the opposite directions to those found for the control participants. Total intracranial volume and both left and right hippocampal volumes were associated with greater errors on the Austin Maze. Hippocampal volumes were also associated with longer time taken to complete 10 trials of the Austin Maze. This suggests that the shift workers were not able to adequately recruit structures that were nonetheless intact (when compared to the control participants) in order to complete the Austin Maze.

It is difficult to say that the shift workers' relatively reduced performance on the Austin Maze, compared to control participants, was due to poorer hippocampal function. Nor is it possible to attribute it to reduced visual-memory ability only. Austin Maze performance clearly has a visual memory component in later trials, but mainly calls upon visual spatial abilities in early trials (Crowe et al., 1999). As with all complex cognitive tasks, the availability of attentional resources also impacts upon performance. Attentional abilities tend to be affected by fatigue (Frey et al., 2004), so it is possible that the shift workers' poor performance on the Austin Maze and WAIS-III Digit Span

represents the effects of fatigue on attention rather than true deficits in memory functioning. Shift workers reported significantly fewer hours of sleep on average, and higher levels of fatigue and lower levels of vigour on the POMS. Fatigue also tends to affect motivation and effort (Blagrove et al., 1995; Chmiel et al., 1995). The Austin Maze is a challenging and frustrating task even when one is not fatigued, so it would not be surprising if effort and motivation to complete it were reduced with increased fatigue and tiredness.

Increased T2 relaxation times are associated with a reduction in neuronal cell density and increased gliosis (Jackson & Connelly, 1999). In the current study it was hypothesised that increased hippocampal T2 signal would be associated with reduced cognitive performances. This hypothesis was partially supported for both shift workers and controls participants. For controls, increased left hippocampal T2 signal was associated with increased errors on the test d2. For shift workers, increased right hippocampal T2 signal was associated with longer time taken on the Austin Maze and poorer performance on the WAIS-III Block Design task and WMS-III Word List initial learning. With the exception of the finding for the list learning task, these results were consistent with theoretical assumptions and imaging findings about the role of the right hemisphere in visually based cognitive skills such as visual-spatial memory (as measured by the Austin Maze) and visuo-spatial and visuo-constructional intellectual abilities (as measured by WAIS-III Block Design). Shift workers' increased left hippocampal T2 signal was associated with poorer delayed recall of a word list (WMS-III Word List 2). This finding is also consistent with the role of the left hemisphere in language processing and the left hippocampus in particular in auditory-verbal learning and memory.

4.4.2. Cognitive performance and MR spectroscopy

Alterations in brain metabolite levels as measured by magnetic resonance spectroscopy have been linked to measurable changes in brain structure. Such alterations can also occur as precursors to structural change (Woermann et al., 1999), and have been linked to reductions in cognitive performance (Ross & Sachdev, 2004). It was hypothesised in the current study that changes in brain

metabolites, such as reductions in N-acetyl-aspartate (NAA; a marker of neuronal density or viability) or increases in choline (Cho; indicative of a breakdown in cell membrane integrity) or myo-inositol (mI; indicative of gliosis) as absolute concentrations or as ratios over creatine (Cr), would be associated with reduced cognitive performance.

There was some support for this hypothesis. For shift workers, a higher left hippocampal mI/Cr ratio was associated with more errors on the Austin Maze. Higher right hippocampal mI and mI/Cr levels were associated with poorer performance on both initial and delayed recognition of faces on the WMS-III. A higher left mI/Cr ratio was associated with poorer short-term auditory attention and working memory (overall WAIS-III Digit Span scaled score). Lower right NAA+NAAG levels were associated with poorer performance on the WAIS-III Block Design subtest, a measure of visuo-spatial and visuo-constructional abilities. As with the findings for correlations between cognitive performance and MR volumetrics and relaxometry, these results are consistent with the known functional delineations between left and right hemispheres. Higher right mI and lower right NAA+NAAG were associated with poorer performance on tasks related to right hemisphere functions such as face recognition and visuo-constructional ability. Higher left mI was associated with poorer auditory-verbal working memory, a left hemisphere-mediated skill. These results are also consistent with the findings of Brown and colleagues (2004) who reported decreased NAA ratios associated with poorer cognitive performance in participants undergoing treatment with corticosteroids for a variety of different illnesses.

In contrast, control participants showed fewer and less consistent associations between MRS values and cognitive performance. For controls, higher levels of left hippocampal NAA+NAAG were associated with longer time taken on the Austin Maze (a test of visuo-spatial memory), but increased right hippocampal ratios of NAA+NAAG/Cr were associated with more accurate performance on a measure of visual attention (test d2).

It is possible that the differences between the two groups in terms of relationships between MRS and cognitive performance are related to both sleep

reduction and the significant age difference between the shift workers and control participants. Previous work by Urrila and colleagues (2004) found that sleep-deprivation related MRS changes were associated with poorer performance on a word generation task in older participants only. It is difficult to comment on the relative effects of sleep disruption and age in the current study, as the shift workers were both older and had less sleep than the control participants.

4.4.3. Cognitive performance and cortisol levels

Increases in cortisol caused by the exogenous administration of glucocorticoids, either experimentally or therapeutically, have been shown to cause measurable declines in cognitive performance (de Quervain et al., 2000; Keenan et al., 1995; Kuhlmann et al., 2005; Quarton et al., 1955). Endogenous disruptions to the HPA axis such as in Cushing's Disease, depression and PTSD have also been associated with cognitive deficits (Belanoff, Kalehzan et al., 2001; Forget et al., 2000; Yehuda, 2001). In the current study it was hypothesised that higher levels of salivary cortisol would be associated with poorer performance on the cognitive tasks administered.

For shift workers, this hypothesis was partly supported. Increased cortisol levels at some points over a day shift were associated with reduced performance on some memory tasks. Higher cortisol levels at 0300h on a day shift were associated with longer time taken on the Austin Maze. Higher cortisol levels at 1100h on a day shift were associated with poorer delayed recall of a word list (WMS-III Word List 2). In contrast, increased cortisol levels over a night shift were associated with improved performance on a task of visual attention and concentration. Higher night shift 0300h cortisol levels were associated with fewer errors on the test d2. Total cortisol levels over the 24-hours containing a night shift were also associated with better test d2 performance. It is possible that shift workers have adapted or habituated to the continued disruption to the cortisol rhythm caused by their work schedule, and are no longer as sensitive to the effects of heightened cortisol. This is consistent with the findings of Brown

and colleagues (2006), who reported a lesser reduction in cognitive performance following repeat administration of prednisolone.

For control participants, higher cortisol levels were associated with better performance on a number of cognitive tasks. Higher cortisol levels at 0300h were associated with fewer errors on the test d2. Higher cortisol levels at 1500h were associated with better WAIS-III Vocabulary, Arithmetic and Digit Span forward performance. Better Digit Span forward performance was also associated with higher cortisol levels at 1100h.

Given that the cognitive tasks were not performed during the shift cycle in which cortisol was collected, it is difficult to directly attribute cognitive performance to cortisol levels. It is particularly difficult to do this for levels at particular time points. However, assuming that the shift cycles sampled were representative of participants' normal working conditions and therefore normal levels of cortisol, some speculative interpretations can be offered. For shift workers, increased cortisol levels over a day shift were associated with reduced performance on a visual memory task and an auditory-verbal memory task. Increased cortisol levels over a night shift were associated with better performance on a visual attention/concentration task. It is possible that for shift workers, increases in cortisol are able to raise arousal levels enough to aid initial attention and concentration. An increase in arousal that raises vigilance and attention may be detrimental to later consolidation and recall of information, as seen in the shift workers' reductions in memory performance associated with increased cortisol.

Control participants, in contrast, were better able to utilise the increased arousal levels afforded by increases in cortisol, possibly because they were not subjected to the same levels of fatigue seen in shift workers.

4.4.4. Cortisol levels and MR imaging and spectroscopy

Previous research on Cushing's Disease and post-traumatic stress disorder (PTSD) has suggested that disease-associated increases in cortisol are related to decreased hippocampal volumes as measured by MRI (Bremner et al., 1997;

Starkman et al., 1999). Long-term therapeutic use of prednisolone, a medicinal corticosteroid, has also been associated with reduced hippocampal volume (E. S. Brown et al., 2004). It was therefore hypothesised in the current study that increased cortisol levels in both shift workers and controls would be associated with reductions in hippocampal and temporal lobe volumes and increased hippocampal T2 relaxation times.

This hypothesis was not supported for shift workers. Despite the presence of a chronic stressor (shift work schedule), shift workers did not show negative associations between cortisol and brain volumes. High day shift cortisol at 2300h was associated with larger total intracranial volume. Larger right hippocampal percentages of total intracranial volume were associated with higher night shift cortisol levels at 1500h, and higher total 24-hour cortisol levels over a night shift. These results are not consistent with previous research showing reduced brain volumes and increased cortisol in participants with PTSD (Bremner et al., 1995; Bremner et al., 1997; Stein et al., 1997) and Cushing's syndrome (Starkman et al., 1999; Starkman et al., 2003).

For control participants, higher cortisol levels at 1900h were associated with smaller left and right total temporal lobe volumes. Neither the shift workers nor the controls showed any significant associations between cortisol levels and T2 relaxation times.

Reduced NAA levels have been reported in association with long-term therapeutic use of prednisolone (E. S. Brown et al., 2004). Higher cortisol levels in the current study were hypothesised to be associated with decreased levels of NAA-group metabolites and increased levels of choline-group metabolites and myo-Inositol. This hypothesis was not supported for shift workers. Higher left hippocampal mI/Cr was associated with lower levels of cortisol at 1500h and higher cortisol at 0700h during a day shift. Higher levels of left hippocampal GPC+PCh/Cr were associated with lower cortisol at 1900h and higher cortisol at 1100h on a night shift. For control participants, higher cortisol levels at 2300h and 1900h were associated with lower levels of left and right hippocampal NAA+NAAG respectively, in support of the hypothesis.

However, higher cortisol at a variety of different times was also associated with lower levels of mI and GPC+PCh.

Neylan et al., (2003) suggested that in a PTSD-disordered HPA axis, abnormal levels of hippocampal metabolites (such as reduced NAA or increased Cho or mI) are associated with normal range cortisol levels, which nonetheless cause dysregulation of the HPA axis. This may be due to the increased numbers of glucocorticoid receptors proposed to exist in those predisposed to PTSD (Yehuda, 2001). Increased numbers of glucocorticoid receptors may predispose people to a variety of adverse effects related to overstimulation by cortisol, such as poor adaptation to shift work schedules resulting in a shift-lag syndrome. It is possible that once again an overrepresentation of good shift work adapters in the current shift work group masked any adverse effects incurred by potential poor adapters within the group.

4.4.5. MR imaging and spectroscopy

Research in temporal lobe epilepsy suggests that changes in MRS brain metabolite spectra, such as reductions in NAA-group metabolites, are associated with neuronal loss that is measurable with volumetric MRI and T2 relaxometry (Namer et al., 1999). It has also been shown that brain metabolite changes measured with MR are detectable as precursors to clinically significant reductions hippocampal volumes (Woermann et al., 1999). It was therefore hypothesised that volumetric MRI and T2 relaxometry would be negatively correlated with brain metabolite spectra in the current study. That is, reductions in brain volumes and increased T2 signal would be associated with decreased levels of NAA group metabolites and increases in Cho-group metabolites and myo-Inositol.

For shift workers, higher levels of left hippocampal mI were associated with larger total left hippocampal volumes, giving support to the hypothesis. However, higher ratios of right hippocampal NAA+NAAG/Cr were associated with smaller right hippocampal volumes, which is inconsistent with the presumed relationship between heightened NAA and neuronal density and

integrity (Ross & Sachdev, 2004). Control participants showed inconsistent relationships between brain metabolites and size of structures. The absence of significant group differences in MRS as well as inconsistent correlations between MRS and volumetric MRI suggest that unlike the results reported by Schuff et al., (2001) and Neylan et al., (2003) in participants with combat-related PTSD, there are no MRS changes that are indicative of as yet non-measurable volumetric brain changes in the shift work group.

4.5. Strengths and limitations of the current study

A strength of the current study was its utilisation of clinical measures of cognitive function. Most previous studies investigating the effects of shift schedules and work-related sleep disruption on performance have tended utilise subjective measures of fatigue and alertness or measures of reduced work rates and increased work errors. Cho and colleagues (Cho, 2001; Cho et al., 2000) used computerised delayed-match-to-sample and visual spatial memory tasks. Although such tasks are appropriate for research in this area, it is difficult to extrapolate the results to a clinical population or compare them to performance on clinical tasks such as the ones used in the current study. The use of clinical measures makes the current study more useful in terms of the applicability of the results to a clinical setting, The WAIS-III, WMS-III and other psychometrically sound measures that have been normed and validated on the general population are those that will be administered to shift workers who report cognitive deficits. The current study provides some indication of how rotating shift workers are likely to perform on tests that are used in clinical neuropsychological practice.

Although the current study was limited in its statistical power, a strength of the current approach was the use of statistical measures to compare correlations between groups. Initial correlational analysis revealed a number of significant within-group correlations, as discussed in the previous sections. However, comparing correlations between groups using Fisher's r-to-z transformation resulted in the disappearance of many of these effects, showing that they were not true group differences. This is another factor which differentiates the

current study from the work of Cho and colleagues (Cho, 2001; Cho et al., 2000), who did not report Fisher's r-to-z transformation. Analysis of Cho et al's (2000) data using this statistic reveals that although cabin crew showed a significant correlation (r = -.78, p < .05) between cortisol and cognitive performance compared the ground crew (r = -.43, p > .1), there was not a significant difference in strength of association between the two groups, z = -1.10, p (two-tailed) = .27. It appears that the correlations between cortisol and cognition for cabin crew and ground crew reported by Cho et al. are not significantly different. Therefore, the differences in cognitive performance between the ground crew and cabin crew with longer service cannot be attributed solely to elevated cortisol. In contrast, the difference between cortisol levels and right temporal lobe volume correlations for short recovery and long recovery air crew reported in Cho (2001) survive Fisher's r-to-z-transformation.

The current study was limited statistically due to the difficulty accessing suitable participants and subsequently the low number of shift workers recruited. There are a number of reasons for this. Firstly, there are fewer workers undertaking potentially unsafe rotating work schedules than there have been in the past. The detrimental effects of rotating shift systems are now well known (Brugere et al., 1997). Occupational health and safety regulations in Australia place restrictions on the number of nights versus days that can be worked in a particular cycle, and also prescribe the number of days that should be taken off prior to starting a new shift (Australian Council of Trade Unions, 2000; Australian Safety & Compensation Council, 2006). This has led to greater control of the hours worked by shift-workers, and a reduction in unsafe shift-work practices. Fewer people now work rapidly rotating shifts with short recovery times. Secondly, the people who work rotating shifts are often women with family responsibilities to attend to on their non-working days. These women were understandably reluctant to give up their time off and further reduce their sleep in order to participate in the study. Future researchers in this area may consider completing at least part of the assessment (such as the cognitive measures) during a work shift, in order to make participation more attractive to workers.

4.6. Conclusions and future directions

The results of the current study suggest that rotating shift workers who have worked a minimum of three years in their current shift experience few if any cognitive or neuroanatomical deficits as a result their shift schedules. Cortisol rhythm changes including an advance of quiescent period offset and amplitude attenuation over the night shift indicate that they are likely to be people who adapt well to a rotating shift system and are therefore more likely to continue to work such a schedule. However, these results provide no indication of the effect that rotating shifts may have over the long-term on workers who do not easily adapt to ongoing circadian disruption.

Despite the absence of cognitive or neuroanatomical deficits, shift workers still reported that they slept less on average, and felt more tired and less vigorous than the control participants. In addition, there is some suggestion that they do not utilise their intact neuroanatomical resources as effectively as control participants. Fatigue may therefore still affect the shift workers' ability to perform to their optimum levels at work, even in the absence of measurable cognitive differences compared to control participants in the current study.

Changes to the regulation of shift work have led to a reduction in people working unsafe shift systems, and in general better control and awareness of the effects of fatigue in the workplace. However, it is still the case that people must subject themselves to potentially unhealthy work practices in order to see whether they are able to cope with rotating shifts. Future research should look at functional imaging in potential shift workers in order to screen for "good adapters". Studies in sleep deprived participants suggest that consistent, individual functional changes are likely to exist (Caldwell et al., 2005; Strangman et al., 2005; Stricker et al., 2006). Ideally, studies in this area should take a longitudinal approach and follow workers during the development of their careers. Such an approach would enable researchers to measure change in cognitive and brain functioning over time, as well as develop screening tools (like functional imaging) to identify those workers who will be well suited to shift work.

REFERENCES

Abbott, D., & Jackson, G. (2001). iBrain® - Software for analysis and visualisation of functional MR images. *NeuroImage, 13*(6, Suppl. 1), 59.

Abercrombie, H. C., Kalin, N. H., Thurow, M. E., Rosenkranz, M. A., & Davidson, R. J. (2003). Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behavioral Neuroscience, 117*(3), 505-516.

Åkerstedt, T. (1990). Psychological and psychophysiological effects of shift work. *Scandinavian Journal of Work, Environment & Health, 16*(1), 67-73.

Åkerstedt, T., Fredlund, P., Gillberg, M., & Jansson, B. (2002). A prospective study of fatal occupational accidents-relationship to sleeping difficulties and occupational factors. *Journal of Sleep Research, 11*(1), 69-71.

Åkerstedt, T., Kecklund, G., Gillberg, M., & Bjorvatn, B. (1998). Subjective sleepiness in shift work. In Y. Touitou (Ed.), *Biological Clocks: Mechanisms and Applications* (pp. 235-242). Amsterdam: Elsevier.

Åkerstedt, T., Kecklund, G., Gillberg, M., Lowden, A., & Axelsson, J. (2000). Sleepiness and days of recovery. *Transportation Research Part F: Traffic Psychology & Behaviour, 3*(4), 251-261.

Åkerstedt, T., Palmblad, J., de la Torre, B., Marana, R., & Gillberg, M. (1980). Adrenocortical and gonadal steroids during sleep deprivation. *Sleep, 3*(1), 23-30.

Åkerstedt, T., & Torsvall, L. (1981). Shift work: Shift-dependent well-being and individual differences. *Ergonomics, 24*(4), 265-273.

Alchanatis, M., Deligiorgis, N., Zias, N., Amfilochiou, A., Gotsis, E., Karakatsani, A., et al. (2004). Frontal brain lobe impairment in obstructive sleep apnoea: a

proton MR spectroscopy study. *European Respiratory Journal, 24*(6), 980-986.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association.

Aschoff, J. (1979). Circadian rhythms: General features and endocrinological aspects. In D. T. Krieger (Ed.), *Endocrine Rhythms* (pp. 1-61). New York: Raven Press.

Aschoff, J., Saint-Paul, U., & Wever, R. (1977). Die lebensdauer von fliegen unter dem einfluss von zeitverschiebungen. *Naturwissenschaften, 58*, 574.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry - the methods. *NeuroImage, 11*(6), 805-821.

Australian Bureau of Statistics. (2003). *Working Arrangements, Australia* (No. 6342.0). Canberra: Australian Bureau of Statistics.

Australian Council of Trade Unions. (2000). *Health and Safety Guidelines for Shift Work and Extended Working Hours* (No. 66/2000). Melbourne: ACTU.

Australian Safety & Compensation Council. (2006). *Work-Related Fatigue: Summary of Recent Regulatory Developments*. Canberra: Australian Government.

Axelsson, J., Åkerstedt, T., Kecklund, G., Lindqvist, A., & Attefors, R. (2003). Hormonal changes in satisfied and dissatisfied shift workers across a shift cycle. *Journal of Applied Physiology, 95*(5), 2099-2105.

Barker, P. B. (2005). Fundamentals of MR spectroscopy. In J. Gillard, A. Waldman & P. B. Barker (Eds.), *Clinical MR Neuroimaging: Diffusion, Perfusion and Spectroscopy* (pp. 7-26). Cambridge, UK: Cambridge.

Barnes, P. J., & Pederson, S. S. (1993). Efficacy and safety of inhaled corticosteroids in asthma. *American Review of Respiratory Diseases, 148*(Suppl), S1-S26.

Bartlett, D. J., Rae, C., Thompson, C. H., Byth, K., Joffe, D. A., Enright, T., et al. (2004). Hippocampal area metabolites relate to severity and cognitive function in obstructive sleep apnea. *Sleep Medicine, 5*(6), 593-596.

Belanoff, J. K., Gross, K., Yager, A., & Schatzberg, A. F. (2001). Corticosteroids and cognition. *Journal of Psychiatric Research, 35*, 127-145.

Belanoff, J. K., Kalehzan, M., Sund, B., Fleming Ficek, S. K., & Schatzberg, A. F. (2001). Cortisol activity and cognitive changes in psychotic Major Depression. *America Journal of Psychiatry, 158*(10), 1612-1616.

Bjerner, B., Holm, Å., & Swensson, Å. (1955). Diurnal variation of mental performance: A study of three-shift workers. *British Journal of Industrial Medicine, 12*, 103-110.

Blagrove, M., Alexander, C., & Horne, J. A. (1995). The effects of chronic sleep reduction on the performance of cognitive tasks sensitive to sleep deprivation. *Applied Cognitive Psychology, 9*(1), 21-40.

Blatter, D. D., Bigler, E. D., Gale, S. D., Johnson, S. C., Anderson, C. V., Burnett, B. M., et al. (1995). Quantitative volumetric analysis of brain MR: Normative database spanning 5 decades of life. *American Journal Of Neuroradiology, 16*(2), 241-251.

Bloche, M. G., & Marks, J. H. (2005). Doctors and interrogators at Guantanamo Bay. *New England Journal Of Medicine, 353*(1), 6-8.

Bohnen, N., Houx, P., Nicholson, N., & Jolles, J. (1990). Cortisol reactivity and cognitive performance in a continuous mental task paradigm. *Biological Psychology, 31*, 107-116.

Bohnen, N., Jolles, J., Twijnstra, A., Mellink, R., & Sulon, J. (1992). Coping style, cortisol reactivity, and performance in a vigilance task of patients with persistent concussive symptoms after mild head injury. *International Journal of Neuroscience, 64*, 97-105.

Bohnen, N., Nicholson, N., Sulon, J., & Jolles, J. (1991). Coping style, trait anxiety, and cortisol reactivity during mental stress. *Journal of Psychosomatic Research, 35*, 141-147.

Bourdouxhe, M. A., Queinnec, Y., Granger, D., Baril, R. H., Guertin, S. C., Massicotte, P. R., et al. (1999). Aging and shiftwork: The effects of 20 years of rotating 12-hour shifts among petroleum refinery operators. *Experimental Aging Research, 25*(4), 323-329.

Bowden, S., Dumendzic, J., Clifford, C., Hopper, J., Kinsella, G., & Tucker, A. (1992). Healthy adults' performance on the Austin Maze. *Clinical Psychologist, 6*, 43-52.

Bremner, J. D. (2001). Hypotheses and controversies related to effects of stress on the hippocampus: An argument for stress-induced damage to the hippocampus in patients with posttraumatic stress disorder. *Hippocampus, 11*(2), 75-81.

Bremner, J. D., Krystal, J. H., Southwick, S. M., & Charney, D. S. (1995). Functional neuroanatomical correlates of the effects of stress on memory. *Journal of Traumatic Stress, 8*(4), 527-553.

Bremner, J. D., Randall, P., Vermetten, E., Staib, L., Bronen, R. A., Mazure, C., et al. (1997). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse: A preliminary report. *Biological Psychiatry, 41*(1), 23-32.

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Nazeer, A., et al. (2003). MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and

posttraumatic stress disorder. *American Journal of Psychiatry, 160*(5), 924-932.

Brickencamp, R. (1981). *Test d2:/Aufmerksamkeits-Belastungs-Test Handanweisung* (7th ed.). Goettingen: Verlag fuer Psychologie, C. J. Hogrefe.

Briellman, R. S., Berkovic, S. F., & Jackson, G. D. (2000). Men may be more vulnerable to seizure-associated brain damage. *Neurology, 55*, 1479-1485.

Briellmann, R. S., Pell, G. S., Wellard, R. M., Mitchell, L. A., Abbott, D. F., & Jackson, G. D. (2003). MR imaging of epilepsy: State of the art at 1.5 T and potential of 3 T. *Epileptic Disorders, 5*(1), 3-20.

Briellmann, R. S., Wellard, R. M., & Jackson, G. D. (2005). MR spectroscopy in seizure disorders. In J. Gillard, A. Waldman & P. B. Barker (Eds.), *Clinical MR Neuroimaging: Diffusion, Perfusion and Spectroscopy* (pp. 488-506). Cambridge, UK: Cambridge.

Brown, E. S., Beard, L., Frol, A. B., & Rush, A. J. (2006). Effect of two prednisone exposures on mood and declarative memory. *Neurobiology of Learning and Memory, 86*(1), 28-34.

Brown, E. S., Woolston, D. L., Frol, A., Bobadilla, L., Khan, D. A., Hanczyc, M., et al. (2004). Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. *Biological Psychiatry, 55*, 538-545.

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and the hippocampus? *Nature Reviews Neuroscience, 2*, 51-61.

Browne, R. C. (1949). The day and night performance of teleprinter switchboard operators. *Occupational Psychology, 23*, 121-126.

Brugere, D., Barrit, J., Butat, C., Cosset, M., & Volkoff, S. (1997). Shiftwork, age, and health: An epidemiologic investigation. *International Journal of Occupational and Environmental Health, 3*(Suppl 2), S15-S19.

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., et al. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *NeuroImage, 23*(2), 724-738.

Cajochen, C., Jewett, M. E., & Dijk, D.-J. (2003). Human circadian melatonin rhythm phase delay during a fixed sleep-wake schedule interspersed with nights of sleep deprivation. *Journal of Pineal Research, 35*(3), 149-157.

Cajochen, C., Kräuchi, K., & Wirz-Justice, A. (2003). Role of melatonin in the regulation of human circadian rhythms and sleep. *Journal of Neuroendocrinology, 15*(4), 432-437.

Caldwell, J. A., Caldwell, J. L., Brown, D. L., & Smith, J. K. (2004). The effects of 37 hours of continuous wakefulness on the physiological arousal, cognitive performance, self-reported mood, and simulator flight performance of F-117A pilots. *Military Psychology, 16*(3), 163-181.

Caldwell, J. A., Mu, Q., Smith, J. K., Mishory, A., Caldwell, J. L., Peters, G., et al. (2005). Are individual differences in fatigue vulnerability related to baseline differences in cortical activation? *Behavioral Neuroscience, 119*(3), 694-707.

Cannon, W. B. (1927). The James-Lange theory of emotions: A critical examination and an alternative theory. *American Journal of Psychology, 39*, 106-124.

Catalani, A., Marinelli, M., Scaccianoce, S., Nicolai, R., Muscolo, L. A., Porcu, A., et al. (1993). Progeny of mothers drinking corticosterone during lactation has lower stress-induced corticosterone secretion and better cognitive performance. *Brain Research, 624*, 209-215.

Caufriez, A., Moreno-Reyes, R., Leproult, R., Vertongen, F., Van Cauter, E., & Copinschi, G. (2002). Immediate effects of an 8-h advance shift of the rest-activity cycle on 24-h profiles of cortisol. *American Journal of Physiology, 282*(5), E1147-E1153.

Cavallo, A., Jaskiewicz, J., & Ris, M. D. (2002). Impact of night-float rotation on sleep, mood, and alertness: The resident's perception. *Chronobiology International, 19*(5), 893-902.

Chapotot, F., Buguet, A., Gronfier, C., & Brandenberger, G. (2001). Hypothalamo-pituitary-adrenal axis activity is related to the level of central arousal: Effect of sleep deprivation on the association of high-frequency waking electroencephalogram with cortisol release. *Neuroendocrinology, 73*(5), 312-321.

Chee, M. W. L., Chuah, L. Y. M., Venkatraman, V., Chan, W. Y., Philip, P., & Dinges, D. F. (2006). Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: Correlations of fronto-parietal activation with performance. *NeuroImage, 31*(1), 419-428.

Chmiel, N., Totterdell, P., & Folkard, S. (1995). On adaptive control, sleep loss and fatigue. *Applied Cognitive Psychology, 9*, S39-S53.

Cho, K. (2001). Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. *Nature Neuroscience, 4*(6), 567-568.

Cho, K., Ennaceur, A., Cole, J. C., & Kook Suh, C. (2000). Chronic jet lag produces cognitive deficits. *Journal of Neuroscience, 20*(6), RC66.

Chuah, Y. M. L., Venkatraman, V., Dinges, D. F., & Chee, M. W. L. (2006). The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. *Journal of Neuroscience, 26*(27), 7156-7162.

Cohen, N. J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., & Nash, C. (1999). Hippocampal memory system and declarative (relational) memory: Summarizing the data from functional neuroimaging studies. *Hippocampus, 9*, 83-98.

Constantinidis, I. (2000). MRS methodology. *Advances In Neurology, 83*, 235-246.

Copinschi, G., Spiegel, K., Leproult, R., & Van Cauter, E. (2000). Pathophysiology of human circadian rhythms. In D. J. Chadwick & J. A. Goode (Eds.), *Mechanisms and Biological Significance of Pulsatile Hormone Secretion: Novartis Foundation Symposium* (Vol. 227, pp. 143-162). Chichester: Wiley.

Costa, G. (1996). The impact of shift and night work on health. *Applied Ergonomics, 27*(1), 9-16.

Costa, G. (1997). The problem: Shiftwork. *Chronobiology International, 14*(2), 89-98.

Coull, J. T. (1998). Neural correlates of attention and arousal: Insights from electrophysiology, functional neuroimaging and psychopharmacology. *Progress In Neurobiology, 55*(4), 343-361.

Criglington, A. J. (1998). Do professionals get jet lag? A commentary on jet lag. *Aviation, Space, and Environmental Medicine, 69*(8), 810.

Crowe, S. F., Barclay, L., Brennan, S., Farkas, L., Gould, E., Katchmarsky, S., et al. (1999). The cognitive determinants of performance on the Austin Maze. *Journal of the International Neuropsychological Society, 5*, 1-9.

Cullinan, W. E., Herman, J. P., Helmreich, D. L., & Watson, S. J. J. (1995). A neuroanatomy of stress. In M. J. Friedman, D. S. Charney & A. Y. Deutch (Eds.), *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder* (pp. 3-26). Philadelphia: Lippincott-Raven Publishers.

Dachir, S., Kadar, T., Robinson, B., & Levy, A. (1993). Cognitive deficits induced in young rats by long-term corticosterone administration. *Behavioral & Neural Biology, 60*, 103-109.

de Quervain, D. J.-F., Roozendaal, B., Nitsch, R. M., McGaugh, J. L., & Hock, C. (2000). Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nature Neuroscience, 3*(4), 313-314.

Deacon, S., & Arendt, J. (1996). Adapting to phase shifts: I. An experimental model for jet lag and shift work. *Physiology & Behavior, 59*(4), 665-673.

Deary, I. J., & Tait, R. (1987). Effects of sleep disruption on cognitive performance and mood in medical house officers. *British Medical Journal, 295*(6612), 1513-1516.

Désir, D., Van Cauter, E., Fang, V. S., Martino, E., Jadot, C., Spire, J.-P., et al. (1981). Effects of "jet lag" on hormonal patterns. I. Procedures, variations in total plasma-proteins, and disruption of adrenocorticotropin-cortisol periodicity. *Journal of Clinical Endocrinology & Metabolism, 52*(4), 628-641.

Désir, D., Van Cauter, E., Refetoff, S., Fang, V. S., Golstein, J., Fevre-Montange, M., et al. (1983). Hormonal changes after jet lag in normal man. In J. Mendlewicz & H. M. van Praag (Eds.), *Biological Rhythms and Behavior* (Vol. 11, pp. 60-63). Basel: Karger.

Deweer, B., Pillon, B., Pochon, J. B., & Dubois, B. (2001). Is the HM story only a "remote memory"? Some facts about hippocampus and memory in humans. *Behavioural Brain Research, 127*(1), 209-224.

Di Costanzo, A., Trojsi, F., Tosetti, M., Giannatempo, G. M., Nemore, F., Piccirillo, M., et al. (2003). High-field proton MRS of human brain. *European Journal of Radiology, 48*(2), 146-153.

Ding, X. Q., Kucinski, T., Wittkugel, O., Goebell, E., Grzyska, U., Gorg, M., et al. (2004). Normal brain maturation characterized with age-related T2 relaxation times: An attempt to develop a quantitative imaging measure for clinical use. *Investigative Radiology, 39*(12), 740-746.

Drachman, D. A., & Arbit, J. (1966). Memory and the hippocampal complex. II. Is memory a multiple process? *Archives of Neurology, 15*(1), 52-61.

Drake, C. L., Roehrs, T., Richardson, G., Walsh, J. K., & Roth, T. (2004). Shift work sleep disorder: Prevalence and consequences beyond that of symptomatic day workers. *Sleep, 27*(8), 1453-1462.

Drummond, S. P. A., & Brown, G. G. (2001). The effects of total sleep deprivation on cerebral responses to cognitive performance. *Neuropsychopharmacology, 25*, S68-S73.

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.

Drummond, S. P. A., Brown, G. G., Stricker, J. L., Buxton, R. B., Wong, E. C., & Gillin, J. C. (1999). Sleep deprivation-induced reduction in cortical functional response to serial subtraction. *NeuroReport, 10*, 3745-3748.

Dula, D. J., Dula, N. L., Hamrick, C., & Wood, G. C. (2001). The effect of working serial night shifts on the cognitive functioning of emergency physicians. *Annals of Emergency Medicine, 38*(2), 152-155.

Engle-Friedman, M., Riela, S., Golan, R., Ventuneac, A. M., Davis, C. M., Jefferson, A. D., et al. (2003). The effect of sleep loss on next day effort. *Journal of Sleep Research, 12*(2), 113-124.

Falleti, M. G., Maruff, P., Collie, A., Darby, D. G., & McStephen, M. (2003). Qualitative similarities in cognitive impairment associated with 24 h of

sustained wakefulness and a blood alcohol concentration of 0.05%. *Journal of Sleep Research, 12*(4), 265-274.

Fehm-Wolfsdorf, G., Reutter, D., Zenz, H., Born, J., & Fehm, H. L. (1993). Are circadian variations in taste thresholds cortisol-dependent? *Journal of Psychophysiology*, 65-72.

Filipini, D., Gijsbers, K., Birmingham, M. K., & Dubrovsky, B. (1991). Effects of adrenal steroids and the reduced metabolites in hippocampal long-term potentiation. *Journal of Steroid Biochemistry and Molecular Biology, 40*, 87-91.

Folkard, S. (1990). Circadian performance rhythms: Some practical and theoretical implications. *Philosophical Transactions of the Royal Society of London., 327*(1241), 543-553.

Folkard, S., & Tucker, P. (2003). Shift work, safety and productivity. *Occupational Medicine, 53*(2), 95-101.

Forget, H., Lacroix, A., Somma, M., & Cohen, H. (2000). Cognitive decline in patients with Cushing's syndrome. *Journal of the International Neuropsychological Society, 6*(1), 20-29.

Fossati, P., Radtchenko, A., & Boyer, P. (2004). Neuroplasticity: From MRI to depressive symptoms. *European Neuropsychopharmacology, 14*, S503-S510.

Free, S., Bergin, P., Fish, D., Cook, M., Shorvon, S., & Stevens, J. (1995). Methods for normalization of hippocampal volumes measured with MR. *American Journal of Neuroradiology, 16*(4), 637-643.

Frey, D. J., Badia, P., & Wright, K. P., Jr. (2004). Inter- and intra-individual variability in performance near the circadian nadir during sleep deprivation. *Journal of Sleep Research, 13*(4), 305-315.

Fuchs, E., & Flügge, G. (1998). Stress, glucocorticoids and structural plasticity of the hippocampus. *Neuroscience and Behavioural Reviews, 23*, 295-300.

Fukui, T., & Kertesz, A. (2000). Volumetric study of lobar atrophy in Pick complex and Alzheimer's disease. *Journal of the Neurological Sciences, 174*(2), 111-121.

Goh, V. H., Tong, T. Y., Lim, C. L., Low, E. C., & Lee, L. K. (2001). Effects of one night of sleep deprivation on hormone profiles and performance efficiency. *Military Medicine, 166*(5), 427-431.

Goichot, B., Weibel, L., Chapotot, F., Gronfier, C., Piquard, F., & Brandenberger, G. (1998). Effect of the shift of the sleep-wake cycle on three robust endocrine markers of the circadian clock. *American Journal of Physiology, 275*(2 Pt 1), E243-E248.

Golier, J., & Yehuda, R. (1998). Neuroendocrine activity and memory-related impairments in posttraumatic stress disorder. *Development & Psychopathology, 10*(4), 857-869.

Gomez, R. G., Fleming, S. H., Keller, J., Flores, B., Kenna, H., DeBattista, C., et al. (2006). The neuropsychological profile of psychotic major depression and its relation to cortisol. *Biological Psychiatry, 60*(5), 472-478.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N. A., Friston, K. J., & Frackowiak, R. S. J. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *NeuroImage, 14*(1), 21-36.

Gronfier, C., & Brandenberger, G. (1998). Ultradian rhythms in pituitary and adrenal hormones: Their relations to sleep. *Sleep Medicine Reviews, 2*(1), 17-29.

Gurvits, T. G., Shenton, M. R., Hokama, H., Ohta, H., Lasko, N. B., Gilbertson, M. W., et al. (1996). Magnetic resonance imaging study of hippocampal volume

in chronic combat-related posttraumatic stress disorder. *Biological Psychiatry, 40*, 192-199.

Halberg, F., Nelson, W. L., & Cadotte, L. (1977). Living routine shifts simulated on mice by weekly or twice-weekly manipulation of light-dark cycle. In F. Halberg (Ed.), *XII International Conference Proceedings, International Society for Chronobiology* (pp. 133-138). Milan: Il Ponte.

Harrison, Y., & Horne, J. A. (1998). Sleep loss impairs short and novel language tasks having a prefrontal focus. *Journal of Sleep Research, 7*(2), 95-100.

Harrison, Y., & Horne, J. A. (2000). Sleep loss and temporal memory. *Quarterly Journal of Experimental Psychology A, 53*(1), 271-279.

Heiser, P., Dickhaus, B., Schreiber, W., Clement, H. W., Hasse, C., Hennig, J., et al. (2000). White blood cells and cortisol after sleep deprivation and recovery sleep in humans. *European Archives of Psychiatry & Clinical Neuroscience, 250*(1), 16-23.

Hennig, J., Kieferdorf, P., Moritz, C., Huwe, S., & Netter, P. (1998). Changes in cortisol secretion during shiftwork: Implications for tolerance to shiftwork? *Ergonomics, 41*(5), 610-621.

Het, S., Ramlow, G., & Wolf, O. T. (2005). A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology, 30*, 771-784.

Hildebrandt, G., Rohmert, W., & Rutenfranz, J. (1974). 12 and 24 hour rhythms in error frequency of locomotive drivers and the influence of tiredness. *International Journal of Chronobiology, 2*, 175-180.

Ho, S. S., Kuzniecky, R. I., Gilliam, F., Faught, E., & Morawetz, R. (1998). Temporal lobe developmental malformations and epilepsy: Dual pathology and bilateral hippocampal abnormalities. *Neurology, 50*(3), 748-754.

Hoffman, R., & al'Absi, M. (2004). The effect of acute stress on subsequent neuropsychological test performance (2003). *Archives of Clinical Neuropsychology, 19*(4), 497-506.

Hornak, J. P. (2006). *The Basics of MRI*. Retrieved 28 January, 2006, from http://www.cit.ris.edu/htbooks/mri

Horne, J. A., & Pettitt, A. N. (1985). High incentive effects on vigilance performance during 72 hours of total sleep deprivation. *Acta Psychologica, 58*(2), 123-139.

Ilias, I., Vgontzas, A. N., Provata, A., & Mastorakos, G. (2002). Complexity and non-linear description of diurnal cortisol and growth hormone secretory patterns before and after sleep deprivation. *Endocrine Regulations, 36*(2), 63-72.

Jackson, G. D., & Connelly, A. (1999). New NMR measurements in epilepsy. T2 relaxometry and magnetic resonance spectroscopy. *Advances In Neurology, 79*, 931-937.

Jameison, K., & Dinan, T. G. (2001). Glucocorticoids and cognitive function: From physiology to pathophysiology. *Human Psychopharmacology: Clinical & Experimental, 16*(4), 293-302.

Jauhar, P., & Weller, M. (1982). Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. *British Journal of Psychiatry, 140*(3), 231-235.

Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., et al. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology Of Aging, 22*(4), 581-594.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep, 14*(6), 540-545.

Jutila, L., Ylinen, A., Partanen, K., Alafuzoff, I., Mervaala, E., Partanen, J., et al. (2001). MR volumetry of the entorhinal, perirhinal, and temporopolar cortices in drug-refractory temporal lobe epilepsy. *American Journal Of Neuroradiology, 22*(8), 1490-1501.

Kalus, P., Buri, C., Slotboom, J., Gralla, J., Remonda, L., Dierks, T., et al. (2004). Volumetry and diffusion tensor imaging of hippocampal subregions in schizophrenia. *Neuroreport, 15*(5), 867-871.

Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (Eds.). (2000). *Principles of Neural Science* (4th ed.). New York: McGraw-Hill.

Kaneko, S.-Y., Maeda, T., Sasaki, A., Sato, A., Tanaka, K., Kobayashi, T., et al. (2004). Effect of shift work on mental state of factory workers. *Fukushima Journal of Medical Science, 50*(1), 1-9.

Kantarci, K., & Jack, C. R., Jr. (2003). Neuroimaging in Alzheimer disease: An evidence-based review. *Neuroimaging Clinics of North America, 13*(2), 197-209.

Karacan, I., Williams, R. L., & Moore, C. A. (1989). Sleep disorders. In H. I. Kaplan & B. J. Sadock (Eds.), *Comprehensive Textbook of Psychiatry* (5th ed., pp. 1118-1120). Baltimore: Williams & Wilkins.

Karlamangla, A. S., Singer, B. H., Chodosh, J., McEwen, B. S., & Seeman, T. E. (2005). Urinary cortisol excretion as a predictor of incident cognitive impairment. *Neurobiology of Aging, 26*(1, Supplement 1), 80-84.

Katz, G., Knobler, H. Y., Laibel, Z., Strauss, Z., & Durst, R. (2002). Time zone change and major psychiatric morbidity: The results of a 6-year study in Jerusalem. *Comprehensive Psychiatry, 43*(1), 37-40.

Keenan, P. A., Jacobson, M. W., Soleymani, R. M., & Newcomer, J. W. (1995). Commonly used therapeutic doses of glucocorticoids impair explicit memory. *Annals of the New York Academy of Sciences, 761*, 400-402.

Kennedy, P. G. E., & Chaudhuri, A. (2002). Herpes simplex encephalitis. *Journal of Neurology, Neurosurgery & Psychiatry, 73*(3), 237-238.

Kerr, D. S., Campbell, L. W., Applegate, M. D., Brodish, A., & Landfield, P. W. (1991). Chronic stress-induced acceleration of electrophysiologic and morphometric biomarkers of hippocampal aging. *Journal of Neuroscience, 11*, 1316.

Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., & Hellhammer, D. H. (1999). Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosomatic Medicine, 61*, 157-162.

Klein, E., Caspi, Y., & Gil, S. (2003). The relation between memory of the traumatic event and PTSD: Evidence from studies of traumatic brain injury. *Canadian Journal of Psychiatry, 48*(1), 28-33.

Klein, K. E., & Wegmann, H. M. (1979). Circadian rhythms in air operations. In A. N. Nicholson (Ed.), *Sleep, Wakefulness and Circadian Rhythms* (Vol. 105, pp. 10.10 -10.25). Neuilly sur Seine, France: NATO Advisory Group for Aerospace Research and Development.

Knott, R., & Marslen-Wilson, W. (2001). Does the medial temporal lobe bind phonological memories? *Journal of Cognitive Neuroscience, 13*(5), 593-609.

Knutsson, A., & Åkerstedt, T. (1992). The healthy-worker effect: self-selection among Swedish shift workers. *Work & Stress, 6*, 163-167.

Knutsson, A., Hallquist, J., Reuterwall, C., Theorell, T., & Akerstedt, T. (1999). Shiftwork and myocardial infarction: A case-control study. *Occupational & Environmental Medicine, 56*(1), 46-50.

Kogi, K. (1998). International regulations on the organization of shift work. *Scandinavian Journal of Work, Environment & Health, 24 Suppl 3*, 7-12.

Krieger, D. T., & Hauser, H. (1978). Comparison of synchronization of circadian corticosteroid rhythms by photoperiod and food. *Proceedings of the National Academy of Sciences, 75*(3), 1577-1581.

Kruggel, F. (2006). MRI-based volumetry of head compartments: Normative values of healthy adults. *NeuroImage, 30*(1), 1-11.

Kuhlmann, S., Kirschbaum, C., & Wolf, O. T. (2005). Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words. *Neurobiology of Learning & Memory, 83*, 158-162.

Kuzniecky, R., Ho, S. S., Martin, R., Faught, E., Morawetz, R., Palmer, C., et al. (1999). Temporal lobe developmental malformations and hippocampal sclerosis: Epilepsy surgical outcome. *Neurology, 52*(3), 479-484.

Lac, G., & Chamoux, A. (2003). Elevated salivary cortisol levels as a result of sleep deprivation in a shift worker. *Occupational Medicine, 53*(2), 143-145.

Lac, G., & Chamoux, A. (2004). Biological and psychological responses to two rapid shiftwork schedules. *Ergonomics, 47*(12), 1339-1349.

Lamond, N., Dorrian, J., Roach, G. D., Burgess, H. J., Holmes, A. L., McCulloch, K., et al. (2001). Performance, sleep and circadian phase during a week of simulated night work. *Journal of Human Ergology, 30*(1-2), 137-142.

Laudat, M., Cerdas, S., Fournier, C., Guiban, D., Guilhaume, B., & Luton, J. (1988). Salivary cortisol measurement: a practical approach to assess pituitary-adrenal function. *Journal of Clinical Endocrinology & Metabolism, 66*(2), 343-348.

Lee, A. L., Ogle, W. O., & Sapolsky, R. M. (2002). Stress and depression: Possible links to neuron death in the hippocampus. *Bipolar Disorders, 4*, 117-128.

Leese, G., Chattington, P., Fraser, W., Vora, J., Edwards, R., & Williams, G. (1996). Short-term night-shift working mimics the pituitary-adrenocortical dysfunction in chronic fatigue syndrome. *Journal of Clinical Endocrinology & Metabolism, 81*(5), 1867-1870.

Leproult, R., Copinschi, G., Buxton, O., & Van Cauter, E. (1997). Sleep loss results in an elevation of cortisol levels the next evening. *Sleep, 20*(10), 865-870.

Leritz, E. C., Grande, L. J., & Bauer, R. M. (2006). Temporal lobe epilepsy as a model to understand human memory: The distinction between explicit and implicit memory. *Epilepsy & Behavior, 9*(1), 1-13.

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Lindauer, R. J. L., Vlieger, E.-J., Jalink, M., Olff, M., Carlier, I. V. E., Majoie, C. B. L. M., et al. (2004). Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. *Biological Psychiatry, 56*(5), 356-363.

Lupien, S. J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N. P., et al. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience, 1*(1), 69-73.

Lupien, S. J., Wilkinson, C. W., Briere, S., Menard, C., Ng Ying Kin, N. M. K., & Nair, N. P. V. (2002). The modulatory effects of corticosteroids on cognition: Studies in young human populations. *Psychoneuroendocrinology, 27*(3), 401-416.

Maheu, F. S., Collicutt, P., Kornik, R., Moszkowski, R., & Lupien, S. J. (2005). The perfect time to be stressed: A differential modulation of human memory by stress applied in the morning or in the afternoon. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29*(8), 1281-1288.

Maislin, G., Pack, A. I., Kribbs, N. B., Smith, P. L., Schwartz, A. R., Kline, L. R., et al. (1995). A survey screen for prediction of apnea. *Sleep, 18*(3), 158-166.

Marquié, J.-C., & Foret, J. (1999). Sleep, age, and shiftwork experience. *Journal of Sleep Research, 8*(4), 297-304.

Mauri, M., Sinforiani, E., Bono, G., Vignati, F., Berselli, M. E., Attanasio, R., et al. (1993). Memory impairment in Cushing's Disease. *Acta Neurologica Scandinavica, 87*, 52-55.

McClay, R. N., Freeman, S. M., & Zadina, J. E. (1998). Chronic Corticosterone Impairs Memory Function in the Barnes Maze. *Physiology and Behavior, 63*(5), 933-937.

McCormick, C. M., McNamara, M., Kelsey, J. F., & Klecker, N. W. (1995). Acute corticosterone replacement three months after adrenalectomy improves performance in a Morris Water Maze despite degeneration in the dentate gyrus. *Society for Neuroscience. Abstracts., 21*, 1944.

McCoy, A. W. (2006). *A question of torture: CIA interrogation, from the Cold War to the War on Terror.* New York: Metropolitan Book/Henry Holt and Company, LLC.

McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism: Clinical And Experimental, 55*(10 Suppl 2), S20-23.

McEwen, B. S., Magarinos, A. M., & Reagan, L. P. (2002). Studies of hormone action in the hippocampal formation: Possible relevance to depression and diabetes. *Journal of Psychosomatic Research, 53*(4), 883-890.

McEwen, B. S., Weiss, J. M., & Schwartz, L. S. (1968). Selective retention of corticosterone by limbic structures in rat brain. *Nature, 220*, 911-912.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1971). *Manual for the Profile of Mood States*. San Diego: Educational and Industrial Testing Services.

Meddis, R. (1982). Cognitive dysfunction following loss of sleep. In A. Burton (Ed.), *The Pathology and Psychology of Cognition* (pp. 225-252). London: Methuen.

Meijman, T., van der Meer, O., & van Dormolen, M. (1993). The after-effects of night work on short-term memory performance. *Ergonomics, 36*(1-3), 37-42.

Menezes, M. C. R., Pires, M. L. N., Benedito-Silva, A. A., & Tufik, S. (2004). Sleep parameters among offshore workers: An initial assessment in the Campos Basin, Rio De Janeiro, Brazil. *Chronobiology International, 21*(6), 889-897.

Mikulincer, M., Babkoff, H., Caspy, T., & Sing, H. (1989). The effects of 72 hours of sleep loss on psychological variables. *British Journal of Psychology, 80 (Pt 2)*, 145-162.

Milner, B. (1965). Visually-guided maze learning in man: effects of bilateral hippocampal, bilateral frontal, and unilateral cerebral lesions. *Neuropsychologia, 3*, 317-338.

Milner, B. (2005). The medial temporal-lobe amnesic syndrome. *Psychiatric Clinics of North America, 28*(3), 599-611.

Molina, V., Sanz, J., Sarramea, F., Luque, R., Benito, C., & Palomo, T. (2006). Dorsolateral prefrontal and superior temporal volume deficits in first-episode

psychoses that evolve into schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience, 256*(2), 106-111.

Moore-Ede, M. C., Sulzman, F. M., & Fuller, C. A. (1982). *The Clocks that Time Us*. Cambridge,MA: Harvard University Press.

Motohashi, Y. (1992). Alteration of circadian rhythm in shift-working ambulance personnel: Monitoring of salivary cortisol rhythm. *Ergonomics, 35*(11), 1331-1340.

Mu, Q., Nahas, Z., Johnson, K. A., Yamanaka, K., Mishory, A., Koola, J., et al. (2005). Decreased cortical response to verbal working memory following sleep deprivation. *Sleep, 28*, 55-67.

Muecke, S. (2005). Effects of rotating night shifts: literature review. *Journal of Advanced Nursing, 50*(4), 433-439.

Müller, M. B., Lucassen, P. J., Yassouridis, A., Hoogendijk, W. J. G., Holsboer, F., & Swaab, D. F. (2001). Neither major depression nor glucocorticoid treatment affects the cellular integrity of the human hippocampus. *European Journal of Neuroscience, 14*, 1603-1612.

Muller-Gass, A., & Campbell, K. (2002). Event-related potential measures of the inhibition of information processing: I. Selective attention in the waking state. *International Journal Of Psychophysiology, 46*(3), 177-195.

Murck, H., Struttmann, T., Czisch, M., Wetter, T., Steiger, A., & Auer, D. P. (2002). Increase in amino acids in the pons after sleep deprivation: A pilot study using proton magnetic resonance spectroscopy. *Neuropsychobiology, 45*(3), 120-123.

Namer, I. J., Bolo, N. R., Sellal, F., Nguyen, V. H., Nedelec, J. F., Hirsch, E., et al. (1999). Combined measurements of hippocampal n-acetyl-aspartate and T2 relaxation time in the evaluation of mesial temporal lobe epilepsy: Correlation

with clinical severity and memory performances. *Epilepsia, 40*(10), 1424-1432.

Newcomer, J. W., Selke, G., Melson, A. K., Hershey, T., Craft, S., Richards, K., et al. (1999). Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of General Psychiatry, 56*, 527-533.

Neylan, T. C., Schuff, N., Lenoci, M., Yehuda, R., Weiner, M. W., & Marmar, C. R. (2003). Cortisol levels are positively correlated with hippocampal *N*-acetylaspartate. *Biological Psychiatry, 54*, 1118-1121.

Nicol, A.-M., & Botterill, J. S. (2004). On-call work and health: A review. *Environmental Health: A Global Access Science Source, 3*(1), 15.

Nilsson, J. P., Söderström, M., Karlsson, A. U., Lekander, M., Åkerstedt, T., Lindroth, N. E., et al. (2005). Less effective executive functioning after one night's sleep deprivation. *Journal of Sleep Research, 14*(1), 1-6.

Nunn, J. A., Graydon, F. J. X., Polkey, C. E., & Morris, R. G. (1999). Differential spatial memory impairment after right temporal lobectomy demonstrated using temporal titration. *Brain, 122*(47-59).

O'Donoghue, F. J., Briellmann, R. S., Rochford, P. D., Abbott, D. F., Pell, G. S., Chan, C. H. P., et al. (2005). Cerebral structural changes in severe Obstructive Sleep Apnea. *American Journal of Respiratory and Critical Care Medicine, 171*(10), 1185-1190.

Ohayon, M. M., Lemoine, P., Arnaud-Briant, V., & Dreyfus, M. (2002). Prevalence and consequences of sleep disorders in a shift worker population. *Journal of Psychosomatic Research, 53*(1), 577-583.

Olsson, K., Kandolin, I., & Kauppinen-Toropainen, K. (1990). Stress and coping strategies of three-shift workers. *Travail Humain, 53*(2), 175-188.

Orion Diagnostica. (2005). *Spectria Cortisol RIA: Coated Tube Radionimmunoassay. Instructions for Use*. Espoo, Finland: Orion Diagnostica.

Orton, D. I., & Gruzelier, J. H. (1989). Adverse changes in mood and cognitive performance of house officers after night duty. *British Medical Journal, 298*(6665), 21-23.

Owen, A. M., Sahakian, B. J., Semple, J., Polkey, C. E., & Robbins, T. W. (1995). Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia, 33*(1), 1-24.

Oyewumi, L. K. (1998). Jet lag and relapse of schizoaffective psychosis despite maintenance clozapine treatment. *British Journal of Psychiatry, 173*, 268.

Patrick, G. T. W., & Gilbert, J. A. (1896). Studies from the psychological laboratory of the University of Iowa. On the effects of sleep loss. *Psychological Review, 3*, 486-483.

Picton, T. W. (1992). The P300 wave of the human event-related potential. *Journal Of Clinical Neurophysiology, 9*(4), 456-479.

Portela, L. F., Rotenberg, L., & Waissmann, W. (2004). Self-reported health and sleep complaints among nursing personnel working under 12h night and day shifts. *Chronobiology International, 21*(6), 859-870.

Porter, N. M., & Landfield, P. W. (1998). Stress hormones and brain aging: Adding injury to insult. *Nature Neuroscience, 1*(1), 3-4.

Provencher, S. W. (1993). Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magnetic Resonance in Medicine, 30*(6), 672-679.

Provencher, S. W. (2006). LCModel (Version 6.10). Ontario: Stephen Provencher Incorporated.

Quarton, G. C., Clark, L. D., Cobb, S., & Bauer, W. (1955). Mental disturbances associated with ACTH and cortisone: A review of explanatory hypotheses. *Medicine, 34*, 13-50.

Rasband, W. (2006). ImageJ (Version 1.36b). Bethesda, MD: Research Services Branch, National Institutes of Mental Health.

Redwine, L., Hauger, R. L., Gillin, J. C., & Irwin, M. (2000). Effects of sleep and sleep deprivation on Interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *Journal of Clinical Endocrinology & Metabolism, 85*(10), 3597-3603.

Regestein, Q. R., & Monk, T. H. (1991). Is the poor sleep of shift workers a disorder? *American Journal of Psychiatry, 148*, 1487-1493.

Roden, M., Koller, M., Pirich, K., Vierhapper, H., & Waldhauser, F. (1993). The circadian melatonin and cortisol secretion pattern in permanent night shift workers. *American Journal of Physiology, 265*(1 Pt 2), R261-267.

Rollinson, D., Rathlev, N., Moss, M., Killiany, R., Sassower, K., Auerbach, S., et al. (2003). The effects of consecutive night shifts on neuropsychological performance of interns in the emergency department: A pilot study. *Annals of Emergency Medicine, 41*(3), 400-406.

Rome, H. P., & Braceland, F. L. (1952). The psychological response to ACTH, cortisone, hydrocortisone and related steroid substances. *American Journal of Psychiatry, March 1952*, 641-651.

Roozendaal, B., Okuda, S., de Quervain, D. J.-F., & McGaugh, J. L. (2006). Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience, 138*(3), 901-910.

Ross, A. J., & Sachdev, P. S. (2004). Magnetic resonance spectroscopy in cognitive research. *Brain Research Reviews, 44*, 83-102.

Rouch, I., Wild, P., Ansiau, D., & Marquié, J.-C. (2005). Shiftwork experience, age and cognitive performance. *Ergonomics, 48*(10), 1282-1293.

Sachar, E. J. (1967). Corticosteroids in depressive illness. II. A longitudinal psychoendocrine study. *Archives of General Psychiatry, 17*, 554-567.

Sapolsky, R. M. (1992). *Stress, the Aging Brain, and the Mechanisms of Neuron Death*. Cambridge, MA: MIT Press.

Sapolsky, R. M. (2000a). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry, 57*, 925-935.

Sapolsky, R. M. (2000b). The possibility of neurotoxicity in the hippocampus in Major Depression: A primer on neuron death. *Biological Psychiatry, 48*, 755-765.

Sapolsky, R. M. (2001). Atrophy of the hippocampus in Posttraumatic Stress Disorder: How and when? *Hippocampus, 11*, 90-91.

Schteingart, D. E., Tsao, H. S., McKenzie, A., Victoria, A., & Therrian, B. A. (1980). Sustained remission of Cushing's Disease with mitotane and pituitary irradiation. *Annals of Internal Medicine, 92*, 613-620.

Schuff, N., Neylan, T. C., Lenoci, M. A., Du, A.-T., Weiss, D. S., Marmar, C. R., et al. (2001). Decreased hippocampal N-acetylaspartate in the absence of atrophy in posttraumatic stress disorder. *Biological Psychiatry, 50*(12), 952-959.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry, 20*, 11-21.

Skipper, J. K., Jr, Jung, F. D., & Coffey, L. C. (1990). Nurses and shiftwork: Effects on physical health and mental depression. *Journal of Advanced Nursing, 15*(7), 835-842.

Smith, M. E., McEvoy, L. K., & Gevins, A. (2002). The impact of moderate sleep loss on neurophysiologic signals during working-memory task performance. *Sleep, 25*(7), 784-794.

Smith-Coggins, R., Rosekind, M. R., Hurd, S., & Buccino, K. R. (1994). Relationship of day versus night sleep to physician performance and mood. *Annals of Emergency Medicine, 24*(5), 928-934.

Sonino, N., & Fava, G. A. (2001). Psychiatric disorders associated with Cushing's syndrome: Epidemiology, pathophysiology and treatment. *CNS Drugs, 15*(5), 361-373.

Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet, 354*(9188), 1435-1439.

Spreen, O., & Strauss, E. (1998). *A Compendium of Neuropsychological Tests* (2nd ed.). New York: Oxford University Press.

Squire, L. R., Amaral, D. G., & Press, G. A. (1990). Magnetic resonance imaging of the hippocampal formation and mamillary nuclei distinguish medial temporal lobe and diencephalic amnesia. *Journal of Neuroscience, 10*, 3106-3117.

Starkman, M. N., Giordani, B., Berent, S., Schork, M. A., & Schteingart, D. E. (2001). Elevated cortisol levels in Cushing's disease are associated with cognitive decrements. *Psychosomatic Medicine, 63*(6), 985-993.

Starkman, M. N., Giordani, B., Gebarski, S. S., Berent, S., Schork, M. A., & Schteingart, D. E. (1999). Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biological Psychiatry, 46*(12), 1595-1602.

Starkman, M. N., Giordani, B., Gebarski, S. S., & Schteingart, D. E. (2003). Improvement in learning associated with increase in hippocampal formation volume. *Biological Psychiatry, 53*, 233-238.

Stein, M. B., Koverola, C., Hanna, C., Torchia, M. G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine, 27*, 951-959.

Steyvers, F. J., & Gailard, A. W. (1993). The effects of sleep deprivation and incentives on human performance. *Psychological Research, 55*, 64-70.

Strangman, G., Thompson, J. H., Strauss, M. M., Marshburn, T. H., & Sutton, J. P. (2005). Functional brain imaging of a complex navigation task following one night of total sleep deprivation: A preliminary study. *Journal of Sleep Research, 14*(4), 369-375.

Stricker, J. L., Brown, G. G., Wetherell, L. A., & Drummond, S. P. A. (2006). The impact of sleep deprivation and task difficulty on networks of fMRI brain response. *Journal of the International Neuropsychological Society, 12*(5), 591-597.

Sutano, W., & de Kloet, E. R. (1994). The use of various animal models in the study of stress and stress-related phenomena. *Laboratory Animals, 28*, 293-306.

Suzuki, S., Sakai, O., & Jara, H. (2006). Combined volumetric T1, T2 and secular-T2 quantitative MRI of the brain: Age-related global changes (preliminary results). *Magnetic Resonance Imaging, 24*(7), 877-887.

Takebe, K., Setaishi, C., & Hirami, M. (1966). Effects of bacterial pyrogen on pituitary-adrenal axis at various times in the 24 hours. *Journal of Clinical Endocrinology & Metabolism, 26*, 437-442.

Taylor, P. J., & Pocock, S. J. (1972). Mortality of shift and day workers, 1956-68. *British Journal of Industrial Medicine, 29*, 201-207.

Tepas, D. I., Barnes-Farrell, J. L., Bobko, N., Fischer, F. M., Iskra-Golec, I., & Kaliterna, L. (2004). The impact of night work on subjective reports of well-

being: An exploratory study of health care workers from five nations. *Revista de Saúde Pública, 38*(Suppl), 26-31.

Thakore, J. H. (1998). Stabilisation of the hypothalamic-pituitary-adrenal axis as a treatment modality for mood disorders. *Human Psychopharmacology: Clinical & Experimental, 13*(2), 77-81.

Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., et al. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research, 9*(4), 335-352.

Totterdell, P., Spelten, E., Smith, L., Barton, J., & Folkard, S. (1995). Recovery from work shifts: How long does it take? *Journal of Applied Psychology, 80*(1), 43-57.

Touitou, Y., Motohashi, Y., Reinberg, A., Touitou, C., Bourdeleau, P., Bogdan, A., et al. (1990). Effect of shift work on the night-time secretory patterns of melatonin, prolactin, cortisol and testosterone. *European Journal of Applied Physiology & Occupational Physiology, 60*, 288-292.

Tucker, A., Kinsella, G., Gawith, M., & Harrison, G. (1987). Performance on the Austin Maze: Steps towards normative data. *Australian Psychologist, 22*, 353-359.

Urrila, A. S., Hakkarainen, A., Heikkinen, S., Vuori, K., Stenberg, D., Häkkinen, A.-M., et al. (2004). Stimulus-induced brain lactate: Effects of aging and prolonged wakefulness. *Journal Of Sleep Research, 13*(2), 111-119.

Van Paesschen, W., Connelly, A., Johnson, C. L., & Duncan, J. S. (1996). The amygdala and intractable temporal lobe epilepsy: A quantitative magnetic resonance imaging study. *Neurology, 47*(4), 1021-1031.

Van Paesschen, W., Connelly, A., King, M. D., Jackson, G. D., & Duncan, J. S. (1997). The spectrum of hippocampal sclerosis: A quantitative magnetic resonance imaging study. *Annals of Neurology, 41*, 41-51.

Van Paesschen, W., Sisodiya, S., Connelly, A., Duncan, J. S., Free, S. L., Raymond, A. A., et al. (1995). Quantitative hippocampal MRI and intractable temporal lobe epilepsy. *Neurology, 45*(12), 2233-2240.

Verleger, R. (1997). On the utility of P3 latency as an index of mental chronometry. *Psychophysiology, 34*(2), 131-156.

Vgontzas, A. N., Mastorakos, G., Bixler, E. O., Kales, A., Gold, P. W., & Chrousos, G. P. (1999). Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: Potential clinical implications. *Clinical Endocrinology, 51*(2), 205-215.

Voderholzer, U., Hohagen, F., Klein, T., Jungnickel, J., Kirschbaum, C., Berger, M., et al. (2004). Impact of sleep deprivation and subsequent recovery sleep on cortisol in unmedicated depressed patients. *American Journal of Psychiatry, 161*(8), 1404-1410.

Wagner, U., Degirmenci, M., Drosopoulos, S., Perras, B., & Born, J. (2005). Effects of cortisol suppression on sleep-associated consolidation of neutral and emotional memory. *Biological Psychiatry, 58*(11), 885-893.

Wahlund, L. O., Julin, P., Johansson, S. E., & Scheltens, P. (2000). Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: A comparative study. *Journal of Neurology, Neurosurgery, and Psychiatry, 69*(5), 630-635.

Walsh, K. W. (1978). Frontal lobe problems. In G. V. Stanley & K. W. Walsh (Eds.), *Brain Impairment: Proceedings of the 1976 Brain Impairment Workshop* (pp. 23-28). Parkville: Department of Psychology, University of Melbourne.

Wechsler, D. (1997a). *Wechsler Adult Intelligence Scale - III*. San Antonio: The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale - III*. San Antonio: The Psychological Corporation.

Wehr, T. A., & Wirz-Justice, A. (1982). Circadian mechanisms in affective illness and in antidepressant drug action. *Pharmacopsychiatry, 15*, 31-39.

Weibel, L., Spiegel, K., Follenius, M., Ehrhart, J., & Brandenberger, G. (1996). Internal dissociation of the circadian markers of the cortisol rhythm in night workers. *American Journal Of Physiology, 270*(4 Pt 1), E608-E613.

Wellard, R. M., Briellmann, R. S., Prichard, J. W., Syngeniotis, A., & Jackson, G. D. (2003). Myoinositol abnormalities in temporal lobe epilepsy. *Epilepsia, 44*(6), 815-821.

Wever, R. A. (1979). *The Human Circadian System*. Berlin: Springer.

Whelan, T. B., Schteingart, D. E., Starkman, M. N., & Smith, A. (1980). Neuropsychological deficits in Cushing's syndrome. *Journal of Nervous & Mental Diseases, 168*, 753-757.

Wiedenmayer, C. P., Bansal, R., Anderson, G. M., Zhu, H., Amat, J., Whiteman, R., et al. (2006). Cortisol levels and hippocampus volumes in healthy preadolescent children. *Biological Psychiatry, 60*(8), 856-861.

Winget, C. M., DeRoshia, C. W., Markley, C. L., & Holley, D. C. (1984). A review of human physiological and performance changes associated with desynchronosis of biological rhythms. *Aviation, Space, and Environmental Medicine, 55*(12), 1085-1096.

Wirz-Justice, A. (2000). Biological rhythms in mood disorders. In F. E. Bloom & D. E. Kupfer (Eds.), *Neuropsychopharmacology: the Fourth Generation of*

Progress. Retrieved 14th December, 2005 from: http://www.acnp.org/g4/GN401000099/Default.htm.

Woermann, F. G., McLean, M. A., Bartlett, P. A., Parker, G. J., Barker, G. J., & Duncan, J. S. (1999). Short echo time single-voxel 1H magnetic resonance spectroscopy in magnetic resonance imaging-negative temporal lobe epilepsy: different biochemical profile compared with hippocampal sclerosis. *Annals of Neurology, 45*(3), 369-376.

Wolf, O. T., Dziobek, I., McHugh, P., Sweat, V., de Leon, M. J., Javier, E., et al. (2005). Subjective memory complaints in aging are associated with elevated cortisol levels. *Neurobiology of Aging, 26*(10), 1357-1363.

Wright, J. E., Vogel, J. A., Sampson, J. B., Knapik, J. J., Patton, J. F., & Daniels, W. L. (1983). Effects of travel across time zones (jet-lag) on exercise capacity and performance. *Aviation, Space, and Environmental Medicine, 54*(2), 132-137.

Wu, J. C., Gillin, J. C., Buschbaum, M. S., Hershey, T., Hazlett, E., Sicotte, N., et al. (1991). The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. *Sleep, 14*, 155-162.

Yasukouchi, H., Wada, S., Urasaki, E., & Yokota, A. (1995). Effects of night work on the cognitive function in young and elderly subjects with specific reference to the auditory P300. *Journal of UOEH, 17*(4), 229-246.

Yehuda, R. (2001). Are glucocortoids responsible for putative hippocampal damage in PTSD? How and when to decide. *Hippocampus, 11*, 85-89.

Yehuda, R., Boisoneau, D., Lowry, M. T., & Giller, E. L. (1995). Dose response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. *Archives of General Psychiatry, 52*, 583-593.

Yonelinas, A. P., Kroll, N. E. A., Quamme, J. R., Lazzara, M. M., Sauve, M.-J., Widaman, K. F., et al. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nature Neuroscience, 5*(11), 1236-1241.

Young, D. M. (1995). Psychiatric morbidity in travelers to Honolulu, Hawaii. *Comprehensive Psychiatry, 36*(3), 224-228.

Young, E. A., & Breslau, N. (2004). Saliva cortisol in posttraumatic stress disorder: A community epidemiologic study. *Biological Psychiatry, 56*(3), 205-209.

Zuzewicz, K., Kwarecki, K., & Waterhouse, J. (2000). Circadian rhythm of heart rate, urinary cortisol excretion, and sleep in civil air traffic controllers. *International Journal of Occupational Safety & Ergonomics, 6*(3), 383-392.

Appendix 1: Recruitment advertisement

Ever wondered what night-shift is doing to you?

Participants wanted for research study

It will come as no surprise to the many nurses who work rotating night shifts that shift work is associated with a variety of adverse consequences. Shift work, like jet-lag, disrupts circadian rhythms and affects sleep patterns. It can negatively affect work performance and efficiency, health, and family and social relationships. In the short-term adverse effects may include sleep disturbances, psychosomatic illnesses, work-errors and accidents at work and while travelling to and from work. Longer-term, there is increased risk of gastrointestinal, psychological disorders and cardiovascular diseases, and women may be more vulnerable in relation to reproductive function and family duties. More recent research looking at flight attendants, who suffer chronic jet-lag due to frequent flights across multiple time zones, has suggested that cognitive functions including memory and attention may also be affected by prolonged disruptions to the sleep-wake cycle.

Victoria University School of Psychology in conjunction with the Sleep Disorders Unit and Brain Research Institute at Austin & Repatriation Medical Centre is conducting a study looking at the effects of long-term night shift work on memory and attention, and invites female nurses under the age of 45 years to participate. We require women who have worked a rotating night shift for at least 3 years, alternating between nights and another shift on a weekly or fortnightly basis. Control participants who have not worked nights are also invited to participate. The study involves neuropsychological assessment, brain MRI, keeping a sleep diary and collecting saliva samples. Participation requires attendance at Austin Health Repatriation Campus in Heidelberg for MRI. People with chronic medical or psychiatric disorders or recent stressful life events are not eligible to participate.

Please contact Alexia Pavlis (0418 ### ###; alexia.pavlis@email.au) for additional information about participating in this study.

Appendix 2: Participant information sheet and informed consent

Project Title:

The effect of long-term nightshift work on the temporal lobe and related performance and cognitive functions

Introduction

You are invited to take part in this research study. Before you decide whether to participate, it is important for you to understand why the research is being done, what it will involve and possible benefits, risks and discomforts. Please take time to read the following information carefully and discuss it with your family doctor, if you wish.

What is the background and purpose of the study?

This project is designed to look at the affect of prolonged night shift on areas of the brain and their associated functions.

In this study magnetic resonance imaging of the brain will be used to detect any areas of abnormality that might be present in workers who have worked night shift for a prolonged period of time. We will also be looking for reductions in brain function e.g. memory that may be present in people who worked prolonged night shift.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given a Written Informed Consent Form to sign. The study is not related to your employment at Austin Health or elsewhere.

What will happen to me if I take part?

During the study you will need to make two visits to the Hospital. At the first visit, a brief medical history will be taken, followed by a number of brief neuropsychological tests of cognitive function. This stage will take approximately two hours. On the second visit two weeks later you will need to attend the hospital for one hour between 8am and 12pm to have a MRI scan to measure relative sizes of various sections of the brain. This will involve laying still in the scanner for up to an hour while images are being collected. In the two weeks between the Hospital visits you will be required to keep a Sleep Log, and to collect saliva samples and store them in a cool box (provided to you by the researchers).

Risks

MRI is a safe procedure since radiation is not involved and no contrast media are needed. It is a tunnel shaped machine in which you will be asked to lie for up to an hour at a time while images are being collected. There is knocking sound associated with MRI scanning but this will be masked by headphones. The headphones also allow a means for staff to give you instructions. To allay any feelings of claustrophobia, trained staff will be on hand to assist and a buzzer will be available to call for assistance if needed.

For safety reasons, metallic objects are not permitted within the scanning unit. For this reason, if you have metallic implants of any kind (e.g. pacemakers, artificial joints etc) you will not be able to participate in this study.

There are no risks of harm associated with the neuropsychological and saliva tests.

Benefits

Your participation will help in improving our understanding of the pathological and neuropsychological effects of night shift work.

What if new information becomes available?
If any disorder or pathology is found on the MRI scans or Neuropsychological tests, arrangements will be made for you to have appropriate clinical consultations.

Voluntary Participation
Your participation is entirely voluntary and can be terminated at any time without prejudice. You may contact Dr Gerard Kennedy at anytime during the course of the study on (03) 9### ####.

Costs
There is no cost associated with participating in this study.

Confidentiality
All information obtained during the course of the study is strictly confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. Your data will be identified by code-number only, and your name will not be included in databases. Data may be reported in scientific journals and will not include any information that identifies you as a subject in this study.

Who to contact with questions
For the duration of the study, you will be under the supervision of Dr Mark Howard, Dr Gerard Kennedy and Dr Bruce Thompson. During the course of the study, if you have any questions concerning the nature of the research or your rights as a subject, or you believe you have sustained a research-related injury, please contact:

Dr Mark Howard on (03) 9### #### or Dr Gerard Kennedy on (03) 9### ####

If you wish to contact someone independent of the study about ethical issues or your rights you may contact Mr Max Griffiths, Chairman of the Austin Health Human Research Ethics Committee. Phone 9### #### OR the Secretary, University Human Research Ethics Committee, Victoria University, PO Box 14428 MCMC, Melbourne, 8001. Phone no: 9### ####.

Thank you for your interest in this study.

Victoria University of Technology

Consent Form for Participants Involved in Research

INFORMATION TO PARTICIPANTS:

We would like to invite you to be a part of a study looking at the effect of prolonged night shift work on areas of the brain, and their associated functions.

CERTIFICATION BY PARTICIPANT

I, _____

of _____

certify that I am at least 17 years old* and that I am voluntarily giving my consent to participate in the study entitled:

The effect of long term night shift work on the temporal lobe and related performance and cognitive functions.

being conducted at Victoria University of Technology by:

Dr Gerard Kennedy and Alexia Pavlis

I certify that the objectives of the study, together with any risks to me associated with the procedures listed below to be carried out in the study, have been fully explained to me by: Alexia Pavlis or Emra Oguzkaya

and that I freely consent to participation involving the use of these procedures.

Procedures: Performance of Magnetic Resonance Imaging (MRI) of the brain
Neuropsychological testing
Collection of saliva samples

I certify that I have had the opportunity to have any questions answered and that I understand that I can withdraw from this study at any time and that this withdrawal will not jeopardise me in any way.

I have been informed that the information I provide will be kept confidential.

Signed: **.....** **Date: .....**

Witness other than the experimenter (as appropriate) **.....**

Any queries about your participation in this project may be directed to the researcher (Dr. Gerard Kennedy ph. 9### ####). If you have any queries or complaints about the way you have been treated, you may contact the Secretary, University Human Research Ethics Committee, Victoria University of Technology, PO Box 14428 MCMC, Melbourne, 8001 (telephone no: 03-9### ####).

[*please note: where the subject/s is aged under 18, separate parental consent is required; where the subject is unable to answer for themselves due to mental illness or disability, parental or guardian consent may be required.]

Appendix 3: Sleep health instruments

Appendix 3A

Sleep Health Questionnaire

PART 1

1. What is your age? _____

3. What is your weight? _____

4. What is your height? _____

5. What is your current occupation? _____

6. How many years have you been employed in your current occupation? _____

7. How many years have you been in the work force in total? _____

8. What education have you completed?

(Please tick one of the categories listed below to indicate your answer)

____ (1) None; 0 years
____ (2) 1-3 years (some primary school)
____ (3) 4-6 years (completed primary school)
____ (4) 7-9 years (some secondary school)
____ (5) 10-12 years (completed secondary school)
____ (6) Some college/university; no degree
____ (7) College/university degree
____ (8) Postgraduate or professional education

9. What language(s) do you speak at home? _____
(if not English, about what percent of the time do you speak English at home
_____%)

10. Are you a smoker? Yes ☐ No ☐

If Yes, how many cigarettes do you smoke per day? _____

How many years have you been smoking? _____

11. Do you drink alcohol? Yes ☐ No ☐

If yes, how many standard drinks would you have in a normal week? _____

(one standard drink equals one pot beer, one glass wine, one 30ml shot spirits or liqueur)

How long have you been drinking at this level? _____

12. Are you LEFT ☐ or RIGHT ☐ handed, or AMBIDEXTROUS ☐ ? (please tick)

13. Have you ever lost consciousness as a result of being struck in the head? If so, please describe the circumstances:

_____
_____
_____
_____

14. Do you have a diagnosed neurological condition (stroke, epilepsy, brain tumour, other)?

_____

15. Do you have a diagnosed psychiatric condition (depression, schizophrenia other)?

_____

16. Please list any medications you regularly take and the condition for which

you take them, excluding common pain-killers such as Panadol:

_____
_____
_____
_____

17. In the past year, have you experienced an extremely stressful life event, such as the death of an immediate family member or friend, a life threatening event, a divorce etc?

_____
_____
_____
_____

PART 2

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

1. **During the past month, what time have you usually gone to bed at night?**

   BED TIME: _____

2. **During the past month, how long (in minutes) has it usually taken you to fall asleep each night?**

   NUMBER OF MINUTES: _____

3. **During the past month, what time have you usually woken up and gotten up in the morning?**

   WAKING UP TIME: _____
   GETTING UP TIME: _____

4. **During the past month, how many hours of actual sleep did you get at night? (this may be different than the number of hours you spent in bed)**

   HOURS OF SLEEP PER NIGHT: _____

For each of the following questions, tick ✓ the box [ ] of the one response that best describes your sleeping patterns. Please answer all questions.

5. **During the past month, how often have you had trouble sleeping because you:**

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes	[ ]	[ ]	[ ]	[ ]
b. Wake up in the middle of the night or early morning	[ ]	[ ]	[ ]	[ ]
c. Have to get up to use the bathroom	[ ]	[ ]	[ ]	[ ]
d. Cannot breath comfortably	[ ]	[ ]	[ ]	[ ]
e. Cough or snore loudly	[ ]	[ ]	[ ]	[ ]
f. Feel too cold	[ ]	[ ]	[ ]	[ ]

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
g. Feel to hot	[ ]	[ ]	[ ]	[ ]
h. Had bad dreams	[ ]	[ ]	[ ]	[ ]
i. Have pain	[ ]	[ ]	[ ]	[ ]

j. Other reason(s), please describe:

_____
_____
_____

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
k. How often during the past have you had trouble sleeping because of the above reason(s)	[ ]	[ ]	[ ]	[ ]

6. During the past month, how would you rate your sleep quality overall?

- Very good [ ]
- Fairly good [ ]
- Fairly bad [ ]
- Very bad [ ]

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

- Not during the past month [ ]
- Less than once a week [ ]
- Once or twice a week [ ]
- Three or more times a week [ ]

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

- Not during the past month [ ]
- Less than once a week [ ]
- Once or twice a week [ ]
- Three or more times a week [ ]

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

- No problem at all [ ]
- Only a very slight problem [ ]
- Somewhat of a problem [ ]
- A very big problem [ ]

10. Do you have a bed partner or room mate?

- No bed partner or room mate [ ]
- Partner/room mate in other room [ ]
- Partner in same room, but not same bed [ ]
- Partner in same bed [ ]

If you have a room mate or bed partner, ask him/her how often in the past month you have had:

	Not during the past month	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
a. Loud snoring	[ ]	[ ]	[ ]	[ ]
b. Long pauses between breaths while asleep	[ ]	[ ]	[ ]	[ ]
c. Legs twitching or jerking while you sleep	[ ]	[ ]	[ ]	[ ]
d. Episode of disorientation or confusion during sleep	[ ]	[ ]	[ ]	[ ]

e. Other restlessness while you sleep; please describe:

_____

_____

f. How often during the past have you had trouble sleeping because of the above reason?	[ ]	[ ]	[ ]	[ ]

PART 3

Now we would like to ask you some more questions about your sleep. Please tick the box [ ] of the one response that best describes your sleep.

During the last month, have you had, or have you been told about the following symptoms.

Symptoms	(0) never	(1) rarely less than once a week	(2) 1-2 times a week	(3) 3-4 times a week	(4) 5-7 times a week	(5) don't know
1. Snoring or gasping	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
2. Loud snoring	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
3. Breathing stops, choke or struggle for breath	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
4. Frequent awakenings	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
5. Tossing, turning or thrashing	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
6. Difficulty falling asleep	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
7. Legs feel jumpy or jerky	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
8. Morning headaches	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
9. Falling asleep when at work or school	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
10. Falling asleep when driving	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
11. Excessive sleepiness during the day	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
12. Awaken feeling paralysed, unable to move for short periods	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
13. Find yourself in a vivid dreamlike state when falling asleep or awakening even though you know you're awake	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

PART 4

The following questions refer to sleepiness or the tendency to doze off when relaxed.

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you haven't done some of these things recently, try to work out how they would have affected you.

(Choose the most appropriate number for each situation by putting a tick in one box for each question).

Situation	**(0) would never doze**	**(1) slight chance of dozing**	**(2) moderate chance of dozing**	**(3) high chance of dozing**
1. Sitting and reading	☐	☐	☐	☐
2. Watching TV	☐	☐	☐	☐
3. Sitting, inactive in a public place (eg. theatre or a meeting)	☐	☐	☐	☐
4. As a passenger in a car for an hour without a break	☐	☐	☐	☐
5. Lying down to rest in the afternoon when circumstances permit	☐	☐	☐	☐
6. Sitting and talking to someone	☐	☐	☐	☐
7. Sitting quietly after a lunch without alcohol	☐	☐	☐	☐
8. In a car, while stopped for a few minutes in traffic	☐	☐	☐	☐

Code number:_____ **Please complete this diary of your sleep and work habits for two weeks prior to your MRI**

Each Morning Co mplete The Following (see example below):

1. Write in the day and date
2. With an arrow pointing down mark the ti me you got into bed last night
3. With a plain line mark the ti me you think you fell asleep and woke up in the morning
4. With plain lines, mark ti mes when you woke up and went back to sleep during the night
5. Colour in the blocks of ti me you were asleep
6. With an arrow pointing up mark when you got out of bed
7. With plain lines mark any naps you have during the day
8. With an X mark hours that you were at work

9. Answer the following questions each day

	Day	Date	8 pm	9 pm	10 pm	11 pm	12 pm	1 pm	2 am	3 am	4 am	5 am	6 am	7 am	8 am	9 am	10 am	11 am	no on	1 pm	2 pm	3 pm	4 pm	5 pm	6 pm	7 pm	8 pm
1																											
2																											
3																											
4																											
5																											
6																											
7																											
8																											
9																											
10																											
11																											
12																											
13																											
14																											

E X A M P L E ***E X A M P L E***

List for question 4 above: did any of the following keep you awake at night

1. Noise in the neighbourhood or house
2. Children
3. Pain
4. Too hot or cold
5. Sleeping partner
6. Mind too active
7. Need to go to the toilet
8. Worried about something
9. Other (specify reason and which day)

_____
_____
_____

Appendix 4: Saliva collection instructions and log sheet

Instructions for the collection of saliva samples

Preparation:

- Nothing should be eaten for at least 20 minutes prior to the collection of the saliva. You can drink water.
- You should take a drink of water and swallow it before collecting the saliva sample, in order to rinse your mouth.
- Make sure you have the appropriate container for the sample you are collecting e.g. Day, 0300 (3am); Night, 1900 (7pm).

Collecting the sample:

- Before commencing to collect the sample, take an initial swallow. This will help to stimulate saliva production.
- Sitting in an upright chair, tilt your head forward so that saliva collects in the front of your mouth under your tongue.
- Allow saliva to accumulate under your tongue for about one minute, then spit it directly into the container provided.
- Repeat this procedure until you have collected about 3-5mls (marked on the container).
- The entire procedure for each sample should take about 5 minutes.
- If you forget to take a sample at the appropriate time please

  DO NOT SUBSTITUTE ANOTHER TIME INSTEAD!

  The timing of the samples is important- it's better to miss one than to replace it with a sample collected at the wrong time.

Storing and transporting the samples:

- Initially the samples can be stored in the fridge (up to 2 days) but should be transferred to the freezer as soon as possible until bringing it in for analysis.
- Store the saliva samples in the freezer until the second appointment. Transport the samples to the experimenter in the cool box provided.

Saliva Sampling Timetable

Control and Shift Work participants:
DAY-shift samples- please tick once the sample has been collected

0300 (3am) ●
0700 (7am) ●
1100 (11am) ●
1500 (3pm) ●
1900 (7pm) ●
2300 (11pm) ●

Shift Work participants only:
NIGHT-shift samples- please tick once the sample has been collected

0300 (3am) ●
0700 (7am) ●
1100 (11am) ●
1500 (3pm) ●
1900 (7pm) ●
2300 (11pm) ●

Appendix 5: Tests of normality

	group	Shapiro-Wilk		
		Statistic	df	Sig.
Age of participant	Shift work	0.849	12	0.035
	control	0.901	17	0.072
weight	Shift work	0.948	11	0.623
	control	0.961	16	0.677
height	Shift work	0.961	10	0.802
	control	0.907	16	0.105
years in current occupation	Shift work	0.929	12	0.372
	control	0.557	17	0.000
total years in work force	Shift work	0.909	12	0.208
	control	0.893	17	0.052
estimated years in education	Shift work	0.768	12	0.004
	control	0.829	17	0.005
Epworth Sleepiness Scale Score	Shift work	0.949	11	0.629
	control	0.951	15	0.540
Sleep Diary- Average sleep 24 hr prd	Shift work	0.924	11	0.356
	control	0.933	15	0.306
Austin Maze errors	Shift work	0.938	11	0.501
	control	0.899	17	0.065
Austin Maze time	Shift work	0.898	11	0.173
	control	0.890	17	0.046
Test d2 Concentration raw score (GZ-F)	Shift work	0.951	12	0.658
	control	0.908	17	0.092
Test d2 Total Error Score	Shift work	0.721	12	0.001
	control	0.836	17	0.007
WMS-III Faces 1 Recognition _ Scaled score	Shift work	0.913	12	0.231
	control	0.863	17	0.017
WMS-III Faces 2 Recognition_Scaled Score	Shift work	0.897	12	0.144
	control	0.943	17	0.354
WMS-III Word list 1 recall total score_ scaled score	Shift work	0.911	12	0.217
	control	0.966	17	0.739
WMS-III Word list 2 total recall _ scaled score	Shift work	0.902	12	0.168
	control	0.925	17	0.178
WAIS-III Block Design scaled score	Shift work	0.863	12	0.053
	control	0.902	17	0.074
WAIS-III Vocab scaled score	Shift work	0.937	12	0.463
	control	0.950	17	0.449
WAIS-III Arithmetic scaled score	Shift work	0.883	12	0.097
	control	0.977	17	0.920
WAIS-III Digit Span forward raw score	Shift work	0.893	12	0.131
	control	0.869	16	0.026
WAIS-III Digit Span backward raw score	Shift work	0.946	12	0.575
	control	0.959	16	0.649
WAIS-III Digit Span scaled score	Shift work	0.945	12	0.568
	control	0.874	16	0.031
cortisol dayshift 1500	Shift work	0.854	10	0.065
	control	0.892	16	0.059
cortisol dayshift 1900	Shift work	0.887	10	0.157
	control	0.903	14	0.127
cortisol dayshift 2300	Shift work	0.899	9	0.246
	control	0.677	16	0.000

cortisol dayshift 0300	Shift work	0.641	9	0.000
	control	0.931	16	0.251
cortisol dayshift 0700	Shift work	0.979	10	0.959
	control	0.974	17	0.878
cortisol dayshift 1100	Shift work	0.894	9	0.218
	control	0.943	17	0.360
d_total	Shift work	0.927	10	0.416
	control	0.958	17	0.590
mean 24h dayshift cortisol	Shift work	0.960	10	0.782
	control	0.951	17	0.480
cortisol nightshift 1500	Shift work	0.969	10	0.880
cortisol nightshift 1900	Shift work	0.798	9	0.019
cortisol nightshift 2300	Shift work	0.886	9	0.181
cortisol nightshift 0300	Shift work	0.511	10	0.000
cortisol nightshift 0700	Shift work	0.937	8	0.581
cortisol nightshift 1100	Shift work	0.957	8	0.783
n_total	Shift work	0.937	10	0.520
mean 24h nightshift cortisol	Shift work	0.944	10	0.596
total volume of R hippocampus mm3	Shift work	0.916	10	0.328
	control	0.958	16	0.621
percentage of intracranial volume R hippocampus	Shift work	0.920	10	0.359
	control	0.879	16	0.037
total volume of L hippocampus mm3	Shift work	0.806	10	0.017
	control	0.958	16	0.619
percentage of intracranial volume L hippocampus	Shift work	0.821	10	0.026
	control	0.983	16	0.985
total volume of R TL mm3	Shift work	0.888	10	0.159
	control	0.976	16	0.927
percentage of intracranial volume R TL	Shift work	0.934	10	0.488
	control	0.957	16	0.607
total volume of L TL mm3	Shift work	0.990	10	0.997
	control	0.945	16	0.415
percentage of intracranial volume L TL	Shift work	0.904	10	0.239
	control	0.935	16	0.291
total intracranial volume in mm3	Shift work	0.972	10	0.905
	control	0.820	16	0.005
Creatine L	Shift work	0.885	10	0.150
	control	0.960	15	0.700
myo-Inositol L	Shift work	0.954	10	0.712
	control	0.894	15	0.078
mI/Cr L	Shift work	0.976	10	0.940
	control	0.893	15	0.075
Guanine L	Shift work	0.916	10	0.327
	control	0.772	15	0.002
Gua/Cr L	Shift work	0.927	10	0.418
	control	0.873	15	0.037
Glycerophosphocholine + Phosphorylcholine L	Shift work	0.816	10	0.023
	control	0.984	15	0.990
GPC+PCh/Cr L	Shift work	0.808	10	0.018
	control	0.966	15	0.794
N-acetyl aspartate + N-acetyl aspartate glutamate L	Shift work	0.914	10	0.310
	control	0.950	15	0.524
NAA+NAAG/Cr L	Shift work	0.931	10	0.461
	control	0.927	15	0.247

Glutamate + Glutamine L	Shift work	0.820	10	0.025
	control	0.925	15	0.233
Glu+Gln/Cr L	Shift work	0.742	10	0.003
	control	0.955	15	0.604
Creatine R	Shift work	0.928	10	0.427
	control	0.955	15	0.610
myo-Inositol R	Shift work	0.890	10	0.170
	control	0.911	15	0.138
mI/Cr R	Shift work	0.930	10	0.447
	control	0.313	15	0.000
Guanine R	Shift work	0.880	10	0.132
	control	0.985	15	0.993
Gua/Cr R	Shift work	0.857	10	0.070
	control	0.960	15	0.691
Glycerophosphocholine + Phosphorylcholine R	Shift work	0.934	10	0.485
	control	0.932	15	0.291
GPC+PCh/Cr R	Shift work	0.925	10	0.405
	control	0.961	15	0.713
N-acetyl aspartate + N-acetyl aspartate glutamate R	Shift work	0.970	10	0.892
	control	0.955	15	0.598
NAA+NAAG/Cr R	Shift work	0.966	10	0.850
	control	0.970	15	0.854
Glutamate + Glutamine R	Shift work	0.837	10	0.040
	control	0.940	15	0.386
Glu+Gln/Cr R	Shift work	0.851	10	0.060
	control	0.972	15	0.887

Appendix 6: Fisher's r-to-z transformations

Appendix 6A

Cognitive versus MRI correlations

Austin Maze time

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	0.49	-0.03	0.54	-0.03	1.23	0.22
R hipp. % TIV	0.27	0.18	0.28	0.19	0.19	0.85
L hipp. TV	0.63	-0.40	0.74	-0.43	2.49	0.01
L hipp. % TIV	0.31	-0.10	0.33	-0.10	0.91	0.36
R temp. lobe TV	0.02	-0.25	0.02	-0.26	0.60	0.55
R temp. lobe % TIV	-0.16	0.10	-0.16	0.10	-0.55	0.58
L temp. lobe TV	-0.16	-0.42	-0.16	-0.45	0.62	0.53
L temp. lobe % TIV	-0.29	-0.17	-0.30	-0.17	-0.27	0.79
TIV	0.27	-0.59	0.28	-0.68	2.03	0.04
N	10	16				

Austin Maze errors

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	0.45	-0.18	0.48	-0.19	1.43	0.15
R hipp. % TIV	0.13	0.00	0.14	0.00	0.29	0.77
L hipp. TV	0.67	-0.38	0.82	-0.40	2.61	0.01
L hipp. % TIV	0.09	-0.18	0.09	-0.19	0.59	0.56
R temp. lobe TV	0.33	-0.17	0.35	-0.17	1.10	0.27
R temp. lobe % TIV	0.07	0.08	0.07	0.08	-0.04	0.97
L temp. lobe TV	0.24	-0.33	0.25	-0.35	1.27	0.20
L temp. lobe % TIV	0.02	-0.18	0.02	-0.19	0.44	0.66
TIV	0.58	-0.37	0.67	-0.38	2.25	0.02
N	10	16				

Test d2 Concentration raw score (GZ-F)

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	0.04	0.37	0.04	0.39	-0.73	0.46
R hipp. % TIV	-0.09	0.15	-0.09	0.15	-0.52	0.60
L hipp. TV	-0.09	0.22	-0.09	0.22	-0.67	0.51
L hipp. % TIV	-0.40	0.07	-0.43	0.07	-1.06	0.29
R temp. lobe TV	0.24	0.02	0.25	0.02	0.50	0.62
R temp. lobe % TIV	0.42	-0.20	0.45	-0.20	1.40	0.16
L temp. lobe TV	-0.02	-0.02	-0.02	-0.02	-0.01	0.99
L temp. lobe % TIV	-0.07	-0.20	-0.07	-0.20	0.29	0.77
TIV	0.27	0.12	0.28	0.12	0.34	0.74
N	10	16				

Test d2 Total Error Score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.23	-0.08	-0.23	-0.08	-0.32	0.75
R hipp. % TIV	-0.55	0.02	-0.62	0.02	-1.36	0.17
L hipp. TV	-0.09	0.05	-0.09	0.05	-0.30	0.76
L hipp. % TIV	-0.09	0.00	-0.09	0.00	-0.20	0.84
R temp. lobe TV	0.07	-0.03	0.07	-0.03	0.22	0.83
R temp. lobe % TIV	-0.20	0.00	-0.21	0.00	-0.44	0.66
L temp. lobe TV	0.34	0.07	0.36	0.07	0.61	0.54
L temp. lobe % TIV	0.16	0.00	0.16	0.00	0.34	0.73
TIV	0.18	-0.07	0.19	-0.07	0.54	0.59
N	10	16				

WMS-III Faces 1 Recognition _ Scaled score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	0.03	0.21	0.03	0.22	-0.41	0.68
R hipp. % TIV	0.23	0.08	0.23	0.08	0.32	0.75
L hipp. TV	0.28	-0.08	0.29	-0.08	0.79	0.43
L hipp. % TIV	0.18	-0.05	0.18	-0.05	0.48	0.63
R temp. lobe TV	0.03	0.27	0.03	0.28	-0.53	0.59
R temp. lobe % TIV	0.18	0.14	0.18	0.14	0.08	0.93
L temp. lobe TV	-0.43	0.05	-0.46	0.05	-1.08	0.28
L temp. lobe % TIV	-0.38	-0.06	-0.40	-0.06	-0.71	0.48
TIV	-0.13	0.10	-0.13	0.10	-0.49	0.62
N	10	16				

WMS-III Faces 2 Recognition_Scaled Score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	0.28	0.15	0.29	0.15	0.30	0.77
R hipp. % TIV	0.14	0.11	0.14	0.12	0.06	0.95
L hipp. TV	0.24	-0.01	0.24	-0.01	0.53	0.60
L hipp. % TIV	-0.19	0.04	-0.19	0.04	-0.50	0.62
R temp. lobe TV	0.07	0.13	0.07	0.13	-0.13	0.89
R temp. lobe % TIV	0.02	0.06	0.02	0.06	-0.08	0.93
L temp. lobe TV	-0.26	-0.19	-0.26	-0.19	-0.16	0.87
L temp. lobe % TIV	-0.21	-0.22	-0.21	-0.22	0.02	0.98
TIV	0.24	0.13	0.24	0.13	0.23	0.82
N	10	16				

WMS-III Word list 1 recall total score_ scaled score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.03	0.01	-0.03	0.01	-0.07	0.94
R hipp. % TIV	0.13	-0.13	0.13	-0.13	0.55	0.58
L hipp. TV	-0.53	-0.16	-0.59	-0.17	-0.90	0.37
L hipp. % TIV	-0.43	-0.27	-0.46	-0.28	-0.39	0.70
R temp. lobe TV	0.10	0.22	0.10	0.22	-0.26	0.80
R temp. lobe % TIV	0.20	0.10	0.20	0.10	0.23	0.82
L temp. lobe TV	0.00	0.08	0.00	0.08	-0.17	0.87
L temp. lobe % TIV	0.15	-0.01	0.15	-0.01	0.34	0.73
TIV	-0.13	0.13	-0.13	0.13	-0.55	0.58
N	10	16				

WMS-III Word list 2 total recall _ scaled score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	0.17	-0.10	0.17	-0.10	0.57	0.57
R hipp. % TIV	0.02	-0.08	0.02	-0.08	0.22	0.83
L hipp. TV	-0.07	-0.29	-0.07	-0.30	0.49	0.63
L hipp. % TIV	-0.31	-0.22	-0.32	-0.22	-0.20	0.84
R temp. lobe TV	-0.05	-0.01	-0.05	-0.01	-0.08	0.93
R temp. lobe % TIV	-0.05	0.10	-0.05	0.10	-0.31	0.76
L temp. lobe TV	0.47	-0.17	0.51	-0.17	1.45	0.15
L temp. lobe % TIV	0.24	-0.11	0.24	-0.12	0.76	0.45
TIV	0.17	0.03	0.17	0.03	0.30	0.76
N	10	16				

WAIS-III Block Design scaled score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.44	0.12	-0.47	0.12	-1.27	0.20
R hipp. % TIV	-0.10	-0.14	-0.10	-0.14	0.10	0.92
L hipp. TV	-0.68	0.25	-0.84	0.25	-2.33	0.02
L hipp. % TIV	-0.44	0.04	-0.47	0.04	-1.08	0.28
R temp. lobe TV	-0.05	0.21	-0.05	0.22	-0.56	0.57
R temp. lobe % TIV	0.34	-0.05	0.35	-0.05	0.87	0.39
L temp. lobe TV	0.10	0.37	0.10	0.39	-0.63	0.53
L temp. lobe % TIV	0.29	0.14	0.30	0.14	0.33	0.74
TIV	-0.34	0.39	-0.36	0.41	-1.64	0.10
N	10	16				

WAIS-III Arithmetic scaled score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	0.05	0.10	0.05	0.10	-0.11	0.91
R hipp. % TIV	0.16	-0.09	0.16	-0.09	0.52	0.60
L hipp. TV	0.05	-0.07	0.05	-0.07	0.26	0.80
L hipp. % TIV	0.16	-0.24	0.16	-0.25	0.86	0.39
R temp. lobe TV	-0.29	0.16	-0.29	0.16	-0.96	0.34
R temp. lobe % TIV	-0.08	-0.10	-0.08	-0.10	0.06	0.96
L temp. lobe TV	-0.08	-0.03	-0.08	-0.03	-0.09	0.93
L temp. lobe % TIV	0.08	-0.29	0.08	-0.30	0.81	0.42
TIV	-0.21	0.21	-0.21	0.21	-0.90	0.37
N	10	16				

WAIS-III Vocabulary scaled score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.38	0.08	-0.40	0.08	-1.01	0.31
R hipp. % TIV	-0.14	-0.11	-0.14	-0.11	-0.06	0.95
L hipp. TV	-0.75	0.16	-0.98	0.16	-2.44	0.01
L hipp. % TIV	-0.33	-0.09	-0.34	-0.09	-0.53	0.60
R temp. lobe TV	-0.16	0.21	-0.16	0.22	-0.82	0.41
R temp. lobe % TIV	0.12	-0.06	0.12	-0.06	0.38	0.71
L temp. lobe TV	-0.26	0.33	-0.26	0.35	-1.30	0.19
L temp. lobe % TIV	0.02	0.13	0.02	0.13	-0.23	0.82
TIV	-0.42	0.25	-0.45	0.25	-1.51	0.13
N	10	16				

WAIS-III Digit Span forward raw score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.73	0.15	-0.93	0.15	-2.27	0.02
R hipp. % TIV	-0.33	-0.09	-0.34	-0.09	-0.52	0.60
L hipp. TV	-0.38	0.30	-0.40	0.31	-1.48	0.14
L hipp. % TIV	-0.03	-0.13	-0.03	-0.13	0.23	0.82
R temp. lobe TV	-0.10	0.42	-0.10	0.45	-1.15	0.25
R temp. lobe % TIV	0.20	0.01	0.20	0.01	0.40	0.69
L temp. lobe TV	-0.30	0.32	-0.31	0.33	-1.34	0.18
L temp. lobe % TIV	-0.10	0.01	-0.10	0.01	-0.23	0.82
TIV	-0.43	0.42	-0.46	0.45	-1.90	0.06
N	10	15				

	WAIS-III Digit Span backward raw score					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
R hipp. TV	-0.24	0.11	-0.25	0.11	-0.76	0.45
R hipp. % TIV	0.00	0.01	0.00	0.01	-0.02	0.98
L hipp. TV	0.00	0.26	0.00	0.26	-0.55	0.58
L hipp. % TIV	0.00	0.24	0.00	0.24	-0.50	0.61
R temp. lobe TV	-0.21	0.28	-0.22	0.28	-1.06	0.29
R temp. lobe % TIV	-0.07	0.26	-0.07	0.26	-0.70	0.48
L temp. lobe TV	-0.21	0.46	-0.22	0.50	-1.51	0.13
L temp. lobe % TIV	-0.21	0.54	-0.22	0.61	-1.74	0.08
TIV	-0.29	0.15	-0.30	0.15	-0.95	0.34
N	10	15				

Appendix 6B

Cognitive versus MRS correlations

Left MRS	Austin Maze time					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	-0.29	0.21	-0.30	0.21	-1.07	0.28
myo-Inositol (mI)	0.16	-0.06	0.16	-0.06	0.45	0.65
mI/Cr	0.29	-0.15	0.30	-0.15	0.95	0.34
GPC + PCh	0.16	0.17	0.16	0.17	-0.04	0.97
GPC + PCh/Cr	0.38	-0.08	0.40	-0.08	1.00	0.32
NAA + NAAG	-0.20	0.40	-0.20	0.43	-1.32	0.19
NAA + NAAG/Cr	0.24	0.33	0.25	0.34	-0.19	0.85
N	10	15				

Left MRS	Austin Maze errors					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	0.02	0.20	0.02	0.20	-0.38	0.70
myo-Inositol (mI)	0.38	0.05	0.40	0.05	0.74	0.46
mI/Cr	0.51	-0.09	0.56	-0.09	1.37	0.17
GPC + PCh	0.29	0.09	0.30	0.09	0.44	0.66
GPC + PCh/Cr	0.07	-0.22	0.07	-0.22	0.61	0.54
NAA + NAAG	-0.07	0.20	-0.07	0.20	-0.57	0.57
NAA + NAAG/Cr	0.02	0.10	0.02	0.11	-0.17	0.86
N	10	15				

Left MRS	Test d2 Concentration raw score (GZ-F)					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	0.56	-0.10	0.63	-0.10	1.52	0.13
myo-Inositol (mI)	0.20	-0.23	0.20	-0.23	0.92	0.36
mI/Cr	-0.02	-0.21	-0.02	-0.21	0.40	0.69
GPC + PCh	0.02	0.02	0.02	0.02	0.01	0.99
GPC + PCh/Cr	-0.29	0.21	-0.30	0.21	-1.07	0.28
NAA + NAAG	0.20	-0.10	0.20	-0.10	0.63	0.53
NAA + NAAG/Cr	-0.07	0.19	-0.07	0.19	-0.55	0.58
N	10	15				

Left MRS	Test d2 Total Error Score					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	-0.16	-0.07	-0.16	-0.07	-0.20	0.84
myo-Inositol (mI)	-0.07	-0.07	-0.07	-0.07	0.00	1.00
mI/Cr	-0.11	-0.07	-0.11	-0.07	-0.10	0.92
GPC + PCh	0.16	-0.20	0.16	-0.20	0.77	0.44
GPC + PCh/Cr	0.16	-0.03	0.16	-0.03	0.40	0.69
NAA + NAAG	-0.57	-0.11	-0.65	-0.11	-1.14	0.26
NAA + NAAG/Cr	-0.43	0.09	-0.46	0.09	-1.15	0.25
N	10	15				

Left MRS	WMS-III Faces 1 Recognition _ Scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.08	-0.02	-0.08	-0.02	-0.12	0.91
myo-Inositol (mI)	-0.08	0.12	-0.08	0.13	-0.42	0.67
mI/Cr	0.08	0.19	0.08	0.19	-0.24	0.81
GPC + PCh	-0.48	0.25	-0.52	0.26	-1.63	0.10
GPC + PCh/Cr	-0.13	0.25	-0.13	0.26	-0.80	0.42
NAA + NAAG	0.23	0.17	0.23	0.17	0.13	0.89
NAA + NAAG/Cr	0.28	0.08	0.28	0.08	0.42	0.67
N	10	15				

Left MRS	WMS-III Faces 2 Recognition_Scaled Score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.12	0.05	-0.12	0.05	-0.35	0.72
myo-Inositol (mI)	-0.40	0.07	-0.42	0.07	-1.03	0.30
mI/Cr	-0.16	-0.07	-0.16	-0.07	-0.20	0.84
GPC + PCh	-0.26	0.17	-0.26	0.17	-0.92	0.36
GPC + PCh/Cr	-0.07	0.05	-0.07	0.05	-0.25	0.80
NAA + NAAG	0.12	0.17	0.12	0.17	-0.12	0.90
NAA + NAAG/Cr	0.40	0.05	0.42	0.05	0.77	0.44
N	10	15				

Left MRS	WMS-III Word list 1 recall total score_ scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.25	0.24	0.25	0.24	0.03	0.98
myo-Inositol (mI)	0.00	0.32	0.00	0.33	-0.69	0.49
mI/Cr	-0.10	0.12	-0.10	0.12	-0.46	0.65
GPC + PCh	0.05	0.08	0.05	0.08	-0.06	0.95
GPC + PCh/Cr	0.00	-0.18	0.00	-0.18	0.38	0.71
NAA + NAAG	0.35	0.22	0.36	0.22	0.30	0.76
NAA + NAAG/Cr	0.15	0.00	0.15	0.00	0.32	0.75
N	10	15				

Left MRS	WMS-III Word list 2 total recall _ scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.05	0.20	-0.05	0.20	-0.53	0.60
myo-Inositol (mI)	0.05	0.34	0.05	0.36	-0.65	0.52
mI/Cr	0.05	0.20	0.05	0.20	-0.33	0.74
GPC + PCh	0.52	0.24	0.57	0.25	0.69	0.49
GPC + PCh/Cr	0.19	-0.06	0.19	-0.06	0.53	0.60
NAA + NAAG	-0.38	0.30	-0.40	0.31	-1.49	0.14
NAA + NAAG/Cr	-0.19	-0.04	-0.19	-0.04	-0.32	0.75
N	10	15				

Left MRS	WAIS-III Block Design scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.24	-0.12	0.25	-0.12	0.77	0.44
myo-Inositol (mI)	-0.10	-0.02	-0.10	-0.02	-0.16	0.87
mI/Cr	-0.24	0.02	-0.25	0.02	-0.56	0.57
GPC + PCh	-0.24	0.08	-0.25	0.08	-0.69	0.49
GPC + PCh/Cr	-0.34	0.32	-0.35	0.33	-1.44	0.15
NAA + NAAG	0.15	-0.10	0.15	-0.10	0.52	0.60
NAA + NAAG/Cr	-0.24	-0.08	-0.25	-0.08	-0.35	0.73
N	10	15				

Left MRS	WAIS-III Arithmetic scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.44	-0.09	-0.47	-0.09	-0.81	0.42
myo-Inositol (mI)	-0.13	0.01	-0.13	0.01	-0.30	0.77
mI/Cr	0.08	-0.13	0.08	-0.13	0.44	0.66
GPC + PCh	-0.08	-0.01	-0.08	-0.01	-0.14	0.89
GPC + PCh/Cr	0.13	0.13	0.13	0.13	0.00	1.00
NAA + NAAG	-0.08	-0.09	-0.08	-0.09	0.02	0.98
NAA + NAAG/Cr	0.49	0.05	0.54	0.05	1.03	0.30
N	10	15				

Left MRS	WAIS-III Vocab scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.12	0.01	-0.12	0.01	-0.27	0.79
myo-Inositol (mI)	-0.40	-0.05	-0.42	-0.05	-0.78	0.44
mI/Cr	-0.49	-0.03	-0.53	-0.03	-1.06	0.29
GPC + PCh	-0.02	-0.05	-0.02	-0.05	0.05	0.96
GPC + PCh/Cr	0.12	0.15	0.12	0.15	-0.07	0.95
NAA + NAAG	-0.16	-0.25	-0.16	-0.25	0.18	0.86
NAA + NAAG/Cr	-0.12	-0.09	-0.12	-0.09	-0.06	0.95
N	10	15				

Left MRS	WAIS-III Digit Span forward raw score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.20	-0.37	0.20	-0.38	1.21	0.23
myo-Inositol (mI)	-0.20	-0.18	-0.20	-0.18	-0.05	0.96
mI/Cr	-0.45	-0.15	-0.48	-0.15	-0.68	0.50
GPC + PCh	-0.40	-0.39	-0.42	-0.41	-0.02	0.98
GPC + PCh/Cr	-0.40	0.04	-0.42	0.04	-0.94	0.35
NAA + NAAG	0.00	-0.37	0.00	-0.38	0.79	0.43
NAA + NAAG/Cr	-0.30	-0.06	-0.31	-0.06	-0.51	0.61
N	10	14				

Left MRS	WAIS-III Digit Span backward raw score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.36	0.08	-0.37	0.08	-0.95	0.34
myo-Inositol (mI)	-0.41	0.11	-0.43	0.11	-1.11	0.27
mI/Cr	-0.36	0.18	-0.37	0.18	-1.15	0.25
GPC + PCh	-0.17	0.04	-0.17	0.04	-0.42	0.67
GPC + PCh/Cr	-0.07	0.06	-0.07	0.06	-0.27	0.79
NAA + NAAG	-0.36	-0.08	-0.37	-0.08	-0.60	0.55
NAA + NAAG/Cr	-0.17	-0.11	-0.17	-0.11	-0.13	0.90
N	10	14				

Left MRS	WAIS-III Digit Span scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.24	-0.03	-0.24	-0.03	-0.42	0.67
myo-Inositol (mI)	-0.38	-0.01	-0.40	-0.01	-0.80	0.43
mI/Cr	-0.52	0.03	-0.57	0.03	-1.26	0.21
GPC + PCh	-0.24	-0.10	-0.24	-0.11	-0.28	0.78
GPC + PCh/Cr	-0.14	0.03	-0.14	0.03	-0.37	0.71
NAA + NAAG	-0.33	-0.27	-0.34	-0.27	-0.14	0.89
NAA + NAAG/Cr	-0.28	-0.10	-0.29	-0.11	-0.38	0.70
N	10	14				

Right MRS	Austin Maze time					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.42	-0.02	-0.45	-0.02	-0.91	0.36
myo-Inositol (mI)	-0.24	-0.08	-0.25	-0.08	-0.36	0.72
mI/Cr	-0.11	-0.19	-0.11	-0.19	0.17	0.86
GPC + PCh	-0.29	-0.23	-0.30	-0.23	-0.13	0.89
GPC + PCh/Cr	0.24	-0.31	0.25	-0.32	1.20	0.23
NAA + NAAG	-0.33	0.27	-0.35	0.27	-1.31	0.19
NAA + NAAG/Cr	-0.07	0.25	-0.07	0.25	-0.67	0.50
N	10	15				

Right MRS	Austin Maze errors					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.20	-0.03	-0.20	-0.03	-0.37	0.71
myo-Inositol (mI)	0.07	0.03	0.07	0.03	0.08	0.94
mI/Cr	0.02	0.03	0.02	0.03	-0.01	0.99
GPC + PCh	-0.07	-0.16	-0.07	-0.16	0.20	0.84
GPC + PCh/Cr	0.11	-0.26	0.11	-0.27	0.79	0.43
NAA + NAAG	-0.38	0.03	-0.40	0.03	-0.90	0.37
NAA + NAAG/Cr	-0.29	-0.03	-0.30	-0.03	-0.57	0.57
N	10	15				

Right MRS	Test d2 Concentration raw score (GZ-F)					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.33	-0.13	0.35	-0.13	1.01	0.31
myo-Inositol (mI)	0.16	-0.33	0.16	-0.34	1.04	0.30
mI/Cr	0.02	-0.36	0.02	-0.38	0.85	0.40
GPC + PCh	0.38	-0.15	0.40	-0.15	1.16	0.25
GPC + PCh/Cr	0.11	0.06	0.11	0.06	0.11	0.91
NAA + NAAG	0.42	0.00	0.45	0.00	0.95	0.34
NAA + NAAG/Cr	-0.02	0.48	-0.02	0.52	-1.14	0.25
N	10	15				

Right MRS	Test d2 Total Error Score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.25	-0.01	-0.26	-0.01	-0.52	0.61
myo-Inositol (mI)	-0.02	-0.03	-0.02	-0.03	0.01	0.99
mI/Cr	0.02	0.03	0.02	0.03	-0.01	0.99
GPC + PCh	-0.25	-0.03	-0.26	-0.03	-0.48	0.63
GPC + PCh/Cr	-0.20	0.28	-0.21	0.29	-1.04	0.30
NAA + NAAG	-0.30	-0.13	-0.30	-0.13	-0.38	0.71
NAA + NAAG/Cr	-0.07	-0.20	-0.07	-0.20	0.29	0.77
N	10	15				

Right MRS	WMS-III Faces 1 Recognition _ Scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.03	-0.02	0.03	-0.02	0.10	0.92
myo-Inositol (mI)	-0.53	0.15	-0.59	0.15	-1.55	0.12
mI/Cr	-0.53	0.06	-0.59	0.06	-1.37	0.17
GPC + PCh	-0.38	-0.06	-0.40	-0.06	-0.70	0.48
GPC + PCh/Cr	-0.28	-0.15	-0.28	-0.15	-0.29	0.77
NAA + NAAG	0.08	0.37	0.08	0.39	-0.67	0.50
NAA + NAAG/Cr	-0.18	0.31	-0.18	0.32	-1.05	0.29
N	10	15				

Right MRS	WMS-III Faces 2 Recognition_Scaled Score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.02	0.03	0.02	0.03	-0.01	0.99
myo-Inositol (mI)	-0.58	0.17	-0.67	0.17	-1.76	0.08
mI/Cr	-0.72	0.07	-0.91	0.07	-2.07	0.04
GPC + PCh	-0.44	-0.07	-0.48	-0.07	-0.85	0.40
GPC + PCh/Cr	-0.49	-0.34	-0.53	-0.35	-0.39	0.70
NAA + NAAG	0.02	0.33	0.02	0.35	-0.68	0.50
NAA + NAAG/Cr	-0.02	0.23	-0.02	0.24	-0.55	0.58
N	10	15				

Right MRS	WMS-III Word list 1 recall total score_ scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.55	-0.28	0.61	-0.28	1.89	0.06
myo-Inositol (mI)	0.25	0.02	0.25	0.02	0.49	0.62
mI/Cr	0.20	0.26	0.20	0.26	-0.13	0.90
GPC + PCh	0.50	-0.34	0.55	-0.35	1.88	0.06
GPC + PCh/Cr	-0.10	-0.04	-0.10	-0.04	-0.13	0.90
NAA + NAAG	0.40	-0.04	0.42	-0.04	0.97	0.33
NAA + NAAG/Cr	0.00	0.26	0.00	0.26	-0.55	0.58
N	10	15				

Right MRS	WMS-III Word list 2 total recall _ scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.09	-0.22	-0.09	-0.23	0.27	0.78
myo-Inositol (mI)	0.19	0.02	0.19	0.02	0.36	0.72
mI/Cr	0.14	0.14	0.14	0.14	0.00	1.00
GPC + PCh	0.05	-0.14	0.05	-0.14	0.40	0.69
GPC + PCh/Cr	0.09	0.06	0.09	0.06	0.07	0.94
NAA + NAAG	0.14	0.06	0.14	0.06	0.17	0.86
NAA + NAAG/Cr	0.19	0.12	0.19	0.12	0.15	0.88
N	10	15				

Right MRS	WAIS-III Block Design scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.13	0.04	-0.13	0.04	-0.36	0.72
myo-Inositol (mI)	-0.13	0.08	-0.13	0.08	-0.44	0.66
mI/Cr	-0.13	0.04	-0.13	0.04	-0.36	0.72
GPC + PCh	-0.23	0.06	-0.24	0.06	-0.63	0.53
GPC + PCh/Cr	-0.18	0.10	-0.18	0.10	-0.60	0.55
NAA + NAAG	0.08	0.20	0.08	0.20	-0.27	0.79
NAA + NAAG/Cr	0.03	0.20	0.03	0.20	-0.37	0.71
N	10	15				

Right MRS	WAIS-III Arithmetic scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.21	-0.03	0.21	-0.03	0.51	0.61
myo-Inositol (mI)	0.16	-0.07	0.16	-0.07	0.49	0.62
mI/Cr	0.02	-0.03	0.02	-0.03	0.11	0.91
GPC + PCh	0.12	-0.03	0.12	-0.03	0.31	0.76
GPC + PCh/Cr	-0.21	0.01	-0.21	0.01	-0.47	0.64
NAA + NAAG	0.44	-0.07	0.48	-0.07	1.15	0.25
NAA + NAAG/Cr	0.21	0.17	0.21	0.17	0.09	0.93
N	10	15				

Right MRS	WAIS-III Vocab scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.10	-0.01	0.10	-0.01	0.23	0.82
myo-Inositol (mI)	0.05	-0.11	0.05	-0.11	0.33	0.74
mI/Cr	0.05	-0.07	0.05	-0.07	0.25	0.80
GPC + PCh	0.10	0.05	0.10	0.05	0.11	0.92
GPC + PCh/Cr	-0.05	0.21	-0.05	0.21	-0.55	0.58
NAA + NAAG	0.20	-0.13	0.20	-0.13	0.69	0.49
NAA + NAAG/Cr	0.10	0.09	0.10	0.09	0.02	0.98
N	10	15				

Right MRS	WAIS-III Digit Span forward raw score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.31	-0.01	-0.32	-0.01	-0.64	0.52
myo-Inositol (mI)	-0.41	-0.13	-0.43	-0.13	-0.62	0.53
mI/Cr	-0.36	-0.04	-0.37	-0.04	-0.70	0.48
GPC + PCh	-0.50	0.15	-0.55	0.15	-1.46	0.14
GPC + PCh/Cr	-0.12	0.18	-0.12	0.18	-0.62	0.53
NAA + NAAG	0.07	-0.32	0.07	-0.33	0.83	0.41
NAA + NAAG/Cr	0.21	-0.15	0.22	-0.15	0.77	0.44
N	10	14				

Right MRS	WAIS-III Digit Span backward raw score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	-0.14	0.39	-0.14	0.42	-1.16	0.25
myo-Inositol (mI)	-0.14	0.20	-0.14	0.21	-0.72	0.47
mI/Cr	-0.09	0.16	-0.09	0.16	-0.52	0.60
GPC + PCh	-0.19	0.44	-0.19	0.47	-1.38	0.17
GPC + PCh/Cr	-0.14	0.21	-0.14	0.21	-0.73	0.47
NAA + NAAG	0.14	0.06	0.14	0.06	0.17	0.86
NAA + NAAG/Cr	0.24	-0.20	0.24	-0.21	0.92	0.36
N	10	14				

Right MRS	WAIS-III Digit Span scaled score					
	SW	C	z1	z2	z-test	2 tail sig
Creatine (Cr)	0.48	0.27	0.53	0.27	0.52	0.60
myo-Inositol (mI)	0.34	0.10	0.35	0.11	0.51	0.61
mI/Cr	0.24	0.10	0.25	0.11	0.29	0.77
GPC + PCh	0.34	0.34	0.35	0.35	0.00	1.00
GPC + PCh/Cr	-0.24	0.15	-0.25	0.15	-0.83	0.41
NAA + NAAG	0.53	-0.06	0.59	-0.06	1.35	0.18
NAA + NAAG/Cr	0.05	-0.13	0.05	-0.13	0.37	0.71
N	10	14				

Appendix 6C

Cognitive versus dayshift cortisol correlations

Austin Maze time

Day shift	SW	C	z1	z2	z-test	2 tail sig
d1500	-0.08	-0.22	-0.08	-0.22	0.29	0.77
N	9	16				
d1900	-0.24	-0.01	-0.24	-0.01	-0.46	0.64
N	9	14				
d2300	-0.03	-0.11	-0.03	-0.11	0.16	0.87
N	9	16				
d0300	0.57	0.10	0.65	0.10	1.11	0.27
N	9	16				
d0700	0.20	-0.12	0.20	-0.12	0.66	0.51
N	9	17				
d1100	-0.25	-0.17	-0.26	-0.17	-0.16	0.87
N	8	17				
d_total	0.11	-0.16	0.11	-0.16	0.56	0.58
N	9	17				
d_mean	0.11	-0.08	0.11	-0.08	0.39	0.70
N	9	17				

Austin Maze errors

Day shift	SW	C	z1	z2	z-test	2 tail sig
d1500	-0.03	-0.07	-0.03	-0.07	0.08	0.94
N	9	16				
d1900	-0.29	0.13	-0.30	0.13	-0.85	0.40
N	9	14				
d2300	0.33	0.05	0.34	0.05	0.59	0.55
N	9	16				
d0300	0.33	-0.07	0.34	-0.07	0.84	0.40
N	9	16				
d0700	0.25	0.03	0.26	0.03	0.46	0.64
N	9	17				
d1100	-0.25	-0.17	-0.26	-0.17	-0.16	0.87
N	8	17				
d_total	0.06	-0.04	0.06	-0.04	0.21	0.84
N	9	17				
d_mean	0.06	0.05	0.06	0.05	0.02	0.98
N	9	17				

Test d2 Concentration raw score (GZ-F)

Day shift	SW	C	z1	z2	z-test	2 tail sig
d1500	0.07	0.31	0.07	0.32	-0.53	0.59
N	10	16				
d1900	0.09	-0.07	0.09	-0.07	0.34	0.73
N	10	14				
d2300	0.39	0.02	0.41	0.02	0.79	0.43
N	9	16				
d0300	0.21	0.04	0.21	0.04	0.35	0.73
N	9	16				
d0700	-0.13	0.14	-0.13	0.14	-0.59	0.56
N	10	17				

d1100	-0.20	0.05	-0.20	0.05	-0.52	0.60
N	9	17				
d_total	0.11	0.13	0.11	0.13	-0.04	0.97
N	10	17				
d_mean	-0.02	0.04	-0.02	0.04	-0.13	0.90
N	10	17				

Test d2 Total Error Score

Day shift	**SW**	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.12	-0.38	-0.12	-0.40	0.60	0.55
N	10	16				
d1900	0.19	-0.09	0.20	-0.09	0.60	0.55
N	10	14				
d2300	0.09	0.04	0.09	0.04	0.10	0.92
N	9	16				
d0300	-0.15	0.05	-0.15	0.05	-0.41	0.68
N	9	16				
d0700	-0.14	0.15	-0.14	0.15	-0.63	0.53
N	10	17				
d1100	-0.11	0.28	-0.11	0.29	-0.82	0.41
N	9	17				
d_total	-0.39	0.10	-0.41	0.10	-1.11	0.27
N	10	17				
d_mean	-0.25	0.11	-0.26	0.11	-0.79	0.43
N	10	17				

WMS-III Faces 1 Recognition _ Scaled score

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.15	-0.22	-0.15	-0.22	0.15	0.88
N	10	16				
d1900	-0.08	-0.45	-0.08	-0.48	0.84	0.40
N	10	14				
d2300	-0.47	-0.31	-0.51	-0.32	-0.38	0.70
N	9	16				
d0300	0.27	-0.04	0.28	-0.04	0.64	0.52
N	9	16				
d0700	0.15	-0.17	0.15	-0.17	0.70	0.49
N	10	17				
d1100	-0.15	-0.13	-0.15	-0.13	-0.04	0.97
N	9	17				
d_total	0.19	-0.27	0.19	-0.28	1.01	0.31
N	10	17				
d_mean	0.24	-0.28	0.24	-0.29	1.15	0.25
N	10	17				

WMS-III Faces 2 Recognition_Scaled Score

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.05	-0.05	0.05	-0.05	0.21	0.83
N	10	16				
d1900	-0.12	-0.04	-0.12	-0.04	-0.17	0.87
N	10	14				
d2300	0.03	-0.23	0.03	-0.23	0.54	0.59
N	9	16				

d0300	-0.03	-0.18	-0.03	-0.18	0.31	0.76
N	9	16				
d0700	0.12	-0.06	0.12	-0.06	0.39	0.70
N	10	17				
d1100	-0.29	-0.32	-0.30	-0.33	0.07	0.95
N	9	17				
d_total	-0.14	-0.10	-0.14	-0.10	-0.09	0.93
N	10	17				
d_mean	0.00	-0.17	0.00	-0.17	0.37	0.71
N	10	17				

WMS-III Word list 1 recall total score_ scaled score

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.12	0.11	0.12	0.11	0.02	0.98
N	10	16				
d1900	0.03	-0.10	0.03	-0.10	0.27	0.79
N	10	14				
d2300	0.20	-0.11	0.20	-0.11	0.63	0.53
N	9	16				
d0300	-0.13	-0.40	-0.13	-0.42	0.59	0.55
N	9	16				
d0700	-0.02	-0.01	-0.02	-0.01	-0.02	0.98
N	10	17				
d1100	0.36	0.11	0.38	0.11	0.55	0.59
N	9	17				
d_total	0.15	-0.03	0.38	0.11	0.58	0.56
N	10	17				
d_mean	0.10	-0.12	0.15	-0.03	0.39	0.70
N	10	17				

WMS-III Word list 2 total recall _ scaled score

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.46	-0.05	0.50	-0.05	1.17	0.24
N	10	16				
d1900	-0.28	0.10	-0.29	0.10	-0.80	0.42
N	10	14				
d2300	0.19	-0.30	0.19	-0.31	1.02	0.31
N	9	16				
d0300	-0.29	-0.33	-0.30	-0.34	0.09	0.93
N	9	16				
d0700	-0.34	-0.32	0.10	-0.12	0.48	0.63
N	10	17				
d1100	-0.75	-0.11	-0.97	-0.11	-1.77	0.08
N	9	17				
d_total	-0.26	-0.34	-0.27	-0.35	0.19	0.85
N	10	17				
d_mean	-0.41	-0.43	-0.44	-0.46	0.05	0.96
N	10	17				

WAIS-III Block Design scaled score

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.25	0.04	0.26	0.04	0.46	0.65
N	10	16				
d1900	0.15	-0.30	0.15	-0.31	0.95	0.34

N	10	14				
d2300	-0.10	-0.29	-0.10	-0.30	0.40	0.69
N	9	16				
d0300	-0.41	0.01	-0.44	0.01	-0.90	0.37
N	9	16				
d0700	-0.27	0.04	-0.28	0.04	-0.68	0.49
N	10	17				
d1100	-0.03	0.16	-0.03	0.16	-0.39	0.69
N	9	17				
d_total	-0.15	0.07	-0.15	0.07	-0.48	0.63
N	10	17				
d_mean	-0.24	-0.08	-0.24	-0.08	-0.36	0.72
N	10	17				

WAIS-III Arithmetic scaled score

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.18	0.54	0.18	0.60	-0.90	0.37
N	10	16				
d1900	-0.36	0.06	-0.38	0.06	-0.90	0.37
N	10	14				
d2300	-0.37	0.05	-0.39	0.05	-0.89	0.37
N	9	16				
d0300	0.07	-0.11	0.07	-0.11	0.37	0.71
N	9	16				
d0700	-0.25	0.25	-0.26	0.26	-1.10	0.27
N	10	17				
d1100	-0.41	0.10	-0.44	0.10	-1.10	0.27
N	9	17				
d_total	-0.12	0.20	-0.12	0.20	-0.70	0.48
N	10	17				
d_mean	-0.27	0.07	-0.28	0.07	-0.75	0.45
N	10	17				

WAIS-III Vocab scaled score

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.09	0.47	0.09	0.51	-0.90	0.37
N	10	16				
d1900	0.12	-0.17	0.12	-0.17	0.60	0.55
N	10	14				
d2300	-0.22	0.02	-0.22	0.02	-0.49	0.62
N	9	16				
d0300	-0.06	0.05	-0.06	0.05	-0.22	0.82
N	9	16				
d0700	-0.35	0.20	-0.37	0.20	-1.23	0.22
N	10	17				
d1100	-0.03	0.42	-0.03	0.45	-0.98	0.33
N	9	17				
d_total	-0.18	0.27	-0.18	0.28	-0.99	0.32
N	10	17				
d_mean	-0.23	0.22	-0.23	0.22	-0.99	0.32
N	10	17				

WAIS-III Digit Span forward raw score

	SW	C	z1	z2	z-test	2 tail sig
d1500	-0.31	0.45	-0.32	0.48	-1.72	0.09
N	10	16				
d1900	0.43	0.05	0.46	0.05	0.85	0.40
N	10	14				
d2300	-0.35	0.35	-0.37	0.37	-1.46	0.14
N	9	15				
d0300	0.10	-0.24	0.10	-0.24	0.69	0.49
N	9	15				
d0700	-0.05	0.38	-0.05	0.40	-0.96	0.34
N	10	16				
d1100	0.29	0.08	0.30	0.08	0.44	0.66
N	9	16				
d_total	-0.08	0.34	-0.08	0.35	-0.93	0.35
N	10	16				
d_mean	0.03	0.38	0.03	0.40	-0.79	0.43
N	10	16				

WAIS-III Digit Span backward raw score

	SW	C	z1	z2	z-test	2 tail sig
d1500	0.48	-0.05	0.52	-0.05	1.22	0.22
N	10	16				
d1900	0.30	-0.33	0.31	-0.34	1.35	0.18
N	10	14				
d2300	-0.51	-0.01	-0.56	-0.01	-1.11	0.27
N	9	15				
d0300	-0.06	0.04	-0.06	0.04	-0.2	0.84
N	9	15				
d0700	-0.33	0.14	-0.34	0.14	-1.03	0.30
N	10	16				
d1100	-0.35	0.32	-0.37	0.33	-1.41	0.16
N	9	16				
d_total	-0.12	0.14	-0.12	0.14	-0.56	0.58
N	10	16				
d_mean	-0.26	0.08	-0.27	0.08	-0.74	0.46
N	10	16				

WAIS-III Digit Span scaled score

	SW	C	z1	z2	z-test	2 tail sig
d1500	0.19	0.19	0.19	0.19	0.00	1.00
N	10	16				
d1900	0.43	-0.31	0.46	-0.32	1.61	0.11
N	10	14				
d2300	-0.53	0.12	-0.59	0.12	-1.42	0.16
N	9	15				
d0300	0.13	-0.10	0.13	-0.10	0.46	0.64
N	9	15				
d0700	-0.31	0.31	-0.32	0.32	-1.37	0.17
N	10	16				
d1100	-0.15	0.29	-0.15	0.30	-0.91	0.36
N	9	16				
d_total	-0.14	0.29	-0.14	0.30	-0.94	0.35
N	10	16				
d_mean	-0.28	0.23	-0.29	0.23	-1.11	0.27
N	10	16				

Appendix 6D

Shift workers' dayshift versus nightshift cortisol correlations

Austin Maze time

	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.08	0.33	-0.08	0.34	-0.73	0.46
N	9	9				
1900	-0.24	-0.15	-0.24	-0.15	-0.15	0.88
N	9	8				
2300	-0.03	-0.11	-0.03	-0.11	0.13	0.89
N	9	8				
0300	0.57	0.00	0.65	0.00	1.12	0.26
N	9	9				
0700	0.20	-0.04	0.20	-0.04	0.40	0.69
N	9	8				
1100	-0.25	0.44	-0.26	0.47	-1.15	0.25
N	8	8				
total	0.11	0.03	0.11	0.03	0.14	0.89
N	9	9				
mean	0.11	0.00	0.11	0.00	0.19	0.85
N	9	9				

Austin Maze errors

	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.03	-0.06	-0.03	-0.06	0.05	0.96
N	9	9				
1900	-0.29	0.15	-0.30	0.15	-0.74	0.46
N	9	8				
2300	0.33	-0.11	0.34	-0.11	0.75	0.45
N	9	8				
0300	0.33	-0.18	0.34	-0.18	0.91	0.36
N	9	9				
0700	0.25	-0.11	0.26	-0.11	0.60	0.55
N	9	8				
1100	-0.25	0.07	-0.26	0.07	-0.51	0.61
N	8	8				
total	0.06	-0.03	0.06	-0.03	0.16	0.88
N	9	9				
mean	0.06	-0.06	0.06	-0.06	0.21	0.84
N	9	9				

Test d2 Concentration raw score (GZ-F)

	Ns	Ds	z1	z2	z-test	2 tail sig
1500	0.07	-0.09	0.07	-0.09	0.30	0.76
N	10	10				
1900	0.09	0.09	0.09	0.09	0.00	1.00
N	10	9				
2300	0.39	0.27	0.41	0.28	0.23	0.82
N	9	9				
0300	0.21	0.45	0.21	0.48	-0.49	0.63
N	9	10				
0700	-0.13	0.04	-0.13	0.04	-0.29	0.77
N	10	8				

1100	-0.20	-0.22	-0.20	-0.22	0.03	0.97
N	9	8				
total	0.11	0.27	0.11	0.28	-0.31	0.76
N	10	10				
mean	-0.02	0.38	-0.02	0.40	-0.79	0.43
N	10	10				

Test d2 Total Error Score

	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.12	-0.46	-0.12	-0.50	0.70	0.48
N	10	10				
1900	0.19	0.28	0.19	0.29	-0.17	0.86
N	10	9				
2300	0.09	0.03	0.09	0.03	0.10	0.92
N	9	9				
0300	-0.15	-0.58	-0.15	-0.66	0.92	0.36
N	9	10				
0700	-0.14	-0.38	-0.14	-0.40	0.44	0.66
N	10	8				
1100	-0.11	-0.11	-0.11	-0.11	0.00	1.00
N	9	8				
total	-0.39	-0.74	-0.41	-0.95	1.01	0.31
N	10	10				
mean	-0.25	-0.80	-0.26	-1.10	1.58	0.11
N	10	10				

WMS-III Faces 1 Recognition _ Scaled score

	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.15	0.22	-0.15	0.22	-0.70	0.48
N	10	10				
1900	-0.08	0.20	-0.08	0.20	-0.51	0.61
N	10	9				
2300	-0.47	0.20	-0.51	0.20	-1.23	0.22
N	9	9				
0300	0.27	0.24	0.28	0.24	0.06	0.95
N	9	10				
0700	0.15	-0.37	0.15	-0.39	0.92	0.36
N	10	8				
1100	-0.15	-0.08	-0.15	-0.08	-0.12	0.91
N	9	8				
total	0.19	0.22	0.19	0.22	-0.06	0.95
N	10	10				
mean	0.24	0.19	0.24	0.19	0.10	0.92
N	10	10				

WMS-III Faces 2 Recognition_Scaled Score

	Ns	Ds	z1	z2	z-test	2 tail sig
1500	0.05	-0.07	0.05	-0.07	0.22	0.82
N	10	10				
1900	-0.12	0.13	-0.12	0.13	-0.45	0.65
N	10	9				
2300	0.03	0.09	0.03	0.09	-0.10	0.92
N	9	9				
0300	-0.03	-0.03	-0.03	-0.03	0.00	1.00

N	9	10				
0700	0.12	-0.11	0.12	-0.11	0.39	0.69
N	10	8				
1100	-0.29	-0.31	-0.30	-0.32	0.04	0.97
N	9	8				
total	-0.14	0.07	-0.14	0.07	-0.39	0.69
N	10	10				
mean	0.00	-0.09	0.00	-0.09	0.17	0.87
N	10	10				

WMS-III Word list 1 recall total score_ scaled score

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.12	0.12	0.12	0.12	0.00	1.00
N	10	10				
1900	0.03	-0.29	0.03	-0.30	0.59	0.55
N	10	9				
2300	0.20	-0.03	0.20	-0.03	0.40	0.69
N	9	9				
0300	-0.13	0.35	-0.13	0.37	-0.89	0.37
N	9	10				
0700	-0.02	0.43	-0.02	0.46	-0.82	0.41
N	10	8				
1100	0.36	0.08	0.38	0.08	0.49	0.62
N	9	8				
total	0.15	0.34	0.15	0.35	-0.38	0.70
N	10	10				
mean	0.10	0.29	0.10	0.30	-0.37	0.71
N	10	10				

WMS-III Word list 2 total recall _ scaled score

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.46	0.05	0.50	0.05	0.84	0.40
N	10	10				
1900	-0.28	-0.35	-0.29	-0.37	0.14	0.89
N	10	9				
2300	0.19	-0.23	0.19	-0.23	0.74	0.46
N	9	9				
0300	-0.29	0.11	-0.30	0.11	-0.74	0.46
N	9	10				
0700	-0.34	0.47	-0.35	0.51	-1.48	0.14
N	10	8				
1100	-0.75	-0.04	-0.97	-0.04	-1.54	0.12
N	9	8				
total	-0.26	0.10	-0.27	0.10	-0.69	0.49
N	10	10				
mean	-0.41	0.07	-0.44	0.07	-0.95	0.34
N	10	10				

WAIS-III Block Design scaled score

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.25	-0.07	0.26	-0.07	0.61	0.54
N	10	10				
1900	0.15	-0.03	0.15	-0.03	0.33	0.74
N	10	9				

2300	-0.10	0.13	-0.10	0.13	-0.40	0.69
N	9	9				
0300	-0.41	0.43	-0.44	0.46	-1.61	0.11
N	9	10				
0700	-0.27	0.11	-0.28	0.11	-0.66	0.51
N	10	8				
1100	-0.03	-0.39	-0.03	-0.41	0.63	0.53
N	9	8				
total	-0.15	0.32	-0.15	0.33	-0.90	0.37
N	10	10				
mean	-0.24	0.34	-0.24	0.35	-1.12	0.26
N	10	10				

WAIS-III Arithmetic scaled score

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.18	0.25	0.18	0.26	-0.14	0.89
N	10	10				
1900	-0.36	-0.42	-0.38	-0.45	0.13	0.90
N	10	9				
2300	-0.37	-0.33	-0.39	-0.34	-0.08	0.94
N	9	9				
0300	0.07	0.41	0.07	0.44	-0.66	0.51
N	9	10				
0700	-0.25	0.16	-0.26	0.16	-0.71	0.48
N	10	8				
1100	-0.41	-0.04	-0.44	-0.04	-0.65	0.51
N	9	8				
total	-0.12	0.37	-0.12	0.39	-0.95	0.34
N	10	10				
mean	-0.27	0.27	-0.28	0.28	-1.04	0.30
N	10	10				

WAIS-III Vocab scaled score

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.09	0.26	0.09	0.27	-0.33	0.74
N	10	10				
1900	0.12	-0.50	0.12	-0.55	1.20	0.23
N	10	9				
2300	-0.22	-0.15	-0.22	-0.15	-0.13	0.90
N	9	9				
0300	-0.06	0.51	-0.06	0.56	-1.12	0.26
N	9	10				
0700	-0.35	0.38	-0.37	0.40	-1.31	0.19
N	10	8				
1100	-0.03	0.00	-0.03	0.00	-0.05	0.96
N	9	8				
total	-0.18	0.21	-0.18	0.21	-0.74	0.46
N	10	10				
mean	-0.23	0.32	-0.23	0.33	-1.06	0.29
N	10	10				

WAIS-III Digit Span forward raw score

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	-0.31	-0.05	-0.32	-0.05	-0.51	0.61

N	10	10				
1900	0.43	0.23	0.46	0.23	0.41	0.68
N	10	9				
2300	-0.35	0.24	-0.37	0.24	-1.06	0.29
N	9	9				
0300	0.10	0.06	0.10	0.06	0.07	0.94
N	9	10				
0700	-0.05	-0.29	-0.05	-0.30	0.42	0.67
N	10	8				
1100	0.29	-0.17	0.30	-0.17	0.78	0.44
N	9	8				
total	-0.08	-0.23	-0.08	-0.23	0.29	0.77
N	10	10				
mean	0.03	-0.03	0.03	-0.03	0.11	0.91
N	10	10				

WAIS-III Digit Span backward raw score

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.48	0.33	0.52	0.34	0.34	0.74
N	10	10				
1900	0.30	-0.03	0.31	-0.03	0.61	0.54
N	10	9				
2300	-0.51	0.25	-0.56	0.26	-1.42	0.16
N	9	9				
0300	-0.06	0.21	-0.06	0.21	-0.49	0.62
N	9	10				
0700	-0.33	-0.24	-0.34	-0.24	-0.17	0.87
N	10	8				
1100	-0.35	-0.20	-0.37	-0.20	-0.27	0.79
N	9	8				
total	-0.12	0.19	-0.12	0.19	-0.59	0.56
N	10	10				
mean	-0.26	0.16	-0.27	0.16	-0.80	0.42
N	10	10				

WAIS-III Digit Span scaled score

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.19	0.14	0.19	0.14	0.10	0.92
N	10	10				
1900	0.43	0.03	0.46	0.03	0.77	0.44
N	10	9				
2300	-0.53	0.29	-0.59	0.30	-1.54	0.12
N	9	9				
0300	0.13	0.21	0.13	0.21	-0.15	0.88
N	9	10				
0700	-0.31	-0.31	-0.32	-0.32	0.00	1.00
N	10	8				
1100	-0.15	-0.15	-0.15	-0.15	0.00	1.00
N	9	8				
total	-0.14	0.02	-0.14	0.02	-0.30	0.76
N	10	10				
mean	-0.28	0.09	-0.29	0.09	-0.71	0.48
N	10	10				

Appendix 6E

Cortisol versus POMS correlations

POMS - total mood disturbance score

	SW	C	z1	z2	z-test	2 tail sig
1500h	0.114286	-0.04256	0.11	-0.04	0.3	0.76
N		16				
1900h	0.507972	0.140546	0.56	0.14	0.83	0.41
N		14				
2300h	-0.24287	0.220523	-0.24	0.22	-0.95	0.34
0300h	-0.12144	0.201029	-0.12	0.2	-0.66	0.51
N		16				
0700h	0.228571	0.20226	0.23	0.2	0.06	0.95
N	9					
1100h	0.296296	0.237689	0.31	0.24	0.12	0.45
N	8					
total	0.197203	0.289965	0.2	0.3	-0.2	0.84
mean	0.197203	0.37037	0.2	0.39	-0.38	0.7
		17				

POMS - tension-anxiety score

	SW	C	z1	z2	z-test	2 tail sig
1500h	-0.08697	-0.12069	-0.09	-0.12	0.06	0.95
N		16				
1900h	0.576022	0.189512	0.66	0.19	0.93	0.35
N		14				
2300h	-0.18481	-0.0089	-0.18	-0.01	-0.35	0.73
0300h	0.030802	-0.08853	0.03	-0.09	0.24	0.81
N		16				
0700h	0.144943	0.030303	0.14	0.03	0.23	0.82
N	9					
1100h	0.490653	0.069786	0.54	0.07	0.89	0.37
N	8					
total	0.285831	0.060152	0.3	0.06	0.49	0.63
mean	0.285831	0.097384	0.3	0.1	0.41	0.68
		17				

POMS - depression-dejection score

	SW	C	z1	z2	z-test	2 tail sig
1500h	0.029881	-0.13914	0.03	-0.14	0.35	0.73
N		16				
1900h	0.65625	0.192827	0.79	0.19	1.18	0.24
N		14				
2300h	-0.1905	0.036049	-0.19	0.04	-0.47	0.64
0300h	-0.0635	0.252262	-0.06	0.26	-0.64	0.52
N		16				
0700h	0.089642	-0.07693	0.09	-0.08	0.35	0.73
N	9					
1100h	0.339683	0.157485	0.35	0.16	0.37	0.71
N	8					
total	0.235702	0.015271	0.24	0.02	0.46	0.65
mean	0.235702	0.053251	0.24	0.05	0.4	0.69
		17				

POMS- anger-hostility score

	SW	C	z1	z2	z-test	2 tail sig
1500h	0.4	-0.06114	0.42	-0.06	0.98	0.33
N		16				
1900h	0.209165	-0.01212	0.21	-0.01	0.44	0.66
N		14				
2300h	-0.42502	0.378517	-0.46	0.4	-1.74	0.08
0300h	-0.36431	0.063349	-0.38	0.06	-0.89	0.38
N		16				
0700h	0.171429	0.054064	0.17	0.05	0.25	0.8
N	9					
1100h	-0.10911	-0.01581	-0.11	-0.02	-0.17	0.86
N	8					
total	0.140859	0.076656	0.14	0.08	0.12	0.9
mean	0.140859	0.175654	0.14	0.18	-0.08	0.93
		17				

POMS- fatigue score

	SW	C	z1	z2	z-test	2 tail sig
1500h	0.285714	-0.03509	0.3	-0.04	0.69	0.49
N		16				
1900h	-0.08964	-0.0241	-0.09	-0.02	-0.14	0.89
N		14				
2300h	-0.30359	0.270369	-0.31	0.28	-1.19	0.23
0300h	0.121435	0.2883	0.12	0.3	-0.36	0.72
N		16				
0700h	0.4	0.230797	0.42	0.23	0.39	0.7
N	9					
1100h	-0.10911	0.188982	-0.11	0.19	-0.58	0.56
N	8					
total	0.366234	0.305424	0.39	0.32	0.14	0.89
mean	0.366234	0.342327	0.39	0.35	0.07	0.94
		17				

POMS- confusion-bewilderment score

	SW	C	z1	z2	z-test	2 tail sig
1500h	0.285714	0.008734	0.3	0.01	0.58	0.56
N		16				
1900h	0.239046	0.084362	0.24	0.08	0.32	0.75
N		14				
2300h	-0.36431	0.181042	-0.38	0.18	-1.13	0.26
0300h	-0.30359	0.090094	-0.31	0.09	-0.81	0.42
N		16				
0700h	0.342857	0.230797	0.35	0.23	0.25	0.81
N	9					
1100h	0.254588	0.125988	0.26	0.13	0.24	0.81
N	8					
total	0.30989	0.320695	0.32	0.33	-0.02	0.98
mean	0.30989	0.342327	0.32	0.35	-0.07	0.95
		17				

	POMS- vigor score					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
1500h	-0.17143	-0.04329	-0.17	-0.04	-0.27	0.79
N		16				
1900h	-0.44821	0.178685	-0.48	0.18	-1.31	0.19
N		14				
2300h	-0.06072	0.017946	-0.06	0.02	-0.16	0.87
0300h	0.030359	-0.13337	0.03	-0.13	0.33	0.74
N		16				
0700h	-0.34286	-0.13741	-0.35	-0.14	-0.44	0.66
N	9					
1100h	-0.51852	-0.50787	-0.58	-0.56	-0.03	0.98
N	8					
total	-0.42258	-0.24245	-0.45	-0.24	-0.42	0.68
mean	-0.42258	-0.2491	-0.45	-0.26	-0.39	0.69
		17				

Appendix 6F

Cortisol versus MRI correlations

total volume of R hippocampus mm3

	SW	C	z1	z2	z-test	2 tail sig
d1500	0.37	-0.08	0.39	-0.08	0.94	0.35
N	9	15				
d1900	-0.29	-0.27	-0.30	-0.28	-0.04	0.97
N	9	13				
d2300	0.45	0.32	0.48	0.33	0.31	0.76
N	9	15				
d0300	0.15	0.16	0.15	0.16	-0.02	0.98
N	9	15				
d0700	0.31	0.10	0.32	0.10	0.45	0.66
d1100	-0.18	-0.17	-0.18	-0.17	-0.02	0.98
d_total	0.22	0.06	0.22	0.06	0.33	0.74
d_mean	0.22	0.15	0.22	0.15	0.15	0.88
N	9	16				

percentage of intracranial volume R hippocampus

	SW	C	z1	z2	z-test	2 tail sig
d1500	0.48	-0.23	0.52	-0.23	1.51	0.13
N	9	15				
d1900	-0.35	0.00	-0.37	0.00	-0.71	0.48
N	9	13				
d2300	-0.15	0.44	-0.15	0.47	-1.25	0.21
N	9	15				
d0300	0.09	0.22	0.09	0.22	-0.27	0.79
N	9	15				
d0700	0.48	-0.02	0.52	-0.02	1.10	0.27
d1100	0.04	-0.21	0.04	-0.21	0.51	0.61
d_total	0.44	-0.03	0.47	-0.03	1.02	0.31
d_mean	0.44	0.13	0.47	0.13	0.69	0.49
N	9	16				

total volume of L hippocampus mm3

	SW	C	z1	z2	z-test	2 tail sig
d1500	-0.08	0.00	-0.08	0.00	-0.16	0.87
N	9	15				
d1900	-0.29	-0.22	-0.30	-0.22	-0.15	0.88
N	9	13				
d2300	0.15	0.18	0.15	0.18	-0.06	0.95
N	9	15				
d0300	0.27	0.04	0.28	0.04	0.47	0.64
N	9	15				
d0700	0.31	0.07	0.32	0.07	0.51	0.61
d1100	-0.25	-0.12	-0.26	-0.12	-0.27	0.78
d_total	0.22	0.14	0.22	0.14	0.17	0.87
d_mean	0.22	0.18	0.22	0.18	0.08	0.93
N	9	16				

percentage of intracranial volume L hippocampus

	SW	C	z1	z2	z-test	2 tail sig
d1500	-0.31	-0.21	-0.32	-0.21	-0.21	0.83
N	9	15				
d1900	-0.41	0.00	-0.44	0.00	-0.84	0.40
N	9	13				
d2300	-0.45	0.18	-0.48	0.18	-1.33	0.18
N	9	15				
d0300	0.09	0.22	0.09	0.22	-0.27	0.79
N	9	15				
d0700	0.25	-0.07	0.26	-0.07	0.66	0.51
d1100	0.11	-0.14	0.11	-0.14	0.51	0.61
d_total	0.17	0.03	0.17	0.03	0.29	0.77
d_mean	0.17	0.12	0.17	0.12	0.10	0.92
N	9	16				

total volume of R TL mm3

	SW	C	z1	z2	z-test	2 tail sig
d1500	-0.20	0.04	-0.20	0.04	-0.49	0.63
N	9	15				
d1900	0.12	-0.46	0.12	-0.50	1.20	0.23
N	9	13				
d2300	0.33	0.04	0.34	0.04	0.61	0.54
N	9	15				
d0300	0.15	-0.34	0.15	-0.35	1.01	0.31
N	9	15				
d0700	0.31	-0.03	0.32	-0.03	0.71	0.48
d1100	0.11	-0.02	0.11	-0.02	0.26	0.79
d_total	0.33	-0.19	0.34	-0.19	1.08	0.28
d_mean	0.33	-0.07	0.34	-0.07	0.84	0.40
N	9	16				

percentage of intracranial volume R TL

	SW	C	z1	z2	z-test	2 tail sig
d1500	-0.25	-0.17	-0.26	-0.17	-0.17	0.87
N	9	15				
d1900	0.12	-0.24	0.12	-0.24	0.71	0.48
N	9	13				
d2300	-0.03	-0.08	-0.03	-0.08	0.10	0.92
N	9	15				
d0300	0.03	-0.26	0.03	-0.27	0.59	0.55
N	9	15				
d0700	0.25	-0.20	0.26	-0.20	0.93	0.35
d1100	0.18	-0.09	0.18	-0.09	0.55	0.58
d_total	0.22	-0.34	0.22	-0.35	1.17	0.24
d_mean	0.22	-0.22	0.22	-0.22	0.91	0.36
N	9	16				

total volume of L TL mm3

	SW	C	z1	z2	z-test	2 tail sig
d1500	0.20	0.02	0.20	0.02	0.37	0.71
N	9	15				
d1900	-0.35	-0.46	-0.37	-0.50	0.26	0.80
N	9	13				

d2300	0.33	-0.06	0.34	-0.06	0.81	0.42
N	9	15				
d0300	-0.39	-0.08	-0.41	-0.08	-0.66	0.51
N	9	15				
d0700	0.31	-0.05	0.32	-0.05	0.75	0.45
d1100	-0.18	0.17	-0.18	0.17	-0.72	0.47
d_total	0.00	0.03	0.00	0.03	-0.06	0.95
d_mean	0.00	0.03	0.00	0.03	-0.06	0.95
N	9	16				

percentage of intracranial volume L TL

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.08	-0.19	-0.08	-0.19	0.22	0.82
N	9	15				
d1900	-0.47	-0.32	-0.51	-0.33	-0.35	0.73
N	9	13				
d2300	0.03	-0.10	0.03	-0.10	0.26	0.79
N	9	15				
d0300	-0.45	-0.10	-0.48	-0.10	-0.77	0.44
N	9	15				
d0700	0.37	-0.14	0.39	-0.14	1.07	0.28
d1100	0.11	0.10	0.11	0.10	0.02	0.98
d_total	0.06	-0.06	0.06	-0.06	0.24	0.81
d_mean	0.06	-0.05	0.06	-0.05	0.22	0.82
N	9	16				

total intracranial volume in mm3

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.03	0.17	0.03	0.17	-0.28	0.78
N	9	15				
d1900	0.00	-0.11	0.00	-0.11	0.21	0.83
N	9	13				
d2300	0.69	0.02	0.85	0.02	1.66	0.10
N	9	15				
d0300	0.15	-0.14	0.15	-0.14	0.58	0.56
N	9	15				
d0700	-0.03	-0.03	-0.03	-0.03	0.00	1.00
d1100	-0.33	-0.05	-0.34	-0.05	-0.59	0.55
d_total	-0.11	-0.01	-0.11	-0.01	-0.20	0.84
d_mean	-0.11	-0.03	-0.11	-0.03	-0.16	0.87
N	9	16				

SW **total volume of R hippocampus mm3**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	0.37	0.11	0.39	0.11	0.48	0.63
N	9	9				
n1900	-0.29	-0.23	-0.30	-0.23	-0.11	0.92
N	9	8				
n2300	0.45	-0.11	0.48	-0.11	0.98	0.33
N	9	8				
n0300	0.15	-0.12	0.15	-0.12	0.47	0.64
N	9	9				
n0700	0.31	0.25	0.32	0.26	0.11	0.91
N	9	8				

n1100	-0.18	0.30	-0.18	0.31	-0.78	0.44
N	8	8				
n_total	0.22	0.14	0.22	0.14	0.14	0.89
N	9	9				
n_mean	0.22	0.11	0.22	0.11	0.20	0.84
N	9	9				

SW **percentage of intracranial volume R hippocampus**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	0.48	0.56	0.52	0.63	-0.19	0.85
N	9	9				
n1900	-0.35	-0.31	-0.37	-0.32	-0.07	0.94
N	9	8				
n2300	-0.15	-0.11	-0.15	-0.11	-0.07	0.95
N	9	8				
n0300	0.09	0.12	0.09	0.12	-0.05	0.96
N	9	9				
n0700	0.48	0.47	0.52	0.51	0.02	0.98
N	9	8				
n1100	0.04	0.37	0.04	0.39	-0.55	0.58
N	8	8				
n_total	0.44	0.59	0.47	0.68	-0.36	0.72
N	9	9				
n_mean	0.44	0.56	0.47	0.63	-0.28	0.78
N	9	9				

SW **total volume of L hippocampus mm3**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	-0.08	0.00	-0.08	0.00	-0.14	0.89
N	9	9				
n1900	-0.29	0.23	-0.30	0.23	-0.88	0.38
N	9	8				
n2300	0.15	0.11	0.15	0.11	0.07	0.95
N	9	8				
n0300	0.27	-0.30	0.28	-0.31	1.02	0.31
N	9	9				
n0700	0.31	-0.25	0.32	-0.26	0.95	0.34
N	9	8				
n1100	-0.25	0.15	-0.26	0.15	-0.64	0.52
N	8	8				
n_total	0.22	-0.03	0.22	-0.03	0.44	0.66
N	9	9				
n_mean	0.22	-0.11	0.22	-0.11	0.58	0.56
N	9	9				

SW **percentage of intracranial volume L hippocampus**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	-0.31	0.39	-0.32	0.41	-1.27	0.20
N	9	9				
n1900	-0.41	-0.15	-0.44	-0.15	-0.47	0.64
N	9	8				
n2300	-0.45	-0.34	-0.48	-0.35	-0.22	0.83
N	9	8				

n0300	0.09	-0.18	0.09	-0.18	0.47	0.64
N	9	9				
n0700	0.25	-0.04	0.26	-0.04	0.49	0.63
N	9	8				
n1100	0.11	0.44	0.11	0.47	-0.57	0.57
N	8	8				
n_total	0.17	0.03	0.17	0.03	0.25	0.81
N	9	9				
n_mean	0.17	-0.06	0.17	-0.06	0.40	0.69
N	9	9				

SW **total volume of R TL mm3**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	-0.20	-0.22	-0.20	-0.22	0.04	0.97
N	9	9				
n1900	0.12	0.54	0.12	0.60	-0.80	0.42
N	9	8				
n2300	0.33	0.42	0.34	0.45	-0.17	0.86
N	9	8				
n0300	0.15	0.00	0.15	0.00	0.26	0.79
N	9	9				
n0700	0.31	-0.25	0.32	-0.26	0.95	0.34
N	9	8				
n1100	0.11	-0.15	0.11	-0.15	0.41	0.68
N	8	8				
n_total	0.33	0.08	0.34	0.08	0.45	0.65
N	9	9				
n_mean	0.33	0.11	0.34	0.11	0.40	0.69
N	9	9				

SW **percentage of intracranial volume R TL**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	-0.25	-0.11	-0.26	-0.11	-0.25	0.80
N	9	9				
n1900	0.12	0.46	0.12	0.50	-0.62	0.53
N	9	8				
n2300	-0.03	0.49	-0.03	0.54	-0.93	0.35
N	9	8				
n0300	0.03	0.37	0.03	0.39	-0.62	0.53
N	9	9				
n0700	0.25	-0.18	0.26	-0.18	0.72	0.47
N	9	8				
n1100	0.18	-0.37	0.18	-0.39	0.90	0.37
N	8	8				
n_total	0.22	0.31	0.22	0.32	-0.17	0.87
N	9	9				
n_mean	0.22	0.44	0.22	0.47	-0.43	0.67
N	9	9				

SW **total volume of L TL mm3**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	0.20	-0.44	0.20	-0.47	1.17	0.24
N	9	9				

n1900	-0.35	0.46	-0.37	0.50	-1.42	0.15
N	9	8				
n2300	0.33	-0.11	0.34	-0.11	0.75	0.45
N	9	8				
n0300	-0.39	-0.61	-0.41	-0.71	0.51	0.61
N	9	9				
n0700	0.31	-0.04	0.32	-0.04	0.60	0.55
N	9	8				
n1100	-0.18	-0.22	-0.18	-0.22	0.07	0.95
N	8	8				
n_total	0.00	-0.37	0.00	-0.39	0.67	0.50
N	9	9				
n_mean	0.00	-0.33	0.00	-0.34	0.59	0.55
N	9	9				

SW **percentage of intracranial volume L TL**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	-0.08	-0.28	-0.08	-0.29	0.36	0.72
N	9	9				
n1900	-0.47	0.23	-0.51	0.23	-1.23	0.22
N	9	8				
n2300	0.03	-0.34	0.03	-0.35	0.63	0.53
N	9	8				
n0300	-0.45	-0.43	-0.48	-0.46	-0.04	0.97
N	9	9				
n0700	0.37	0.04	0.39	0.04	0.58	0.57
N	9	8				
n1100	0.11	-0.30	0.11	-0.31	0.66	0.51
N	8	8				
n_total	0.06	-0.08	0.06	-0.08	0.24	0.81
N	9	9				
n_mean	0.06	-0.17	0.06	-0.17	0.40	0.69
N	9	9				

SW **total intracranial volume in mm3**

	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
n1500	0.03	-0.33	0.03	-0.34	0.65	0.52
N	9	9				
n1900	0.00	0.15	0.00	0.15	-0.25	0.80
N	9	8				
n2300	0.69	0.19	0.85	0.19	1.08	0.28
N	9	8				
n0300	0.15	-0.24	0.15	-0.24	0.69	0.49
N	9	9				
n0700	-0.03	-0.04	-0.03	-0.04	0.02	0.99
N	9	8				
n1100	-0.33	-0.07	-0.34	-0.07	-0.43	0.67
N	8	8				
n_total	-0.11	-0.31	-0.11	-0.32	0.36	0.72
N	9	9				
n_mean	-0.11	-0.22	-0.11	-0.22	0.20	0.84
N	9	9				

Appendix 6G

Cortisol versus MRS correlations

DAY SHIFT	Creatine L					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.14	-0.03	-0.14	-0.03	-0.22	0.83
N	9	14				
d1900	0.18	-0.03	0.18	-0.03	0.40	0.69
N	9	12				
d2300	0.39	-0.45	0.41	-0.48	1.77	0.08
d0300	-0.15	-0.18	-0.15	-0.18	0.06	0.95
N	9	14				
d0700	0.25	-0.03	0.26	-0.03	0.57	0.57
d1100	0.25	0.10	0.26	0.10	0.31	0.76
d_total	0.22	0.02	0.22	0.02	0.41	0.68
d_mean	0.22	-0.20	0.22	-0.20	0.85	0.39
N	9	15				

DAY SHIFT	myo-Inositol L					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.14	-0.01	-0.14	-0.01	-0.26	0.80
N	9	14				
d1900	-0.35	-0.06	-0.37	-0.06	-0.58	0.56
N	9	12				
d2300	0.21	-0.52	0.21	-0.58	1.56	0.12
d0300	-0.03	-0.14	-0.03	-0.14	0.22	0.83
N	9	14				
d0700	0.54	-0.24	0.60	-0.24	1.70	0.09
d1100	0.18	0.16	0.18	0.16	0.04	0.97
d_total	0.33	-0.10	0.34	-0.10	0.89	0.38
d_mean	0.33	-0.24	0.34	-0.24	1.18	0.24
N	9	15				

DAY SHIFT	mI/Cr L					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.14	-0.10	-0.14	-0.10	-0.08	0.94
N	9	14				
d1900	-0.59	0.00	-0.68	0.00	-1.29	0.20
N	9	12				
d2300	0.03	-0.09	0.03	-0.09	0.24	0.81
d0300	-0.03	0.00	-0.03	0.00	-0.06	0.95
N	9	14				
d0700	0.54	-0.42	0.60	-0.45	2.10	0.04
d1100	0.04	-0.06	0.04	-0.06	0.20	0.84
d_total	0.22	-0.23	0.22	-0.23	0.92	0.36
d_mean	0.22	-0.22	0.22	-0.22	0.89	0.37
N	9	15				

DAY SHIFT	Glycerophosphocholine + Phosphorylcholine L					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.31	-0.12	0.32	-0.12	0.87	0.38
N	9	14				
d1900	-0.18	-0.55	-0.18	-0.62	0.83	0.41

N	9	12				
d2300	0.45	-0.75	0.48	-0.97	2.87	0.00
d0300	0.03	0.14	0.03	0.14	-0.22	0.83
N	9	14				
d0700	0.08	-0.24	0.08	-0.24	0.65	0.52
d1100	-0.18	0.04	-0.18	0.04	-0.44	0.66
d_total	-0.06	-0.19	-0.06	-0.19	0.26	0.79
d_mean	-0.06	-0.43	-0.06	-0.46	0.80	0.42
N	9	15				

DAY SHIFT	**GPC+PCh/Cr L**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.08	0.06	0.08	0.06	0.04	0.97
N	9	14				
d1900	-0.18	-0.36	-0.18	-0.38	0.37	0.71
N	9	12				
d2300	0.03	-0.12	0.03	-0.12	0.30	0.77
d0300	0.39	0.25	0.41	0.26	0.31	0.76
N	9	14				
d0700	-0.08	-0.13	-0.08	-0.13	0.10	0.92
d1100	0.04	-0.02	0.04	-0.02	0.12	0.90
d_total	0.06	-0.11	0.06	-0.11	0.34	0.73
d_mean	0.06	-0.20	0.06	-0.20	0.53	0.60
N	9	15				

DAY SHIFT	**N-acetyl aspartate + N-acetyl aspartate glutamate L**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.25	-0.17	-0.26	-0.17	-0.17	0.87
N	9	14				
d1900	-0.12	-0.23	-0.12	-0.23	0.22	0.83
N	9	12				
d2300	0.09	-0.49	0.09	-0.54	1.23	0.22
d0300	-0.03	-0.14	-0.03	-0.14	0.22	0.83
N	9	14				
d0700	0.42	-0.13	0.45	-0.13	1.16	0.25
d1100	0.40	-0.02	0.42	-0.02	0.89	0.37
d_total	0.33	-0.15	0.34	-0.15	0.99	0.32
d_mean	0.33	-0.31	0.34	-0.32	1.33	0.18
N	9	15				

DAY SHIFT	**NAA+NAAG/Cr L**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.20	-0.17	-0.20	-0.17	-0.06	0.95
N	9	14				
d1900	-0.53	-0.10	-0.59	-0.10	-0.93	0.35
N	9	12				
d2300	-0.21	0.12	-0.21	0.12	-0.66	0.51
d0300	0.33	0.16	0.34	0.16	0.36	0.72
N	9	14				
d0700	0.08	0.09	0.08	0.09	-0.02	0.98
d1100	0.04	-0.08	0.04	-0.08	0.24	0.81
d_total	0.11	-0.06	0.11	-0.06	0.34	0.73
d_mean	0.11	0.01	0.11	0.01	0.20	0.84
N	9	15				

SW	Creatine L					
	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.33	-0.14	-0.34	-0.14	-0.35	0.73
N	9	9				
1900	0.54	0.18	0.60	0.18	0.70	0.49
N	8	9				
2300	0.34	0.39	0.35	0.41	-0.10	0.92
N	8	9				
300	-0.06	-0.15	-0.06	-0.15	0.16	0.87
N	9	9				
700	-0.11	0.25	-0.11	0.26	-0.60	0.55
N	8	9				
1100	-0.44	0.25	-0.47	0.26	-1.15	0.25
N	8	8				
total	-0.03	0.22	-0.03	0.22	-0.44	0.66
N	9	9				
mean	0.11	0.22	0.11	0.22	-0.20	0.84
N	9	9				

SW	myo-Inositol L					
	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.22	-0.14	-0.22	-0.14	-0.14	0.89
N	9	9				
1900	0.54	-0.35	0.60	-0.37	1.60	0.11
N	8	9				
2300	-0.11	0.21	-0.11	0.21	-0.53	0.59
N	8	9				
300	-0.24	-0.03	-0.24	-0.03	-0.37	0.71
N	9	9				
700	-0.18	0.54	-0.18	0.60	-1.30	0.19
N	8	9				
1100	-0.07	0.18	-0.07	0.18	-0.40	0.69
N	8	8				
total	-0.03	0.33	-0.03	0.34	-0.65	0.52
N	9	9				
mean	0.00	0.33	0.00	0.34	-0.59	0.55
N	9	9				

SW	mI/Cr L					
	Ns	Ds	z1	z2	z-test	2 tail sig
1500	0.00	-0.14	0.00	-0.14	0.24	0.81
N	9	9				
1900	0.23	-0.59	0.23	-0.68	1.51	0.13
N	8	9				
2300	-0.26	0.03	-0.27	0.03	-0.49	0.62
N	8	9				
300	-0.18	-0.03	-0.18	-0.03	-0.26	0.79
N	9	9				
700	-0.11	0.54	-0.11	0.60	-1.18	0.24
N	8	9				
1100	0.07	0.04	0.07	0.04	0.05	0.96
N	8	8				
total	0.08	0.22	0.08	0.22	-0.25	0.80
N	9	9				

mean	0.00	0.22	0.00	0.22	-0.39	0.70
N	9	9				

SW	**Glycerophosphocholine + Phosphorylcholine L**					
	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.06	0.31	0.06	0.32	-0.45	0.65
N	9	9				
1900	-0.31	-0.18	-0.32	-0.18	-0.23	0.82
N	8	9				
2300	-0.34	0.45	-0.35	0.48	-1.39	0.17
N	8	9				
300	-0.18	0.03	-0.18	0.03	-0.37	0.71
N	9	9				
700	0.55	0.08	0.62	0.08	0.89	0.37
N	8	9				
1100	0.37	-0.18	0.39	-0.18	0.90	0.37
N	8	8				
total	-0.14	-0.06	-0.14	-0.06	-0.14	0.89
N	9	9				
mean	-0.06	-0.06	-0.06	-0.06	0.00	1.00
N	9	9				

SW	**GPC+PCh/Cr L**					
	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.50	0.08	0.55	0.08	0.81	0.42
N	9	9				
1900	-0.77	-0.18	-1.02	-0.18	-1.38	0.17
N	8	9				
2300	-0.26	0.03	-0.27	0.03	-0.49	0.62
N	8	9				
300	0.06	0.39	0.06	0.41	-0.61	0.54
N	9	9				
700	0.33	-0.08	0.34	-0.08	0.70	0.48
N	8	9				
1100	0.82	0.04	1.16	0.04	1.77	0.08
N	8	8				
total	0.08	0.06	0.08	0.06	0.03	0.97
N	9	9				
mean	-0.06	0.06	-0.06	0.06	-0.21	0.84
N	9	9				

SW	**N-acetyl aspartate + N-acetyl aspartate glutamate L**					
	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.00	-0.25	0.00	-0.26	0.44	0.66
N	9	9				
1900	0.31	-0.12	0.32	-0.12	0.73	0.47
N	8	9				
2300	0.11	0.09	0.11	0.09	0.03	0.97
N	8	9				
300	0.30	-0.03	0.31	-0.03	0.59	0.56
N	9	9				
700	-0.11	0.42	-0.11	0.45	-0.92	0.36
N	8	9				

1100	-0.30	0.40	-0.31	0.42	-1.16	0.25
N	8	8				
total	0.31	0.33	0.32	0.34	-0.04	0.97
N	9	9				
mean	0.33	0.33	0.34	0.34	0.00	1.00
N	9	9				

SW	**NAA+NAAG/Cr L**					
	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.33	-0.20	0.34	-0.20	0.94	0.34
N	9	9				
1900	-0.39	-0.53	-0.41	-0.59	0.29	0.77
N	8	9				
2300	-0.57	-0.21	-0.65	-0.21	-0.72	0.47
N	8	9				
300	0.24	0.33	0.24	0.34	-0.17	0.87
N	9	9				
700	0.40	0.08	0.42	0.08	0.57	0.57
N	8	9				
1100	0.30	0.04	0.31	0.04	0.43	0.67
N	8	8				
total	0.42	0.11	0.45	0.11	0.58	0.56
N	9	9				
mean	0.22	0.11	0.22	0.11	0.20	0.84
N	9	9				

DAY SHIFT	**Creatine R**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.14	-0.06	-0.14	-0.06	-0.16	0.87
N	9	14				
d1900	0.00	-0.19	0.00	-0.19	0.36	0.72
N	9	12				
d2300	-0.09	-0.12	-0.09	-0.12	0.06	0.95
N	9	14				
d0300	-0.15	0.14	-0.15	0.14	-0.58	0.56
N	9	14				
d0700	0.25	0.07	0.26	0.07	0.37	0.71
N	9	15				
d1100	0.33	0.10	0.34	0.10	0.46	0.65
N	8	15				
d_total	0.22	0.15	0.22	0.15	0.15	0.88
N	9	15				
d_mean	0.22	0.10	0.22	0.10	0.25	0.81
N	9	15				

DAY SHIFT	**myo-Inositol R**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.37	-0.19	-0.39	-0.19	-0.39	0.70
N	9	14				
d1900	-0.18	-0.06	-0.18	-0.06	-0.23	0.82
N	9	12				
d2300	0.27	-0.35	0.28	-0.37	1.27	0.21
N	9	14				

d0300	0.03	-0.07	0.03	-0.07	0.20	0.84
N	9	14				
d0700	0.08	-0.09	0.08	-0.09	0.34	0.73
N	9	15				
d1100	0.33	0.12	0.34	0.12	0.42	0.68
N	8	15				
d_total	0.00	0.04	0.00	0.04	-0.08	0.94
N	9	15				
d_mean	0.00	-0.07	0.00	-0.07	0.14	0.89
N	9	15				

DAY SHIFT	**ml/Cr R**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.37	-0.03	-0.39	-0.03	-0.71	0.48
N	9	14				
d1900	-0.18	-0.06	-0.18	-0.06	-0.23	0.82
N	9	12				
d2300	0.15	-0.28	0.15	-0.29	0.86	0.39
N	9	14				
d0300	0.03	-0.20	0.03	-0.20	0.46	0.65
N	9	14				
d0700	0.08	-0.07	0.08	-0.07	0.30	0.76
N	9	15				
d1100	0.33	0.20	0.34	0.20	0.26	0.79
N	8	15				
d_total	0.00	0.04	0.00	0.04	-0.08	0.94
N	9	15				
d_mean	0.00	-0.07	0.00	-0.07	0.14	0.89
N	9	15				

DAY SHIFT	**Glycerophosphocholine + Phosphorylcholine R**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.25	-0.06	-0.26	-0.06	-0.38	0.70
N	9	14				
d1900	-0.06	-0.06	-0.06	-0.06	0.00	1.00
N	9	12				
d2300	0.27	-0.05	0.28	-0.05	0.64	0.52
N	9	14				
d0300	0.09	0.23	0.09	0.23	-0.28	0.78
N	9	14				
d0700	0.14	-0.03	0.14	-0.03	0.34	0.73
N	9	15				
d1100	0.33	-0.16	0.34	-0.16	0.95	0.34
N	8	15				
d_total	0.11	-0.04	0.11	-0.04	0.30	0.76
N	9	15				
d_mean	0.11	-0.03	0.11	-0.03	0.28	0.78
N	9	15				

DAY SHIFT	**GPC+PCh/Cr R**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	-0.08	0.15	-0.08	0.15	-0.46	0.65
N	9	14				
d1900	-0.24	0.07	-0.24	0.07	-0.60	0.55

N	9	12				
d2300	0.03	0.25	0.03	0.26	-0.44	0.66
N	9	14				
d0300	0.09	0.14	0.09	0.14	-0.10	0.92
N	9	14				
d0700	0.03	0.03	0.03	0.03	0.00	1.00
N	9	15				
d1100	-0.04	0.00	-0.04	0.00	-0.08	0.94
N	8	15				
d_total	0.00	0.06	0.00	0.06	-0.12	0.90
N	9	15				
d_mean	0.00	0.03	0.00	0.03	-0.06	0.95
N	9	15				

DAY SHIFT	**N-acetyl aspartate + N-acetyl aspartate glutamate R**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.25	-0.19	0.26	-0.19	0.88	0.38
N	9	14				
d1900	0.24	-0.45	0.24	-0.48	1.38	0.17
N	9	12				
d2300	0.15	-0.35	0.15	-0.37	1.02	0.31
N	9	14				
d0300	-0.03	-0.09	-0.03	-0.09	0.12	0.91
N	9	14				
d0700	-0.31	-0.17	-0.32	-0.17	-0.30	0.77
N	9	15				
d1100	-0.11	-0.14	-0.11	-0.14	0.06	0.95
N	8	15				
d_total	-0.11	-0.17	-0.11	-0.17	0.12	0.90
N	9	15				
d_mean	-0.11	-0.33	-0.11	-0.34	0.46	0.64
N	9	15				

DAY SHIFT	**NAA+NAAG/Cr R**					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
d1500	0.48	0.10	0.52	0.10	0.83	0.40
N	9	14				
d1900	0.18	-0.29	0.18	-0.30	0.91	0.36
N	9	12				
d2300	-0.09	-0.12	-0.09	-0.12	0.06	0.95
N	9	14				
d0300	-0.09	-0.05	-0.09	-0.05	-0.08	0.94
N	9	14				
d0700	-0.31	-0.11	-0.32	-0.11	-0.42	0.67
N	9	15				
d1100	-0.18	-0.06	-0.18	-0.06	-0.23	0.82
N	8	15				
d_total	-0.22	-0.11	-0.22	-0.11	-0.23	0.82
N	9	15				
d_mean	-0.22	-0.28	-0.22	-0.29	0.13	0.90
N	9	15				

SW	Creatine R					
	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.11	-0.14	-0.11	-0.14	0.05	0.96
N	9	9				
1900	0.23	0.00	0.23	0.00	0.39	0.70
N	8	9				
2300	0.19	-0.09	0.19	-0.09	0.47	0.64
N	8	9				
0300	0.43	-0.15	0.46	-0.15	1.06	0.29
N	9	9				
0700	-0.11	0.25	-0.11	0.26	-0.60	0.55
N	8	9				
1100	-0.37	0.33	-0.39	0.34	-1.16	0.25
N	8	8				
total	0.31	0.22	0.32	0.22	0.17	0.87
N	9	9				
mean	0.33	0.22	0.34	0.22	0.21	0.84
N	9	9				

SW	myo-Inositol R					
	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.33	-0.37	-0.34	-0.39	0.08	0.94
N	9	9				
1900	0.00	-0.18	0.00	-0.18	0.30	0.76
N	8	9				
2300	-0.34	0.27	-0.35	0.28	-1.04	0.30
N	8	9				
0300	-0.06	0.03	-0.06	0.03	-0.16	0.88
N	9	9				
0700	0.25	0.08	0.26	0.08	0.29	0.77
N	8	9				
1100	0.00	0.33	0.00	0.34	-0.54	0.59
N	8	8				
total	-0.08	0.00	-0.08	0.00	-0.14	0.89
N	9	9				
mean	0.11	0.00	0.11	0.00	0.19	0.85
N	9	9				

SW	mI/Cr R					
	Ns	Ds	z1	z2	z-test	2 tail sig
1500	-0.33	-0.37	-0.34	-0.39	0.08	0.94
N	9	9				
1900	0.08	-0.18	0.08	-0.18	0.43	0.67
N	8	9				
2300	-0.34	0.15	-0.35	0.15	-0.83	0.40
N	8	9				
0300	-0.18	0.03	-0.18	0.03	-0.37	0.71
N	9	9				
0700	0.11	0.08	0.11	0.08	0.05	0.96
N	8	9				
1100	0.00	0.33	0.00	0.34	-0.54	0.59
N	8	8				
total	-0.20	0.00	-0.20	0.00	-0.35	0.73
N	9	9				

mean	0.00	0.00	0.00	0.00	0.00	1.00
N	9	9				

SW	**Glycerophosphocholine + Phosphorylcholine R**					
	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	-0.22	-0.25	-0.22	-0.26	0.06	0.96
N	9	9				
1900	0.08	-0.06	0.08	-0.06	0.23	0.82
N	8	9				
2300	-0.11	0.27	-0.11	0.28	-0.64	0.52
N	8	9				
0300	0.18	0.09	0.18	0.09	0.16	0.87
N	9	9				
0700	0.25	0.14	0.26	0.14	0.19	0.85
N	8	9				
1100	-0.07	0.33	-0.07	0.34	-0.65	0.51
N	8	8				
total	0.03	0.11	0.03	0.11	-0.14	0.89
N	9	9				
mean	0.22	0.11	0.22	0.11	0.20	0.84
N	9	9				

SW	**GPC+PCh/Cr R**					
	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.22	-0.08	0.22	-0.08	0.53	0.60
N	9	9				
1900	-0.23	-0.24	-0.23	-0.24	0.02	0.99
N	8	9				
2300	-0.42	0.03	-0.45	0.03	-0.79	0.43
N	8	9				
0300	-0.12	0.09	-0.12	0.09	-0.37	0.71
N	9	9				
0700	0.47	0.03	0.51	0.03	0.79	0.43
N	8	9				
1100	0.52	-0.04	0.58	-0.04	0.97	0.33
N	8	8				
total	-0.08	0.00	-0.08	0.00	-0.14	0.89
N	9	9				
mean	0.11	0.00	0.11	0.00	0.19	0.85
N	9	9				

SW	**N-acetyl aspartate + N-acetyl aspartate glutamate R**					
	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	-0.11	0.25	-0.11	0.26	-0.63	0.53
N	9	9				
1900	-0.15	0.24	-0.15	0.24	-0.65	0.51
N	8	9				
2300	0.19	0.15	0.19	0.15	0.07	0.95
N	8	9				
0300	0.55	-0.03	0.62	-0.03	1.12	0.26
N	9	9				
0700	0.33	-0.31	0.34	-0.32	1.10	0.27
N	8	9				
1100	-0.15	-0.11	-0.15	-0.11	-0.06	0.95

N	8	8				
total	0.14	-0.11	0.14	-0.11	0.44	0.66
N	9	9				
mean	0.33	-0.11	0.34	-0.11	0.79	0.43
N	9	9				

SW	**NAA+NAAG/Cr R**					
	Ns	**Ds**	**z1**	**z2**	**z-test**	**2 tail sig**
1500	0.11	0.48	0.11	0.52	-0.71	0.47
N	9	9				
1900	-0.46	0.18	-0.50	0.18	-1.12	0.26
N	8	9				
2300	-0.11	-0.09	-0.11	-0.09	-0.03	0.97
N	8	9				
0300	0.06	-0.09	0.06	-0.09	0.26	0.79
N	9	9				
0700	0.47	-0.31	0.51	-0.32	1.37	0.17
N	8	9				
1100	0.22	-0.18	0.22	-0.18	0.64	0.52
N	8	8				
total	0.03	-0.22	0.03	-0.22	0.44	0.66
N	9	9				
mean	0.11	-0.22	0.11	-0.22	0.58	0.56
N	9	9				

Appendix 6H

T1-MRI versus MRS correlations

	L temp. lobe TV					
Left	**SW**	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	-0.18	-0.18	-0.18	-0.18	0.00	1.00
myo-Inositol (mI)	0.22	0.01	0.22	0.01	0.45	0.65
mI/Cr	0.36	0.18	0.38	0.18	0.41	0.68
GPC + PCh	0.04	-0.22	0.04	-0.22	0.55	0.58
GPC + PCh/Cr	0.09	0.01	0.09	0.01	0.17	0.87
NAA + NAAG	0.00	-0.37	0.00	-0.39	0.82	0.41
NAA + NAAG/Cr	0.18	-0.16	0.18	-0.16	0.72	0.47
N	10	15				

	L temp. lobe % TIV					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	-0.31	0.09	-0.32	0.09	-0.86	0.39
myo-Inositol (mI)	0.18	0.09	0.18	0.09	0.19	0.85
mI/Cr	0.40	0.26	0.42	0.27	0.33	0.74
GPC + PCh	-0.09	-0.07	-0.09	-0.07	-0.04	0.97
GPC + PCh/Cr	0.22	-0.14	0.22	-0.14	0.77	0.44
NAA + NAAG	0.04	-0.07	0.04	-0.07	0.23	0.82
NAA + NAAG/Cr	0.22	-0.12	0.22	-0.12	0.72	0.47
N	10	15				

	L hipp. TV					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	0.33	-0.05	0.34	-0.05	0.83	0.41
myo-Inositol (mI)	0.60	0.22	0.69	0.22	0.99	0.32
mI/Cr	0.47	0.39	0.51	0.41	0.21	0.84
GPC + PCh	0.33	-0.09	0.34	-0.09	0.91	0.36
GPC + PCh/Cr	-0.07	0.07	-0.07	0.07	-0.29	0.77
NAA + NAAG	-0.02	-0.35	-0.02	-0.37	0.73	0.47
NAA + NAAG/Cr	-0.29	-0.41	-0.30	-0.44	0.29	0.77
N	10	15				

	L hipp. % TIV					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	0.29	0.28	0.30	0.29	0.02	0.98
myo-Inositol (mI)	0.47	0.31	0.51	0.32	0.40	0.69
mI/Cr	0.42	0.45	0.45	0.48	-0.08	0.94
GPC + PCh	0.11	0.09	0.11	0.09	0.04	0.97
GPC + PCh/Cr	-0.20	-0.14	-0.20	-0.14	-0.13	0.90
NAA + NAAG	0.11	0.01	0.11	0.01	0.21	0.83
NAA + NAAG/Cr	-0.16	-0.39	-0.16	-0.41	0.53	0.60
N	10	15				

	R temp. lobe TV					
Right	**SW**	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	-0.27	-0.14	-0.28	-0.14	-0.29	0.78
myo-Inositol (mI)	-0.13	-0.43	-0.13	-0.46	0.69	0.49
mI/Cr	-0.18	-0.35	-0.18	-0.37	0.39	0.70

GPC + PCh	-0.13	-0.12	-0.13	-0.12	-0.02	0.98
GPC + PCh/Cr	0.13	0.01	0.13	0.01	0.25	0.80
NAA + NAAG	-0.09	0.03	-0.09	0.03	-0.25	0.80
NAA + NAAG/Cr	0.09	0.31	0.09	0.32	-0.48	0.63
N	10	15				

R temp. lobe % TIV

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	-0.22	-0.01	-0.22	-0.01	-0.45	0.65
myo-Inositol (mI)	-0.27	-0.33	-0.28	-0.34	0.14	0.89
mI/Cr	-0.22	-0.41	-0.22	-0.44	0.45	0.66
GPC + PCh	-0.09	-0.07	-0.09	-0.07	-0.04	0.97
GPC + PCh/Cr	0.27	-0.03	0.28	-0.03	0.65	0.52
NAA + NAAG	0.13	-0.03	0.13	-0.03	0.34	0.74
NAA + NAAG/Cr	0.31	0.14	0.32	0.14	0.38	0.71
N	10	15				

R hipp. TV

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	0.38	-0.22	0.40	-0.22	1.31	0.19
myo-Inositol (mI)	0.20	-0.09	0.20	-0.09	0.62	0.54
mI/Cr	0.07	-0.01	0.07	-0.01	0.17	0.87
GPC + PCh	0.07	-0.05	0.07	-0.05	0.25	0.80
GPC + PCh/Cr	-0.29	0.05	-0.30	0.05	-0.73	0.46
NAA + NAAG	-0.16	0.07	-0.16	0.07	-0.49	0.63
NAA + NAAG/Cr	-0.60	0.31	-0.69	0.32	-2.13	0.03
N	10	15				

R hipp. % TIV

	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
Creatine (Cr)	0.64	0.16	0.76	0.16	1.25	0.21
myo-Inositol (mI)	0.29	0.18	0.30	0.18	0.25	0.81
mI/Cr	0.16	0.03	0.16	0.03	0.28	0.78
GPC + PCh	0.33	0.14	0.34	0.14	0.42	0.67
GPC + PCh/Cr	-0.29	-0.20	-0.30	-0.20	-0.20	0.84
NAA + NAAG	0.11	0.37	0.11	0.39	-0.58	0.56
NAA + NAAG/Cr	-0.51	0.12	-0.56	0.12	-1.44	0.15
N	10	15				

Appendix 6I

T2-MRI versus cognitive correlations

ROI T2 right hippocampal measures

	SW	C	z1	z2	z-test	2 tail sig
Austin Maze time	**0.56***	0.07	0.63	0.07	1.18	0.24
Austin Maze errors	0.42	0.08	0.45	0.08	0.77	0.44
Test d2 Concentration	0.07	-0.38	0.07	-0.4	0.99	0.32
Test d2 Total Errors	0.30	**0.46***	0.31	0.5	-0.39	0.69
WMS-III Faces 1	0.28	-0.07	0.29	-0.07	0.75	0.45
WMS-III Faces 2	0.40	-0.06	0.42	-0.06	1.02	0.31
WMS-III Word list 1	**-0.57***	0.09	-0.62	0.09	-1.49	0.14
WMS-III Word list 2	-0.09	0.27	-0.09	0.28	-0.77	0.44
WAIS-III Vocab	-0.35	-0.14	-0.37	-0.14	-0.47	0.64
WAIS-III Block Design	**-0.68****	-0.11	-0.83	-0.11	-1.51	0.13
WAIS-III Arithmetic	-0.03	-0.14	-0.03	-0.14	0.23	0.82
N		15				
WAIS-III Digit Span	-0.05	-0.07	-0.05	-0.07	0.04	0.97
WAIS-III Digit Span f	-0.20	-0.17	-0.2	-0.17	-0.06	0.95
WAIS-III Digit Span b	0.12	0.11	0.12	0.11	0.02	0.98
N	10	14				

ROI T2 left hippocampal measures

	SW	C	z1	z2	z-test	2 tail sig
Austin Maze time	0.09	-0.30	0.09	-0.31	0.84	0.40
Austin Maze errors	-0.13	-0.04	-0.13	-0.04	-0.19	0.85
Test d2 Concentration	-0.22	-0.18	-0.22	-0.18	-0.09	0.93
Test d2 Total Errors	0.05	0.06	0.05	0.06	-0.02	0.98
WMS-III Faces 1	0.25	0.01	0.26	0.01	0.52	0.61
WMS-III Faces 2	0.19	0.16	0.19	0.16	0.07	0.95
WMS-III Word list 1	-0.18	0.07	-0.18	0.07	-0.53	0.60
WMS-III Word list 2	**-0.58***	0.23	-0.62	0.23	-1.79	0.07
WAIS-III Vocab	-0.14	-0.10	-0.14	-0.1	-0.09	0.93
WAIS-III Block Design	-0.46	0.09	-0.5	0.09	-1.24	0.22
WAIS-III Arithmetic	-0.26	0.12	-0.27	0.12	-0.81	0.42
N		15				
WAIS-III Digit Span	0.17	0.02	0.17	0.02	0.31	0.75
WAIS-III Digit Span f	0.20	0.07	0.2	0.07	0.27	0.78
WAIS-III Digit Span b	0.14	-0.02	0.14	-0.02	0.33	0.74
N	10	14				

Appendix 6J

T2-MRI versus cortisol correlations

ROI T2 right hippocampal measures

	SW	C	z1	z2	z-test	2 tail sig
d1500	-0.03	-0.16	-0.03	-0.16	0.26	0.80
N		14				
d1900	0.18	0.18	0.18	0.18	0.00	1.00
N		12				
d2300	0.09	-0.15	0.09	-0.15	0.48	0.63
d0300	0.27	-0.24	0.28	-0.24	1.03	0.30
N		14				
d0700	0.03	0.12	0.03	0.12	-0.18	0.86
N	9					
d1100	-0.25	0.09	-0.26	0.09	-0.65	0.52
N	8					
d_total	0.06	0.03	0.06	0.03	0.06	0.95
mean d24h	0.06	0.00	0.06	0.00	0.12	0.90
N	9	15				

ROI T2 left hippocampal measures

	SW	C	z1	z2	z-test	2 tail sig
d1500	0.00	0.04	0.00	0.04	-0.08	0.94
N		14				
d1900	0.54	0.21	0.60	0.21	0.74	0.46
N		12				
d2300	-0.18	-0.20	-0.18	-0.20	0.04	0.97
d0300	0.18	-0.31	0.18	-0.32	0.99	0.32
N		14				
d0700	0.06	-0.06	0.06	-0.06	0.24	0.81
N	9					
d1100	0.22	-0.13	0.22	-0.13	0.67	0.51
N	8					
d_total	0.25	-0.01	0.26	-0.01	0.53	0.60
mean d24h	0.25	-0.15	0.26	-0.15	0.81	0.42
N	9	15				

Appendix 6K

T1- & T2-MRI versus POMS correlations

POMS - total mood disturbance score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.29545	0.209207	-0.31	0.21	-1.11	0.26
R hipp. % TIV	-0.20455	0.276153	-0.2	0.29	-1.05	0.3
L hipp. TV	-0.15909	0.108788	-0.16	0.11	-0.58	0.56
L hipp. % TIV	-0.15909	0.19247	-0.16	0.19	-0.75	0.45
R temp. lobe TV	0.314627	-0.14226	0.32	-0.14	0.98	0.32
R temp. lobe % TIV	0.224733	-0.20921	0.22	-0.21	0.93	0.35
L temp. lobe TV	0.13484	-0.04184	0.13	-0.04	0.36	0.72
L temp. lobe % TIV	0.044947	-0.09205	0.04	-0.09	0.28	0.78
TIV	-0.06818	0.058578	-0.07	0.06	-0.28	0.78
N		16				
ROI T2 R hipp	0.224733	-0.06731	0.22	-0.07	0.62	0.54
ROI T2 L hipp	0.340909	-0.22115	0.35	-0.22	1.21	0.22
N	10	15				

POMS - tension-anxiety score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.2299	0.042197	-0.23	0.04	-0.58	0.56
R hipp. % TIV	-0.13794	0.194108	-0.14	0.19	-0.71	0.48
L hipp. TV	-0.18392	-0.12659	-0.18	-0.13	-0.11	0.91
L hipp. % TIV	-0.13794	-0.00844	-0.14	-0.01	-0.28	0.78
R temp. lobe TV	0.340997	0.042197	0.35	0.04	0.67	0.5
R temp. lobe % TIV	0.295531	0.109713	0.31	0.11	0.42	0.67
L temp. lobe TV	-0.15913	-0.02532	-0.16	-0.03	-0.28	0.78
L temp. lobe % TIV	-0.2046	0.075955	-0.2	0.08	-0.6	0.55
TIV	-0.09196	0.042197	-0.09	0.04	-0.28	0.78
N		16				
ROI T2 R hipp	0.113666	0.251211	0.11	0.26	-0.3	0.76
ROI T2 L hipp	0.482791	-0.25121	0.52	-0.26	1.64	0.1
N	10	15				

POMS - depression-dejection score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.28968	0.034503	-0.3	0.03	-0.7	0.48
R hipp. % TIV	-0.28968	0.172516	-0.3	0.17	-1	0.32
L hipp. TV	-0.19312	-0.05175	-0.19	-0.05	-0.3	0.76
L hipp. % TIV	-0.2414	0.172516	-0.24	0.17	-0.89	0.37
R temp. lobe TV	**0.405798**	**-0.34503**	**0.44**	**-0.37**	**1.71**	**0.09**
R temp. lobe % TIV	0.358057	-0.13801	0.38	-0.14	1.1	0.27
L temp. lobe TV	-0.02387	-0.20702	-0.02	-0.21	0.41	0.68
L temp. lobe % TIV	-0.11935	-0.06901	-0.12	-0.07	-0.11	0.91
TIV	-0.04828	-0.06901	-0.05	-0.07	0.04	0.97
N		16				
ROI T2 R hipp	0.262575	-0.12877	0.27	-0.13	0.83	0.4
ROI T2 L hipp	0.362103	-0.16839	0.38	-0.17	1.15	0.25
N	10	15				

POMS- anger-hostility score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.20455	0.307794	-0.2	0.32	-1.12	0.26
R hipp. % TIV	-0.06818	0.273594	-0.07	0.28	-0.74	0.46
L hipp. TV	-0.02273	0.222295	-0.02	0.22	-0.52	0.6
L hipp. % TIV	-0.15909	0.119697	-0.16	0.12	-0.6	0.55
R temp. lobe TV	0.179787	-0.0342	0.18	-0.03	0.45	0.65
R temp. lobe % TIV	0.26968	-0.25649	0.28	-0.27	1.16	0.25
L temp. lobe TV	0.314627	-0.1368	0.32	-0.14	0.98	0.32
L temp. lobe % TIV	0.224733	-0.27359	0.22	-0.28	1.07	0.29
TIV	-0.15909	0.068399	-0.16	0.07	-0.49	0.62
N		16				
ROI T2 R hipp	0	-0.27595	0	-0.29	0.6	0.55
ROI T2 L hipp	-0.02273	-0.27595	-0.02	-0.29	0.56	0.57
N	10	15				

POMS- fatigue score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.02273	-0.0345	-0.02	-0.03	0.02	0.98
R hipp. % TIV	0.204545	0.034503	0.2	0.03	0.37	0.71
L hipp. TV	0.204545	0.069007	0.2	0.07	0.28	0.78
L hipp. % TIV	-0.15909	0.20702	-0.16	0.21	-0.8	0.42
R temp. lobe TV	0.40452	-0.20702	0.42	-0.21	1.36	0.17
R temp. lobe % TIV	0.494413	-0.15526	0.54	-0.16	1.49	0.14
L temp. lobe TV	0.044947	0.069007	0.04	0.07	-0.06	0.95
L temp. lobe % TIV	0.044947	0.120761	0.04	0.12	-0.17	0.86
TIV	0.022727	-0.13801	0.02	-0.14	0.34	0.73
N		16				
ROI T2 R hipp	0.13484	-0.14858	0.13	-0.15	0.59	0.55
ROI T2 L hipp	-0.02273	0.029716	-0.02	0.03	-0.11	0.92
N	10	15				

POMS- confusion-bewilderment score

	SW	C	z1	z2	z-test	2 tail sig
R hipp. TV	-0.32186	0.163164	-0.33	0.16	-1.05	0.29
R hipp. % TIV	0	0.231864	0	0.23	-0.5	0.62
L hipp. TV	-0.27588	0.197514	-0.29	0.2	-1.05	0.3
L hipp. % TIV	0	0.369265	0	0.39	-0.83	0.41
R temp. lobe TV	0.068199	-0.23186	0.07	-0.23	0.65	0.52
R temp. lobe % TIV	0.250065	-0.23186	0.26	-0.23	1.04	0.3
L temp. lobe TV	0.250065	-0.04294	0.26	-0.04	0.63	0.53
L temp. lobe % TIV	0.295531	0.008588	0.31	0.01	0.64	0.52
TIV	-0.32186	-0.14599	-0.33	-0.15	-0.39	0.7
N		16				
ROI T2 R hipp	-0.0682	-0.28726	-0.07	-0.3	0.48	0.63
ROI T2 L hipp	0.09196	-0.08915	0.09	-0.09	0.38	0.7
N	10	15				

	POMS- vigor score					
	SW	**C**	**z1**	**z2**	**z-test**	**2 tail sig**
R hipp. TV	0.04598	-0.0855	0.05	-0.09	0.3	0.76
R hipp. % TIV	0	-0.1368	0	-0.14	0.3	0.76
L hipp. TV	0.09196	0	0.09	0	0.19	0.85
L hipp. % TIV	0.13794	0.034199	0.14	0.03	0.24	0.81
R temp. lobe TV	-0.29553	-0.1368	-0.31	-0.14	-0.36	0.72
R temp. lobe % TIV	-0.2046	0.102598	-0.2	0.1	-0.65	0.52
L temp. lobe TV	-0.0682	-0.2223	-0.07	-0.22	0.33	0.74
L temp. lobe % TIV	0.068199	-0.0855	0.07	-0.09	0.34	0.73
TIV	0.04598	-0.1368	0.05	-0.14	0.41	0.68
N		16				
ROI T2 R hipp	-0.0682	-0.09757	-0.07	-0.1	0.06	0.95
ROI T2 L hipp	-0.32186	0.390286	-0.33	0.41	-1.56	0.12
N	10	15				

Appendix 7: Correlation matrix for shift workers' cortisol levels and WAIS-III scores

Shift workers

WAIS-III subtest scaled scores

Day shift	BDesign	Arithmetic	Vocabulary	DSpan fwd	DSpan bwd	DSpan
1500h	0.25	0.18	0.09	-0.31	0.48	0.19
1900h	0.15	-0.36	0.12	0.43	0.30	0.43
2300h	-0.10	-0.37	-0.22	-0.35	-0.51	-0.53
0300h	-0.41	0.07	-0.06	0.10	-0.06	0.13
0700h	-0.27	-0.25	-0.35	-0.05	-0.33	-0.31
1100h	-0.03	-0.41	-0.03	0.29	-0.35	-0.15
total dayshift	-0.15	-0.12	-0.18	-0.08	-0.12	-0.14
mean dayshift	-0.24	-0.27	-0.23	0.03	-0.26	-0.28
Night Shift						
1500h	-0.07	0.25	0.26	-0.05	0.33	0.14
1900h	-0.03	-0.42	-0.50	0.23	-0.03	0.03
2300h	0.13	-0.33	-0.15	0.24	0.25	0.29
0300h	0.43	0.41	0.51	0.06	0.21	0.21
0700h	0.11	0.16	0.38	-0.29	-0.24	-0.31
1100h	-0.39	-0.04	0.00	-0.17	-0.20	-0.15
total night shift	0.32	0.37	0.21	-0.23	0.19	0.02
mean night shift	0.34	0.27	0.32	-0.03	0.16	0.09

Appendix 8: Correlation matrix for shift workers' right MRS and cortisol

	Shift workers: day shift							
	1500h	**1900h**	**2300h**	**0300h**	**0700h**	**1100h**	**24h total**	**24h mean**
Creatine (Cr)	-0.14	0.00	-0.09	-0.15	0.25	0.33	0.22	0.22
myo-Inositol (mI)	-0.37	-0.18	0.27	0.03	0.08	0.33	0.00	0.00
mI/Cr	-0.37	-0.18	0.15	0.03	0.08	0.33	0.00	0.00
Guanine (Gua)	0.08	-0.06	0.15	-0.21	0.25	0.18	0.11	0.11
Gua/Cr	0.08	-0.12	0.15	-0.09	0.25	0.04	0.11	0.11
GPC + PCh	-0.25	-0.06	0.27	0.09	0.14	0.33	0.11	0.11
GPC + PCh/Cr	-0.08	-0.24	0.03	0.09	0.03	-0.04	0.00	0.00
NAA + NAAG	0.25	0.24	0.15	-0.03	-0.31	-0.11	-0.11	-0.11
NAA + NAAG/Cr	0.48	0.18	-0.09	-0.09	-0.31	-0.18	-0.22	-0.22
Glu + Gln	-0.20	-0.18	0.33	0.15	-0.03	0.04	0.00	0.00
Glu+Gln/Cr	-0.42	0.00	0.15	0.45	-0.25	0.18	0.00	0.00

	Shift workers: night shift							
	1500h	**1900h**	**2300h**	**0300h**	**0700h**	**1100h**	**24h total**	**24h mean**
Creatine (Cr)	-0.11	0.23	0.19	0.43	-0.11	-0.37	0.31	0.33
myo-Inositol (mI)	-0.33	0.00	-0.34	-0.06	0.25	0.00	-0.08	0.11
mI/Cr	-0.33	0.08	-0.34	-0.18	0.11	0.00	-0.20	0.00
Guanine (Gua)	-0.22	0.31	-0.04	-0.06	0.18	-0.37	0.03	0.22
Gua/Cr	-0.22	0.39	-0.04	-0.12	0.11	-0.22	-0.08	0.11
GPC + PCh	-0.22	0.08	-0.11	0.18	0.25	-0.07	0.03	0.22
GPC + PCh/Cr	0.22	-0.23	-0.42	-0.12	0.47	0.52	-0.08	0.11
NAA + NAAG	-0.11	-0.15	0.19	0.55	0.33	-0.15	0.14	0.33
NAA + NAAG/Cr	0.11	-0.46	-0.11	0.06	0.47	0.22	0.03	0.11
Glu + Gln	-0.11	-0.08	-0.11	0.24	-0.25	0.00	0.08	-0.11
Glu+Gln/Cr	0.11	-0.31	-0.04	0.18	-0.11	0.44	-0.03	-0.22