The relationship between circadian integrity and delirium: A prospective study of an elderly population in an acute hospital setting.

by

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Collaborators

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**Declaration**

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of MSc. is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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Abstract

In this thesis, several aspects of the relationship between circadian integrity and delirium are explored. Delirium is a complex phenomenological entity of which circadian integrity is a significant element. The intimate relationship between the components of circadian integrity, namely the sleep-wake cycle and motor activity, are critical aspects of modern conceptualisation of how consciousness and cognition become disrupted in delirium. Therefore, it was hypothesised that exploring the elements of circadian integrity would illuminate the underlying pathological processes of delirium. To explore these elements, in Part I, chapter 1, a synthetic study of all the pertinent literature related to the relationship of circadian integrity and delirium was undertaken. This relationship was examined in terms of a wide variety of perspectives, from the historical medical literature, to modern neuro physiological studies and integrated with the contemporary developments in the field focused upon treatment and phenomenological analysis of delirium. In Part II, chapter 2, the phenomenology of elderly medical inpatients was explored in the hospital setting. This study aimed at exploring the incidence and prevalence of subsyndromal delirium and full syndromal delirium, as well as the phenomenological features that compose these entities. In Part II, chapter 3, the sleep-wake cycles of elderly medical inpatients was explored both at baseline and longitudinally. The patterns of sleep-wake cycle and sleeping were also investigated in terms of the existence of neurocognitive disorders. In Part III, chapter 4, the inter rater reliability between the Delirium motor subtyping scale (DMSS) and the 4 item Delirium motor subtyping scale (DMSS-4) was investigated in elderly medical inpatients between three raters, doctor, nurse, and medical student. In Chapter 5, the studies are reflected upon as a whole, with a focus upon methodological considerations for future studies.
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Background to Chapter 1

This thesis describes a series of studies conducted over a four year period that explore the relationship between circadian integrity and delirium. Associated conditions are also considered due to the well-established fact that delirium exists in a mixed neuropsychiatric population. The principal aims of this work were to elucidate the common but understudied condition of delirium by a detailed analysis of its phenomenology (see table 1). A particular focus on sleep and circadian dimensions to this state was undertaken. In order to do this successfully, a clear account of the current research pertaining to this topic was undertaken and organized into a literature review. From there, validated measures of cognition, phenomenology and sleep quality were identified to assess these patients both at admission into the study and then longitudinally. Areas of future research were discussed with a view to structuring the discourse on delirium in light of the findings of this research.

Overall, this study has not only explored many particular areas of this complex relationship, but has illustrated the utility of various methods by which this area can be studied scientifically.

Contributions of the authors: The initial idea and scope of the literature review was set out by the author James Fitzgerald and supervisor Prof. David Meagher. Once a broad based literature review was conducted, the collaborators Paula Trzepacz, Colum Dunne, Suzanne Timmons, Niamh O’Regan and Dimistrios Adamis were invited to review the theory and helped bridge the gap between fundamental neuroscience and clinical research. All collaborators contributed to reviewing the finished chapter.
Table 1. Aims of this research programme

1. Examine via a synthetic literature review the phenomenological, pathophysiological, and therapeutic studies that have implications for our understanding of the relevance of disturbed circadian integrity to delirium.
2. Explore the delirium phenomenology of elderly general medical admissions.
3. Identify the point prevalence of full syndromal delirium (FSD) and subsyndromal delirium (SSD) defined by systematic categorical methods.
4. Identify the features of this phenomenological profile that characterise FSD and SSD.
5. Examine sleep patterns in elderly general medical admissions.
6. Explore how these patterns relate to the presence of dementia, depression and onset of delirium.
7. Explore the attribution of clinical subtype in elderly medical inpatients at risk of delirium and to specifically examine the level of agreement between the DMSS and DMSS-4.
8. Examine concordance between the DMSS and DMSS-4 over time.
9. Examine the inter-rater reliability of the DMSS and DMSS-4 between doctor, medical student and nursing staff.
Chapter 1 - Delirium- A disorder of circadian integrity?

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\textbf{Key words:} Delirium; cognition; circadian; pathophysiology; treatment
Abstract

Delirium is a serious neuropsychiatric syndrome of acute onset that occurs in approximately one in five general hospital patients and is associated with serious adverse outcomes that include loss of adaptive function, persistent cognitive problems and increased mortality. Recent studies indicate a three-domain model for delirium that includes generalised cognitive impairment, disturbed executive cognition, and disruption of behaviours that are under circadian control such as sleep-wake cycle and motor activity levels. As a consequence, attention has focused upon the possible role of the circadian timing system (CTS) in the pathophysiology of delirium. We explored this possibility by reviewing evidence that (1) many symptoms that occur in delirium are influenced by circadian rhythms, (2) many features of recognised circadian rhythm disorders are similar to characteristic features of delirium, (3) common risk factors for delirium are known to disrupt circadian systems, (4) physiological disturbances of circadian systems have been noted in delirious patients, and (5) positive effects in the treatment of delirium have been demonstrated for melatonin and related agents that influence the circadian timing system. A programme of future studies that can help to clarify the relevance of circadian integrity to delirium is described. Such work can provide a better understanding of the pathophysiology of delirium while also identifying opportunities for more targeted therapeutic efforts.
Introduction.

Delirium is a complex neuropsychiatric syndrome that is characterised by acute generalised disturbance of brain function in the context of physical illness. It occurs in 11-42% of general medical inpatients (Siddiqi et al., 2006), with even higher rates in those with pre-existing cognitive impairment, terminal illness or in intensive care units (Cole, 2004; Leonard et al., 2008). Delirium impacts adversely upon a variety of healthcare outcomes that include more prolonged hospitalisation, reduced likelihood of subsequent socio-adaptive independence, persistent or ‘long-term’ cognitive impairments in older persons and elevated mortality rates (Trzepacz et al., 2010; Witlox et al., 2010). Delirium is thus a major health care concern (MacLullich et al., 2009).

Delirium involves a complex range of cognitive and behavioural components. Attentional deficits are cardinal and a required feature of DSM-IV and ICD-10 criteria for delirium. Additionally, there are impairments of other cognitive domains (orientation, executive function, higher-order thinking, memory, visuospatial function) and disturbances to language, affective regulation, sleep-wake cycle and motor behaviour. Delirium is characterised by a temporal course that is highly fluctuating over short time frames (e.g., minutes or hours) (Meagher et al., 2007; Gupta et al., 2008). While no single cognitive or behavioural disturbance is specific to delirium, the pattern and context of its features are distinctive.

The circadian timing system (CTS) is an important mechanism by which environmental factors can regulate biological rhythms. This system couples environmental cues (or zeitgebers) with structures that regulate a variety of physiological functions, including the integrity of the sleep-wake cycle, motor activity, arousal and cognition. This role makes the CTS a logical target for studies exploring delirium pathophysiology. In this review we examine phenomenological, pathophysiological and therapeutic studies that have implications for our understanding of the relevance of disturbed circadian integrity to delirium.

Neurobiology of circadian mechanisms and circadian rhythm disorders (CRD).

Circadian rhythms are biological cycles that occur with a periodicity of approximately 24 hours. In humans, they are generated and regulated by the circadian timing system (CTS)
(Moore, 1997). The primary functions of the CTS are to facilitate adequate restorative periods and allow the organism as a whole to anticipate and adapt to the changing challenges of the environment (Schibler and Sassone-Corsi, 2002). The CTS is composed of three functional elements; (1) entrainment mechanisms, (2) a pacemaker, and (3) effector systems that regulate biological rhythms (Moore, 1997). In humans, light is a pivotal zeitgeber (environmental time signalling stimulus) that allows for the entrainment or synchronisation of circadian rhythms to the 24 hour cycle. The main photic entrainment pathway is the retinohypothalamic tract which terminates at the principal circadian pacemaker, the suprachiasmatic nucleus (SCN). Other (non-photic) environmental factors such as social exchanges / schedules, physical activity and availability of food can also act as zeitgebers but appear less potent (Schibler and Sassone-Corsi, 2002). The SCN in the hypothalamus functions as the circadian pacemaker that directs or drives biological rhythms.

Circadian control of sleep is achieved through projections from the SCN to the ventrolateral preoptic area – an area of the hypothalamus that is sleep-promoting, as well as by promoting arousal via connections from the posterior hypothalamus to areas located subcortically and in the neocortex. This balance facilitates temporal regulation of sleep-wake cycle to allow for optimal restorative effects from sleep and conservation of energy (Mieda et al., 2006). The SCN is coupled to the pineal gland which is involved in the rhythmic release of melatonin. Melatonin is synthesized from tryptophan during the dark phase when its production is promoted by a major increase (up to 150 fold) in the activity of serotonin-N-acetyltransferase. In humans, melatonin receptors are present in most physiological systems (e.g., reproductive system, renal system, immune system) (Daan et al., 1984). These receptors have been proposed as the main molecular mechanism by which the CTS regulates physiological cycles systemically (Reiter, 2003).
Fig. 1 The Circadian timing system (CTS).

Neocortical regions

Preoptic area (sleep promotion)

Posterior hypothalamus (arousal promotion)

Subcortical regions

Retina (non-cone/non-rod retinal ganglion cells)

SCN Core (Exogenous rhythmicity)

SCN Shell (Endogenous rhythmicity)

Pineal gland (melatonin synthesis)

Melatonin Receptors (MT1; MT2)

Photic stimuli (environmental light exposure)

Peripheral circadian oscillators e.g. clock genes & circadian molecular mechanisms
The 'circadian resonance hypothesis' posits that optimal health requires precise alignment of the environment and the CTS. Transient desynchrony between endogenous circadian oscillators and environmental cues occurs in humans undergoing phase-shifts or shift-work with effects upon sleep drive, motor activity, core body temperature and hormone release, but circadian rhymicity is typically restored after several cycles of re-entrainment. More chronic circadian desynchrony (e.g., with work schedules that significantly disrupt circadian entrainment) is linked to obesity, diabetes, infertility and cardiovascular disease (Caumo et al., 2007; Haus and Smolensky, 2006; Lange et al., 2010). In conditions with no external zeitgeber (e.g., constant darkness/light) the normal 24 hour cycle is absent and a free running period occurs (Schulz and Steimer, 2009). Other circadian rhythm disorders (CRDs) relate to shift work, jet lag and delayed sleep phase syndrome (DSPS) involve less extreme disruption of the integrity of this system (Turek and Gillette, 2004; Srinivasan et al., 2008).

CRDs can include a variety of problems with cognitive functioning, affective disturbances, and motor and sleep activity. The so-called “sundowning syndrome” has received particular attention as an example of the link between disturbed circadian rhythmicity and neuropsychiatric disturbance that may be relevant to delirious states (de Jonghe et al., 2011). Sundowning syndrome is characterised by a circadian phase delay where the severity of behavioural disturbances correlates with the degree of circadian disruption (Volicer et al., 2001) and factors such as daylight exposure, medication and active medical morbidity increase propensity for the behavioural features of sundowning syndrome (Bachman and Rabins, 2006, Meagher et al., 2008). However, the concept of sundowning lacks clear definition and has unclear relevance to actual delirium.

**Disturbed circadian integrity and the phenomenology of delirium.**

The features of delirium can be divided into ‘core’ features that are almost invariably present (e.g., inattention) and non-core features that occur less consistently (e.g., perceptual disturbance, labile affect). Detailed studies have documented that, in addition to generalised cognitive impairment, sleep-wake cycle and motor activity disturbances are almost invariably
present in patients with full syndromal delirium (Meagher et al, 2007; Meagher et al, 2008; Jabbar et al, 2011; Mattoo et al, 2012; Meagher et al, 2012). As a consequence, current phenomenological models of delirium suggest three principal domains; (i) generalized disturbance of cognition with disproportionate impairment of attention, (ii) disorganization of higher-order thinking, and (iii) alterations to sleep-wake cycle and motor activity. This final domain relates to functions that are subject to considerable circadian regulation which, along with the fluctuation of delirium features over the 24 hour cycle, points towards disturbed circadian integrity.

Cognitive impairment

Disturbed ability to focus, sustain and shift attention is considered the primary cognitive deficit of delirium and is disproportionately and consistently disturbed (Meagher et al, 2008; Meagher et al, 2010). As such, any comprehensive explanation of the pathophysiology of delirium needs to consider the neural processes that serve attention. Evidence from human and animal studies suggests a bilateral relationship between cognitive performance and circadian systems where disturbed circadian functions is associated with impaired cognition, while attention and related cognitive functions can also act as entrainment signals to the CTS by virtue of connections between forebrain structures that subserve attentional processes, the locus coeruleus and the SCN (Gritton et al, 2009). Tranah et al (2011) found that the development of mild cognitive impairment and dementia was predicted by significantly decreased activity level combined with a later peak in activity. Such findings were proposed to be as a result of deregulated phase and amplitude of circadian rhythms. Disturbances in sleep (e.g., reduced time spent in REM sleep and increased time spent in stage 1 NREM sleep) have been shown to have a significant association with age-related decline of cognitive integrity (Barnes et al., 2008; Blackwell et al., 2011). However the precise relationship between the circadian disturbance and cognitive decline remains unclear.
Sleep-wake cycle

Sleep disturbance in delirium has been recognised since ancient times; Hippocrates described acute disturbances of behaviour, sleep and cognitive function associated with fever. Later, Quincy (1719) described delirium as “the dreams of waking persons”, while James (1745) was the first to stress the importance of altered sleep-wake cycle in delirium (Adamis et al, 2007).

More recent work has characterised these disturbances in greater detail. Alterations of sleep-wake cycle involve a variety of patterns including sleeplessness, increased somnolence, and varying degrees of fragmentation. Delirious patients often experience severe disruption with fragmentation or sleep-wake cycle reversal, that is far in excess of the more minor problems with insomnia that commonly occur in hospitalised elderly patients (Meagher et al, 2007; Gupta et al 2008). Meagher et al (2007) found that 73% of delirious patients experienced at least moderate disturbances of sleep-wake cycle, while Mattoo et al (2012) found that 99% of delirious patients without comorbid dementia had at least some sleep disturbance with moderate or greater disturbances in 80%. Even higher frequencies (98%) have been noted in older patients, many of whom had comorbid dementia (Jabbar et al, 2011). As such, although sleep disturbance is not specific to delirium, more severe disturbances are highly indicative of active delirium (Meagher et al 2008).

The nature of causality between sleep disturbances and the occurrence of delirium is less clear - Studies have implicated prior sleep disturbances as a risk factor for developing delirium (Heller et al, 1970; Sveinsson et al, 1975; Yildezeli et al 2005) but have lacked objective sleep measurement or used retrospective designs. Prospective studies indicate close correlation between reduced nocturnal and excessive daytime sleep and post-operative delirium risk and identify sleep-disturbance as an indicator of prodromal or early delirium (Kaneko et al, 1997; Fann et al (2005). A small study of postoperative patients in ICU using polysomnography found that sleep disturbances preceded the emergence of delirium (Trompeo et al 2011). Matsushima et al (1997) prospectively found prodromal changes of background slowing on EEG (theta/alpha ratio) and sleep disturbance associated with changing consciousness in CCU patients developing delirium. Moreover, sleep enhancement strategies and avoidance of hypnotics can reduce delirium risk (Inouye et al 1999; Flaherty et al., 2003). Thus, there is a link between sleep...
disturbances and delirium but it remains unclear whether sleep disturbances cause delirium or reflect the emergence of delirium, or perhaps both contribute to an escalating cycle of delirium and disturbed circadian integrity.

Motor activity

The majority of patients with delirium experience discernible alterations in their activity levels with loss of control of activity levels and/or activity that is inappropriate in its timing (e.g., nocturnal agitation) that suggest disruption of systems that regulate the temporal pattern of behaviour (Meagher et al, 2008). Recent work has highlighted altered motor functional performance (measured by the Trunk Control Test and the Tinetti Scale) as a relatively specific marker of emerging and resolving delirium and that distinguishes the delirious state from dementia without delirium (Bellelli et al, 2011). Disturbances of motor activity can include hypoactive and/or hyperactive presentations, with some ‘mixed subtype’ patients exhibiting features of both within short time frames. What underlies these patterns and their clinical significance remains uncertain, but they may reflect the influence of differing aetiologies, treatment exposures, and individual patient characteristics such as genetics, frailty, age and prior cognitive functioning (Meagher, 2009). Relative hypoactivity is linked to frailty, severity of physical illness, comorbid dementia, and older age (O’Keeffe and Lavan, 1999; Peterson et al, 2006). Other work has highlighted differences between motor subtypes in the degree of sleep-wake cycle disruption (Leonard et al, 2011) and in melatonergic metabolism (Balan et al, 2003).

Temporal fluctuation of motor activity and physical activity is subject to circadian regulation (Ivanov et al, 2007) such that SCN lesions in animals disrupt patterns of motor activity (Hu et al., 2007). There has been limited direct investigation of the processes that regulate circadian activity in delirious patients but one study indicated disruptions to melatonergic function ( urinary 6-SMT) according to motor subtypes of delirium (Balan et al, 2003).

Prodromal features
Prodromal features of delirium also overlap with symptoms of Circadian Rhythm Disorders. These include difficulty concentrating, sleep-wake cycle changes, vivid dreams, disorientation soon after waking, lassitude, irritability, anxiety, depression, restlessness, noise sensitivity and altered pain perception (Gupta et al, 2008; Gagnon et al, 2001).

In summary, the characteristic presentation of delirium, with marked fluctuation of its features over the 24 hour cycle and disturbance of cognitive and behavioural functions that are subject to significant circadian influence points towards disturbed circadian integrity.

Disturbed circadian integrity and pathological mechanisms of delirium.

Neurotransmitters in circadian rhythms and delirium

The primary neurochemical hypothesis of delirium links impaired cerebral oxidative metabolism with decreased cholinergic / GABAergic and increased dopaminergic / noradrenergic / glutamatergic activity (Trzepacz, 1999). In particular, imbalance between cholinergic and dopaminergic systems is emphasised as the principal neurochemical disturbance underpinning delirium. The interactions between these neurochemical systems and circadian rhythms has not been directly studied in delirious patients, but animal studies indicate significant connectivity.

Cholinergic mechanisms

The SCN has extensive connections with cholinergic forebrain structures (e.g., nucleus basalis) but their precise function remains unclear. Brain stem cholinergic projections to the thalamus and mid-brain have a key role in regulation of the sleep wake cycle, including REM vs non REM dreaming cycles with increased cholinergic activity during wakefulness and REM sleep (Pepeu and Giovannini, 2004; Reinoso-Suarez et al, 2001). In addition, the release of acetylcholine at sites that serve key cognitive functions (e.g., hippocampus) follows a circadian rhythm that is modified by activity. Acetylcholine and cholinergic agonists (e.g., carbachol) can induce phase-shifting of the circadian cycle (Gritton et al, 2009) while acetylcholinesterase
inhibitors can improve sleep architecture in both demented and non-demented elderly (Moraes et al, 2006; Cooke et al, 2006).

There are also significant interactions between cholinergic and melatonergic mechanisms. Melatonin induces increased Ach release at the nucleus accumbens that is associated with increased motor activity and nicotinic receptor efficiency is modulated by melatonin (Paredes et al., 1999). In short, evidence points to complex and bilateral communications between cholinergic activity and circadian mechanisms, although their relevance to the pathophysiology of delirium requires more direct investigation.

Dopaminergic mechanisms

Delirium occurs in states of dopaminergic dysregulation - both hypodopaminergic and hyperdopaminergic (Trzepacz et al, 2010). Dopamine-blocking antipsychotic agents are first line pharmacological intervention for both prophylaxis and treatment of delirium (NICE, 2010) and are thought to act by correcting imbalance between dopaminergic and cholinergic systems (Meagher, 2010). Plasma and CSF levels of the DA metabolite Homovanillic Acid (HVA) are altered in delirium, with greater dopaminergic disturbance in those with psychosis (Ramirez-Bermudez et al, 2008; van der Cammen et al, 2006). Circadian variation in dopamine receptor sensitivity, striatal dopamine turnover, and plasma HVA concentration occurs in healthy humans (Eisenberg et al, 2010; Doran et al 1990) and is thought to be mediated by striatal dopamine-melatonin interactions (Zisapel, 2001). Melatonin has complex interaction with dopaminergic systems, both directly inhibiting postsynaptic striatal dopaminergic signalling and promoting presynaptic dopamine neuronal integrity (Zisapel, 2001; Venero et al, 2003; Eisenberg et al, 2010). These effects are site-specific, with for example, melatonin inhibiting DA release in hippocampal and hypothalamic centres (Parades et al, 1999) while dopamine and melatonin act as mutually inhibitory signalling molecules of day/night status in the retina (Guido et al, 2010).

Tryptophan and serotonin

The 'abnormal tryptophan metabolism' model of delirium emphasises tryptophan’s role as a precursor for both melatonin and serotonin. Disturbance in the balance between these
compounds may underpin a link between delirium and CRD disturbance (Lewis and Barnett, 2004; Balan et al, 2003). A direct link between tryptophan and the development of delirium has been suggested. Van der Mast et al (1991) found significantly lower tryptophan concentration in delirious patients compared to controls. Moreover, patients who develop postoperative delirium have significantly lower serum levels of tryptophan (Robinson et al. 2008) and tryptophan infusion can protect against delirium development (Hebenstreit et al, 1989).

**GABAergic mechanisms**

GABAergic mechanisms implicated in delirium include the upregulation of GABA-A receptors, increased synthesis of endogenous GABA agonists or stimulation from exogenous GABA agonists (Sanders, 2011). Similar mechanisms have been speculated in alcohol withdrawal delirium (Caputo and Bernardi, 2010) although existing evidence indicates considerable differences in the pathophysiology of alcohol-withdrawal delirium versus other causes. Of note, cellular signalling in the SCN involves prominent GABAergic neurotransmission (Liu and Reppert, 2000; Mintz et al., 2002; Wang et al, 2003), while administration of GABAergic compounds (e.g., GABA-RB positive allosteric modulators) has been shown to enhance the inhibitory effect of baclofen and thus significantly impact upon light-induced phase shifts of circadian rhythms displayed by hamster wheel running activity (Gannon and Millan, 2011).

**Melatonergic mechanisms**

Disturbed melatonergic activity is also implicated in delirium pathogenesis. Risk factors for delirium, such as dementia, old age and psychotropic medication use are all associated with impaired melatonergic function. Shigeta et al (2001) examined melatonin secretion in patients after major abdominal surgery and found that patients developing delirium had reduced melatonin levels where delirium was not associated with complications and markedly elevated melatonin levels where particular complications (infection, shock, cardiac failure) occurred. The most significant finding reported was the apparent sleep disturbance (e.g., delayed sleep onset and reversal of sleep-wake cycle) found in all patients diagnosed as having post-operative
delirium. Similarly, Olofsson et al (2004) reported disrupted circadian rhythm of melatonin secretion in ICU patients who developed delirium. Furthermore, altered urinary levels of the melatonin metabolite (6-SMT) have been demonstrated in delirious patients where, in comparison with non-delirious controls, levels were elevated in hypoactive patients and lower in hyperactive patients (Balan et al, 2003).

It has been proposed that melatonin supplementation can ameliorate delirium symptoms by inducing a negative feedback signalling cascade that leads to decreased serotonin and tryptophan catabolism. Alternatively, melatonin may have an indirect role in the prevention of delirium by resetting the sleep/wake cycle and CTS (Lewis and Barnett, 2004; Balan et al, 2003). In support, Hanania and Kitain (2002) reported successful treatment of severe postoperative delirium unresponsive to antipsychotics or benzodiazepines with melatonin. Subsequent studies (see table 2) suggest that the incidence of delirium can be significantly reduced with prophylactic melatonin. These studies suggest that disturbed melatonergic metabolism has a primary role in delirium pathogenesis rather than representing a mere marker of delirium emergence.

**Hypothalamic-pituitary-adrenal (HPA)-Stress axis**

HPA axis dysregulation also appears relevant to both delirium and circadian systems. O’Keeffe and Devlin (1994) linked delirium risk to DST non-suppression. Other work has identified and association between elevated plasma cortisol levels and increased delirium risk post cardiac surgery (Plaschke et al, 2010; Mu et al, 2010) and non-cardiac surgery (Kudoh et al 2005; Shi et al, 2010). Similarly, Pearson et al (2010) found that median CSF cortisol levels were elevated in post-operative patients who subsequently developed delirium. Macullich et al. (2008) postulated a model whereby aberrant stress responses related to disrupted function of the limbic-HPA axis and it's interaction with inflammatory mechanisms may underpin the elevated risk of delirium that is associated with ageing and CNS disease, including dementia.

Melatonin is involved in HPA axis modulation. For example, adrenal hypertrophy induced by pinealectomy can be reversed by administration of exogenous melatonin (Wurtman et al, 1959; Malhotra et al, 2004). Melatonin release is influenced by vasopressin receptors located on the SCN (Reghunandan et al, 1991) that are activated by cortisol (Buckley and
Various evidence indicates significant linkage between the CRS, inflammatory mechanisms, key physiological functions that are disrupted in delirium and the delirious state itself. Infectious states that are commonly associated with delirium activate inflammatory mechanisms that are associated with increased daytime sleepiness and reduced NREM sleep (Hermann et al. 1998). Inflammatory mechanisms impact considerably upon sleep-wake cycle. TNF-α as well as IL-1, IL-1α, IL-1β and IFN-γ have recognised somnogenic effects and induce increased NREM sleep (Obal et al, 1990; Krueger et al, 1998; Takahashi et al, 1999). Sleep deprivation can elevate circulating levels of IL-1 (Takahashi et al. 1999) while elevated peripheral levels of TNF-α are associated with EEG slow wave activity (Darko et al., 1995) which is the typical EEG pattern seen in delirium (Plaschke, 2007; Thomas et al.,2008; Trzepacz,1994). Endotoxin administration to healthy volunteers provokes an elevation of TNF-α, IL-6 and IL-1Ra, increased subjective sleepiness (peaking in 3 hours after injection) and a reduction of the total sleep time and NREM sleep. Mullington et al (2000) found that a small nocturnal dose of endotoxin increases cytokines (TNF-α, IL-6, IL-1Ra) but also induces increased NREM sleep, while a high dose of endotoxin disrupts sleep, concluding that sleep–wake behaviour is very sensitive to levels of inflammatory cytokines.

Other studies have highlighted the significant role of inflammatory mechanisms in delirium pathogenesis (MacLullich et al, 2008; Murray et al, 2012). Patients with active delirium have low levels of anti-inflammatory markers such as IL-1Ra and Insulin-like growth factor and significantly elevated levels of inflammatory markers such as IFN-gamma and C-reactive protein (Beloozesky et al, 2007; Adamis et al, 2009). In addition, hip fracture patients that develop delirium have significantly higher levels of IL-6 during and IL-8 before delirium onset compared to control patients who do not develop delirium (van Munster et al, 2008).

It has been proposed that the SCN exerts a circadian regulation of the inflammatory response via melatonin and cortisol signalling (Scheff, 2010). In support, melatonin specific receptors are present on leukocytes and diurnal rhythms of leucocyte proliferation, cytokine production and NK cell activity in mammalian bone marrow cells are controlled by melatonin.
(Del Gobbo et al, 1989; Drazen et al, 2001; Scheff et al, 2010). Melatonin has also been reported to enhance therapeutic outcomes in states of organ failure and systemic infection (Bubenik et al, 1998; Escames et al, 2006; Korkmaz et al, 2009) that are commonly complicated by delirium. In summary, various sources of evidence suggest that delirium risk is related to interactions between circadian mechanisms and the inflammatory response.

Electroencephalography/ Polysomnography

Polysomnography and electroencephalography have considerable potential for exploring the relationship between delirium and circadian functions but have received limited study. Desynchronisation of the EEG occurs in both delirium and circadian rhythm disorders - delirium is classically associated with generalised slowing on the EEG (Plaschke, 2007; Thomas et al., 2008; Trzepacz, 1994) while disruption of circadian systems is associated with desynchronisation of the EEG and pinealectomy increases the likelihood of seizures. Administration of exogenous melatonin or bright light therapy can synchronise the EEG (Jacobson et al., 2008).

Overall, these reports highlight the many complex interactions involving possible pathophysiologies that may underpin the relationship between circadian systems and the neurobiological functions that are thought to be disrupted in delirium. Future work needs to focus upon clarifying the extent to which disturbances of neurochemical, circadian, stress and inflammatory mechanisms occur independently or as a highly interconnected system that contributes to a cycle of escalating circadian dysregulation and delirium and that is central to delirium pathogenesis.

Pharmacokinetics

Finally, the relationship between medication use, circadian systems and delirium may also relate to pharmacokinetic influences. The SCN has been shown to regulate hepatic metabolism, detoxification and renal elimination in a circadian manner (Clarke, 1984). Patients with dementia or age related degeneration of SCN may have circadian dysregulation of pharmacological metabolism and predispose patient to developing delirium. These actions may
also underlie the loss of circadian patterns of analgesia that have been noted in delirium (Gagnon et al, 2002).

Overall, these reports highlight the complexity in the interactions between circadian systems and the neurobiological functions that are thought to be disrupted in delirium. However, the primary disturbances are unknown and it remains unclear whether pathophysiological disturbances of delirium have knock on effects on circadian systems (or vice versa) or if both mechanisms can contribute to a cycle of escalating circadian dysregulation and delirium.
<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Population and Setting</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Aama et al., 2011</td>
<td>Elderly 65+ (n= 145) Internal Medicine</td>
<td>Randomized, double-blinded trial</td>
<td>0.5 mg melatonin vs. placebo</td>
<td>Melatonin use associated with a lower risk of delirium</td>
</tr>
<tr>
<td>Sultan, 2010</td>
<td>Elderly 65+ (n=222 ) Orthopaedic surgery</td>
<td>Randomized, double-blinded trial</td>
<td>4 groups: control, melatonin 5mg, midazolam 7.5 mg, clonidine 100 μg.</td>
<td>Significant decrease of rate of delirium in melatonin group</td>
</tr>
<tr>
<td>Kain et al., 2009</td>
<td>Children (n= 148 ) Post-operative</td>
<td>Randomized trial</td>
<td>Oral midazolam 0.5 mg/kg or oral melatonin 0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg</td>
<td>Melatonin reduced the occurrence of delirium and the effect was dose related</td>
</tr>
<tr>
<td>Hanania and Kitain, 2002</td>
<td>53 years and 78 years old (n=2) Orthopaedic surgery</td>
<td>Case reports</td>
<td>2 mg melatonin for treatment (1st case), 2mg for prevention of delirium in the 2nd case</td>
<td>Successful treatment and prevention</td>
</tr>
<tr>
<td>Taguchi et al., 2007</td>
<td>Adults (27-71) years old (n= 11) ICU after surgery for oesophageal cancer</td>
<td>Randomized Trial</td>
<td>Phototherapy</td>
<td>Phototherapy reduced the incidence of delirium</td>
</tr>
<tr>
<td>Fortuyn and Schoemaker, 1997</td>
<td>68 years (n= 1 ) ICU</td>
<td>Case report</td>
<td>Phototherapy</td>
<td>Successfully treated</td>
</tr>
</tbody>
</table>
7. What is the relationship between circadian mechanisms and delirium?

Fig. 2. A model of interaction between the circadian timing system and delirium. (Dotted lines reflect probable / possible effects, while full lines represent well demonstrated effects).
Figure 2. shows interactions between elements of the CTS, risk factors for both CRD and delirium, and specific symptom domains of the syndrome of delirium. This highlights a number of possible explanations for the relationship between delirium and dysregulation of circadian systems. These include;

1. Delirium reflects a generalised disturbance of neural function that includes circadian systems. Disruption of circadian systems may account for specific elements of the overall syndrome of delirium such as disturbed sleep-wake cycle, altered motor activity patterns, impaired cognition and the overall propensity for symptom fluctuation during an episode.

2. The occurrence of delirium causes circadian dysregulation through its impact upon the capacity to comprehend and interact normally with the environment and to engage with zeitgebers, resulting in uncoupling of circadian entrainment mechanisms and the external environment.

3. Delirium represents a primary circadian rhythm disorder where severe disturbance of the circadian rhythm system results in impaired cognition and neuropsychiatric symptoms that comprise delirium. The severity of these disturbances in delirium suggests severe disruptions to CTS (such as a free running phase) whereby the synchronising effect of a range of zeitgebers has been lost.

4. Delirium and CRDs are discrete but share specific symptoms which increase the likelihood of the other occurring (i.e., are mutually aggravating). For example, sleep disturbances occurring in delirium may uncouple the CTS and / or sleep disturbances in circadian dysregulation may predispose towards developing delirium in high risk patients exposed to other precipitating factors. Exercise and cognition are also recognised zeitgebers and may have similar influences in destabilising the CTS and / or increasing delirium proneness.

5. Circadian disturbance occurring with increasing age or dementia or through exposure to anticholinergic, benzodiazipine or opioid medications may predispose to delirium or initiate an at-risk prodromal state that progresses to delirium in patients with other delirium-vulnerabilities.
(6) Delirium and CRDs co-occur by chance and reflect loss of physiological integrity due to factors such as advancing age, dementia etc. This explanation seems unlikely in the context of evidence for therapeutic effects of interventions that modify the circadian system in the management of delirium and the specific pathophysiological disturbances of circadian systems identified in delirious patients (Balan et al., 2003).

Based on the available evidence the most likely hypothesis is a combination of points one and two whereby the generalised disturbance of neural functioning in delirium induces a disturbed CTS. This highly interconnected system contributes to specific features of delirium such as disturbed motor-activity, impaired cognition and fragmented sleep-wake cycle. This relationship in turn induces a cycle of escalating circadian dysregulation and delirium. However, the other hypotheses cannot be entirely ruled out and an inclusion of more detailed neurobiological mechanisms into the discourse need to be considered when exploring the framework of how the relationship between circadian integrity and delirium operates.

8. Conclusions, future studies and recommendations

Delirium is a key target for improved healthcare in our increasingly aged society. In particular, our limited understanding of the complex pathophysiology that underpins delirium poses a major obstacle to improved detection and management of this serious condition. Evidence from a variety of sources suggests that circadian mechanisms are relevant to the pathophysiology of delirium and may even be of principal importance. A refined theory of delirium that integrates our knowledge of the symptoms of delirium, the biological processes that serve these functions, and risk factors for disruption of the key physiological processes that are disrupted in delirium (such as the CTS) can enhance detection and management strategies. Existing evidence indicates that the etiological factors associated with delirium activate inflammatory mechanisms and the stress axis which in turn imbalances the CTS, especially where it is vulnerable due to factors such as advanced age and dementia that also predispose
towards delirium. Circadian dysregulation is associated with a range of cognitive and neuropsychiatric disturbances that occur in delirium while the delirious state itself dysregulates circadian integrity by interfering with its links to environmental regulators. Once this disconnected state is established, a cycle of escalating circadian dysregulation and worsening delirium occurs. Therapeutic interventions that ameliorate delirium symptoms can allow the CTS to recalibrate but gathering evidence also indicates that interventions that are primarily directed towards the circadian system can prevent delirium and may also impact positively in patients with established delirium. This model can be further refined by studies (see table 1) that explore phenomenological disturbances in delirium and how they relate to circadian dysregulation.
References


unmet needs. Journal of Psychopharmacology, 22, 4-8.


National Institute for Health and Clinical Excellence: Delirium: diagnosis, prevention and management. (Clinical guideline 103.). 2010. www.nice.org.uk/CG103. 12/12/12 17:30pm GMT


Commentary chapter 1

This literature review collects and organizes the wide variety of relevant studies and theories that have helped sculpted the framework for this research programme. This literature review serves as the basis of the theory for the remainder chapters and as a point of reference for the research findings. As such this literature review of the fundamental sciences is integrated at various levels to the remainder chapters in a way that enhances the translatability of sleep and circadian research to the growing body of research dedicated to delirium and associated conditions. From this literature review, various theories were utilized to translate basic sciences into clinical research in real world healthcare settings. As the first point of departure, a detailed phenomenological profile of the elderly medical admission cohort was undertaken in chapter 2.

Background chapter 2

This chapter explores delirium phenomenology in two ways. Firstly, it explores patient phenomenology at the point of admission into the study and then longitudinally throughout the study. This is an important perspective as delirium is a fluctuating phenomenon and requires a detailed longitudinal analysis for an accurate empirical account of its trajectory. Secondly, this study explored delirium using consensus derived algorithm for a validated method for determining delirium diagnosis. This is a useful adjunct to delirium research as delirium is an under detected phenomenon in the clinical setting. More complex still is the existence of subsyndromal delirium which has approximately half the phenomenological features and half the consequences of full syndromal delirium. Mapping out the broad based phenomenological profile of this patient cohort is important for a more detailed analysis of the sleep and circadian patterns.
Contributions of the authors:

Although the majority of this work was undertaken by the author (James Fitzgerald [JF]) each of the components of the study was developed by collaboration with senior researchers, David Meagher, Colum Dunne, Paula Trzepacz, Niamh O’ Regan, Suzanne Timmons and Dimitrios Adamis. Although the ideas and study design was initiated by JF, the structure and rationale behind how best to execute this study was developed in consultation with these collaborators. Moreover, given the complex variety of data required to investigate this issue in elderly medical admissions, data collection was shared between the author and senior researcher Dr. O’Regan. In addition, detailed statistical instruction was given by Dr. Adamis and in particular instances, statistical analysis was conducted by Dr. Adamis (GEE method). All collaborators contributed to reviewing the finished chapters.
Chapter 2 - Delirium phenomenology in elderly general medical admissions: A longitudinal study in an acute hospital setting.

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Abstract

Introduction: The phenomenology of delirium is understudied, including features that characterise full syndromal delirium (FSD) and subsyndromal delirium (SSD). We assessed delirium phenomenology in elderly general medical admissions to identify features that are most characteristic of FSD and SSD.

Methods: Elderly general medical admissions (n=145) were assessed daily for up to 7 days using the Delirium Rating Scale-Revised-98 (DRS-R98) and systematic diagnostic algorithms for DSM 5 FSD and SSD. Patients were assessed at admission using the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF) and the Geriatric Depression scale (GDS). The generalised estimating equation (GEE) method was used to identify features that distinguish FSD from SSD.

Results: Mean age was 80 (SD: 6; range 70-94) and sixty nine (47.6%) were female. Thirty one participants (21.4%) had a previous history of dementia. Six participants (4.3%) were depressed at admission. FSD was 20.0% (n=29) at admission, while a further 18.5% (n=27) developed delirium over the study period. SSD was 5.5% (n=8) at admission, while the total frequency of SSD episodes was 14.5% (n=21). Fifteen cases (71%) of SSD transitioned to FSD over the study period. Longitudinal analysis of these patients’ phenomenological profiles using the GEE method revealed that sleep-wake cycle disturbance, perceptual disturbances and hallucinations, lability of affect, thought process abnormalities, motor agitation, motor retardation, attention, long-term memory and visuospatial ability were all significantly higher (more impaired) in FSD vs. SSD.

Conclusions: FSD differs from SSD delirium over time by the severity and consistency of a variety of features that are elementary to both states and reflect a dimensional relationship between SSD and FSD.
Introduction

Delirium is a complex neuropsychiatric syndrome that is common in the hospitalised elderly (Ryan et al., 2013). It is associated with a variety of adverse outcomes that include reduced adaptive functioning and increased mortality (Witlox et al., 2010). Delirium phenomenology can be divided into ‘core’ features that are almost invariably present (disturbances of attention, memory, orientation, thought process, sleep-wake cycle, and motor behaviour) and ‘associated’ features that are more variable in presentation (e.g. psychotic symptoms, affective disturbances, language disturbances) (Trzepacz et al., 2011). Recent work has conceptualised delirium phenomenology as consisting of three core domains: (a) general cognition with disproportionate impairment of attention; (b) circadian integrity characterised by sleep–wake cycle and motor alterations; and (c) disturbances of executive cognition (comprehension, language, and thinking processes) (Mattoo et al., 2012; Franco et al., 2013). Previous work using cross-sectional studies provide a valuable insight into the manifestation and frequency of delirium features in at risk patient groups (Meagher et al., 2007; Franco et al., 2009; Meagher et al., 2010). However, given its heterogeneous and highly fluctuating profile, delirium phenomenology requires detailed longitudinal analysis with a focus upon the temporal pattern of features and their severity (Adamis et al., 2013).

Subsyndromal delirium (SSD) is a state characterised by the presence of delirium symptoms but without full syndromal delirium (FSD) criteria. It is associated with outcomes intermediate between FSD and no delirium (Dosa et al, 2007; Cole et al, 2013). Although it is thought to include many features of FSD, such as disturbances in motor behaviour, consciousness and sleep-wake rhythmicity, a comprehensive account has been impeded by the
lack of clear criteria. However, recent work has applied a discriminate analysis approach and multinomial logistic regression methods to the phenomenological profiles of delirious and non-delirious cases to generate a conceptual phenotype of SSD. It was found that an intermediate severity of a range of neurocognitive features attributed to the FSD phenotype characterised SSD (Trzepacz et al. 2012). Other work has suggested a definition of SSD that can allow for reliable and consistent diagnosis (Trzepacz et al., 2011; Meagher et al, 2014).

Although the frequency of delirium has been reported to occur in 11-42% of medical in-patients, the frequency of SSD is less well defined and is estimated to occur in approximately 7-50% of cases, according to clinical population studied and definition applied (Ouimet et al, 2007; Bond et al, 2012). Other work has suggested that pharmacological intervention may reduce transition from SSD to FSD (Hakim et al., 2012). As such, a better understanding of the phenomenology of SSD may enable researchers and clinicians to address the many negative outcomes associated with SSD (Bourd el et al., 2004; Marcantonio et al., 2005). Therefore, the aim of this study is to; (1) explore the delirium phenomenology of elderly general medical admissions (2) identify the frequency of FSD and SSD defined by systematic categorical methods, and (3) identify the features of this phenomenological profile that characterise FSD and SSD.
Methods

Study design

Over a one year period between August 2012 and August 2013, 277 older general medical patients admitted through the emergency department of Cork University Hospital in the Republic of Ireland were screened for inclusion in a prospective study of sleep and neurocognitive disturbance. During the recruitment, older (≥70 years) general medical patients admitted within the prior 36 hours were invited to participate in the study. The inclusion of patients 70 years and older was chosen to include a more exclusive cohort of patients who were slightly older than the general cut off age of 65. Criteria for patient exclusion from this study were, 1) requiring specialist intervention (e.g. haematology, oncology, orthopaedic surgery and psychiatry), 2) patients who were deemed too unwell to participate, 3) early discharge from hospital, 4) insufficient data collected and 5) refusal to participate.

Ethical approval

The procedures and rationale for the study were explained to all patients but because many patients had cognitive impairment at entry to the study, it was presumed that most were not capable of giving informed written consent. Due to the non-invasive nature of the study, Cork Research Ethics Committee (CREC) approval was given to augment patient assent with proxy consent from next of kin (where possible) or a responsible caregiver in accordance with the
Helsinki Guidelines for Medical Research involving human subjects (World Medical Association, 2008).

Medication use

All medications prescribed for each patient were documented at each visit, including regular and as required doses. The use of psychoactive agents was a specific focus, especially the use of antipsychotics, opioids, benzodiazepines, psychostimulants and corticosteroids (Clegg and Young, 2011). Dose equivalents over the 24 hours prior to assessment were calculated for each drug class according to accepted conversion rates (i.e. antipsychotics in chlorpromazine equivalents; opioids in morphine equivalents; benzodiazepines in diazepam equivalents; corticosteroids in prednisolone equivalents) (Taylor et al., 2015).

Instruments and assessments

Delirium assessment

The Revised Delirium Rating Scale (DRS-R98) is a widely used instrument to measure symptom profile in delirium and can be used both as a diagnostic and severity assessment tool (Trzepacz et al, 2001). The DRS-R98 is designed to rate symptoms over the prior 24 hours. The DRS-R98 has high inter-rater reliability, validity, sensitivity and specificity for distinguishing delirium from mixed neuropsychiatric populations including dementia, depression, and schizophrenia (Trzepacz et al, 2001). It is a 16-item clinician-rated scale with 13 severity items
and 3 diagnostic items. All items are anchored by text descriptions which guide rating along a continuum from 0=absent; 1=present but possibly normal variation; 2=abnormal; 3=severe impaired. The 13-item severity section can be scored separately from the 3-item diagnostic section; their sum constituting the total scale score. Thus, DRS-R98 severity scores range from 0-39 with higher scores indicating more severe delirium. The DRS-R98 Total scale score ranges from 0 to a maximum of 46. A cutoff score of ≥18 is often applied to delirium diagnosis, especially where high specificity is desirable, but other work suggests that such cutoffs exclude many cases of DSM-IV delirium and lower cutoff scores are advocated where diagnostic sensitivity is the primary goal (Franco et al 2009; Kato et al., 2010; Meagher et al., 2012).

**DSM 5 Criteria**

The systematic algorithm-based methods adopted to identify DSM 5 full syndromal delirium (FSD) and subsyndromal delirium (SSD) were those published by our group previously. These algorithm based methods are based upon all available data for each patient, including clinical interview of patient, the use of validated assessments methods and supported by collateral interview with nursing staff, medical record, and collateral history from caregivers (Meagher et al., 2014a; 2014b).

**Dementia assessment**

For all patients, medical case notes were reviewed for a diagnosis of pre-existing cognitive impairment or dementia. In addition, the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF) was used to assess pre-admission cognitive
status. This 16 item scale was scored by a caregiver or close relative. A mean item cut off score of $\geq 3.5$ was used to diagnose dementia (Jorm, 2004). Consensus discussion was used to apply diagnosis in borderline cases. In the absence of an available informant, patients were considered not to have dementia if they scored $\geq 27/30$ on the MMSE. A previous study has shown only 2% of older in-patients with dementia are missed using this MMSE cut-off (Travers, 2013).

**Depression**

The short form of the Geriatric Depression Scale (GDS-SF) was used to screen for depression status. This 15 item scale is rated by a trained interviewer with scores of 0-4 indicating normal (depending on education, age and complaints), 5-8 considered mild depression, 9-11 indicating moderate depression; and 12-15 indicating severe depression (Greenberg, 2007). For the purpose of this study, depression status was designated as a binary variable with patients either having depression ($\geq 5$) or not (0-4).

**Statistical analysis**

Statistical analysis was conducted using the SPSS-19 package. Continuous variables are reported as means plus standard deviation, categorical variables are reported as counts and percentages. Little’s MCAR (missing completely at random) indicated that there was no systematic pattern of missing values [$\chi^2 = 27.114$, DF = 33, Sig. = .755]. ANOVA (Bonferroni correction), Post hoc Tukey test and Chi-square test were used for item comparisons. The generalised estimating equations method (GEE) was used to analyse longitudinal data for patterns of individual items from the DRS-R98 and between defined groups for full syndromal
delirium (FSD), subsyndromal delirium (SSD) and no delirium ever (ND) over the study period. The group designation at baseline and at each subsequent assessment (FSD/SSD) was determined according to the validated DSM 5 algorithm for FSD and SSD. The GEE approach was used to find pattern changes across the visits. The GEE method takes into account the fact that observations within a participant are correlated and estimates the population average across time. The estimated coefficients reflect the relationship between the longitudinal development of the dependent variable (grouped by delirium status FSD versus SSD) and the longitudinal development of the predictor variables (for example, age, gender, DRS-R98 items) using all data. All scale items were analysed in each analysis, although only those that were significantly different are shown in the results tables, with the reference group listed first. Given that the outcome (dependent) variable has 3 categories (no delirium, SSD, and FSD) the multinomial distribution was assumed, and the link function the Cumulative logit. For the GEE model the independent variables (predictors) were the 13 severity items of the DRS-R98.

Results

Of the 277 assessed, 145 (52%) were included and 132 (48%) were excluded from the study. The reasons for exclusion were: (1) refusal to participate (n=65), (2) patients who were deemed too unwell to participate (n=32), (3) early discharge from hospital (n=28), and (4) patients requiring non general medical treatment (n=7).

The sample consisted of 145 patients. The mean age was 80 (SD: 6; range 70-94). Sixty nine (47.6%) were females. Only 6 participants were in receipt of one or more classes of psychotropic/sedative medication. Three were in receipt of antipsychotic medications throughout
the hospitalisation, 2 antidepressants, 4 benzodiazepines, 4 hypnotics and 6 other sedative medications (e.g. opioids).

From the 145 participants, 31 (21.4%) had a previous history of dementia. Six participants (4.3%) were depressed at admission according to GDS. However, 30 (22%) participants had at least one feature of depression as measured by the GDS. Full syndromal delirium was 20.0% (n=29) at admission, while a further 18.5% (n=27) developed delirium over the study period. SSD was 5.5% (n=8) at admission, while the total frequency of SSD episodes was 14.5% (n=21). Fifteen cases of SSD (71.4%) of episodes of SSD transitioned to FSD over the course of the 7 days. The number of patients who did not develop either SSD or FSD i.e. ND was 56% (n=81). The average length of an episode of FSD was 2 days, while the average length of an episode of SSD was 1.1 days (see Table 1). Using the GEE method, the total number of observations was 655 from 145 participants who ranged from 1 to 7 observations. The distribution of delirium categories across time was 495 (76.2%) with no delirium, 129 (19.8%) observations with FSD and 26 (4%) with SSD.

For all the episodes of FSD, co-morbid depression was found to be 7.5 % (n=4), while for all the episodes of SSD there were no cases of co-morbid depression. However, for all the episodes of FSD and SSD it was found that 34% (n=19) and 24% (n=5) respectively had at least one feature of depression. Co-morbid dementia was found to be 33.3% (n=19) and 22.4% (n=5) in all the episodes of FSD and SSD, respectively. Co-morbid dementia was significantly more common in those with FSD compared to no delirium ($\chi^2 = 24.08$, DF = 2, p <0.0001), while gender, age and co-morbid depression were not significantly different in frequency (see Table 2).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean age (years)</td>
<td>80 (SD: 6.3) (Range 70-94)</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>76/69</td>
</tr>
<tr>
<td>Comorbid dementia (%)</td>
<td>21.4</td>
</tr>
<tr>
<td>Comorbid depression (%)</td>
<td>4.3</td>
</tr>
<tr>
<td>FSD at admission (%)</td>
<td>20.0</td>
</tr>
<tr>
<td>Incident FSD during first 7 days (%)</td>
<td>18.5</td>
</tr>
<tr>
<td>FSD at any stage (%)</td>
<td>38.5</td>
</tr>
<tr>
<td>Average length of episode of FSD (days)</td>
<td>2</td>
</tr>
<tr>
<td>SSD at admission (%)</td>
<td>5.5</td>
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</table>
Table 2. Comparison of demographic features between all episodes of FSD, all episodes of SSD and No delirium ever (n=145; number of assessments =655)

<table>
<thead>
<tr>
<th></th>
<th>No delirium ever (n=81)</th>
<th>Total SSD (N=21)</th>
<th>Total FSD (n=56)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ±SD)</td>
<td>79 ±6</td>
<td>82 ±7</td>
<td>80±6</td>
<td>NS</td>
</tr>
<tr>
<td>Female / Male (n)</td>
<td>40/41</td>
<td>9/12</td>
<td>21/34</td>
<td>NS</td>
</tr>
<tr>
<td>Co-morbid dementia (%)</td>
<td>10.0*</td>
<td>33.3</td>
<td>22.4*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Co-morbid depression (%)</td>
<td>4.0</td>
<td>0.0</td>
<td>7.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P values refer to Chi squared test for item comparisons.
Delirium Phenomenology

The frequency (%) and severity (mean ± SD) of individual delirium features as rated on the DRS-R98 are shown in Table 3. For total FSD (n=56), the most common and consistent DRS-R98 features present (at any severity) over time were: sleep wake cycle disturbance (100%), inattention (100%), visuospatial ability (100%), thought process abnormalities (98%), motor retardation (100%) and short term memory (100%), while hallucinations/perceptual disturbances (43%) and delusions (34%) occurred least frequently. The most common and consistent FSD DRS-R98 features reaching moderate or greater severity (score ≥2) were: Sleep-wake cycle disturbance (89%), short term memory (87.5%) and visuospatial ability (80%).

For all the episodes of SSD (n=21), the most common and consistent DRS-R98 features manifesting (at any severity) over time were: sleep wake cycle disturbance (100%), lability of affect (100%), visuospatial ability (100%), thought process abnormalities (100%), inattention (100%) and short term memory (100%), disorientation (100%) and delusions (71.4%), language (76.2%), while perceptual disturbances and hallucinations (47.6%) were the least frequent. For all the episodes of SSD, DRS-R98 items found to be most common with ≥2 severity were: sleep-wake cycle disturbances (85.7%), short term memory disturbances (100%), and visuospatial ability (85.7%).

For all the episodes of FSD, temporal onset and fluctuation of features were 100% and 92.9% at any severity, while the score ≥2 of these items was 89.3% and 8.9%, respectively. For all the episodes of SSD, temporal onset and fluctuation of features was similar at 90.5% and 100% at any severity, while the pathological severity (score ≥2) of these items was 81.0 % and 32.1%, respectively. Peak item scores for ND and FSD were all significantly different (with the
exception of the item for delusions), while only peak item scores for fluctuation of features were
significantly different for the ND and SSD groups (see Table 3).
Table 3. Comparison of DRS-R98 items scores between no delirium ever (ND), all episodes of SSD and all episodes of FSD (n=145; number of assessments = 655).

<table>
<thead>
<tr>
<th>DRS-R98 items</th>
<th>ND (n=81)</th>
<th>All episodes of SSD (n=21)</th>
<th>All episodes of FSD (n=56)</th>
<th>P value†*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
</tr>
<tr>
<td>Sleep-wake cycle disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>97.5(78)</td>
<td>100(21)</td>
<td>100(56)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>48.2(39)</td>
<td>85.7(18)</td>
<td>89.3(50)</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>1.5±0.6*</td>
<td>1.8±0.4</td>
<td>1.9±0.3*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perceptual disturbances and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hallucinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>4.8(3)</td>
<td>47.6(10)</td>
<td>42.8(24)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>3.6(2)</td>
<td>47.6(10)</td>
<td>23.2(13)</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>1.1±0.4*</td>
<td>1.4±0.5</td>
<td>1.1±0.4*</td>
<td>&lt;0.001</td>
</tr>
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<td>Delusions</td>
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<td></td>
</tr>
<tr>
<td>≥1</td>
<td>15.6(13)</td>
<td>71.4(15)</td>
<td>33.9(19)</td>
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</tr>
<tr>
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<td>1.2(1)</td>
<td>47.6(10)</td>
<td>8.9(5)</td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>0.4±0.2</td>
<td>0.9±0.2</td>
<td>0.8±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Lability of affect</td>
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<td></td>
<td></td>
<td></td>
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<td>6(5)</td>
<td>66.7(14)</td>
<td>33.9(34)</td>
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</tr>
<tr>
<td>Mean ±SD</td>
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<td>1.4±0.3</td>
<td>1.2±0.7*</td>
<td>&lt;0.001</td>
</tr>
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<td>Language</td>
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</tr>
<tr>
<td>≥1</td>
<td>38.5(31)</td>
<td>76.2(16)</td>
<td>82.1(46)</td>
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<td>0(0)</td>
<td>42.9(9)</td>
<td>5.4(3)</td>
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</tr>
<tr>
<td>Mean ±SD</td>
<td>0.5±0.3*</td>
<td>0.7±0.4</td>
<td>0.9±0.5*</td>
<td>&lt;0.001</td>
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<td>Thought process</td>
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<td>≥1</td>
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<tr>
<td>abnormities</td>
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<td>3.6(3)</td>
<td>76.2(16)</td>
<td>53.6(30)</td>
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</tr>
<tr>
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<td>1.5±0.5*</td>
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<tr>
<td>Motor agitation</td>
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<tr>
<td>≥1</td>
<td>37.3(30)</td>
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<td>67.9(38)</td>
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<tr>
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<td>66.7(14)</td>
<td>3.2(2)</td>
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</tr>
<tr>
<td>Mean ± SD</td>
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<tr>
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<tr>
<td>≥1</td>
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<td>Mean ± SD</td>
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<td>1.3±0.5</td>
<td>1.7±0.4*</td>
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</tr>
<tr>
<td>Orientation</td>
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<td>≥1</td>
<td>13.2(10)</td>
<td>100(21)</td>
<td>73.2(41)</td>
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<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.4±0.1*</td>
<td>0.9±0.3</td>
<td>1.1±0.8*</td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>57.8(47)</td>
<td>100(21)</td>
<td>100(56)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>9.6(8)</td>
<td>71.4(15)</td>
<td>67.9(38)</td>
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</tr>
<tr>
<td>Mean ± SD</td>
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<td>1.6±0.4</td>
<td>1.8±0.7*</td>
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</tr>
<tr>
<td>Short-term memory</td>
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<td></td>
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</tr>
<tr>
<td>≥1</td>
<td>92.7(75)</td>
<td>100(21)</td>
<td>100(56)</td>
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<td>≥2</td>
<td>57.6(47)</td>
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<td>87.5(49)</td>
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<tr>
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<td>38.5(31)</td>
<td>85.7(18)</td>
<td>71.4(40)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>1.2(1)</td>
<td>52.7(11)</td>
<td>23.2(13)</td>
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</tr>
<tr>
<td>Mean ± SD</td>
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<td>1.5±0.5</td>
<td>1.0±0.8*</td>
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<tr>
<td>Visuospatial ability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>95.2(73)</td>
<td>100(21)</td>
<td>100(56)</td>
<td></td>
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<td></td>
<td>≥2</td>
<td>31.3(25)</td>
<td>85.7(18)</td>
<td>80.3(45)</td>
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<td>--------------------------------------</td>
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<tr>
<td><strong>Temporal onset</strong></td>
<td>≥1</td>
<td>19.2(15)</td>
<td>90.5(19)</td>
<td>100(56)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>6.1(5)</td>
<td>81.0(17)</td>
<td>89.3(50)</td>
</tr>
<tr>
<td><strong>Fluctuation of features</strong></td>
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<td>9.6(8)</td>
<td>100(21)</td>
<td>92.9(52)</td>
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<td>≥2</td>
<td>1.2(1)</td>
<td>32.1(8)</td>
<td>8.9(9)</td>
</tr>
<tr>
<td><strong>Physical disorder</strong></td>
<td>≥1</td>
<td>81.9(66)</td>
<td>100(21)</td>
<td>100(56)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>2.4(2)</td>
<td>71.4(15)</td>
<td>67.9(38)</td>
</tr>
</tbody>
</table>

ANOVA (Bonferroni correction)
Post Hoc Tukey HSD test†*
A radar graph of mean peak DRS-R98 severity scale item scores over the total assessment period (Figure 1) indicates disturbances in sleep-wake cycle, lability of affect, thought process abnormalities, motor retardation, attention, short term memory and visuospatial ability are most pronounced in FSD and SSD. This graph also illustrates the phenomenological congruency between SSD and FSD supporting the notion that these are states that exist on a continuum of neurocognitive impairment.

**Fig. 1 Radar graph of mean peak DRS-R98 severity scale item scores for delirium phenomenology over the total assessment period.**
The generalised equation estimation (GEE) method was used to identify the items that exerted a significant effect on delirium status over time. Firstly, ND was compared with either SSD or FSD (see Table 4) determining that sleep-wake cycle disturbance, perceptual disturbances and hallucinations, lability of affect, motor retardation, attention and long term memory distinguished ND from either SSD or FSD. Further, GEE was used to compare SSD versus ND or FSD (see table 5) demonstrating that sleep wake cycle disturbance, perceptual disturbances and hallucinations, lability of affect, thought process abnormalities, motor hyperactivity, motor retardation, attention, long term memory and visuospatial ability distinguished SSD from either FSD or ND.

<table>
<thead>
<tr>
<th>Table 4. Generalised equation estimation (GEE) model findings for Delirium Rating Scale – Revised-98 (DRS-R98) severity item scores comparing no delirium versus either SSD or FSD delirium.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Coefficient</td>
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<td>----------------------------------------------------------------</td>
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<tr>
<td>Sleep-wake cycle disturbance</td>
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<tr>
<td>Perceptual disturbances and hallucinations</td>
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<tr>
<td>Lability of affect</td>
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<tr>
<td>Thought process abnormalities</td>
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<tr>
<td>Motor retardation</td>
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<tr>
<td>Attention</td>
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<tr>
<td>Long term memory</td>
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<tr>
<td>Visuospatial ability</td>
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<td>--------------------------------</td>
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<tr>
<td>Sleep-wake cycle disturbance</td>
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<tr>
<td>Perceptual disturbances and Hallucinations</td>
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<tr>
<td>Lability of affect</td>
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<td>Motor agitation</td>
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<td>Motor retardation</td>
</tr>
<tr>
<td>Attention</td>
</tr>
<tr>
<td>Long term memory</td>
</tr>
</tbody>
</table>
Discussion

This study investigated delirium phenomenology in general medical admissions with serial assessment over 7 days using validated methods for phenomenological assessment and delirium syndromal diagnosis. Both the prevalence of delirium at admission (20%) and incidence of delirium during the study period (18.5%) were consistent with other studies of delirium in the general hospital setting (Ryan et al., 2013; Inouye et al., 2014; Kennedy et al., 2014; Richie et al., 2014). In contrast, the frequency of SSD at admission was quite low (5.5%), however the frequency increased over the study period to 14.5%. The frequency of episodes of SSD transitioning to FSD was 10.3% (n=15). This is in keeping with the literature which estimates that SSD exists in 7-50% of patients (Ouimet et al., 2007; Bond et al., 2012). There are two aspects to the relationship between SSD and FSD. The first is the endogenous pathological mechanism of delirium onset and how critically unwell patients can escalate from a state of SSD to FSD. The second is the exogenous factors such as medical intervention and how this may prevent patients from descending into FSD. Given the inconsistent detection methods of identifying delirium in hospital based systems, it is difficult to parse out this important issue.

Moreover, the criteria that we applied are more stringent in terms of the requirements for SSD diagnosis as we believe that this can allow for greater precision for what has previously been a vague and ill-defined concept. The frequency and severity of phenomenology in FSD provides further evidence that delirium is a complex neuropsychiatric syndrome with core features (inattention, sleep-wake cycle disturbance and motor disturbances) that are particularly consistently present, along with a variety of associated features (delusions, perceptual disturbance and hallucinations) that are more variable in frequency. In support of this, we found
that the more pronounced features of SSD were sleep-wake cycle disturbances, visuospatial ability, thought process abnormality and inattention.

The diagnosis and phenomenological assessment of delirium is complicated by a wide differential diagnosis, with depression and dementia especially relevant. In this study, 22.4 % of patients with FSD also had comorbid dementia which is in keeping with the literature estimating that 22-89% of cases of dementia are complicated by delirium (Fick et al., 2002). Moreover, the distinction of hypoactive delirium from depression is often challenging and these states are frequently misdiagnosed as ‘hypoactive’ delirium due to the presence of sleep disturbances and motor retardation (Spiller and Keen, 2006; O’Sullivan et al., 2014).

Longitudinal analysis revealed that sleep-wake cycle, lability of affect, thought process abnormalities, motor retardation, attention, short term memory and visuospatial ability were significantly more impaired in FSD and SSD. This supports the notion that SSD and FSD are on a continuum of phenomenological intensity. Importantly, the criteria used for diagnosis of FSD and SSD were independent of DRS-R98 ratings. In addition, SSD and FSD differed by virtue of a broad range of symptoms that are not used diagnostically in these systems. Previous work has found great heterogeneity in the temporal duration of delirium and we found that the average length of an episode of FSD was 2 days, while for SSD it was 1.1 days (Rudberg et al., 1997; Fann et al., 2005; Sylvestre et al., 2006), again suggesting that SSD is an attenuated form of FSD. Almost three quarters of cases of SSD transitioned into FSD, suggesting that SSD may reflect an evolving phase of delirium.

Study limitations
This study describes delirium phenomenology in an elderly general medical population which may limit its generalizability to other delirious populations. This is the first report that we are aware of utilising a systematic algorithm for generating DSM 5 FSD and SSD. A principal limitation of this study was the detection of small numbers of patients with SSD. This may in part be due to the definition of SSD applied to this cohort. However, during the recruitment phase of the study, 132 (48%) of patients were excluded. Many of these patients (particularly those too unwell to participate) may have had SSD and therefore, future studies may need to use more relaxed exclusion criteria. A multi-centre approach whereby pooled elderly medical inpatient data using these operationalized diagnostic algorithm and longitudinal analysis may further enhance our understanding of the phenotype of SSD and its development either into FSD or otherwise. Further studies with larger samples of SSD can allow for more detailed analysis of the relationship with co-morbid dementia, depression, and other relevant medical conditions that may increase the risk of developing SSD. Future research should also focus upon the entire amount of pharmacological substances that patients consume on a daily basis in an effort to explore the existence of the potential impact of ‘pharmacological burden’ upon delirium pathogenesis.

Conclusion

Modern conceptualisations of delirium have been influenced by the assessment methods used to assess, detect and analyse its complex and transient nature (Adamis et al., 2013). Most studies analysing the phenomenology of delirium have been based on cross sectional methods and have thus presented a static picture of delirium (Gupta et al., 2008). Given that delirium is a
fluctuating and often reversible condition, an accurate analysis of its phenomenology must take into account these key features. Longitudinal studies are thus critical to providing clinicians and researchers with a more robust theoretical account of delirium phenomenology that can help to clarify the underlying endophenotype that typifies the neuropsychiatric syndrome of delirium. This study confirms the severity and consistency of features that are elementary to both the FSD and SSD state and reflect a dimensional relationship between the SSD and FSD phenotype. These findings can assist in developing more reliable methods to identify this under recognised syndrome, including its subsyndromal variant that is a frequent precursor to development of full blown delirium.
References


of 768 prospectively evaluated patients using the delirium rating scale-revised-98. BMC Medicine, 12(1), 164.


Commentary chapter 2

Chapter 2 includes a detailed assessment of delirium phenomenology in both its full-syndromal and sub-syndromal form. This chapter highlights the significant differences found between these states longitudinally using validated consensus based methods. This novel approach to delirium phenomenological profiling has generated important findings for this particular area. This chapter builds upon the growing number of studies that explore delirium phenomenology and the associated conditions that exist in such clinical cohorts. The importance of this chapter is not only to be found in the development of improved methods of detecting delirium and sub-syndromal cases, but in exploring the detailed array of features that makes up this heterogenous condition. This then allows researchers to focus on more complex aspects of delirium phenomenology namely, the circadian domain.

Background to Chapter 3

Chapter 3 describes a detailed study of sleep wake cycle patterns in elderly medical admissions. This chapter builds upon the broad phenomenological profiling study of chapter 2 and uses more focused methods of exploring the relationship between disturbed sleep using clinician rated sleep measures and subjective patient rated sleep quality measures. This chapter also explores this relationship in two other fundamental ways. Firstly it explores the relationship between sleep disturbances and other associated conditions like dementia and depression. It also seeks to account for the confounding factors that may exist in this clinical setting. Finally, it explores the relationship between sleep and delirium at both the admission point into the study and longitudinally using advanced statistical methods.
Contributions of the authors:

The initial idea for the study was from the author James Fitzgerald and Prof. David Meagher. Given the complex nature of this particular study, the study design was also amended by the other collaborators Dimitrios Adamis, Paula Trzepacz, Niamh O’ Regan, Colum Dunne and Suzanne Timmons. Data collection was shared between the author James Fitzgerald and Dr. O’Regan. Although the majority of the basic statistical analysis was undertaken by the author, specific guidance was given by Dr. Adamis for suitable tests. For the use of advanced statistical analysis, Dr. Adamis performed the GEE method. All collaborators contributed to reviewing the final chapter.
Chapter 3 - Sleep-wake cycle integrity in elderly acute general medical inpatients: Longitudinal relationship to major neurocognitive disorder.

James M. FitzGerald¹,², Niamh O’Regan³, Dimitrios Adamis²,⁴,⁵, Suzanne Timmons³, Colum P Dunne¹,², Paula T. Trzepacz⁶,⁷, David J. Meagher¹,²,⁸

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Abstract:

Background: Sleep disturbances are common in elderly hospitalised patients but their relationship to neurocognitive disturbance is understudied.

Methods: Sleep performance was assessed daily for a week in elderly acute general hospital admissions using objective (Revised Delirium Rating Scale [DRS-R98]) and subjective (Richards-Campbell Sleep Quality Scale [RCSQ]) measures. The longitudinal relationship between sleep-patterns, delirium and dementia status was examined.

Results: 145 patients [mean age 80±6.3 years; 69(48%) female; 31(21%) with dementia] underwent a total of 661 assessments. Twenty-eight patients had delirium at admission (19%), while 29 (20%) developed incident delirium during the first week. Over three quarters (77%) of those with dementia experienced delirium during their hospitalisation. Objective sleep disturbance occurred in 95% of patients, with more severe disturbances (DRS item 1 score ≥2) associated with active delirium. The absence of DRS-R98 sleep-wake cycle disturbance indicated a low likelihood of delirium with Negative Predictive Values of 96% (score=0) and 90% (score≤1). Subjective sleep quality on the RCSQ did not relate to neurocognitive disorder and had low correlation with DRS-R98 assessments, regardless of delirium status. On longitudinal analysis, severity of DRS-R98 sleep-wake cycle disturbance was significantly linked to delirium status. DRS-R98 sleep scores were elevated on the first day of delirium rather than on either of the two days prior to this.

Conclusions: Objective sleep disturbances are common in neurocognitive disorders, with more severe acute disruptions to sleep-wake cycle highly indicative of possible delirium. Altered sleep patterns may have utility in improving recognition of delirium of this under recognised syndrome.
Introduction

Sleep-wake cycle is a complex, active circadian rhythm involved in a variety of dynamic brain and body physiological processes. Impaired sleep-wake cycle is associated with deficits in cognition (Ellenbogen et al., 2006; Wilckens et al., 2014) including a relationship with abnormal β-amyloid peptide linked to Alzheimer’s disease (Ju et al., 2014). Disturbances in sleep-wake cycle and cognition are common in older medical inpatients, but the relationship is not fully understood. In addition, sleep disturbances are common in mild and major neurocognitive disorders such as traumatic brain injury, dementias and delirium and may herald their onset (Tranah et al., 2011; Blackwell et al., 2011; Yildizeli et al., 2011; Latrielle et al., 2014). As such, there is a strong relationship between sleep and neurocognitive disorders with both these entities impacted upon by the circadian timing system (CTS) (Gritton et al., 2009; Fitzgerald et al., 2013; Naismith et al., 2014).

Delirium is a complex neuropsychiatric syndrome associated with a range of adverse clinical outcomes in hospitalised older people, including elevated risk of mortality (Witlox et al, 2010). It is a common occurrence in the acute hospital setting, with a point prevalence of approximately 20% (Ryan et al., 2013) and can be complicated by presence of other neuropsychiatric conditions, such as depression and dementia (Draper et al., 2011; Ryan et al., 2013). Sleep disturbances form part of the circadian domain – one of three core domains of delirium along with impaired cognition and disturbed higher order thinking (Fitzgerald et al., 2013). These disturbances can present as insomnia, sleep fragmentation, daytime somnolence and reversal of sleep-wake phases (Watson et al., 2012). Sleep disturbances have been reported to be as high as approximately two-thirds in patients with Alzheimer’s disease, while other dementias such as vascular and Lewy-body dementia, have reported circadian shift phases in up to 90% of patients (Guarnieri et al, 2012). In the hospital setting, sleep and cognition can be affected by environment-related, medications, surgery, age, pain, and many different medical and neuropsychiatric conditions.

The longitudinal relationship between sleep-wake cycle disturbance and the onset of delirium has not been previously reported in elderly general medical admissions. The purpose of this study is (i) to prospectively evaluate sleep-wake cycle disturbances in newly admitted, non-
elective elderly general medical patients, and (ii) to explore how these patterns relate to the prevalent and incident delirium with consideration of comorbid dementia and depression.

Methods

Study design

Over a one year period between August 2012 and August 2013, a prospective study of consecutive elderly general medical admissions in an acute hospital setting was conducted. Screening for inclusion into the study was performed on 277 elderly general medical patients, attending the emergency department of Cork University Hospital in the Republic of Ireland. Within the past 36 hours of admission all elderly (70 yrs+) general medical patients were requested to participate in the study. Criteria for patient exclusion from this study were, 1) requiring specialist intervention (e.g. haematology, oncology, orthopaedic surgery and psychiatry), 2) patients who were deemed too unwell to participate, 3) early discharge from hospital, 4) insufficient data collected, and 5) refusal to participate.

Sleep was assessed at baseline and daily thereafter for a week. Two approaches were applied to measure sleep patterns (i) DRS-R98 item for sleep-wake cycle disturbances (item 1) which is a clinician-rated objective clinical assessment of sleep-wake cycle disturbance, and (ii) the Richards-Campbell Sleep Questionnaire (RCSQ), which is a patient self-report scale assessing subjective quality of sleep.

Medication data

For each of the patients, all medications prescribed were documented at each visit, including regular and as required doses. In particular, specific focus was placed upon the use of psychoactive agents, with particular example being antipsychotics, opioids, benzodiazepines, psychostimulants and corticosteroids (Clegg and Young, 2011). Dose equivalents over the 24 hours prior to assessment were calculated for each drug class according to accepted conversion
rates (i.e. antipsychotics in chlorpromazine equivalents; opioids in morphine equivalents; benzodiazepines in diazepam equivalents; corticosteroids in prednisolone equivalents) (Taylor et al., 2015).

Procedures

Delirium assessment

Delirium status was assessed daily using the Confusion Assessment Method (CAM)-Algorithm (Inouye et al, 1990), by a trained and experienced rater (N.O’R). This consists of a 4-item diagnostic algorithm that requires the presence of (a) acute onset or fluctuating course, (b) inattention, and either (c) disturbed consciousness or (d) disorganised thinking. The CAM algorithm was rated thoroughly based on information obtained through interview of the patient, formal cognitive assessment, discussion with treating hospital staff, and screening of medical and nursing records for signs of delirium. The CAM remains the most widely used screening test and has been validated in several languages and replicated in multiple settings (Wei et al, 2008).

Delirium phenomenology was assessed on all patients daily for the duration of the study using the Revised Delirium Rating Scale (DRS-R98) (Trzepacz et al, 2001) (NO’R). This is well-validated and widely used to measure symptom profile and severity in delirium, and rates symptoms up to and including the preceding 24-hour period, utilizing all sources of information. It is a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items. Item rating levels (0-3) are anchored by phenomenological text descriptions and higher scores indicate more severe delirium. It has high inter-rater reliability, validity, sensitivity and specificity for distinguishing delirium in mixed neuropsychiatric populations (Trzepacz et al, 2001). Item 1 of the DRS-R98 assesses sleep-wake cycle on a 4-point scale: “no disturbance (0), mild nocturnal sleep disturbance or occasional daytime drowsiness (1), moderate disorganization of sleep-wake cycle evidenced by daytime napping, brief periods of nocturnal awakening (2), and severe disruption of sleep-wake cycle as evidenced by day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness (3).”
Sleep quality

Sleep quality of all patients was measured daily using the Richards-Campbell Sleep Questionnaire (RCSQ) (Richards et al., 2000). This self-rated visual analog scale measures sleep along a 0 to 100 point scale according to five dimensions: “(1) depth: light sleep (0) to deep sleep (100); (2) latency of sleep: just never could fall asleep (0) to fell asleep almost immediately (100); (3) number of awakenings: awake all night long (0) to awake very little (100); (4) return to sleep: couldn’t get back to sleep (0) to got back to sleep immediately (100); and (5) sleep quality of the previous night: a bad night’s sleep (0) to a good night’s sleep (100).” For each dimension the patient indicated their score along a 100mm line. The total sleep score reflects the average of these five domains, ranging from 0 (poorest possible sleep) to 100 (optimum sleep). The instrument has been validated against polysomnography in ICU patients (Richards et al. 2000).

Dementia assessment

A diagnosis of pre-existing cognitive impairment or dementia was searched for throughout all the patients’ notes. Moreover, the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF) was used to assess pre-admission cognitive status. This 16-item scale was scored by a caregiver or close relative. A mean item cut off score of ≥3.5 was used to diagnose probable dementia (Jorm, 2004). In borderline cases, consensus discussion was used to apply diagnosis. In the absence of an available informant, patients were considered not to have dementia if they scored ≥ 27/30 on the MMSE. A previous study has shown only 2% of older in-patients with dementia are missed using this MMSE cut-off (Travers, 2013).

Depression assessment

The short form of the Geriatric Depression Scale (GDS-SF) was used to screen for depression status. This 15-item scale was rated by a trained interviewer and depression denoted by total scores ≥5 (Greenberg, 2007).
Ethical approval

It was presumed that most patients were not capable of giving informed written consent because many patients had cognitive impairment at entry to the study. However, the procedures and rationale for the study were explained to all patients. Cork Research Ethics Committee (CREC) approval was given to augment patient assent with proxy consent from next of kin (where possible) or a responsible caregiver in accordance with the Helsinki Guidelines for Medical Research involving human subjects, due to the non-invasive nature of the study, (World Medical Association, 2008).

Statistical analysis

Statistical analysis was conducted using the SPSS-19 package. Continuous variables are reported as means plus standard deviation, while categorical variables are reported as counts and percentages. Analysis of variance with Post hoc Tukey tests were used for group comparisons. Spearman’s rho was used to examine the correlation between DRS-R98 and RCSQ ratings. The Generalized Estimating Equations (GEE) method was used to analyse repeated measures for DRS-R98 sleep-wake cycle item and RCSQ quality of sleep scores (Adamis, 2009). For the GEE analysis all sleep-wake cycle scores as measured by DRS-R98 item 1 were included. GEE functions as a form of logistic regression whereby each patient score is included along with a measure for intra-individual correlations. This takes into account the fact that the observations within a subject are interdependent. Also, it has relaxed assumptions about the distribution of data.
Results

Demographic and general clinical characteristics

The sample consisted of 145 patients. The mean age was 80 years (SD: 6.3; Range: 70-94). Sixty nine (48%) were females. These patients underwent a total of 661 assessments over the seven days ranging from 145 on day 1 to 51 on day 7. The number of patients assessed on each of the seven days with CAM-defined delirium status are shown in figure 1. Of note, 129 ratings in total were CAM positive (19.5% of all ratings).

Figure 1. Number of patients assessed on each day with delirium status (as per the CAM)
Thirty one (21%) patients had a previous history of dementia. Six participants (4%) were depressed at admission according to the GDS. The prevalence of delirium at admission was 19% (n=28), while a further 29 patients (20%) developed incident delirium during the week of observation. Of those with dementia (n=31), 9 had prevalent delirium at admission while a further 15 developed incident delirium during the following week. In total, 24 of the 31 patients (77%) with dementia experienced delirium during their hospitalisation.

Medication data

Only 6 participants were in receipt of one or more classes of psychotropic medication during the week of observation: benzodiazepines and hypnotics (n=8), antipsychotics (n=3), antidepressants (n=2), and 6 were administered other sedative medications (e.g. opioids). These numbers were deemed too small to exert a meaningful statistical effect in the overall cohort and this data was not used in the longitudinal analyses.

Sleep patterns

Table 1 shows baseline sleep ratings for the DRS-R98 item 1 and RCSQ for the total population, and then categorised according to the presence of delirium (prevalent at admission or incident cases occurring subsequently) and dementia. Some degree of sleep disturbance was evident for the vast majority of patients (95%), but for most (58%) this was rated with a DRS-R98 score of 1 consistent with some disturbance but within normal limits. Abnormal or
pathological sleep disturbance (as denoted by a score of ≥2 on DRS-R98 item 1) was significantly higher for prevalent delirium compared with all other groups, including those patients who subsequently developed incident delirium during the following week. Eighty-six percent of those with dementia but without delirium at baseline had some form of sleep disturbance (score ≥ 1 on the DRS-R98 item 1), but 68% of these had a score of 1 only (i.e. sleep disturbances within normal ranges), but scores of ≥2 commonly indicated comorbid delirium (6/10).

For the RCSQ ratings, there were no significant differences across the groups regardless of delirium status. The correlation between DRS-R98 sleep item ratings and the total RCSQ score was low for the overall population (r=-0.06), as well as for those who had prevalent delirium (r=-0.27), those who subsequently developed incident delirium (r=-0.19), and for those who did not develop delirium during the study (r=0.08).
Table 1 Sleep ratings for the DRS-R98 item 1 and RCSQ at baseline for the total population and also according to the presence of delirium and dementia.

<table>
<thead>
<tr>
<th></th>
<th>Delirium Status</th>
<th>Dementia Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total population (n=145)</td>
<td>Prevalent delirium (n=28)</td>
</tr>
<tr>
<td>DRS-R98*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score</td>
<td>1.37 ± 0.59</td>
<td>1.79 ± 0.59</td>
</tr>
<tr>
<td>(±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRS-R98 item 1 score</td>
<td>8 (5%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>= 0, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRS-R98 item 1 score</td>
<td>76 (53%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>=1, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRS-R98 item 1 score</td>
<td>61 (42%)</td>
<td>23 (82%)</td>
</tr>
<tr>
<td>≥2, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCSQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency, mean (±SD)</td>
<td>67.1 (±10.5)</td>
<td>68.4 (±11.6)</td>
</tr>
<tr>
<td>Depth,</td>
<td>67.0 (±9.5)</td>
<td>64.5 (±4.5)</td>
</tr>
<tr>
<td>RCSQ</td>
<td>Number of awakenings, mean (±SD)</td>
<td>Quality, mean (±SD)</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>64.4 (±6.9)</td>
<td>65.3 (±8.1)</td>
</tr>
<tr>
<td></td>
<td>63.2 (±5.9)</td>
<td>63.6 (±6.7)</td>
</tr>
<tr>
<td></td>
<td>64.1 (±8.0)</td>
<td>64.7 (±7.9)</td>
</tr>
<tr>
<td></td>
<td>63.7 (±7.0)</td>
<td>64.1 (±7.3)</td>
</tr>
<tr>
<td></td>
<td>64.9 (±6.8)</td>
<td>66.1 (±8.5)</td>
</tr>
<tr>
<td></td>
<td>63.9 (±6.6)</td>
<td>64.6 (±7.7)</td>
</tr>
<tr>
<td></td>
<td>62.7 (±5.9)</td>
<td>64.1 (±6.4)</td>
</tr>
<tr>
<td></td>
<td>63.23 (±6.1)</td>
<td>64.35 (±6.9)</td>
</tr>
<tr>
<td></td>
<td>64.7 (±7.1)</td>
<td>65.6 (±8.4)</td>
</tr>
</tbody>
</table>
Relationship between sleep status and other clinical variables over time

Table 2 shows a GEE model of the relationship over all assessments between sleep-wake cycle integrity (DRS-R98 item 1 score) and other demographic and clinical characteristics. Of note, severity of sleep-wake cycle disturbance was significantly linked to delirium status but not age, gender, dementia or depression status. However, the group with depression was small (n=6).

A similar analysis was performed to examine for variables associated over time with sleep quality according to total scores on the RCSQ scale (see table 3). In contrast to the findings for the DRS-R98, sleep quality was significantly associated with depression status rather than any other clinical or demographic variables.

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>S.E.</th>
<th>P</th>
<th>Wald x2</th>
<th>df</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>-0.54</td>
<td>0.08</td>
<td>&lt;0.001</td>
<td>48.9</td>
<td>1</td>
<td>-0.69 to -0.39</td>
</tr>
<tr>
<td>dementia</td>
<td>0.05</td>
<td>0.08</td>
<td>0.55</td>
<td>0.36</td>
<td>1</td>
<td>-0.10 to 0.19</td>
</tr>
<tr>
<td>Depression status</td>
<td>-0.08</td>
<td>0.14</td>
<td>0.5</td>
<td>0.33</td>
<td>1</td>
<td>-0.35 to 0.19</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>0.00</td>
<td>0.8</td>
<td>0.06</td>
<td>1</td>
<td>-0.009 to 0.012</td>
</tr>
<tr>
<td>Gender</td>
<td>0.02</td>
<td>0.06</td>
<td>0.8</td>
<td>0.06</td>
<td>1</td>
<td>-0.10 to 0.13</td>
</tr>
<tr>
<td>Constant</td>
<td>1.51</td>
<td>0.49</td>
<td>0.002</td>
<td>9.7</td>
<td>1</td>
<td>0.56 to 2.47</td>
</tr>
</tbody>
</table>
Table 3. GEE model for sleep ratings (as per the RCSQ) according to demographic (age, gender) and clinical ratings (delirium status, depression status, dementia).

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>S.E.</th>
<th>p</th>
<th>Wald x2</th>
<th>df</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression status</td>
<td>-1.23</td>
<td>0.62</td>
<td>0.04</td>
<td>3.89</td>
<td>1</td>
<td>-0.35 to 0.19</td>
</tr>
<tr>
<td>Delirium</td>
<td>-0.43</td>
<td>0.63</td>
<td>0.50</td>
<td>0.47</td>
<td>1</td>
<td>-1.66 to 0.80</td>
</tr>
<tr>
<td>Dementia</td>
<td>0.58</td>
<td>0.49</td>
<td>0.23</td>
<td>1.45</td>
<td>1</td>
<td>-1.54 to 0.37</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.04</td>
<td>0.40</td>
<td>0.67</td>
<td>1</td>
<td>-0.04 to 0.11</td>
</tr>
<tr>
<td>Constant</td>
<td>66.9</td>
<td>3.29</td>
<td>&lt;0.001</td>
<td>412.9</td>
<td>1</td>
<td>60.4 to 73.4</td>
</tr>
</tbody>
</table>

Temporal pattern of sleep-wake cycle ratings in incident delirium

Table 4 show DRS-R98 sleep item 1 ratings in the days prior to delirium onset and on the first day of CAM-defined syndromal delirium. In the 29 cases of incident delirium, DRS-R98 scores for the sleep item were significantly higher on the first day of delirium compared to the previous day (1.72±0.46 vs 1.24±0.58; t=-3.7, p<0.001, 95% C.I. for difference = 0.22-0.74). Of these, 11 experienced delirium onset on day 2 of assessment while for 18 the onset was later and thus these had DRS-R98 sleep assessments for at least two days prior to onset of CAM-positive delirium. Of note, sleep scores were significantly elevated only on the first day of delirium but not in the two days immediately prior to this.
Table 4. DRS-R98 sleep-wake cycle disturbance item ratings in the days prior to delirium onset for incident cases and on the first day of CAM-defined syndromal delirium.

<table>
<thead>
<tr>
<th>DRS-R98 Sleep-wake disturbance item rating day</th>
<th>n</th>
<th>DRS-R98 score mean ± SD</th>
<th>Patients with scores ≥ 1</th>
<th>Patients with scores of ≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>29</td>
<td>1.22 ± 0.55</td>
<td>100 (n=29)</td>
<td>39% (n=11)</td>
</tr>
<tr>
<td>First day of delirium</td>
<td>29</td>
<td>1.72 ± 0.46</td>
<td>100 (n=29)</td>
<td>27.5% (n=8)</td>
</tr>
<tr>
<td>Day before delirium onset</td>
<td>29</td>
<td>1.17 ± 0.51</td>
<td>100 (n=29)</td>
<td>27.5% (n=8)</td>
</tr>
<tr>
<td>2 days before delirium onset</td>
<td>18</td>
<td>1.11 ± 0.47</td>
<td>90% (n=16)</td>
<td>11% (n=2)</td>
</tr>
</tbody>
</table>

Relationship between DRS-R98 sleep item ratings and CAM status

Of the 129 CAM positive ratings, 126 (98%) scored ≥1 and 81 (63%) scored ≥2 on the DRS-R98 item for sleep-wake cycle disturbance. There were 580 occasions when the DRS-R98 rating was ≥1 and 126 of these (22%) had active delirium as per CAM status. There were 197 occasions when the DRS-R98 rating was ≥2 and 81 of these (41%) had active delirium as per CAM status. Examining the relationship between DRS-R98 sleep ratings and CAM positive delirium, using a cutoff of ≥1 the sensitivity was 0.98, specificity was 0.15, positive predictive value was 0.22, and negative predictive value was 0.96. Similarly, where a cut-off of ≥2 was applied, sensitivity was 0.63, specificity was 0.78. The positive predictive value was 0.41 and negative predictive value was 0.90.
Discussion

We examined sleep patterns in acute older medical general hospital inpatients using both subjective patient-self ratings and objectively observed assessments. Sleep disturbances in general were extremely common in this population, especially in those with neurocognitive disorders such as dementia and delirium. In addition, we found that more severe disturbances of sleep-wake cycle were more closely linked to the presence of delirium rather than other neuropsychiatric disturbances. Notably, we found that elevated scores on the DRS-R98 item for sleep-wake cycle disturbances were evident during active CAM-defined delirium but not in the period immediately preceding this. In contrast, ratings on the RCSQ were more closely linked to depression status and did not correlate with DRS-R98 ratings both in patients with and without active delirium. A rating of moderate or greater disturbance of sleep-wake cycle on the DRS-R98 was highly indicative of the presence of syndromal delirium.

Both sleep and cognitive disturbances were common in this population. The vast majority of patients had some evidence of disrupted sleep highlighting the frequency of sleep disturbance in the hospitalised older patient. The factors that contribute to this are legion, and range from uncontrolled pain to simple lack of familiarity with the environment. In addition, neurocognitive difficulties were also common, with pre-existing dementia evident in more than one fifth of patients while almost 20% had prevalent delirium at admission and a further 20% developed incident delirium during the first week of hospitalisation. Overall, almost 20% of all assessments were positive for delirium. This is in keeping with other studies of older general hospital inpatients where as a general rule of thumb approximately one in five experience delirium at some point (Ryan et al, 2013; Siddiqi et al, 2006), while a substantial percentage have a pre-
existing dementia (Collins et al, 2010). Similar to previous studies, comorbidity between these conditions was common, with more than three quarters of those with dementia experiencing delirium at some point during the first week of their hospitalisation.

Previous studies have highlighted the frequency of disturbances of sleep-wake cycle in delirium and suggested that although milder disturbances are very common in hospitalised patients, more severe disturbances are indicative of delirium (Meagher et al, 2007; Meagher et al, 2010). We found that sleep disturbance was closely linked to neurocognitive disorder, with ratings on the DRS-R98 for sleep (item 1) particularly linked to the presence of active syndromal delirium as identified with the daily CAM ratings. Ratings of items on the DRS-R98 follow an ascending order of severity whereby scores of ≥2 are considered to be inherently abnormal while a score of 1, although indicating some disturbance, can be equated with normal variation. For the sleep-wake cycle, a score of ≥2 on the DRS-R98 indicates disturbances such as sleep fragmentation, significant daytime napping, frequent nocturnal awakenings, and in more severe cases sleep-wake cycle reversal. We found that delirium was the single significant factor associated with such disturbances over time. Moreover, when present, these disturbances were highly indicative of delirium with high specificity indicating that almost 80% of those experiencing this level of sleep-wake cycle disruption were actively delirious. In addition, the negative predictive value for DRS-R98 sleep-wake cycle disturbances was 96% (score ≥1) and 90% (score ≥2) highlighting how the absence of significant sleep disturbance suggests that a diagnosis of delirium is highly unlikely. Given the poor detection of delirium in real world clinical practice (O’Hanlon et al, 2013), these findings highlight the potential usefulness of including assessment for more severe sleep disturbances in efforts to identify delirium. This is particularly relevant since sleep disturbances are not generally emphasised in commonly used
screening tools for delirium such as the CAM (Inouye, 1991) and NuDESC (Gaudreau et al., 2005).

We found little correlation between the DRS-R98 sleep item and the RCSQ. These two scales differ in a number of aspects. The DRS-R98 is typically clinician-rated and observed according to all available information over the previous 24 hours. In contrast, the RCSQ is subjectively rated by the patient according to their perceptions of sleep over the previous night. In addition, the DRS-R98 focuses upon sleep-wake cycle integrity while the RCSQ is focused upon a variety of characteristics that includes difficulty getting off to sleep, perceived depth of sleep, and subjective quality of the sleep experience. It is well documented that substantial differences can exist between the objective and subjective quality of sleep. Moreover, the presence of significant cognitive disorder in a substantial percentage of our subjects is also likely to have impacted upon the accuracy of self-reported sleep quality (Bourne et al., 2007; Kamder et al., 2013). This is congruent with other work indicating little association between daily observer rated assessments of sleep quality using RCSQ and the transition to delirium (Kamdar et al., 2015). Indeed, our findings support other studies suggesting that presence of delirium precludes the use of the RCSQ (Patel et al., 2014). Interestingly, we found little difference between the ratings of sleep quality between those with and without delirium even though ratings on the DRS-R98 for essentially the same time periods indicated substantial disruptions to sleep wake cycle during active delirium. We found that the RCSQ ratings were more closely linked to depressive illness where the character of sleep disturbance is typically more subtle (increased sleep latency with initial insomnia, reduced depth and perceived quality of sleep) than the often profound changes to sleep-wake cycle that occur in delirium.
Study limitations and recommendations

This study describes the relationship between disturbances to sleep-wake cycle integrity and neurocognitive disorder in acutely hospitalised older people. These findings may not readily generalise to other populations and settings. We found that alterations to sleep-wake cycle occurred in tandem with syndromal delirium but these sleep changes were not useful as prodromal or early indicators of emerging delirium. These measures were conducted during the working day and reflected observations from the previous 24 hours. More continuous monitoring might identify changes earlier. Moreover, we included a relatively modest number of cases of incident delirium such that future work focusing upon incident cases might allow for more fruitful examination of this issue. Similarly, the small number of patients with depressive illness may have impacted upon findings in respect of the relevance of affective changes to sleep-wake cycle and how these might assist in distinguishing neurocognitive disorders in everyday clinical practice (O’Sullivan et al., 2014). Although this study accounted for confounding factors such as medication, age, gender, co-morbid depression and dementia using the GEE method, other potential confounding factors such as noise, light exposure and social zeitgebers have not been accounted for by this longitudinal analysis. Future work should examine the impact of these additional and potential confounding factors upon sleep in particular in elderly medical admissions with cognitive impairment.
Conclusion

Sleep disturbances are extremely common among older hospitalised patients. However, more severe disturbances that reflect fragmentation and sleep-wake cycle reversal are indicative of neurocognitive disorder, especially delirium. Clinician-observed measures of sleep-wake cycle integrity are more sensitive to underlying neurocognitive disorder than subjective reports from patients. Such assessment methods can detect disturbances that occur during syndromal delirium but do not seem to be evident prior to this or as part of any prodromal phase. The inclusion of measures of sleep-wake cycle integrity in delirium assessment could enhance detection rates.
References


Commentary chapter 3

The study described in chapter 3 provides a level of detail regarding the relationship between delirium and sleep disturbances that has not been previously described in the wider literature. Although sleep disturbances have been detected across the entire patient cohort, specific patterns of sleep disturbance have been noted. This study explored delirium longitudinally by exploring sleep disturbances in prevalent versus incident cases. This study is also strengthened by the inclusion of associated conditions such as dementia and depression. This study reinforces the hypothesis that patients with delirium are not capable of accurately reporting their own sleep quality and provides further evidence to indicate that features of delirium phenomenology must be detected in an observer based manner. Following on from this chapter the other aspect of circadian integrity, namely motor behaviour needs to be explored. This is done in a discrete study in chapter 4.

Background to chapter 4

Chapter 4 explores the utility and reliability of different delirium motor subtyping tools by different clinical researchers, namely medical student, senior doctor and nursing staff. This is based on the finding that delirium detection can be a very onerous process and rapid validated tools to detect delirium for both clinical and research purposes are required in the real world clinical setting. This study explores the longer version and short version of delirium motor subtyping, as this aspect of delirium phenomenology lends itself to observer based detection methods. Motor behaviour is also a key component of the circadian domain of delirium phenomenology and may be a more reliable method than complex sleep detection methods. This study explores this issue at two points, at the point of admission in the study and then longitudinally over the course of the study. This study explores the agreement between the different methods, but also between the different raters. The application of the findings are discussed with a view to further research.
Contributions of the authors: The initial idea for this study was from both the author James Fitzgerald and Prof. David Meagher. Moreover, given the type of study i.e. reliability analysis, data collection was shared between the author, senior researcher Dr. O’Regan and the nursing staff at Cork University Hospital. Statistical analysis was undertaken by the author based upon detailed statistical instruction from Dr. Adamis. All collaborators contributed to reviewing the finished chapters.
Chapter 4 - Concordance between the Delirium Motor Subtyping Scale (DMSS) and the abbreviated version (DMSS-4) over longitudinal assessment in elderly medical inpatients

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Abstract

Background: Delirium is a common neuropsychiatric syndrome that includes clinical subtypes identified by the Delirium Motor Subtyping Scale (DMSS). We explored the concordance between the DMSS and an abbreviated 4-item version in elderly medical inpatients.

Methods: Elderly general medical admissions (n=145) were assessed for delirium using the Revised Delirium Rating scale (DRS-R98). Clinical subtype was assessed with the DMSS (which includes the four items included in the DMSS-4). Motor subtypes were generated for all patient assessments using both versions of the scale. The concordance of the original and abbreviated DMSS was examined.

Results: The agreement between the DMSS and DMSS-4 was high, both at initial and subsequent assessments (kappa range 0.75-0.91). ICC for all three raters for the DMSS was high (0.70) and for DMSS-4 was moderate (0.59). Analysis of the agreement between raters for individual DMSS items found higher concordance in respect of hypoactive features compared to hyperactive.

Conclusions: The DMSS-4 allows for rapid assessment of clinical subtype in delirium and has high concordance with the longer and well validated DMSS, including over longitudinal assessment. There is good inter-rater reliability between medical and nursing staff. More consistent clinical subtyping can facilitate better delirium management and more focused research strategies.

Key Words: Delirium; activity; motor; subtypes; phenomenology; assessment
Introduction

Delirium is a common neuropsychiatric syndrome associated with adverse outcomes including long-term functional deterioration, persistent cognitive impairment and mortality (Witlox et al., 2010). It is a complex syndrome that has a highly heterogeneous and fluctuating phenomenological profile whereby approximately 50% of patients with delirium are either missed or diagnosed late across clinical settings. In general, delirium is composed of three domains regarding its clinical phenomenology, and these are higher cognitive processing (e.g. language and thought processing), general cognition (e.g. long term memory, orientation and attention), and circadian integrity which is composed of the interconnected behaviours of the sleep-wake cycle and motor activity. (O’Hanlon et al., 2013). Subsyndromal delirium (SSD) is a state characterised by the presence of delirium symptoms but without full syndromal delirium (FSD) criteria. It is associated with outcomes intermediate between FSD and no delirium (Cole et al., 2013).

Delirium can be further characterised by clinically defined subtypes, with best evidence for the designation of subtypes according to motor activity profile. Lipowski (1983) suggested ‘hyperactive’ and ‘hypoactive’ patterns, characterized by increased and decreased motor activity respectively, before adding a third ‘mixed’ category in recognition that many patients experience elements of both within short time frames. It has been reported that clinical motor subtypes of delirium differ according to a number of factors including, pathophysiology, detection rates, treatment experience, duration of delirium episode and clinical outcome (Slor et al., 2013). In particular, hypoactivity has been associated with organ failure and metabolic causes, while hyperactivity is more connected to substance-related delirium e.g. delirium tremens. Unfortunately such studies have been found to have inconsistent findings due to inconsistent methodology regarding motor subtype profiling. In particular, it has been demonstrated that between four commonly utilised subtype profiling methods that there was concordance of approximately 34% (Meagher et al., 2009). However despite these methodological limitations, hypoactive subtypes have been found to have a significantly poorer prognosis (Yang et al., 2009). In particular, hypoactive motor profiles have been found to have highest associated mortality independent of factors such as co-morbidity, age, delirium, and dementia severity (Kiely et al., 2007). However, the association between hypoactive delirium and elevated
mortality may be reflective of delayed detection of delirium, and hence more prolonged episodes (Gonzalez et al., 2009). Conversely, hyperactive and mixed subtype delirium is associated with more frequent use of antipsychotics, higher detection rates, and better outcomes (Meagher et al., 2011; 2012). Subsequently, a variety of different definitions of motor subtypes have emerged that include a wide range of motor and non-motor features (Lipowski, 1989; Liptzin and Levkoff, 1992; O’Keefe and Lavan, 1999), though only the Delirium Motor Subtyping Scale (DMSS) has been validated using non-delirious controls or independent measurements of motor behaviour. Studies have demonstrated concurrent and predictive validity for the original 13-item DMSS including comparison to objectively measured motor activity levels using bioelectronic methods (Godfrey et al., 2008; 2010). In addition, the DMSS has been applied to the longitudinal study of motor subtype profile in delirium (Meagher et al., 2011; Slor et al., 2013). It has also been translated into Dutch and Japanese versions (Slor et al., 2014; Uchida et al., submitted). No other rating scale for motor subtypes of delirium has been developed and validated with such rigor.

More recently, an abbreviated version of the scale has been developed that can allow for simple and rapid identification of delirium subtypes. Preliminary work with the DMSS-4 has indicated that it has high concordance with the original 13-item DMSS in cross-sectional assessment of at-risk populations (e.g. palliative care, old age psychiatry and general adult psychiatry referrals) (Meagher et al., 2014). However, because delirium is a highly fluctuating condition that requires serial assessment in order to capture its full clinical presentation, the reliability of assessments conducted over time is an important feature of delirium tools. Moreover, the DMSS and DMSS-4 are observational tools that are designed for use by a variety of healthcare professionals who engage with delirious patients and as such the concordance between assessment conducted by different healthcare professionals and the inter-rater reliability of the tool are of interest.

The aims of this study were (i) To explore the attribution of clinical subtype in elderly medical inpatients at risk of delirium and to specifically examine the level of agreement between the DMSS and DMSS-4, (ii) to examine concordance between the DMSS and DMSS-4 over time, (iii) to examine the inter-rater reliability of the DMSS and DMSS-4 between doctor, medical student and nursing staff.
Methods

Study design

Over a one year period between August 2012 and August 2013, all elderly (70 yrs+) general medical patients admitted within the past 36 hours were invited to participate in the prospective study. The emergency department of Cork University Hospital in the Republic of Ireland was the point of screening for inclusion in the study, and 277 elderly general medical patients, attending were screened. During the recruitment. Criteria for patient exclusion from this study were, 1) requiring specialist intervention (e.g. haematology, oncology, orthopaedic surgery and psychiatry), 2) patients who were deemed too unwell to participate, 3) early discharge from hospital, 4) insufficient data collected, and 5) refusal to participate. Of the 277 assessed, 145 (52%) were included and 132 (48%) were excluded from the study. All subjects were assessed for phenomenology, demographic and treatment data in a consistent manner by raters (N. O’R [doctor] and J.F. [medical student]) who were trained by an expert (D.M.) in the use of both the Revised-Delirium Rating Scale (DRS-R98) (Trzepacz et al., 2001) and Delirium Motor Subtyping Scale (DMSS). Patients’ phenomenology was assessed at baseline and also daily (by J.F. and N. O’R) for up to a week using validated methods.

Informed consent.

Many patients had cognitive impairment at entry to the study and it was presumed that most were not capable of giving informed written consent. Regardless, the procedures and rationale for the study were explained to all patients. However, ethics committee approval was given to augment patient assent with proxy consent from next of kin (where possible) or a responsible caregiver in accordance with the Helsinki Guidelines for Medical Research involving human subjects, due to the non-invasive nature of the study (World Medical Association, 2004).
**Medication data**

At each visit, all medications prescribed for each patient were recorded, and this included regular and as required doses. Particular focus was on the use of psychoactive agents, such as antipsychotic, opioids, benzodiazepines, psychostimulants and corticosteroids. Such agents have been reported to be associated with delirium as a risk factor or treatment modality (Clegg and Young, 2011). Over the 24 hours prior to assessment the dose equivalents were calculated for each of these drug classes according to accepted conversion rates, i.e. antipsychotics in chlorpromazine equivalents; opioids in morphine equivalents; benzodiazepines in diazepam equivalents; steroids in prednisolone equivalents (Taylor et al., 2015).

**Delirium assessment**

The Revised Delirium Rating Scale (DRS-R98) is a widely used instrument to measure symptom profile in delirium and can be used both as a diagnostic and severity assessment tool (Trzepacz et al., 2001). It is a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items. The DRS-R98 Total scale score ranges from 0 to a maximum of 46. It is designed to rate symptoms over the previous 24 hours. The DRS-R98 has high inter-rater reliability, sensitivity and specificity for distinguishing delirium from mixed neuropsychiatric populations including dementia, depression, and schizophrenia (Trzepacz et al., 2001). A cutoff score of ≥18 is typically applied to delirium diagnosis, especially where high specificity is desirable, but other work suggests that such cutoffs exclude many cases of DSM-IV delirium and lower cutoff scores are advocated where diagnostic sensitivity is the primary goal (Franco et al., 2006; Kato et al., 2010;). For this general hospital population, in consultation with the DRS-R98 developer (PTT) we applied relaxed cutoff scores to enhance diagnostic sensitivity (especially to milder delirium) to equate total scores of 0-6 with no delirium, 7-11 with SSD (subsyndromal delirium), and ≥12 with FSD (full syndromal delirium).
The Delirium Motor Subtype Scale (DMSS) (Meagher et al., 2008) is a scale comprising 13 (5 hyperactive and 8 hypoactive) symptoms selected according to their reflection of motor phenomenology, relative specificity for delirium relative to controls, and demonstrated correlation with independent and objective measures of motor behaviour (Meagher et al., 2008; Godfrey et al., 2010). The DMSS can be rated by any healthcare professional familiar with the clinical presentation of delirium. Scoring requires at least 2 features to be present from either the hyperactive or hypoactive list to meet subtype criteria. Patients meeting both hyperactive and hypoactive criteria are deemed mixed subtype, while patients meeting neither criteria are labelled ‘no subtype’.

The DMSS-4 is an abbreviated version of the DMSS which includes 2 hyperactive (Increased amount of activity and loss of control of activity) and two hypoactive (decreased speed of actions and decreased speech) features derived through discriminant analysis of the original longer scale. Preliminary work has suggested has high concordance with the DMSS (Meagher et al., 2014).

Dementia assessment

For all patients, the medical case notes were reviewed for a diagnosis of preceding cognitive impairment or dementia made by a suitably trained physician. This was confirmed by the use of the Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-SF) to assess pre-admission cognitive impairment and decline. This 16 item scale was scored by a caregiver or close relative and a mean item cutoff score of $\geq 3.5$ was used to diagnose dementia (Jorm, 2004). Consensus discussion was used to apply diagnosis in borderline cases. In the absence of an assessment from ICQODE-SF/collateral history, patients were considered not to have dementia if they scored greater than or equal to 27 / 30 on MMSE.

Statistical analyses

Continuous variables were presented as means and SD, and categorical variables as proportions and percentages. Cohen's kappa coefficient was used to calculate the agreement
between the full (13 item) DMSS and the DMSS-4. Similarly to estimate the inter-rater reliability among the 3 raters doctor, nurse and student for each of the scales DMSS (13 item) and DMSS-4, Intraclass Correlation Coefficients (ICCs) were calculated. The PAWS (SPSS) v18 software was used for statistical analyses. ICCs and Cohen’s kappa coefficient >0.75, between 0.40–0.75, and <0.40 were interpreted respectively high, moderate and low inter-observer reliability (Landis and Koch, 1977). The PAWS (SPSS) v18 software was used for statistical analyses.

Results

Demographic and medical history

Of the 277 patients assessed, 145 (52%) were included and 132 (48%) were excluded from the study. The reasons for exclusion were: (1) refusal to participate (n=65), (2) patients who were deemed too unwell to participate (n=32), (3) early discharge from hospital (n=28), and (4) patients requiring non general medical treatment (n=7). The mean age was 80.2 (SD: 6.3) (range 70-94 years old). Sixty nine (47.6%) were females. From the 145 participants, 31 (25.4%) had a history of dementia (as indicated by clinical history and case note records, MMSE scores, and IQCODE scores). Only 6 participants were in receipt of one or more classes of psychotropic/sedative medication. Three were in receipt of antipsychotic medications throughout the hospitalisation, 2 antidepressants, 4 benzodiazepines, 4 hypnotics and 6 other sedative medications (e.g. opioids). Up to a third of patients were assessed for 7 days.

Delirium status

The prevalence and incidence of full syndromal delirium was 33.8 % (n=48) and 9% (n=13) respectively. The percentage of patients who reached FSD at any point during the period of study was 42.2% (n= 61). Similarly, the percentage who reached SSD at any point was 37.2 % (n=53). Twenty seven patients who experienced SSD transitioned to FSD during the study period (18.6% of the total study population and 52% of those who exhibited SSD).
**Motor subtypes**

The frequency of motor subtypes according to the DMSS at baseline assessment (n=143) was 47.6% hypoactive (n=69), 4.1% mixed (n=6), 2.8% hyperactive (n=4) and 44.1% no subtype (n=64). The frequency of motor subtypes according to the DMSS-4 across all assessments during the study was 44.8% hypoactive (n=72), 2.1% mixed (n=3), 2.1% hyperactive (n=3) and 44.8% no subtype (n=65). The frequencies of motor subtypes according to the DMSS and DMSS-4 are shown in table 1.

**Table 1. Motor subtypes according to DMSS and DMSS-4 (N=143)**

<table>
<thead>
<tr>
<th></th>
<th>DMSS</th>
<th>DMSS-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoactive</td>
<td>69 (47.6%)</td>
<td>72 (44.8%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (4.1%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>Hyperactive</td>
<td>4 (2.8%)</td>
<td>3 (2.1%)</td>
</tr>
<tr>
<td>No subtype</td>
<td>64 (44.1%)</td>
<td>65 (44.8%)</td>
</tr>
</tbody>
</table>
Agreement between DMSS and DMSS-4

The overall agreement (K) between the DMSS and DMSS-4 was 0.75 across all four subtypes. Further analysis of the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each subtype comparing DMSS to DMSS 4 are shown in Table 2.

Table 2. Agreement (κ), sensitivity, specificity and predictive values between DMSS 4 and DMSS across each motor subtype

<table>
<thead>
<tr>
<th></th>
<th>No subtype</th>
<th>Hypoactive</th>
<th>Mixed</th>
<th>Hyperactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (CI)</td>
<td>89.2 (79.1-95.5)</td>
<td>87.5 (77.5-94.1)</td>
<td>16.6 (2.72-63.9)</td>
<td>33.3 (5.4-88.3)</td>
</tr>
<tr>
<td>Specificity (CI)</td>
<td>92.3 (84.0-97.1)</td>
<td>91.55 (82.5-96.8)</td>
<td>96.34 (91.8-98.8)</td>
<td>97.8 (93.6-99.5)</td>
</tr>
<tr>
<td>PPV (CI)</td>
<td>90.6 (80.7-96.5)</td>
<td>91.3 (82.0-96.7)</td>
<td>16.6 (2.8-63.8)</td>
<td>25.0 (4.7-79.6)</td>
</tr>
<tr>
<td>NPV (CI)</td>
<td>91.0 (82.6-96.3)</td>
<td>87.8 (78.2-94.3)</td>
<td>96.3 (91.7-98.8)</td>
<td>98.7 (94.8-99.8)</td>
</tr>
</tbody>
</table>
**Inter-rater reliability**

Table 3. shows agreement (K) between the DMSS and the DMSS-4 for the three raters separately across the 7 days of assessments. Table 4. shows pairwise ICC between the DMSS and DMSS-4 for the three raters. There was very high concordance between any of the pairs of raters for the DMSS-4 and moderate concordance between any of the pairs for the DMSS. The ICC for ratings conducted by all three raters was 0.70 for the DMSS and 0.59 for the DMSS-4, indicating moderate inter-rater reliability. Analysis of the agreement between raters for individual DMSS items found higher concordance in respect of hypoactive features compared to hyperactive. Items 2 and 3 (Increased speed of actions and Loss of control of movement) were found to have lowest agreement (K) between nursing and medical staff (medical student versus nurse = 0.49, 0.44; doctor versus nurse = 0.56, 0.49), while the remaining items retained high agreement (K ≥ 0.75).
Table 3. Pairwise agreement (k) between DMSS and DMSS-4 for the raters (Doctor, Medical student and Nurse) over 7 days of assessments.

<table>
<thead>
<tr>
<th>Assessment day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group (n)</td>
<td>143</td>
<td>130</td>
<td>113</td>
<td>95</td>
<td>79</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>Total group concordance (K)</td>
<td>0.75</td>
<td>0.72</td>
<td>0.86</td>
<td>0.84</td>
<td>0.91</td>
<td>0.89</td>
<td>0.78</td>
</tr>
<tr>
<td>Between DMSS original and DMSS-4 for Doctor (n)</td>
<td>32</td>
<td>32</td>
<td>28</td>
<td>26</td>
<td>23</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Between DMSS original and DMSS-4 for Doctor agreement (K)</td>
<td>0.62</td>
<td>0.65</td>
<td>0.88</td>
<td>0.92</td>
<td>0.91</td>
<td>0.99</td>
<td>0.66</td>
</tr>
<tr>
<td>Between DMSS original and DMSS-4 for Medical Student (n)</td>
<td>32</td>
<td>32</td>
<td>27</td>
<td>26</td>
<td>23</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Between DMSS original and DMSS-4 for Medical Student agreement (K)</td>
<td>0.53</td>
<td>0.65</td>
<td>0.88</td>
<td>0.98</td>
<td>0.90</td>
<td>0.99</td>
<td>0.67</td>
</tr>
<tr>
<td>Between DMSS original and DMSS-4 for Nurse (n)</td>
<td>32</td>
<td>32</td>
<td>28</td>
<td>26</td>
<td>23</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Between DMSS original and DMSS-4 for Nurse -agreement (K)</td>
<td>0.65</td>
<td>0.55</td>
<td>0.88</td>
<td>0.79</td>
<td>0.82</td>
<td>0.9</td>
<td>0.67</td>
</tr>
</tbody>
</table>
## Table 4. Inter-rater reliability (IRR) between pairs of raters using the DMSS and DMSS-4.

<table>
<thead>
<tr>
<th>Raters</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IRR between raters using the DMSS-4 (n=32)</strong></td>
<td></td>
</tr>
<tr>
<td>Doctor and Nurse</td>
<td>0.77</td>
</tr>
<tr>
<td>Doctor and Medical Student</td>
<td>0.77</td>
</tr>
<tr>
<td>Medical Student and Nurse</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>IRR between raters using the DMSS (n=32)</strong></td>
<td></td>
</tr>
<tr>
<td>Doctor and Nurse</td>
<td>0.65</td>
</tr>
<tr>
<td>Doctor and Medical Student</td>
<td>0.69</td>
</tr>
<tr>
<td>Medical Student and Nurse</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Discussion

In this study of elderly medical admissions, we conducted a longitudinal assessment of motor profiling activity using two validated instruments (DMSS and DMSS-4). The overall concordance between the original DMSS and the abbreviated DMSS-4 was high and this was evident over longitudinal assessments. These findings highlight how the relatively brief four-item DMSS-4 scale can usefully substitute for more detailed and time-consuming methods of defining motor subtypes and thus allow for rapid assessment. These findings are thus relevant to both research that is primarily focused upon clinical subtypes, as well as secondary analyses of the impact of clinical subtype upon treatment response and prognosis – two areas that are particularly lacking in respect of data-based evidence to guide real-world practices (Meagher et al., 2013).

There was very high concordance between any of the pairs of raters for the DMSS-4 and moderate concordance between any of the pairs for the DMSS. Analysis of the agreement between raters regarding the individual items of the DMSS-4 was found to be higher for hypoactive compared to hyperactive items. This may reflect the greater challenge in assessing particular aspects of motor activity, for example, the lowest inter-rater agreement was for items 2 and 3 (Increased speed of actions and involuntary movements), both for medical student versus nurse and doctor versus nurse. The reasons for the lower agreement between nursing and medical staff for some individual items could be attributed to how these raters perceive and conceptualise this behaviour. In particular, these features can be challenging to reliably assess in elderly medical patients (especially if they are sedentary) in the acute hospital setting (Blazer and van Nieuwenhuizenbut, 2012). Improved detection of these items could be facilitated by a more detailed explanation of their characteristics supported by specific training that focuses upon their identification in clinically relevant examples and how this information can be reliably recognised by both nursing and medical staff who typically differ in the consistency of contact with patients over the 24 hour cycle during which these behaviours can fluctuate considerably.
The final aim of this study was to investigate reliability between medical and nursing staff using the DMSS and DMSS-4. The ICC was found to be moderate for the DMSS and high for the DMSS-4. As such, these findings support the use of both the DMSS and DMSS-4 by assessors with nursing and medical backgrounds which is in keeping with the need to engage the multidisciplinary perspectives in order to optimise accurate delirium detection and on-going assessment (O’Hanlon et al, 2014)

Study limitations

The findings from this elderly general medical inpatient cohort do not necessarily generalise to all clinical settings (e.g. ICU and palliative care) where delirium is common and as such further studies specific to these settings are required. Another limitation of this study is the exclusion of 132 (48%) patients, this was due to our stringent exclusion and inclusion criteria applied to this hospital setting. Exclusion of this many patients may have reduced the number of subsyndromal cases and hence may have impacted upon the detected prevalence of the different motor subtypes. Moreover, up to a third of patients were assessed for 7 days which may also have impacted upon the longitudinal assessment of motor subtypes detected. This was largely due to the discharge rate of this cohort by medical teams, as well as in patient changes to eligibility for inclusion in this study e.g. referred for specialist services. The group studied herein was predominantly hypoactive, which is congruent with other studies of older adults and contained relatively few patients with mixed and hyperactive motor subtypes (Meagher, 2009; Blazer and van Nieuwenhuizenbut, 2012). We found relatively few cases of mixed motor subtype, despite the existing evidence suggesting that this type is a distinct subtype rather than a transition state (Meagher et al., 2012). Therefore, the concordance in respect of cases detected as mixed presentations is less convincing. Specificity across the four subtypes was high. However, although sensitivity for hypoactive and no subtype was high, it was lower for mixed and hyperactive subtypes. This may reflect the lower numbers of mixed and hyperactive motor behaviour within this cohort.
Future work and conclusions

This study builds upon the development of the DMSS-4 as a well validated, conceptually robust and simple method of assessing clinical subtypes of delirium. This study supports its usefulness both longitudinally and for use by a variety of healthcare professionals, including both medical and nursing staff by demonstrating high agreement and good reliability. Further work may examine motor subtypes in both SSD and FSD states in terms of bioelectronic analysis (for example in terms of modes of physical activity or energy utilisation) and explore their relationship to issues such as delirium onset/resolution and specific symptom domains such as altered circadian integrity, (Godfrey et al., 2010; Fitzgerald et al., 2013). Further work may also investigate predictors for persistent delirium over the 7 days period.
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Commentary chapter 4

Delirium motor subtyping is a valuable method of exploring delirium phenomenology and may provide a rapid method of delirium detection in the hospital setting. More challenging still is the development of tools that are both reliable and easy to use by a wide variety of staff. This study highlights the importance of the DMSS original and DMSS-4 in addressing both these issues in the acute hospital setting. The possibilities provided by applying the rapid delirium motor subtyping method (DMSS-4) are explored in detail and highlight its use both in the context of research and in the clinical setting by a variety of healthcare professionals. Further research is also highlighted.
Chapter 5 - Summary and Conclusion

Overview

This work significantly develops the role of methods exploring circadian integrity in delirium using well validated and detailed phenomenological assessment tools of a patient cohort of elderly medical inpatients. The studies described herein explore delirium phenomenology both in terms of its severity and duration, but also in terms of its presentation at admission and the connection between subsyndromal delirium and full syndromal delirium. This work also explores delirium in the real world clinical setting by including measures of co-morbid cognitive impairment in depression and dementia. Both of which are often co-occurring with delirium. This work explores delirium phenomenology in both baseline at admission presentations and longitudinally over the course of clinical stay within the hospital setting. This optimises the assessment of delirium phenomenology as it enables researchers to capture both its cross-sectional severity and its longitudinal fluctuation and time course.

This work is novel in that it further develops operationalized algorithms for determining full syndromal and subsyndromal delirium phenomenology. Other novel features include the exploration of the sleep wake cycle and how it is affected in the clinical setting of an acute hospital. Such work enables further studies to design methodologies that may enhance our capacity to focus upon circadian and sleep-wake cycle disturbances as they relate to delirium onset. Such work highlights the utility of observer clinician-based methods of delirium assessment compared to subjective patient-rated measures. This work also highlights the relationship between sleep-wake cycle disturbance and co-occurring neurocognitive disorders, namely depression, dementia and incident delirium. The final novel component of this work is the development of a rapid and easy to use assessment method of delirium motor subtyping (DMSS-4), which demonstrates its reliability both longitudinally and in terms of various raters i.e. medical, student, and nursing.
Part I

Part one of this project focused exclusively on the expanding literature pertaining to the role of circadian integrity in the pathogenesis of delirium. Delirium is a serious and complex neuropsychiatric syndrome characterised by acute onset of generalised brain dysfunction. It exists in the context of a physical insult and/or medical illness and is consequently associated with a plethora of detrimental outcomes such as, loss of socioadaptive functioning, increased risk of long term cognitive impairment, including dementia onset, and a generalised risk of increased mortality. It exists in approximately 20% of general hospital admissions, up to 50 % in elderly medical population and exceeds 80% in critical care and palliative care settings (Witlox et al., 2010). The phenomenology of delirium is highly complex, heterogeneous, and fluctuating. Recent research has highlighted the role of circadian integrity as a cornerstone of understanding delirium onset (Mattoo et al., 2012; Leonard et al., 2011). As a consequence, this synthetic study reviewed the evidence pertaining to several domains of this relationship 1) phenomenology, 2) neurophysiology, and 3) treatment studies that target aspects of circadian integrity that have alleviated delirium features.

The circadian timing system (CTS) has a ubiquitous presence in the cells of mammals including humans. This presence enables the central orchestration of the CTS from the CNS to the peripheral molecular oscillators. The role that the CTS plays in cognition is understudied, but given its broad ranging effects on phenomenology relevant to delirium it is a logical target for further research. The most well studied aspects of circadian dysfunction of cognition is to be found in circadian rhythm disorders. These disorders illustrate the wide variety of cognitive and affective disturbances that can occur during a dysregulation of this key system (Mieda et al., 2006). Furthermore, the role of circadian dysfunction has been seen in other relevant examples of neuropsychiatric disturbance, namely sundown syndrome. This syndrome is largely understudied and the full relevance to delirium manifestation is unknown, but parallels can be drawn between the dysregulated levels of arousal and attention that are core phenomenological features of delirium (de Jonghe et al., 2010).

The phenomenology of delirium has been categorised into three main domains, higher cognition, general cognition and circadian integrity. Regarding circadian integrity, the sleep wake cycle and motor activity continues to be directly regulated by the circadian system in order
to optimise adaptation to the environment. Less well studied domains of higher cognition and general cognition illustrate equally important, yet more tenuous links with the circadian system. Attention, memory, and thought processing all have links with the CTS and when disregulated become detrimentally impacted in a way that parallels delirium.

Beyond phenomenological parallels between studies of circadian integrity and delirium, there exists the critical role circadian regulation plays in the neurophysiological mechanisms that are relevant to delirium. The central neurochemical hypothesis of delirium situates increases in dopaminergic and glutaminergic activity with impaired GABAergic, cholinergic, and oxidative metabolic functions (Trzepacz et al., 2010).

Circadian regulation of the dopaminergic system has been shown to impact upon this system at the level of physiological structures namely the hypothalamus, striatum and nucleus accumbens and at the cellular and molecular levels in regulating dopaminergic signalling and metabolism, both at pre and post synaptic terminals. These broad ranging links have been implicated in the complex physiology of the hypothalamic pituitary adrenal axis, the GABAergic inhibitory system, and the CNS-Immune axis. Overall, there has been limited direct measures of the underlying neural substrate that serves as the phenomenology of delirium.

Treatment studies for restoring circadian integrity are comprised of pharmacological strategies involving melatonin and numerous agonists, while non-pharmacological mechanisms involve re-entrainment via exercise and photic light therapy aimed at restoring the entrainment mechanisms of the CTS to its environmental stimuli (i.e. the zeitgebers) with a view to restoring global circadian functioning. Studies exploring both these strategies have found that they may be of benefit in restoring impaired cognition or preventing the onset of delirium in the first instance. However, in the absence of direct investigations of the neurobiology of delirium, these studies remain rudimentary and subject to further development.

From this synthetic work, a programme of studies was proposed with a view to testing several important hypotheses that would enhance our understanding of the relationship between delirium and circadian integrity in the general medical patient population.
Part II

In Part II, a number of areas unaddressed in the literature were explored in order to enhance our theoretical understanding of the interface between real world situations and conceptually based field work. Chapter 2 focused exclusively upon a phenomenological analysis of full syndromal delirium (FSD) and subsyndromal delirium (SSD) in an elderly medical inpatient population. Although the frequency of delirium has been reported to occur in approximately 11-42% of medical inpatients, the frequency of SSD is less well defined and is estimated to occur in 7-50% of cases, according to a clinical population studied and definitions applied (Ouimet et al., 2007; Bond et al, 2012). Accumulating research indicates that SSD, may be a target of active treatment (Hakim et al., 2012). Hence, research aimed at exploring the relationship between SSD and FSD, with a focus on differences and similarities of phenomenology may enhance this enterprise. Therefore, the aim of this study is to 1) describe the phenomenology of general medical admissions and 2) identify which DRS-R98 items are most affected during FSD and SSD.

In this particular cohort of elderly general admission, prevalent delirium was found to be 20% at admission followed by an incidence of 18.5%. This finding was found to be congruent with other studies investigating delirium in the hospital setting. This study confirms that delirium is indeed a heterogeneous and highly fluctuating syndrome primarily characterised by inattention, sleep wake disturbances, and motor activity disturbances. This study also highlights the negative impact of age and comorbid dementia upon delirium onset and may even explain observed disturbances in visuospatial ability and long term memory. This is congruent with other work that reports that age and co-morbid dementia are robust risk factors for delirium (Trzepacz et al., 2010). In this study, 22.4 % of patients with FSD also had comorbid dementia, which is in keeping with the literature estimating that 22-89% of cases of dementia are complicated by delirium (Fick et al., 2002). Moreover, the distinction of hypoactive delirium from depression is often challenging and these states are frequently misdiagnosed as ‘hypoactive’ delirium due to the presence of sleep disturbances and motor retardation (Spiller and Keen, 2006; O’Sullivan et al., 2014).

This study expands the growing literature on SSD with the use of the systematic operationalised algorithm to generate clinical diagnosis of delirium. However, the detection of
SSD was low at 5.5%, reflecting the exclusion criteria that was applied to this group. This is an issue that can be resolved in further studies of SSD in the hospital setting which may employ either or multi-centred data collection methods or more inclusive selection criteria of patients. This study also highlights the utility of a systematic operationalised algorithm to generate DSM-5 criteria based diagnosis of clinical delirium. Longitudinal analysis of disturbed phenomenology in both SSD and FSD found that key features such as sleep-wake cycle and motor disturbances were elementary to both states, but exhibited a dimensional relationship between the severity of these features. Taken together, this is a novel development that further adds to the repertoire of clinical researchers in field of delirium.

In chapter 3, the sleep-wake cycles and sleeping patterns of elderly medical inpatients were investigated both at baseline and longitudinally. These phenomenological features were also explored in the context of patients with co-occurring neurocognitive disorders. Sleep disturbances are well recognised features in hospitalised patients, but also central to neurocognitive disorders in the elderly, namely delirium, dementia and depression. What is unknown is the extent and severity of these disturbances and what, if any, are the differences between these often co-occurring conditions. Understanding this feature of disturbed neurocognitive phenomenology may enable health care professionals to detect incident delirium with a view towards active management or prophylaxis. This longitudinal study of general medical admissions developing delirium underwent a detailed assessment of sleep. Observer-rated sleep disturbance occurred in the majority (95%) of patients with more severe disturbances associated with active delirium. Patient rated sleep quality measured via the RCSQ did not relate to neurocognitive disorder and had a low correlation with DRS-R98 assessments, regardless of the presence or absence of delirium. This confirmed the notion that patients with cognitive impairment are unreliable raters of their own sleep quality. Longitudinal analysis indicated that the severity of DRS-R98 sleep-wake cycle disturbance was significantly linked to delirium status. DRS-R98 sleep scores become elevated on the first day of delirium rather than on either of the two days prior to this. From these findings, detection of sleep patterns may enable researchers to improve their methods for recognising the onset of delirium. Detection tools may include measures of sleep disturbance in an effort to enhance their capacity to screen for delirium.
In Part III, Chapter 4, the aims of this study were threefold, 1) To explore the attribution of clinical subtype in elderly medical inpatients at risk of delirium and to specifically examine the level of agreement between the DMSS and DMSS-4, 2) To examine concordance between the DMSS and DMSS-4 over time and 3) To examine the inter-rater reliability of the DMSS and DMSS-4 between medical and nursing staff.

Sleep-wake cycle disturbances and motor activity are two inter-related subdomains of circadian integrity. Studies involving delirium motor subtyping have inconsistent designs and subtyping methods (Meagher, 2009). One of the barriers to optimising delirium detection is the absence of reliable, validated methods which can be used in the clinical setting in a prompt manner. In this study, the majority of patients were found to have the hypoactive motor subtype. It was found that the DMSS-4 allows for rapid assessment of clinical subtypes in delirium and has a high concordance with the longer and well validated DMSS, including over longitudinal assessment. More consistent clinical subtyping in delirium can facilitate better delirium management and more focused research effort. This method also has significant utility for health care professionals from different backgrounds, i.e. medical, student, and nurse. Analysis of the agreement between raters for individual DMSS items found higher concordance in respect of hypoactive features compared to hyperactive. Overall, this study contributes to the multidisciplinary approach to delirium research and management.

Methodological considerations, limitations and future studies

This work provides clarity into the relationship between circadian integrity and delirium in the hospital setting, new areas of research need to be explored in order to expand the frontier
of this important clinical issue (see table 1). To do this an exploration of the methodological limitations of this work is required.

This work focuses on delirium occurring in the acute hospital setting where the literature suggests that certain features of delirium such as short duration of stay, and physiological stressors such as surgery may differ from delirium in patients in palliative care compared to patients receiving surgery. As such the findings from this cohort may not be generalizable to these groups, but may require replication studies of circadian integrity in order to identify the core features that are shared across clinical settings.

This group was assessed daily in terms of its delirium phenomenology and syndromal severity using validated measures. Future work may explore how other validated measures of circadian disturbance may impact upon the severity of delirium onset. The sample size of this study, although robust in general, had shortcomings both in terms of numbers with sub syndromal illness and depression. Although this work utilised validated and robust methods for determining delirium, dementia and depression status, future studies may explore different subtypes of dementia e.g. Lewy body dementia or Alzheimer’s disease, in an effort to enhance our understanding of the delirium dementia interface in terms of sleep wake cycle disturbances. Future studies may overcome these shortcomings though collecting data from multiple clinical centres.

Although two methods were utilised for daily assessment of sleep, future studies may utilise other observer-based methods to expand the concept of sleep-wake cycle disturbance, and further examine the features of disturbed sleep in neurocognitive disturbances. Bioelectronic measures of sleep and motor activity may also be of utility in this cohort, but such technology would have to account for the largely sedentary nature of this cohort. In addition, such measures would have to focus upon the elements of the circadian system interface, namely zeitgebers e.g. ambient light levels and their relationship to sleep disturbance in the hospital setting. Finally, the role of sleep-wake cycle disturbance as a target for earlier detection and treatment of delirium and other neurocognitive disorders is understudied and deserving of further exploration.
Table 1. Key areas for study of the delirium-circadian interface

- Detailed study of the CTS in patients with incident delirium, including evidence for phase shifting and the integrity of melatonergic systems. Serial assessment studies can examine patterns of core body temperature and the levels of melatonin and its metabolites (e.g., urinary 6-SMT).

- Exploring the temporal relationship between circadian parameters and specific elements of delirium (e.g., sleep-wake disturbances, motor activity patterns including clinical subtypes and cognition) can help to clarify the pathophysiological evolution of delirium (including prodromal features) and the direction of causality between delirium and circadian dysregulation. This work could include specific studies of the relationship between the integrity of circadian systems and delirium-proneness.

- Specific and detailed investigation of sleep-wake cycle and motor activity can be achieved using polysomnography and actigraphic methods. In particular, studies can explore how changes from baseline profile indicate emerging subsyndromal and full syndromal delirium.

- Studies need to clarify the nature of so-called ‘sundowning syndrome’, including it’s relationship to syndromal and subsyndromal delirium. This requires a clear definition of what constitutes this well recognised but poorly described state. In addition, this work can also explore how circadian dysregulation in neurodegenerative conditions / dementia can predispose towards delirium.

- Clarifying the relationship of biological and neuropsychological markers of delirium proneness (prior cognitive impairments, ageing) to CRS integrity can allow for the development of more accurate delirium-prediction tools that incorporate a more complete range of identifiable risk factors.

- Treatment studies can explore the impact of known interventions for delirium and circadian rhythm disturbance upon physiological mechanisms that are relevant to delirium and CRD. Such studies can be extended to include the impact of novel therapeutic strategies that impact upon circadian systems (e.g., ramelteon, agomelatine).
Conclusion

This study programme focused upon formulating a number of novel theories and testable hypotheses in relation to the phenomenology of delirium and circadian integrity. In general, stringent protocols have emerged within the last couple of decades of research to investigate the functional components of circadian integrity. Modern research protocols aimed at measuring circadian integrity have been organised into three main categories, 1) neurobiological, 2) psychometric, 3) bioelectronic. However, measuring circadian integrity in patients with impaired neurocognitive function (depression, dementia, and delirium) is very challenging. In the absence of robust sleep research facilities, investigations of circadian integrity remain challenging especially in the context of the acute hospital setting. In particular, direct neurobiological measures of these patients circadian metabolism is extremely labour intensive. However, the use of psychometric assessment tools enables researcher to utilise these validated tools which have been standardised against direct biological measures. The central tenet of these papers is to expand the conceptual framework of phenomenological analysis of delirium and integrate it with contemporary developments in neuroscience and psychology. Such innovations will enable researchers to develop improved tools to assess phenomenology, as well as enhance the conceptualisation of the delirium phenotype. Side efforts can enhance our capacity for primary and secondary prevention of this serious neurocognitive disorder.
References


Appendices

A) Consent form

Clinical Research Ethics Committee of The Cork Teaching Hospitals

This is a Consent Form

Participant’s Name: ……………………………

Study Title:

A Prospective Study of the relationship between circadian functioning and the occurrence of Delirium and clinical (motor) subtypes in older people in an acute hospital setting

Chief Investigators: Prof. David Meagher Tel No:

………………………… has given me a full explanation of the nature, purpose and duration of this study. I have also received and read the patient information leaflet. I was able to ask him/ her questions regarding all aspects of the study.

I consent to the study investigators interviewing me on several occasions during my hospital stay, as well as discussing my case with the nursing staff caring for me. I also consent to the investigators speaking to my family about my health and functional abilities before I was admitted.

I accept that data recorded during this study may be processed on a computer by the investigators. My identity will never be disclosed and the data collected will remain confidential. I agree that I will not seek to restrict the use to which results of the study may be put.

After due consideration, I agree to participate in this study and co-operate with the testing required. I understand that at any time I may withdraw from this study without giving a reason.
Signature of investigator Date

Signature of participant Date

Assent from next of kin Date
B) Patient information

Patient Information Sheet:

What is delirium?
Delirium is a sudden, temporary reduced memory and awareness of surroundings during an illness. There are many different symptoms such as confusion, agitation, hallucinations (seeing things that are not there) and poor sleeping and it can vary in severity from day to day. Common causes of delirium include infection, some medications and a change in a person’s surroundings.

Why are we doing this study?
Delirium is common in hospital, particularly in older people, and can be very distressing for patients and families. It leads to higher risk of death, dementia and need for nursing home care which can be reduced by early diagnosis and treatment. However it is often difficult to diagnose correctly. Little research has been done in delirium in Ireland to date. In our study we hope to identify early signs of delirium, assess the impact of delirium on patients and carers, and examine ways to improve its detection. We hope that this will lead to better detection and treatment of delirium in Ireland.

Why am I being considered for this study?
Any patient of 70 years of age and older who is admitted to this ward is being asked to take part in the study. To fully understand delirium, we need to study a large number of patients, so every participant is very important to us.

What do I need to do if I’m interested?
Simply agree to take part in our study. This involves a series of interviews during your hospital stay. The first interview should be less than 30 minutes and the other interviews, sometimes daily,
should last only 10 minutes. We may also need to interview your next-of-kin/ carer. After you are discharged, we will ask you to come to a special clinic to be reviewed twice (at 6 months and 1 year after discharge). We will arrange for the clinic to be as close as possible to where you live and transport will be arranged for you and a carer on each occasion.

**Will all details be confidential?**
Yes. The recorded interview details will not include your name or hospital number.

**Is there any risk?**
The study only involves being interviewed. There will be no procedure and no risk to you. We will stop the interview at any time if you wish to stop.

*Thank you for reading this leaflet.*

*We deeply appreciate your interest and time.*
30th August 2012

Professor David Meagher
Head of Teaching and Research in Psychiatry
Room AM 041
Graduate Entry Medical School
University of Limerick
Limerick

Re: A prospective study of the relationship between circadian integrity and the occurrence of delirium and clinical (motor) subtypes in older people in an acute hospital setting.

Dear Professor Meagher

Expeditied approval is granted to carry out the above study at:
- Cork University Hospital
- Mercy University Hospital.

C)CREC Letter
D) MEDICATION AND DEMOGRAPHICS

Demographics/ Medical History

a) Gender: Male □ Female □ b) married / widowed / single

c) Age: _______ years DOB (dd/mm/yy): ____/_____/____

d) Date of Admission ___/___/___

e) Arrived to A/E ____________ Arrived to ward ____________
   LOS in A&E _______ hrs

f) Reason for Admission
   _______________________________________________________
   _______________________________________________________

g) Working Diagnosis ______________________________________
   _______________________________________________________

h) Medical diagnoses
   _______________________________________________________
   _______________________________________________________

Medication Changes

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<tr>
<th>Day/ time</th>
<th>Meds started</th>
<th>Meds stopped</th>
<th>PRN doses given</th>
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<td>Day/ time</td>
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</table>
E ) DMSS

Questions

Do you think the patient (in comparison with what’s expected for his / her age) ......

- Seems withdrawn / unaware of / disconnected from what’s going on around them?

- Is moving around slowly, as if in slow motion?

- Has lost control over his / her movement?

- Loses focus easily or finds it difficult to remain ‘on task’ when you are talking to him / her?

- Is apathetic, listless or poorly motivated?

- Moves quickly or in “fast motion”?

- Is drowsy during the day or is difficult to rouse from a sleep or nap?

- Is speech low in volume?
• Moves around a lot or seems to be “on the go” a lot of the time?

• Seems hypervigilant or overly alert?

• Speaks less than you would expect? Would he / she have a chat with you?

• Moves around in a restless or fidgety manner?

• Speaks very slowly? Does it take a long time for them to say something?

• Has fewer overall spontaneous body movements than normal / expected?
F) DMSS-4

(a) Hyperactive subtype defined by the presence of either (i) or (ii)

(i) Increased activity levels evidenced by a positive response to either:
   - Is (s)he more active than before?
   - Does (s)he seem overactive?

(ii) Loss of control of activity evidenced by a positive response to either:
   - Are his/her movements unproductive or lacking in purpose?
   - Has (s)he lost a sense of control over their actions?

(b) Hypoactive subtype defined by the presence of either (iii) or (iv)

(iii) Decreased speed of actions evidenced by a positive response to either:
   - Is (s)he moving more slowly than before?
   - Does it take longer than previously to perform simple tasks?

(iv) Decreased amount of speech evidenced by a positive response to either:
   - Does (s)he speak less than before?
   - Is (s)he lacking in spontaneous speech? E.g. only speaks when spoken to.

(c) Mixed subtype defined by the presence of both hyperactive and hypoactive criteria as outlined in (a) and (b) above.

(d) No subtype if neither hyperactive nor hypoactive criteria as outlined in (a) and (b) above.
F ) CAM

CAM Scoring sheet

Positive ☐  Negative ☐

(1a OR 1b) AND 2 AND (3 OR 4) [CAM sensitive]

---

**Item 1**

*(a) Acute onset  Y  N  O  [acute on chronic O]*

______________________________________________

*(b) Fluctuation  Y  O  N  O*

---

**Item 2**

*Inattention  Y  O  N  O*

______________________________________________

*Months Forwards*

<table>
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<tr>
<th>J</th>
<th>F</th>
<th>MH</th>
<th>A</th>
<th>MY</th>
<th>JE</th>
<th>JY</th>
<th>A</th>
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<th>O</th>
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**Item 3**

*Disorganised Thinking  Y  O  N  O*

______________________________________________

*Proverb (cloud / meat / stitch / blood / vessels / actions / book / chickens / leopard / cat)*
### Item 4

**Consciousness**

<table>
<thead>
<tr>
<th>Alert</th>
<th>Y</th>
<th>O</th>
<th>N</th>
<th>O</th>
<th>Other _____________________________</th>
</tr>
</thead>
</table>

*(Hyperalert or vigilant/ lethargic but readily rousable/ stuporose or comatose)*
F) DRS-R98 GENERAL INSTRUCTIONS FOR USE OF THE DRS-R-98

The Delirium Rating Scale-Revised-98 (DRS-R-98) is a 16-item clinician-rated scale with two sections and a score sheet. The 13-item severity section can be scored separately from the 3-item diagnostic section; their sum constitutes the total scale score. The severity section functions as a separate scale for repeated measures at short intervals within an episode of delirium. The total scale can be scored initially to enhance differential diagnosis by capturing characteristic features of delirium, such as acute onset and fluctuation of symptom severity. Concomitant use of diagnostic criteria such as from the International Classification of Disease (ICD)-10 Research Manual or versions of the Diagnostic and Statistical Manual (DSM) will enhance its ability to measure delirium when demented patients are involved because the DRS-R-98 is mostly a severity scale.

All items are anchored by text descriptions as guides for rating along a continuum from normal to severely impaired. Severity items are rated from 0 to 3 points and diagnostic items from 0 to either 2 or 3 points. The scoresheet offers space to circle item ratings and to optionally note characteristics of symptoms (e.g., type of hallucination) or the condition of patients during the ratings (e.g., restrained).

Though designed to be rated by psychiatrists, other physicians, nurses, and psychologists can use it if they have had appropriate clinical training in evaluating psychiatric phenomenology in medically ill patients. It can be used in research or comprehensive clinical evaluations. It does require enough clinical expertise to distinguish, for example, language problems from thought process abnormalities or delusions from confabulation. Even with sufficient clinical expertise, at times it may be difficult to make certain distinctions and more than one item may need to be rated to reflect that presentation (e.g., Wernicke’s aphasia and severe loose associations).

The DRS-R-98 can be used in conjunction with the Delirium Rating Scale (DRS) for certain research purposes because they differ substantially in descriptions of items. For example, the DRS may be more helpful for patients emerging from stupor.

The DRS-R-98 measures symptoms without regard to cause. Thus, preexisting conditions may add points, for example, dysphasia will affect the language item. However, longitudinal ratings will clarify effects of preexisting conditions after the delirium has cleared. The inclusion of mentally retarded and Cognitive Disorder Not Otherwise Specified subjects during the validation study suggests that delirium can still be reliably assessed in the presence of such confounds.

All sources of available information are used to rate the patient—family, visitors, hospital staff, doctors, medical chart, and so on. Even a hospital roommate can contribute information. During interviews for such collateral information, ensure that terms used are mutually understood before accepting others’ interpretation of symptoms.

Any time frame can be chosen for the DRS-R-98. Time frames greater than 24 hours are probably not necessary as this coincides with circadian rhythms and their possible disruptions. Shorter periods (e.g., 4 to 12 hours) may be helpful for intervention assessment—either for clinical or research purposes—though the fluctuating nature of symptom severity may need to be considered when interpreting the scores. Choosing periods less than 2 hours risks not adequately capturing some items (e.g., hallucinations, sleep-wake cycle disturbance) that occur intermittently. In such circumstances, a researcher may wish to use a smaller subset of items to monitor the patient, though such a subscale has not been validated.

Some items are rated based on examination and history, while others incorporate formal testing (e.g., cognitive and language items). It may be useful for a given clinician to standardize the questions used routinely in his/her practice, for example, asking months of the year backwards for attention, clockface or puzzle pieces for visuospatial ability, and particular items for confrontational naming. Adjunctive use of the Cognitive Test for Delirium (CTD) or some of its items offers the advantage of not needing the patient to write or speak. Evaluation of general information included in the longterm memory item should be geared appropriately to the educational and cultural background of the patient.

When both interview behavior and formally elicited responses are used, the relative contribution of each needs to be weighed by the clinician and a scoring judgment needs to be made. For example, on the attention item a patient has difficulty with reciting months of the year backwards but attends fairly well during the interview, or on long-term memory a patient recalls personal remote information accurately, but cannot recall well on formal testing of three words after 15 minutes.

Despite text descriptions for each item rating, the rater may need to exercise judgment in scoring. At times an intermediate rating with a 0.5 point interval may be needed (e.g., 2.5 points) if the rater cannot decide between two choices. Also, the time frame chosen may affect how to weigh the presence of certain symptoms. For example, a patient who has periods of intense hyperactivity and hypoactivity in a 24-hour period would be rated as “3” on both items #7 and 8. If this same patient is rated for a shorter interval that only involved hyperactivity, then item #7 would be rated as “3” and item #8 would be “0”.

In cases where an item cannot be rated at all, the rater should make a notation on the score sheet and decide later how to handle that item’s scoring. If used for research, a statistical consultant may have to advise. If used clinically, altering the denominator of the maximum possible score may be acceptable.

A Trzepacz 1998
This is a revision of the Delirium Rating Scale (Trzepacz et al. 1988). It is used for initial assessment and repeated measurements of delirium symptom severity. The sum of the 13 item scores provides a severity score. All available sources of information are used to rate the items (nurses, family, chart) in addition to examination of the patient. For serial repeated ratings of delirium severity, reasonable time frames should be chosen between ratings to document meaningful changes because delirium symptom severity can fluctuate without interventions.

**DELIRIUM RATING SCALE-R-98 (DRS-R-98)**

**DRS-R-98 SEVERITY SCALE**

1. **Sleep-wake cycle disturbance**
   Rate sleep-wake pattern using all sources of information, including from family, caregivers, nurses’ reports, and patient. Try to distinguish sleep from resting with eyes closed.

   0. Not present
   1. Mild sleep continuity disturbance at night or occasional drowsiness during the day
   2. Moderate disorganization of sleep-wake cycle (e.g., falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion/behavioral changes or very little nighttime sleep)
   3. Severe disruption of sleep-wake cycle (e.g., day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness.)

2. **Perceptual disturbances and hallucinations**
   Illusions and hallucinations can be of any sensory modality. Misperceptions are “simple” if they are uncomplicated, such as a sound, noise, color, spot, or flashes and “complex” if they are multidimensional, such as voices, music, people, animals, or scenes. Rate if reported by patient or caregiver, or inferred by observation.

   0. Not present
   1. Mild perceptual disturbances (e.g., feelings of derealization or depersonalization; or patient may not be able to discriminate dreams from reality)
   2. Illusions present
   3. Hallucinations present

3. **Delusions**
   Delusions can be of any type, but are most often persecutory. Rate if reported by patient, family or caregiver. Rate as delusional if ideas are unlikely to be true yet are believed by the patient who cannot be dissuaded by logic. Delusional ideas cannot be explained otherwise by the patient’s usual cultural or religious background.

   0. Not present
   1. Mildly suspicious, hypervigilant, or preoccupied
   2. Unusual or overvalued ideation that does not reach delusional proportions or could be plausible
   3. Delusional

4. **Lability of affect**
   Rate the patient’s affect as the outward presentation of emotions and not as a description of what the patient feels.

   0. Not present
   1. Affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control
   2. Affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others
   3. Severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others

5. **Language**
   Rate abnormalities of spoken, written or sign language that cannot be otherwise attributed to dialect or stuttering. Assess fluency, grammar, comprehension, semantic content and naming. Test comprehension and naming nonverbally if necessary by having patient follow commands or point.

   0. Normal language
   1. Mild impairment including word-finding difficulty or problems with naming or fluency
   2. Moderate impairment including comprehension difficulties or deficits in meaningful communication (semantic content)
   3. Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension
6. Thought process abnormalities
Rate abnormalities of thinking processes based on verbal or written output. If a patient does not speak or write, do not rate this item.

0. Normal thought processes
1. Tangential or circumstantial
2. Associations loosely connected occasionally, but largely comprehensible
3. Associations loosely connected most of the time

7. Motor agitation
Rate by observation, including from other sources of observation such as by visitors, family and clinical staff. Do not include dyskinesia, tics, or chorea.

0. No restlessness or agitation
1. Mild restlessness of gross motor movements or mild fidgetiness
2. Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing intravenous lines, etc.
3. Severe motor agitation, such as combativeness or a need for restraints or seclusion

8. Motor retardation
Rate movements by direct observation or from other sources of observation such as family, visitors, or clinical staff. Do not rate components of retardation that are caused by parkinsonian symptoms. Do not rate drowsiness or sleep.

0. No slowness of voluntary movements
1. Mildly reduced frequency, spontaneity or speed of motor movements, to the degree that may interfere somewhat with the assessment.
2. Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities or self-care
3. Severe motor retardation with few spontaneous movements.

9. Orientation
Patients who cannot speak can be given a visual or auditory presentation of multiple choice answers. Allow patient to be wrong by up to 7 days instead of 2 days for patients hospitalized more than 3 weeks. Disorientation to person means not recognizing familiar persons and may be intact even if the person has naming difficulty but recognizes the person. Disorientation to person is most severe when one doesn’t know one’s own identity and is rare. Disorientation to person usually occurs after disorientation to time and/or place.

0. Oriented to person, place and time
1. Disoriented to time (e.g., by more than 2 days or wrong month or wrong year) or to place (e.g., name of building, city, state), but not both
2. Disoriented to time and place
3. Disoriented to person

10. Attention
Patients with sensory deficits or who are intubated or whose hand movements are constrained should be tested using an alternate modality besides writing. Attention can be assessed during the interview (e.g., verbal perseverations, distractibility, and difficulty with set shifting) and/or through use of specific tests, e.g., digit span.

0. Alert and attentive
1. Mildly distractible or mild difficulty sustaining attention, but able to refocus with cueing. On formal testing makes only minor errors and is not significantly slow in responses
2. Moderate inattention with difficulty focusing and sustaining attention. On formal testing, makes numerous errors and either requires prodding to focus or finish the task
3. Severe difficulty focusing and/or sustaining attention, with many incorrect or incomplete responses or inability to follow instructions. Distractible by other noises or events in the environment

11. Short-term memory
Defined as recall of information (e.g., 3 items presented either verbally or visually) after a delay of about 2 to 3 minutes. When formally tested, information must be registered adequately before recall is tested. The number of trials to register as well as effect of cueing can be noted on scoresheet. Patient should not be allowed to rehearse during the delay period and should be distracted during that time. Patient may speak or nonverbally communicate to the examiner the identity of the correct items. Short-term deficits noticed during the course of the interview can be used also.

0. Short-term memory intact
1. Recalls 2/3 items; may be able to recall third item after category cueing
2. Recalls 1/3 items; may be able to recall other items after category cueing
3. Recalls 0/3 items
12. **Long-term memory**
Can be assessed formally or through interviewing for recall of past personal (e.g., past medical history or information or experiences that can be corroborated from another source) or general information that is culturally relevant. When formally tested, use a verbal and/or visual modality for 3 items that are adequately registered and recalled after at least 5 minutes. The patient should not be allowed to rehearse during the delay period during formal testing. Make allowances for patients with less than 8 years of education or who are mentally retarded regarding general information questions. Rating of the severity of deficits may involve a judgment about all the ways long-term memory is assessed, including recent and/or remote long-term memory ability informally tested during the interview as well as any formal testing of recent long-term memory using 3 items.

0. No significant long-term memory deficits
1. Recalls 2/3 items and/or has minor difficulty recalling details of other long-term information
2. Recalls 1/3 items and/or has moderate difficulty recalling other long-term information
3. Recalls 0/3 items and/or has severe difficulty recalling other long-term information

13. **Visuospatial ability**
Assess informally and formally. Consider patient’s difficulty navigating one’s way around living areas or environment (e.g., getting lost). Test formally by drawing or copying a design, by arranging puzzle pieces, or by drawing a map and identifying major cities, etc. Take into account any visual impairments that may affect performance.

0. No impairment
1. Mild impairment such that overall design and most details or pieces are correct; and/or little difficulty navigating in his/her surroundings
2. Moderate impairment with distorted appreciation of overall design and/or several errors of details or pieces; and/or needing repeated redirection to keep from getting lost in a newer environment despite, trouble locating familiar objects in immediate environment
3. Severe impairment on formal testing; and/or repeated wandering or getting lost in environment ! Trzepacz 1998

**DRS-R-98 OPTIONAL DIAGNOSTIC ITEMS**

These three items can be used to assist in the differentiation of delirium from other disorders for diagnostic and research purposes. They are added to the severity score for the total scale score, but are NOT included in the severity score.

14. **Temporal onset of symptoms**
Rate the acuteness of onset of the initial symptoms of the disorder or episode being currently assessed, not their total duration. Distinguish the onset of symptoms attributable to delirium when it occurs concurrently with a different preexisting psychiatric disorder. For example, if a patient with major depression is rated during a delirium episode due to an overdose, then rate the onset of the delirium symptoms.

0. No significant change from usual or longstanding baseline behavior
1. Gradual onset of symptoms, occurring over a period of several weeks to a month
2. Acute change in behavior or personality occurring over days to a week
3. Abrupt change in behavior occurring over a period of several hours to a day

15. **Fluctuation of symptom severity**
Rate the waxing and waning of an individual or cluster of symptom(s) over the time frame being rated. Usually applies to cognition, affect, intensity of hallucinations, thought disorder, language disturbance. Take into consideration that perceptual disturbances usually occur intermittently, but might cluster in period of greater intensity when other symptoms fluctuate in severity.

0. No symptom fluctuation
1. Symptom intensity fluctuates in severity over hours
2. Symptom intensity fluctuates in severity over minutes

16. **Physical disorder**
Rate the degree to which a physiological, medical or pharmacological problem can be specifically attributed to have caused the symptoms being assessed. Many patients have such problems but they may or may not have causal relationship to the symptoms being rated.

0. None present or active
1. Presence of any physical disorder that might affect mental state
2. Drug, infection, metabolic disorder, CNS lesion or other medical problem that specifically can be implicated in causing the altered behavior or mental state

! Trzepacz 1998
<table>
<thead>
<tr>
<th>Severity Item</th>
<th>Item Score</th>
<th>Optional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-wake cycle</td>
<td>0 1 2 3</td>
<td>Naps Nocturnal disturbance only Day-night reversal</td>
</tr>
<tr>
<td>Perceptual disturbances</td>
<td>0 1 2 3</td>
<td>Sensory type of illusion or hallucination: olfactory, tactile auditory visual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Format of illusion or hallucination: simple complex</td>
</tr>
<tr>
<td>Delusions</td>
<td>0 1 2 3</td>
<td>Type of delusion: persecutory Nature: poorly formed systematized</td>
</tr>
<tr>
<td>Lability of affect</td>
<td>0 1 2 3</td>
<td>Type: angry anxious elated irritable dysphoric</td>
</tr>
<tr>
<td>Language</td>
<td>0 1 2 3</td>
<td>Check here if intubated, mute, etc.</td>
</tr>
<tr>
<td>Thought process</td>
<td>0 1 2 3</td>
<td>Check here if intubated, mute, etc.</td>
</tr>
<tr>
<td>Motor agitation</td>
<td>0 1 2 3</td>
<td>Check here if restrained Type of restraints:</td>
</tr>
<tr>
<td>Motor retardation</td>
<td>0 1 2 3</td>
<td>Check here if restrained Type of restraints:</td>
</tr>
<tr>
<td>Orientation</td>
<td>0 1 2 3</td>
<td>Date: Place: Person:</td>
</tr>
<tr>
<td>Attention</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>Short-term memory</td>
<td>0 1 2 3</td>
<td>Record # of trials for registration of items: Check here if category cueing helped</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>0 1 2 3</td>
<td>Check here if category cueing helped</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>0 1 2 3</td>
<td>Check here if unable to use hands</td>
</tr>
</tbody>
</table>

**TOTAL SCORE:**

---

**Diagnostic Item**

---

**Name of patient:**

---

**Name of Rater:**

---

**SEVERITY SCORE:**

---

**Date:** / /

---

**Time:**

---

**TOTAL SCORE:**

---
<table>
<thead>
<tr>
<th>Temporal onset of symptoms</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Check here if symptoms appeared on a background of other psychopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluctuation of symptom severity</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
<td>Check here if symptoms only appear during the night</td>
</tr>
</tbody>
</table>
G) RCSQ

RCSQ Taken from Richards et al., 2000

1. **Sleep Depth** My sleep last night was:
   - Light sleep (0)....
   - Deep sleep (100).
   - Score.....

2. **Sleep Latency** Last night the first time I got to sleep I:
   - Just never could fall asleep (0) ....
   - Fell asleep almost immediately (100).
   - Score......

3. **Awakenings** Last night I was:
   - Awake all night long (0)....
   - Awake very little (100).
   - Score.....

4. **Returning to sleep** Last night, when I woke up, I:
Couldn’t get back to sleep (0)....

Got back to sleep immediately (100).

Score......

5. **Sleep Quality** I would describe my sleep last night as:

   A bad night’s sleep (0)....
   
   A good night’s sleep (100).
   
   Score......

6. **Noise** I would describe the noise level last night as

   Very quiet (0)....
   
   Very noisy (100)...
   
   Score......

H ) GDS

AB Clinician Depression Screen (ABCDS)

1. Do you often feel downhearted and blue?
No ☐ ➔ Depression ruled out with 95% certainty

Yes ☐ ➔ Ask the following questions:

2. Do you often feel helpless?    Yes ☐ No ☐

3. Do you feel that your life is empty? Yes ☐ No ☐

4. Do you feel happy most of the time? Yes ☐ No ☐

5. Are you basically satisfied with your life? Yes ☐ No ☐

Score 1 or 2 / total of 5 questions: Not depressed
Score 4 or 5 / total of 5 questions: Depressed.
Score of 3/5: proceed to Geriatric Depression Scale

Date __________  Result __________
I) MMSE

Standardised Mini-Mental State Examination (sMMSE)

DATE_______

Section 1- Orientation

1. Year ____________________ ☐/1 6. Country ________________
2. Season __________________ ☐/1 7. County ________________ ☐/1
3. Month ________________ ☐/1 8. City ________________ ☐/1
4. Today’s Date __________ ☐/1 9. Place ________________ ☐/1
5. Day of the week __________ ☐/1 10. Floor of building _________ ☐/1

Section 2- Cognition

11. Word 1 _____________ ☐/1 15. Pencil ☐/1
   Word 2 _____________ ☐/1 16. No ifs, ands, or buts ☐/1
   Word 3 _____________ ☐/1 17. Subject closes eyes ☐/1
12. DLROW _____________ ☐/5 18. Takes in correct hand ☐/1
13. Word 1 _____________ ☐/1 Folds paper in half ☐/1
   Word 2 _____________ ☐/1 Puts paper on floor ☐/1
   Word 3 _____________ ☐/1 19. Sentence ☐/1
14. Wristwatch ☐/1 20. Copies figure ☐/1
CLOSE YOUR EYES
Write a sentence

__________________________________________________________________

Copy this diagram
J)IQCODE

Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)

by A. F. Jorm

Centre for Mental Health Research The Australian National University Canberra, Australia

There is no copyright on the Short IQCODE. However, the author appreciates being kept informed of research projects which make use of it.

Note: As used in published studies, the IQCODE was preceded by questions to the informant on the subject's sociodemographic characteristics and physical health.

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 19__. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

Compared with 10 years ago how is this person at:

1  2  3  4  5

1. Remembering things about family and friends e.g. occupations, birthdays, addresses
   Much improved
   A bit improved
   Not much change
   A bit worse
   Much worse

2. Remembering things that have happened recently
Much improved
A bit improved
Not much change
A bit worse
Much worse
3. Recalling conversations a few days later
Much improved
A bit improved
Not much change
A bit worse
Much worse
4. Remembering his/her address and telephone number
Much improved
A bit improved
Not much change
A bit worse
Much worse
5. Remembering what day and month it is
Much improved
A bit improved
Not much change
A bit worse
Much worse
6. Remembering where things are usually kept
Much improved
A bit improved
Not much change
A bit worse
Much worse
7. Remembering where to find things which have been put in a different place from usual
Much improved
A bit improved
Not much change
A bit worse
Much worse
8. Knowing how to work familiar machines around the house
Much improved
A bit improved
Not much change
A bit worse
Much worse
9. Learning to use a new gadget or machine around the house
Much improved
A bit improved
Not much change
A bit worse
Much worse
10. Learning new things in general
Much improved
A bit improved
Not much change
A bit worse
Much worse
11. Following a story in a book or on TV
Much improved
A bit improved
Not much change
A bit worse
Much worse
12. Making decisions on everyday matters
Much improved
A bit improved
Not much change
A bit worse
Much worse
13. Handling money for shopping
Much improved
A bit improved
Not much change
A bit worse
Much worse
14. Handling financial matters e.g. the pension, dealing with the bank
Much improved
A bit improved
Not much change
A bit worse
Much worse
15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends
Much improved
A bit improved
Not much change
A bit worse
Much worse
16. Using his/her intelligence to understand what's going on and to reason things through
Much improved
A bit improved
Not much change
A bit worse
Much worse

IQCODE Scoring Methodology
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

To score the IQCODE, add up the score for each question and divide by the number of questions. For the Long IQCODE, you divide by 26. For the Short IQCODE, divide by 16. The result is a score that ranges from 1 to 5. A score of 3 means that the subject is rated on average as 'no change'. A score of 4 means an average of 'a bit worse'. A score of 5 an average of 'much worse'. If the Long IQCODE is used for screening for dementia, a cutting point of 3.27/3.30 balances sensitivity and specificity.

For the Short IQCODE, a cutting point of 3.31/3.38 achieves a balance of sensitivity and specificity. For further information on scoring and cut-points for screening, see: