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A Comparison of Cognitive and Neuropsychiatric Profiles in hospitalised elderly medical patients with Delirium, Dementia and Comorbid Delirium-Dementia

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ABSTRACT

Background and Aims: Differentiation of delirium and dementia is a key diagnostic challenge but there has been limited study of features that distinguish these conditions.

Methods: Consecutive elderly medical inpatients with DSM-IV delirium, dementia, comorbid delirium-dementia, and cognitively intact controls were assessed cross-sectionally using the Revised Delirium Rating Scale (DRS-R98), Cognitive Test for Delirium (CTD) and Neuropsychiatric Inventory (NPI-Q).

Results: 176 patients were assessed with delirium (n=50), dementia (n=32), comorbid delirium-dementia (n=62) and cognitively intact (n=32). Both delirium and comorbid delirium-dementia groups scored higher than the dementia group for DRS-R98 and CTD total scores, but all three neurocognitively impaired groups scored similarly in respect of total NPI-Q scores. For individual DRS-R98 items, delirium groups were distinguished from dementia by a range of non-cognitive symptoms, but only for impaired attention of the cognitive items. For the CTD, attention (p=0.002) and vigilance (p=0.01) distinguished delirium from dementia. No individual CTD item distinguished comorbid delirium-dementia from delirium. For the NPI-Q, there were no differences between the three neurocognitively impaired groups for any individual item severity.

Conclusions: The Neurocognitive profile of delirium is similar with or without comorbid dementia and differs from dementia without delirium. Simple tests of attention and vigilance can help to distinguish delirium from other presentations. The NPI-Q does not readily distinguish between neuropsychiatric disturbances in delirium versus dementia. [218]

Article summary: strengths and Limitations of this study

● This study includes a detailed cross-sectional assessment comparing the phenomenological profile of common neurocognitive disorders in elderly medical patients within a general hospital setting

●The findings highlight that delirium and dementia are characterised by different neuropsychiatric and cognitive disturbances

● Performance on simple bedside tests of attention and vigilance is disproportionately impaired in patients with delirium compared to dementia and thus have distinguishing capacity

●The Neuropsychiatric Inventory (NPI) lacks specificity for the neuropsychiatric disturbances of dementia over delirium

●Further study should examine how these patterns are reflected for different dementia subtypes

Introduction

Delirium and dementia are major neurocognitive disorders that are both common and commonly misdiagnosed in hospitalized elderly. [1, 2] Improved management of these under-recognized neuropsychiatric presentations is a key target within healthcare services. Accurate and timely recognition of these disorders is important because delirium is linked to a variety of adverse outcomes and is frequently the principal presenting feature of urgent physical illness. Gonzalez et al, [3] for example, found that mortality was increased by 11% for each additional 48 hours of active delirium. Bellelli et al [4] showed that patients with delirium superimposed upon dementia experience a two-fold risk of death within one year, emphasizing the need for clear delineation of this presentation. However, distinction is complicated by the considerable phenomenological overlap between these conditions and high comorbidity where the prevalence of delirium superimposed upon dementia in community and hospital settings ranges from 22-89%. [5]

Our understanding of the comparative phenomenological profile of major neurocognitive disorders is based upon studies conducted in a variety of populations. [6-16] These studies have applied different methods to the assessment of neuropsychiatric profile but have focused upon characterizing the neuropsychiatric features of comorbid illness rather than identifying distinguishing features of delirium versus dementia. Moreover, they have included limited account of the range of neuropsychological impairments that occur in these conditions.

We studied the cognitive and neuropsychiatric profiles of consecutive referrals of elderly medical inpatients to a psychiatry for later life consultation-liaison service. In particular, we aimed to address: (i) how does neuropsychiatric and cognitive profile in comorbid delirium-dementia compare to that of either disorder alone when analysed in conjunction with cognitively-intact control patients from the same setting, and (ii) which features best differentiate delirium and dementia, including comorbid cases.

METHODS

Subjects and Design

We conducted a prospective cross-sectional study of neuropsychiatric symptoms and cognitive performance in consecutive referrals to a psychiatry for later life consultation-liaison service of patients with delirium, dementia, comorbid delirium-dementia, as well as cognitively normal comparison subjects. Cases with altered mental state were identified on daily rounds by the medical team and referred for assessment and diagnosis by the research team.

Assessments were conducted by raters (DM, ML, JMcF, SMcI, VL) specifically trained in the use of the tools included herein (see below) and to further enhance inter-rater reliability, ratings associated with any uncertainty were discussed and agreed by consensus between raters.

Delirium was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria [17] based upon a full clinical assessment. Dementia was defined as a clear history of documented DSM-IV dementia (based on all available information at the time of assessment including clinical case notes and collateral history from family and / or carers) *or* a short Informant Questionnaire on Cognitive Decline in the elderly (IQCODE) score of ≥ 3.5. [18-20] Comorbid delirium-dementia was defined as the presence of both disorders. Patients with normal cognition and no prior history of cognitive problems were also recruited for assessment.

Each case was then assessed by first completing the DRS-R98 followed by administration of the CTD. The DRS-R98 rated the preceding 24 hour period whereas the CTD measured cognition at the time of its administration. CTD responses were not used to rate DRS-R98 items. The NPI-Q and IQ-CODE were completed on the same day and after consultation with family and / or carers who were familiar with the day to day functioning of the patient over the recent past.

Informed Consent

The procedures and rationale for the study were explained to all patients but because many patients had cognitive impairment at entry into the study it was presumed that many might not be capable of giving informed written consent. Because of the non-invasive nature of the study, University Hospital Limerick Regional Ethics Committee approved an approach to establishing consent by virtue of augmenting patient assent with proxy consent from next of kin (where

possible) or a responsible caregiver for all participants in accordance with the Helsinki Guidelines for Medical research involving human subjects.[21]

Assessments

Demographic data and medication at the time of the assessment were recorded. All available information from medical records and collateral history was used. Nursing staff were interviewed to assist rating of symptoms over the previous 24 hours.

The Delirium Rating Scale-Revised-98 [DRS-R98][22] is designed for broad phenomenological assessment of delirium. It is a 16-item scale with 13 severity and 3 diagnostic items with high interrater reliability, sensitivity and specificity for detecting delirium in mixed neuropsychiatric and other hospital populations. Each item is rated 0 (absent/normal) to 3 (severe impairment) with descriptions anchoring each severity level. Severity scale scores range from 0-39 with higher scores indicating more severe delirium. Delirium typically involves scores above 15 points (Severity scale) or 18 points (Total scale) when dementia is in the differential diagnosis. For determination of item frequencies in this study, any item score $\geq$ 1 was considered as being "present".

The Cognitive Test for Delirium [CTD][23] was specifically designed to assess hospitalized patients with delirium, in particular those who are intubated or unable to speak or write. It assesses five neuropsychological domains (orientation, attention, memory, comprehension, and vigilance)

emphasizing nonverbal (visual and auditory) modalities. Each individual domain is scored from 0-6 in 2 point increments, except for comprehension (single point increments). Total scores range between 0-30 with higher scores indicating better cognitive function and scores of less than 19 consistent with delirium. It reliably differentiates delirium from other neuropsychiatric conditions including dementia, schizophrenia and depression. [23]

The Neuropsychiatric Inventory (NPI) [24, 25] was developed for assessing neuropsychiatric symptoms in patients with Alzheimer's disease and other neurodegenerative disorders. Studies of cognitively intact older adults indicate extremely low scores suggesting that the NPI is good at distinguishing between healthy people and those with dementia. The NPI-Q is a self-administered short questionnaire version of the NPI [25] intended for use in everyday clinical practice. Neuropsychiatric symptom severity is assessed in the same way as the original NPI. The NPI-Q includes ten behavioural and two neurovegetative items that are assessed by an informed caregiver who is knowledgeable about the patient's daytime and night-time behaviours. Symptoms are rated over the past four weeks. Each of the 12 symptom domains is assessed by a screening question derived from the NPI-Q that covers symptom manifestations with anchor points for symptom severity rated on a three point scale and caregiver distress ratings rated on a five point scale. The questionnaire includes written instructions and the total NPI-Q severity score represents the sum of individual symptom scores and ranges from 0 to 36. [26] The NPI can be further divided into four subscales – Agitation/aggression, frontal, mood and psychosis. [27]

The Informant Questionnaire on Cognitive Decline in the Elderly-Short Form (IQCODE-SF) is a validated screening tool for detecting cognitive impairment.[19] The short version of the IQCODE includes 16 items that rate cognitive change over time, each of which are rated by an informant on a 5 point likert scale. The short-IQCODE takes approximately 10 minutes to administer. The total score divided by the number of questions provides a mean item score where ratings ≥ 3.5 are considered indicative of longstanding cognitive difficulties and dementia.

The Delirium Etiology Checklist (DEC)[28] was used to document etiological underpinnings of delirium. This standardised checklist captures delirium etiology according to twelve categories. The presence and suspected role of multiple potential causes were documented for each case of delirium, rated on a 5-point scale for degree of attribution to the delirium episode, ranging from 'ruled out/not present/not relevant' (0) to 'definite cause' (4).

Statistical Analyses

Statistical analysis was conducted using SPSS-19. Demographic and rating scale data are expressed as means plus standard deviation. Continuous variables (e.g. age, total DRS-R98 and CTD scores) were compared by one way ANOVA with independent t-tests used for post hoc comparisons. Non-normal data (eg, DRS-R98 and CTD item scores) were compared with Mann-Whitney U tests for between group Comparisons.

RESULTS

A total of 176 patients were assessed of whom 50 had delirium without dementia, 62 had both delirium and dementia, 32 had dementia without delirium, and 32 were deemed cognitively intact. Demographic, medication and general clinical data for patients from these four groups are shown in Table 1. There were no significant differences between the four groups in respect of age, gender distribution, number of medications received or use of psychotropic medications.

The principal underlying etiologies for delirium (n=112) as captured on the DEC were systemic infection (66), CNS infection (4), metabolic/ endocrine disturbance (39), drug intoxication (5), drug withdrawal (6) cerebrovascular (28), organ insufficiency (22), seizure-related (12), neoplasm (9), traumatic brain injury. (2)

Table 1 compares mean scores for the four groups for the DRS-R98 total and severity scales, CTD, IQ-CODE and NPI-Q. Both delirium groups were more impaired than the dementia group on total scores for the DRS-R98 and CTD. All three neurocognitively impaired groups scored similarly in respect of total NPI-Q scores. The mean short IQCODE scores distinguished the groups, with both dementia groups scoring well in excess of the suggested cutoff score.[19]

Means and standard deviations for each individual item (1-16) on the DRS-R98 are described in Table 2. The three groups with cognitive impairment differed from cognitively intact controls

across the majority of items, including both cognitive and non-cognitive symptoms. Delirium diagnostic items (symptom fluctuation, acute onset, and attributable physical disorder) significantly distinguished delirium groups from the other groups. In addition, both delirium groups were distinguished from the dementia-only group for sleep-wake cycle disturbances, perceptual disturbances, affective lability, and language abnormalities. Of note, the delirium and dementia alone groups were not distinguished by cognitive items (including either measures of memory) apart from impaired attention which was more severe in both delirium groups. Both delirium groups were very similar in disturbance levels for the majority of items but were distinguished by severity of sleep-wake cycle disturbance, thought process abnormalities and motor agitation.

Table 3 shows the comparison of individual CTD item scores between the four groups. There was a statistically significant difference overall between the four neurocognitive groups for each of the five individual sections ($p < .001$). No item distinguished comorbid delirium-dementia from delirium. Both attention ($p=0.002$) and vigilance ($p=0.01$) distinguished delirium from dementia while only vigilance significantly distinguished delirium-dementia from dementia ($p<0.001$).

The frequencies for each of the 12 individual severity and distress items for the neurocognitive disorder groups (delirium alone, comorbid delirium-dementia, dementia, and control) are shown in tables 4 and 5. There was a significant difference overall between the four patient groups for 10 of the 12 individual distress items of the NPI-Q. All three neurocognitive groups scored more highly than controls for anxiety, while the two delirium groups (but not the dementia-only group)

scored more highly than controls for agitation-aggression, irritability-lability and aberrant motor behaviour. Conversely, the dementia groups (but not delirium alone) scored more highly than controls for depression-dysphoria and sleep disturbances, while only the comorbid delirium-dementia group scored more highly than controls for apathy-indifference. Analysis of the NPI-Q subscale scores [27] showed significant differences between all three neurocognitive groups and controls and broadly replicated these findings (Table 6).

DISCUSSION

We compared the neuropsychiatric profile of elderly medical inpatients with a variety of neurocognitive presentations, including a cognitively-intact group. We used well-validated instruments for both delirium and dementia symptom severity – the DRS-R98, CTD and NPI-Q - which allow for detailed investigation of cognitive and neuropsychiatric profile in these complex syndromes. We found that patients with active delirium – both with and without comorbid dementia – could be distinguished from patients with dementia-alone in respect of a range of neuropsychiatric and cognitive disturbances identified with the DRS-R98 and CTD scales, but less so with the NPI-Q. This suggests that the NPI-Q does not readily distinguish between the neuropsychiatric disturbances of delirium and the so-called Behavioural and Psychological Symptoms of Dementia (BPSD).

We found similar cognitive and neuropsychiatric profile in patients with delirium and comorbid delirium-dementia. However, delirium (both comorbid and without dementia) was

distinguished from dementia without delirium by both a variety of neuropsychiatric symptoms and in terms of cognitive performance on tests of attention and vigilance.

The findings in respect of differences in cognitive profile between delirium and dementia extends previous work using similar instrumentation conducted in palliative care, where attention distinguished both delirium and comorbid delirium-dementia from dementia alone. [12] In addition, this study of elderly medical inpatients found that performance on vigilance distinguished delirium groups from dementia. Attentional disturbances in delirium are in respect of the ability to direct, focus, sustain and shift attention. Vigilance is a term that has many possible meanings, but is most commonly equated with the ability to sustain attention to a task and thus is often referred to as 'vigilant' attention.[29] The vigilance test of the CTD used herein involves a letter recognition test and thus explores the ability to sustain attentional performance. Previous work has highlighted how attention and vigilance are closely linked, including in patients with delirium [30] where there was high correlation between DRS-R98 attention (which emphasizes the months backwards test) and CTD attention (which uses combined performance on the digit span forwards and backwards) (r = -0.73), as well as between DRS–R98 attention and CTD vigilance (r = -0.60). Similarly, Brown et al [31] compared performance among patients with delirium, dementia and unimpaired cognition on a series of tests of sustained visual attention and found that delirious patients could be distinguished across a range of tests, while performance among the patients with dementia was relatively preserved and equivalent to the unimpaired controls. These findings highlight how efforts to

improve detection of delirium (e.g. developing screening tools) can be enhanced by emphasizing sustained attention/vigilance as key elements within the cognitive domain.

Neuropsychiatric profiles

Previous comparisons of delirium versus comorbid delirium-dementia in terms of neuropsychiatric profile measured on the Delirium Symptom Interview in elderly medical inpatients, [6,32] and DRS and BPRS in geropsychiatric patients [7] has found that these conditions are phenomenologically similar. However, other studies using the Organic Brain Scale (OBS) in mixed community-dwelling and hospitalized groups [11,14] found that delirious patients with comorbid dementia have more hyperactive features, more commonly experience psychotic symptoms, have more profound communication difficulties and are more prone to symptom worsening in the evening. Margiotta et al [10] compared DRS profiles in delirious elderly medical inpatients with and without comorbid dementia. They found that comorbid cases had higher overall DRS scores, with greater perceptual disturbances, symptom fluctuation and experienced more prolonged delirium episodes. Otherwise, these groups were similar in terms of other DRS symptoms and MMSE scores. We found that delirium and comorbid-delirium dementia groups were very similar in disturbance levels for the majority of symptoms but were distinguished by severity of DRS-R98 thought process abnormalities and motor agitation.

Studies that have compared profiles in patients with dementia with and without comorbid delirium indicate considerable differences in terms of neuropsychiatric symptom burden.

Landreville et al [15] studied long term care residents using the Behaviour Problem Scale and found that patients with comorbid delirium-dementia had greater sleep problems, wandering, irrational behaviour and aggression. They suggested that BPSD may be a risk factor for delirium. Holtta et al [13] used the NPI in demented patients from acute geriatric inpatient (n=195) and Nursing home settings (n=230) with and without delirium and found that the majority of patients with dementia had multiple neuropsychiatric symptoms (NPS) but, that comorbid delirium was associated with greater NPS and a poorer prognosis. In addition, one third of dementia patients with multiple NPS had comorbid delirium. Hasegawa et al [16] compared dementia to comorbid delirium-dementia in respect of NPI ratings in memory clinic attenders. They found significantly higher total NPI scores for comorbid delirium-dementia, with similar scores across the groups for most individual items except for greater agitation in comorbid delirium-dementia. They concluded that delirium 'exaggerates' BPSD in dementia. We found that in comparison to dementia patients without delirium, comorbid delirium-dementia patients had greater DRS-R98 sleep-wake cycle disturbances, perceptual disturbances, affective lability, and language abnormalities, as well as CTD impairment of vigilance. However, these two groups did not differ in respect of NPI-Q ratings.

Two previous studies [8,12] have compared phenomenological profile in patients with delirium, dementia, comorbid delirium-dementia and without neurocognitive disorder. Laurila et al [8] supplemented a detailed clinical assessment with the WAIS and digit span. Demented patients with and without delirium differed in respect of multiple symptoms including attention, disorganised thinking, perceptual disturbances, sleep difficulties, psychomotor abnormalities,

acuity of onset and presence of etiology - all of which were more prominent in patients with comorbid illness. Specific comparison of delirious patients with and without underlying dementia was not reported. Meagher and colleagues [12] studied palliative care patients and found that delirium and comorbid delirium-dementia groups had comparable DRS-R98 and CTD total scores, which were greater than in dementia or control groups. On the DRS-R98, inattention, disorientation and multiple non-cognitive symptoms (sleep-wake cycle, perceptual abnormality, affective lability, thought process abnormality, motor agitation and motor retardation) were more severe in delirium groups compared with dementia-alone. In this study, we found that both delirium groups were distinguished from the dementia-only group for attention, sleep-wake cycle disturbances, perceptual disturbances, affective lability, language abnormalities and all three diagnostic items (acuity of onset, symptom fluctuation and attributable physical disorder).

Trzepacz and colleagues [33] in a comparison of delirium and dementia without delirium found greater impairment in delirium for disturbances of attention, visuospatial ability, the sleep-wake cycle, perception, thought process, affective lability, motor agitation, comprehension, and acuity of onset and fluctuation of symptoms.

Overall, these findings highlight how delirium symptoms overshadow dementia when comorbid and, along with the greater diagnostic urgency for delirium, emphasise that elderly medical patients with neuropsychiatric symptoms should be presumed to have delirium until otherwise clarified.

Comparison of assessment tools

Although the neuropsychiatric profile of patients varied according to delirium and dementia status, these patterns differed across the assessment tools employed. The instruments that we used differ both in their content and time frames covered – the CTD exclusively focuses on cognitive performance at the time of testing, the DRS-R98 includes cognitive and neurobehavioural elements over the previous 24 hours, while the NPI-Q focuses on neuropsychiatric disturbances over the previous month. Our findings suggest that although patients with delirium and dementia experience a similar range of neurobehavioural disturbances (e.g. over a month as measured with the NPI-Q), the relative acuity of delirium is associated with greater symptom burden in the previous twenty four hours (as captured on the DRS-R98). In addition, although the DRS-R98 and NPI-Q both assess for psychosis, sleep-wake cycle disturbance, motor behaviour and affective alterations, the emphasis for some features is different whereby NPI-Q explores specifically for apathy and sustained affective changes, while in the DRS-R98 the focus is upon lability of affective expression.

In particular, the differences between delirium groups and dementia in respect of DRS-R98 items for sleep, affective lability and perceptual disturbances were not mirrored with the NPI-Q. In addition to the contrasting time frames covered by these tools, their emphasis within these domains is different; the DRS-R98 focuses upon alterations to the sleep-wake cycle over the previous twenty-four hours and emphasizes fragmentation and cycle reversal in severity rating.

The NPI-Q emphasizes sleep at night, with the range and duration of night-time behaviours central to rating of severity. Moreover, the NPI-Q is rated by an informant rather than a psychiatrist. As such, our findings suggest that the character of sleep disturbances differs across neurocognitive disorders and that delirium is particularly characterized by altered sleep-wake cycle. This echoes previous work which has emphasised that more severe disturbances involving altered sleep-wake cycle such as fragmentation and cycle reversal are relatively specific to delirium and occur in 75% or more of patients with active delirium.[30, 34,35]

Similarly, we found different patterns in respect of altered affective functioning. Classically, delirium is associated with affective lability while dementia is often complicated by more sustained disturbances of mood, apathy and indifference. We found that delirium groups had higher scores for the DRS-R98 item for affective lability, while only the dementia groups scored higher than controls for depression-dysphoria on the NPI-Q. Affective disturbances are thus common elements of both delirium and dementia, and are increasingly recognized as risk factors for both conditions.[36,37] More detailed study of affective symptoms and how they differ across neurocognitive disorders is warranted.

Study limitations

Cross-sectional studies cannot fully capture the phenomenological profile of conditions such as delirium where symptom fluctuation is prominent, though the DRS-R98 utilizes a 24-hour reporting period and the NPI-Q captures symptom profile over the previous month. We could not

specify the stage or primary cause of dementia but evidence indicates that the frequency of different neuropsychiatric disturbances varies across dementia types.[38,39] The observations regarding sleep and affective changes can be better explored with tools that have these domains as their primary focus and that explore different aspects of each in greater detail in order to ascertain the different character of disturbances across neurocognitive syndromes.

Implications

Guidance regarding differentiating symptoms between delirium and dementia is relatively lacking in the definition of delirium in DSM-5 [40] or ICD-10 [41], suggesting that these diagnostic systems would be advanced by criteria to guide efforts to distinguish these common conditions. This work suggests that particular neuropsychiatric symptoms and the methods by which these symptoms are assessed, including their character and timeframe are key to accurately distinguishing neurocognitive disorders. This is especially relevant in the assessment of suspected BPSD or major neurocognitive disorder with behavioural disturbance as described in DSM-5.[40] As a general rule, patients with significant neuropsychiatric disturbances as measured on delirium-focused instruments such as the DRS-R98 are highly indicative of delirium, while disturbances captured on tools such as the NPI are less discerning. Given the diagnostic urgency of delirium, our findings favour use of the DRS-R98 as the primary symptom assessment tool. Although delirium and dementia are both characterised by generalised disturbance of cognitive function, this work emphasises how delirium can be distinguished from dementia by virtue of the disproportionate impairment of attention and vigilance. These

cognitive functions should be emphasised in efforts to identify delirium, including in populations where there are high rates of dementia.

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Contributorship statement

Study design was conducted by Maeve Leonard, Shane McInerney, John McFarland, Margaret O'Connor, Paul Reynolds, Anna Maria Meaney, Paula T. Trzepacz, David J. Meagher.

Data collection was conducted by Maeve Leonard, Shane McInerney, John McFarland, David J. Meagher.

Data analysis was performed by Maeve Leonard, Candice Condon, Dimitrios Adamis, Paula T. Trzepacz, David J. Meagher.

Manuscript preparation was performed by Maeve Leonard, Shane McInerney, John McFarland, Candice Condon, Fahad Awan, Margaret O'Connor, Paul Reynolds, Anna Maria Meaney, Dimitrios Adamis, Colum Dunne, Walter Cullen, Paula T. Trzepacz, David J. Meagher.

Data Sharing Statement

We have no data to share.

Competing Interests

The authors have no competing interests to declare

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Table 1. Demographic and medication data for the four patient groups (mean ± SD)

	Delirium (n=50)	Comorbid delirium-dementia (n=62)	Dementia (n=32)	Control (n=32)
Male (%)	55	43	53	41
Age	78.9 ± 9.8	81.1 ± 7.3	80.9 ± 5.0	81.7 ± 7.5
Number of Psychotropics	1.0 ± 1.1	1.4 ± 1.1	1.4± 1.2	0.8 ± 1.1
DRS-R98 total	22.0 ± 8.4†	18.9± 6.9§	14.0± 6.8*	6.1± 5.2
DRS-R98 severity	17.3 ± 7.4‡	15.1 ± 6.1§	11.8 ± 6.3*	4.7± 4.1
CTD total	14.6 ± 9.6	14.2± 7.7	18.1± 8.0*	24.6 ± 4.8
Short IQCODE	3.1 ± 0.3	4.2 ± 1.4	4.1 ±0.7	2.9 ± 0.6
NPI-Q Distress	8.4 ± 6.4	9.9 ± 7.2	6.7 ±6.1*	1.5 ± 2.1
NPI-Q Severity	11.9 ± 10.6	12.3 ± 10.6	10.2 ± 9.5*	1.6 ± 2.7

Note: †delirium > dementia at p<0.001,

‡delirium > dementia at p<0.005,

§comorbid delirium-dementia > dementia at p<0.05,

*all three neurocognitive groups greater than controls at p < 0.001.

Table 2. DRS-R98 item severities (mean scores ± SD) for delirium, comorbid delirium-dementia, dementia alone, and control groups

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)
1. Sleep-wake cycle disturbance	0.5 ± 0.7	2.0 ± 0.9†**	1.5 ± 0.9*	0.9 ± 0.8¶
2. Perceptual disturbances and hallucinations	0.2 ± 0.7	1.0 ± 1.3†	0.7 ± 1.1*	0.2 ± 0.7¶
3. Delusions	0.1 ± 0.6	0.6 ± 1.0	0.4 ± 0.8	0.3 ± 0.7¶
4. Lability of affect	0.2 ± 0.6	1.4 ± 1.1‡	1.0 ± 0.9*	0.5 ± 0.7
5. Language	0.1 ± 0.4	1.1 ± 1.1†	0.8 ± 1.0*	0.3 ± 0.7¶
6. Thought process abnormalities	0.6 ± 0.8	2.5 ± 4.6*§	1.1 ± 1.1	0.8 ± 0.9¶
7. Motor agitation	0.2 ± 0.5	1.5 ± 1.1‡**	0.9 ± 0.9	0.6 ± 0.8
8. Motor retardation	0.1 ± 0.4	0.6 ± 0.9	0.5 ± 0.8	0.3 ± 0.6¶
9. Orientation	0.2 ± 0.4	1.2 ± 1.0	1.5 ± 0.7*	1.0 ± 0.8
10. Attention	0.6 ± 0.8	2.4 ± 1.4‡	2.0 ± 0.9*	1.6 ± 1.1
11. Short term memory	0.9 ± 0.9	1.7 ± 1.2	2.1 ± 0.9	1.7 ± 1.0
12. Long term memory	0.4 ± 0.6	1.4 ± 1.0	1.3 ± 0.9	1.1 ± 1.1
13.Visuospatial ability	0.6 ± 0.9	2.1 ± 1.1	1.8 ± 1.1	1.6 ± 1.2
14. Temporal onset of symptoms	0.4 ± 0.6	2.0 ± 0.6‡§	1.6 ± 0.9‡	0.6 ± 0.7
15. Fluctuation in symptom severity	0.2 ± 0.5	1.2 ± 0.6‡**	0.7 ± 0.7†	0.3 ± 0.4¶
16. Physical disorder	0.8 ± 0.6	1.9 ± 0.4‡	1.8 ± 0.4‡	1.2 ± 0.7

* more impaired than dementia at $p \leq 0.05$

† more impaired than dementia at $p < 0.01$

‡ more impaired than dementia at $p < 0.001$

** more impaired than delirium-dementia at $p < 0.01$

§ more impaired than delirium-dementia at $p \leq 0.05$

¶ no difference between dementia and controls

Table 3. Cognitive Test for Delirium (CTD) section scores for neurocognitive disorder groups, delirium, comorbid delirium-dementia, dementia alone, and control. Controls performed in the normal range for each item.

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)
1. Orientation	5.8 ± 0.6	3.7 ± 2.4	3.2 ± 2.1	4.3 ± 2.1
2. Attention	4.7 ± 1.7	2.1 ± 2.1†*	3.1 ± 2.1	3.8 ± 2.1
3. Memory	5.2 ± 1.1	2.9 ± 2.3	2.3 ± 2.3†	3.6 ± 2.0
4. Comprehension	5.7 ± 0.5	3.8 ± 2.1*	4.1 ± 1.8	4.7 ± 1.7
5. Vigilance	4.3 ± 1.9	1.6 ± 2.2	1.4 ± 2.0*	2.5 ± 2.3

* more impaired than dementia at $p \leq 0.05$

† more impaired than dementia at $p < .01$

‡ more impaired than dementia at $p < .001$

** more impaired than delirium-dementia at $p < .01$

§ more impaired than delirium-dementia at $p \leq 0.05$

¶ no difference between dementia and controls

Table 4. Frequencies for the 12 individual *severity* items of the Neuropsychiatric Inventory (NPI) for delirium, comorbid delirium-dementia, dementia alone, and control groups .

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)	*p*
1. Delusions	1	12	17	5	≤.05
2. Hallucinations	0	14	21	5	<.01
3. Agitation / Aggression	1	23	35	12	<.001
4. Depression / Dysphoria	5	14	30	14	≤.05
5. Anxiety	6	21	31	16	≤.05
6. Elation / Euphoria	0	1	7	2	NS
7. Apathy / Indifference	2	15	30	9	<.001
8. Disinhibition	2	8	18	1	<.01
9. Irritability / Lability	4	23	36	11	<.001
10. Aberrant Motor Behaviour	2	19	25	9	<.01
11. Sleep and Nighttime Disturbances	3	13	32	12	<.001
12. Appetite / Eating Disturbances	7	16	29	10	NS

Table 5. Frequencies for the 12 individual *distress* items of the Neuropsychiatric Inventory (NPI) for delirium, comorbid delirium-dementia, dementia alone, and control groups.

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)	*p*
1. Delusions	1	12	17	5	≤.05
2. Hallucinations	0	15	19	4	<.001
3. Agitation / Aggression	1	23	33	12	<.001
4. Depression / Dysphoria	3	15	28	14	<.01
5. Anxiety	5	20	28	15	≤.05
6. Elation / Euphoria	0	1	6	2	NS
7. Apathy / Indifference	2	12	27	9	<.01
8. Disinhibition	1	8	15	1	≤.05
9. Irritability / Lability	3	21	33	11	<.001
10. Aberrant Motor Behaviour	2	19	20	9	<.01
11. Sleep and Nighttime Disturbances	3	13	31	12	<.01
12. Appetite / Eating Disturbances	5	16	23	9	NS

Table 6. Comparison of NPI-Q subscale scores for delirium, comorbid delirium-dementia, dementia alone, and control groups

	Controls	Delirium	Comorbid delirium-dementia	*Dementia*
NPIQ4-Agitation Aggression	0.3 ± 0.6**	1.8 ± 1.2	1.9 ± 1.4	1.2 ± 1.1*
NPIQ3-Mood	0.7 ± 1.0ǂ	2.6 ± 2.1	3.0 ± 2.4	2.7 ± 2.2
NPIQ4-Frontal	0.4 ± 0.8†	2.3 ± 2.3	2.9 ± 2.5	1.6 ± 2.2
NPIQ- Psychosis	0.0 ± 0.2	1.4 ± 1.7	1.5 ± 2.5	1.4 ± 4.1

*Dementia < Comorbid delirium dementia <0.05;
**Controls < comorbid delirium and dementia; and delirium ≤ 0.05
ǂControls < all other neurocognitive groups ≤0.002
† Controls < Comorbid delirium and dementia; and delirium ≤0.005

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A Comparison of Cognitive and Neuropsychiatric Profiles in hospitalised elderly medical patients with Delirium, Dementia and Comorbid Delirium-Dementia

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ABSTRACT

Objectives: Differentiation of delirium and dementia is a key diagnostic challenge but there has been limited study of features that distinguish these conditions. We examined neuropsychiatric and neuropsychological symptoms in elderly medical inpatients to identify features that distinguish major neurocognitive disorders.

Setting: University teaching hospital in Ireland

Participants and measures: 176 Consecutive elderly medical inpatients [mean age 80.6 ± 7.0 (range 60-96); 85 males (48%)] referred to a psychiatry for later life consultation-liaison service with DSM-IV delirium, dementia, comorbid delirium-dementia, and cognitively intact controls. Subjects were assessed cross-sectionally with comparison of scores (including individual items) for the Revised Delirium Rating Scale (DRS-R98), Cognitive Test for Delirium (CTD) and Neuropsychiatric Inventory (NPI-Q).

Results: The frequency of neurocognitive diagnoses was delirium (n=50), dementia (n=32), comorbid delirium-dementia (n=62) and cognitively intact(n=32). Both delirium and comorbid delirium-dementia groups scored higher than the dementia group forDRS-R98 and CTD total scores, but all three neurocognitively impaired groups scored similarly in respect of total NPI-Q scores. For individual DRS-R98 items, delirium groups were distinguished from dementia by a range of non-cognitive symptoms, but only for impaired attention of the cognitive items. For the CTD, attention (p=0.002) and vigilance (p=0.01) distinguished delirium from dementia. No individual CTD item distinguished comorbid delirium-dementia from delirium. For the NPI-Q, there were no differences between the three neurocognitively impaired groups for any individual item severity.

Conclusions: The Neurocognitive profile of delirium is similar with or without comorbid dementia and differs from dementia without delirium. Simple tests of attention and vigilance can help to distinguish delirium from other presentations. The NPI-Q does not readily distinguish between neuropsychiatric disturbances in delirium versus dementia. Cases of suspected behavioural and psychological symptoms of dementia should be carefully assessed for possible delirium.

Article summary: strengths and Limitations of this study

● This study includes a detailed cross-sectional assessment comparing the phenomenological profile of common neurocognitive disorders in elderly medical patients within a general hospital setting

●The findings highlight that delirium and dementia are characterised by different neuropsychiatric and cognitive disturbances

● Performance on simple bedside tests of attention and vigilance is disproportionately impaired in patients with delirium compared to dementia and thus have distinguishing capacity

●The Neuropsychiatric Inventory (NPI) lacks specificity for the neuropsychiatric disturbances of dementia over delirium

●Further study should examine how these patterns are reflected for different dementia subtypes

Introduction

Delirium and dementia are major neurocognitive disorders that are both common and commonly misdiagnosed in hospitalized elderly. [1, 2] Improved management of these under-recognized neuropsychiatric presentations is a key target within healthcare services. Accurate and timely recognition of these disorders is important because delirium is linked to a variety of adverse outcomes and is frequently the principal presenting feature of urgent physical illness. Gonzalez et al, [3] for example, found that mortality was increased by 11% for each additional 48 hours of active delirium. Bellelli et al [4] found that patients with delirium superimposed upon dementia experience a two-fold risk of death within one year, emphasizing the need for clear delineation of this presentation. However, distinction is complicated by the considerable phenomenological overlap between these conditions and high comorbidity where the prevalence of delirium superimposed upon dementia in community and hospital settings ranges from 22-89%.[5]

Our understanding of the comparative phenomenological profile of major neurocognitive disorders is based upon studies conducted in a variety of populations.[6-16] These studies have applied different methods to the assessment of neuropsychiatric profile but have focused upon characterizing the neuropsychiatric features of comorbid illness rather than identifying distinguishing features of delirium versus dementia. Moreover, they have included limited account of the range of neuropsychological impairments that occur in these conditions.

We studied the cognitive and neuropsychiatric profiles of consecutive referrals of elderly medical inpatients toa psychiatry for later life consultation-liaison service. In particular, we aimed to address: (i) how does neuropsychiatric and cognitive profile in comorbid delirium-dementia

compare to that of either disorder alone when analysed in conjunction with cognitively-intact control patients from the same setting, and (ii) which features best differentiate delirium and dementia, including comorbid cases.

METHODS

Subjects and Design

We conducted a cross-sectional study of neuropsychiatric symptoms and cognitive performance in consecutive referrals to a psychiatry for later life consultation-liaison service at University Hospital Limerick, a 400-bedded tertiary care centre in the Midwestern region of Ireland. Between October 2011 and July 2012 cases with altered mental state suggestive of neurocognitive disorder were identified on daily rounds by the medical team and referred for assessment and diagnosis by the research team. All patients were ≥60 years old. Patients were assessed and classified with delirium, dementia, comorbid delirium-dementia, or cognitively normal.

Assessments were conducted by raters (DM, ML, JMcF, SMcI) specifically trained in the use of the tools included herein (see below) and to further enhance inter-rater reliability, ratings associated with any uncertainty were discussed and agreed by consensus between raters.

Delirium was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria[17] based upon a full clinical assessment at the time of consultation and

independent of the DRS-R98, CTD and NPI assessments. Dementia was defined as a clear history of documented DSM-IV dementia (based on all available information at the time of assessment including clinical case notes and collateral history from family and / or carers) *or*a short Informant Questionnaire on Cognitive Decline in the elderly (IQCODE) score of ≥ 3.5.[18-20] Comorbid delirium-dementia was defined as the presence of both disorders. Patients with normal cognition and no prior history of cognitive problems were also recruited for assessment.

Each case was then assessed by first completing the DRS-R98 followed by administration of the CTD. The DRS-R98 rated the preceding 24 hour period whereas the CTD measured cognition at the time of its administration. CTD responses were not used to rate DRS-R98 items. The NPI-Q and IQ-CODE were completed on the same day and after consultation with family and / or carers who were familiar with the day to day functioning of the patient over the recent past.

Informed Consent

The procedures and rationale for the study were explained to all patients but because many patients had cognitive impairment at entry into the study it was presumed that many might not be capable of giving informed written consent. Because of the non-invasive nature of the study, University Hospital Limerick Regional Ethics Committee approved an approach to establishing consent by virtue of augmenting patient assent with proxy consent from next of kin (where possible) or a responsible caregiver for all participants in accordance with the Helsinki Guidelines for Medical research involving human subjects.[21]

Assessments

Demographic data and medication at the time of the assessment were recorded. All available information from medical records and collateral history was used. Nursing staff were interviewed to assist rating of symptoms over the previous 24 hours.

The Delirium Rating Scale-Revised-98 [DRS-R98][22] is designed for broad phenomenological assessment of delirium. It is a 16-item scale with 13 severity and 3 diagnostic items with high interrater reliability, sensitivity and specificity for detecting delirium in mixed neuropsychiatric and other hospital populations. Each item is rated 0 (absent/normal) to 3 (severe impairment) with descriptions anchoring each severity level. Severity scale scores range from 0-39 with higher scores indicating more severe delirium. Delirium typically involves scores above 15 points (Severity scale) or 18 points (Total scale) when dementia is in the differential diagnosis. For determination of item frequencies in this study, any item score $\geq$ 1 was considered as being "present".

The Cognitive Test for Delirium [CTD][23] was specifically designed to assess hospitalized patients with delirium, in particular those who are intubated or unable to speak or write. It assesses five neuropsychological domains (orientation, attention, memory, comprehension, and vigilance) emphasizing nonverbal (visual and auditory) modalities. Each individual domain is scored from 0-6 in 2 point increments, except for comprehension (single point increments). Total scores range

between 0-30 with higher scores indicating better cognitive function and scores of less than 19 consistent with delirium. It reliably differentiates delirium from other neuropsychiatric conditions including dementia, schizophrenia and depression.[23]

The Neuropsychiatric Inventory (NPI) [24,25]was developed for assessing neuropsychiatric symptoms in patients with Alzheimer's disease and other neurodegenerative disorders. Studies of cognitively intact older adults indicate extremely low scores suggesting that the NPI is relatively specific for dementia-related neuropsychiatric pathology.The NPI-Q is a short questionnaire version of the NPI[25]intended for use in everyday clinical practice. Neuropsychiatric symptom severity is assessed in the same way as the original NPI. The NPI-Q includes ten behavioural and two neurovegetative items that are assessed by an informed caregiver who is knowledgeable about the patient's daytime and night-time behaviours. Symptoms are rated over the past four weeks. Each of the 12 symptom domains is assessed by a screening question derived from the NPI-Q that covers symptom manifestations with anchor points for symptom severity ratedon a three point scale and caregiver distress ratings rated on a five point scale. The questionnaire includes written instructions and the total NPI-Q severity score represents the sum of individual symptom scores and ranges from 0 to 36. [26] The NPI can be further divided into four subscales – Agitation/aggression, frontal, mood and psychosis. [27]

The Informant Questionnaire on Cognitive Decline in the Elderly-Short Form (IQCODE-SF) is a validated screening tool for detecting cognitive impairment.[19] The short version of the

IQCODE includes 16 items that rate cognitive change over time, each of which are rated by an informant on a 5 point likert scale. The short-IQCODE takes approximately 10 minutes to administer. The total score divided by the number of questions provides a mean item score where ratings ≥ 3.5 are considered indicative of longstanding cognitive difficulties and dementia.

The Delirium Etiology Checklist (DEC)[28] was used to document etiological underpinnings of delirium. This standardised checklist captures delirium etiology according to twelve categories. The presence and suspected role of multiple potential causes were documented for each case of delirium, rated on a 5-point scale for degree of attribution to the delirium episode, ranging from 'ruled out/not present/not relevant' (0) to 'definite cause' (4).

Statistical Analyses

Statistical analysis was conducted using SPSS-19. Demographic and rating scale data are expressed as means plus standard deviation. Continuous variables (e.g. age, total DRS-R98 and CTD scores) were compared by one way ANOVA with independent t-tests used for post hoc comparisons. Although data regarding scores for individual items on the DRS-R98 and CTD are shown as means and standard deviations, these data are not normally distributed and as such statistical comparisons relate to non-parametric tests (e.g. Mann-Whitney U tests for between group comparisons). Cohen's d was used to estimate the effect size for key differences (e.g. differences in CTD item scores).

RESULTS

A total of 176 patients [mean age 80.6 ± 7.0 (range 60-96); 85 males (48%)] were assessed of whom 50 had delirium without dementia, 62 had both delirium and dementia, 32 had dementia without delirium, and 32 were deemed cognitively intact. Demographic, medication and general clinical data for patients from these four groups are shown in Table 1. There were no statistically significant differences between the four groups in respect of age, gender distribution, number of medications received or use of psychotropic medications.

The principal underlying etiologies for delirium (n=112) as captured on the DEC were systemic infection (66), CNS infection (4), metabolic/ endocrine disturbance (39), drug intoxication (5), drug withdrawal (6) cerebrovascular (28), organ insufficiency (22), seizure-related (12), neoplasm (9), traumatic brain injury. (2)

Table 1 compares mean scores for the four groups for the DRS-R98 total and severity scales, CTD, IQ-CODE and NPI-Q. Both delirium groups were more impaired than the dementia group on total scores for the DRS-R98 and CTD. All three neurocognitively impaired groups scored similarly in respect of total NPI-Q scores. The mean short IQCODE scores distinguished the groups, with both dementia groups scoring well in excess of the suggested cut-off score and significantly higher than both the delirium without dementia and control groups.[19]

Means and standard deviations for each individual item (1-16) on the DRS-R98 are described in Table 2. The three groups with cognitive impairment differed from cognitively intact controls across the majority of items, including both cognitive and non-cognitive symptoms. Delirium diagnostic items (symptom fluctuation, acute onset, and attributable physical disorder) significantly distinguished delirium groups from the other groups. In addition, both delirium groups were distinguished from the dementia-only group for sleep-wake cycle disturbances, perceptual disturbances, affective lability, and language abnormalities. Of note, the delirium and dementia alone groups were not distinguished by cognitive items (including either measures of memory) apart from impaired attention which was more severe in both delirium groups. Both delirium groups were very similar in disturbance levels for the majority of items but were distinguished by severity of sleep-wake cycle disturbance, thought process abnormalities and motor agitation.

Table 3 shows the comparison of individual CTD item scores between the four groups. There was a statistically significant difference overall between the four neurocognitive groups for each of the five individual sections ($p<0.001$). No item distinguished comorbid delirium-dementia from delirium. Both attention ($p=0.002$; $d=0.81$and vigilance ($p=0.01$; $d=0.4$) distinguished delirium from dementia, while only vigilance significantly distinguished delirium-dementia from dementia ($p<0.001$; $d=1.8$).

The frequencies for each of the 12 individual severity and distress items for the neurocognitive disorder groups (delirium alone, comorbid delirium-dementia, dementia, and control) are shown

in tables 4 and 5. There was a significant difference overall between the four patient groups for 10 of the 12 individual distress items of the NPI-Q. All three neurocognitive groups scored more highly than controls for anxiety, while the two delirium groups (but not the dementia-only group) scored more highly than controls for agitation-aggression, irritability-lability and aberrant motor behaviour. Conversely, the dementia groups (but not delirium alone) scored more highly than controls for depression-dysphoria and sleep disturbances, while only the comorbid delirium-dementia group scored more highly than controls for apathy-indifference. Analysis of the NPI-Q subscale scores[27]showed significant differences between all three neurocognitive groups and controls and broadly replicated these findings (Table 6).

DISCUSSION

We compared the neuropsychiatric profile of elderly medical inpatients with a variety of neurocognitive presentations, including a cognitively-intact group. We used well-validated instruments for both delirium and dementia symptom severity – the DRS-R98, CTD and NPI-Q - which allow for detailed investigation of cognitive and neuropsychiatric profile in these complex syndromes. We found that patients with active delirium – both with and without comorbid dementia – could be distinguished from patients with dementia-alone in respect of a range of neuropsychiatric and cognitive disturbances identified with the DRS-R98 and CTD scales, but less so with the NPI-Q. This suggests that the NPI-Q does not readily distinguish between the neuropsychiatric disturbances of delirium and the so-called Behavioural and Psychological Symptoms of Dementia (BPSD).

We found similar cognitive and neuropsychiatric profile in patients with delirium and comorbid delirium-dementia. However, delirium (both comorbid and without dementia) was distinguished from dementia without delirium by both a variety of neuropsychiatric symptoms and in terms of cognitive performance on tests of attention and vigilance.

The findings in respect of differences in cognitive profile between delirium and dementia extends previous work using similar instrumentation conducted in palliative care, where attention distinguished both delirium and comorbid delirium-dementia from dementia alone.[12] In addition, this study of elderly medical inpatients found that performance on vigilance distinguished delirium groups from dementia. Attentional disturbances in delirium are in respect of the ability to direct, focus, sustain and shift attention. Vigilance is a term that has many possible meanings, but is most commonly equated with the ability to sustain attention to a task and thus is often referred to as 'vigilant' attention.[29]The vigilance test of the CTD used herein involves a letter recognition test and thus explores the ability to sustain attentional performance. Previous work has highlighted how attention and vigilance are closely linked,including in patients with delirium [30] where there was high correlation between DRS-R98 attention (which emphasizes the months backwards test) and CTD attention (which uses combined performance on the digit span forwards and backwards) (r = -0.73), as well as between DRS–R98 attention and CTD vigilance (r = -0.60). Similarly, Brown et al [31] compared performance among patients with delirium, dementia and unimpaired cognition on a series of tests of sustained visual attention and found that delirious patients could be distinguished

across a range of tests, while performance among the patients with dementia was relatively preserved and equivalent to the unimpaired controls. These findings highlight how efforts to improve detection of delirium (e.g. developing screening tools) can be enhanced by emphasizing sustained attention/vigilance as key elements within the cognitive domain.

Neuropsychiatric profiles

Previous comparisons of delirium versus comorbid delirium-dementia in terms of neuropsychiatric profile measured on the Delirium Symptom Interview in elderly medical inpatients,[6,32] and DRS and BPRS in geropsychiatric patients[7]has found that these conditions are phenomenologically similar. However, other studies using the Organic Brain Scale (OBS) in mixed community-dwelling and hospitalized groups [11,14] found that delirious patients with comorbid dementia have more hyperactive features, more commonly experience psychotic symptoms, have more profound communication difficulties and are more prone to symptom worsening in the evening. Margiotta et al[10] compared DRS profiles in delirious elderly medical inpatients with and without comorbid dementia. They found that comorbid cases had higher overall DRS scores, with greater perceptual disturbances, symptom fluctuation and experienced more prolonged delirium episodes. Otherwise, these groups were similar in terms of other DRS symptoms and MMSE scores. We found that delirium and comorbid-delirium dementia groups were very similar in disturbance levels for the majority of symptoms but were distinguished by severity of DRS-R98 thought process abnormalities and motor agitation.

Studies that have compared profiles in patients with dementia with and without comorbid delirium indicate considerable differences in terms of neuropsychiatric symptom burden. Landreville et al[15] studied long term care residents using the Behaviour Problem Scale and found that patients with comorbid delirium-dementia had greater sleep problems, wandering, irrational behaviour and aggression. They suggested that BPSD may be a risk factor for delirium. Holtta et al[13] used the NPI in demented patients from acute geriatric inpatient (n=195) and Nursing home settings (n=230) with and without delirium and found that the majority of patients with dementia had multiple neuropsychiatric symptoms (NPS) but, that comorbid delirium was associated with greater NPS and a poorer prognosis. In addition, one third of dementia patients with multiple NPS had comorbid delirium. Hasegawa et al[16] compared dementia to comorbid delirium-dementia in respect of NPI ratings in memory clinic attenders. They found significantly higher total NPI scoresfor comorbid delirium-dementia, with similar scores across the groups for most individual items except for greater agitation in comorbid delirium-dementia. They concluded that delirium 'exaggerates' BPSD in dementia. We found that in comparison to dementia patients without delirium, comorbid delirium-dementia patients had greater DRS-R98 sleep-wake cycle disturbances, perceptual disturbances, affective lability, and language abnormalities, as well as CTD impairment of vigilance. However, these two groups did not differ in respect of NPI-Q ratings.

Two previous studies [8,12]have compared phenomenological profile in patients with delirium, dementia, comorbid delirium-dementia and without neurocognitive disorder. Laurila et al[8] supplemented a detailed clinical assessment with the WAIS and digit span. Demented patients

with and without delirium differed in respect of multiple symptoms including attention, disorganised thinking, perceptual disturbances, sleep difficulties, psychomotor abnormalities, acuity of onset and presence of etiology - all of which were more prominent in patients with comorbid illness. Specific comparison of delirious patients with and without underlying dementia was not reported. Meagher and colleagues [12] studied palliative care patients and found that delirium and comorbid delirium-dementia groups had comparable DRS-R98 and CTD total scores, which were greater than in dementia or control groups. On the DRS-R98, inattention, disorientation andmultiple non-cognitive symptoms(sleep-wake cycle, perceptual abnormality, affective lability, thought process abnormality, motor agitation and motor retardation) were more severe in delirium groups compared with dementia-alone. In this study, we found that both delirium groups were distinguished from the dementia-only group for attention, sleep-wake cycle disturbances, perceptual disturbances, affective lability, language abnormalities and all three diagnostic items (acuity of onset, symptom fluctuation and attributable physical disorder).

Trzepacz and colleagues [33] in a comparison of delirium and dementia without delirium found greater impairment in delirium for disturbances of attention, visuospatial ability, the sleep-wake cycle, perception, thought process, affective lability, motor agitation, comprehension, and acuity of onset and fluctuation of symptoms.

Overall, these findings highlight how delirium symptoms overshadow dementia when comorbid and, along with the greater diagnostic urgency for delirium, emphasise that elderly medical

patients with neuropsychiatric symptoms should be presumed to have delirium until otherwise clarified.

Comparison of assessment tools

Although the neuropsychiatric profile of patients varied according to delirium and dementia status, these patterns differed across the assessment tools employed. The instruments that we used differ both in their content and timeframes covered – the CTD exclusively focuses on cognitive performance at the time of testing, the DRS-R98 includes cognitive and neurobehavioural elements over the previous 24 hours, while the NPI-Q focuses on neuropsychiatric disturbances over the previous month. Our findings suggest that although patients with delirium and dementia experience a similar range of neurobehavioural disturbances (e.g. over a month as measured with the NPI-Q), the relative acuity of delirium is associated with greater symptom burden in the previous twenty four hours (as captured on the DRS-R98). In addition, although the DRS-R98 and NPI-Q both assess for psychosis, sleep-wake cycle disturbance, motor behaviour and affective alterations, the emphasis for some features is different whereby NPI-Q explores specifically for apathy and sustained affective changes, while in the DRS-R98 the focus is upon lability of affective expression.

In particular, the differences between delirium groups and dementia in respect of DRS-R98 items for sleep, affective lability and perceptual disturbances were not mirrored with the NPI-Q. In addition to the contrasting time frames covered by these tools, their emphasis within these

domains is different; the DRS-R98 focuses upon alterations to the sleep-wake cycle over the previous twenty-four hours and emphasizes fragmentation and cycle reversal in severity rating. The NPI-Q emphasizes sleep at night, with the range and duration of night-time behaviours central to rating of severity. Moreover, the NPI-Q is rated by an informant rather than a psychiatrist. As such, our findings suggest that the character of sleep disturbances differs across neurocognitive disorders and that delirium is particularly characterized by altered sleep-wake cycle. This echoes previous work which has emphasised that more severe disturbances involving altered sleep-wake cycle such as fragmentation and cycle reversal are relatively specific to delirium and occur in 75% or more of patients with active delirium.[30,34,35]

Similarly, we found different patterns in respect of altered affective functioning. Classically, delirium is associated with affective lability while dementia is often complicated by more sustained disturbances of mood, apathy and indifference. We found that delirium groups had higher scores for the DRS-R98 item for affective lability, while only the dementia groups scored higher than controls for depression-dysphoria on the NPI-Q. Affective disturbances are thus common elements of both delirium and dementia, and are increasingly recognized as risk factors for both conditions.[36,37] More detailed study of affective symptoms and how they differ across neurocognitive disorders is warranted.

Study limitations

Cross-sectional studies cannot fully capture the phenomenological profile of conditions such as delirium where symptom fluctuation is prominent, though the DRS-R98 utilizes a 24-hour reporting period and the NPI-Q captures symptom profile over the previous month. Our control group derive from referrals to a psychiatry for later life service and as such are not necessarily representative of elderly medical inpatients in general. However, they do provide an appropriate comparison group who reflect the population in which accurate diagnosis of neuropsychiatric problems is most challenging. We could not specify the stage or primary cause of dementia but evidence indicates that the frequency of different neuropsychiatric disturbances varies across dementia types.[38,39] The observations regarding sleep and affective changes can be better explored with tools that have these domains as their primary focus and that explore different aspects of each in greater detail in order to ascertain the different character of disturbances across neurocognitive syndromes.

Implications

Guidance regarding differentiating symptoms between delirium and dementia is relatively lacking in the definition of delirium in DSM-5[40]or ICD-10[41], suggesting that these diagnostic systems would be advanced by criteria to guide efforts to distinguish these common conditions. This work suggests that particular neuropsychiatric symptoms and the methods by which these symptoms are assessed, including their character and timeframe are key to accurately distinguishing neurocognitive disorders. This is especially relevant in the assessment of suspected BPSD or major neurocognitive disorder with behavioural disturbance as described in

DSM-5.[40] As a general rule, neuropsychiatric disturbances captured on the DRS-R98 are relatively specific for delirium, while disturbances captured on tools such as the NPI are less discerning between these major neurocognitive disorders. Given the diagnostic urgency of delirium, our findings favour use of the DRS-R98 as the primary symptom assessment tool. Although delirium and dementia are both characterised by generalised disturbance of cognitive function, this work emphasises how delirium can be distinguished from dementia by virtue of the disproportionate impairment of attention and vigilance. These cognitive functions should be emphasised in efforts to identify delirium, including in populations where there are high rates of dementia.

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Contributorship statement

Study design was conducted by Maeve Leonard, Shane McInerney, John McFarland, Margaret O'Connor, Paul Reynolds, Anna Maria Meaney, Paula T. Trzepacz, David J. Meagher.

Data collection was conducted by Maeve Leonard, Shane McInerney, John McFarland, David J. Meagher.

Data analysis was performed by Maeve Leonard, Candice Condon, Dimitrios Adamis, Paula T. Trzepacz, David J. Meagher.

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Data Sharing Statement

We have no data to share.

Competing Interests

The authors have no competing interests to declare

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Table 1. Demographic and medication data for the four patient groups (mean ± SD)

	Delirium (n=50)	Comorbid delirium-dementia (n=62)	Dementia (n=32)	Control (n=32)
Male (%)	55	43	53	41
Age	78.9 ± 9.8	81.1 ± 7.3	80.9 ± 5.0	81.7 ± 7.5

Total number of medications	8.7 ± 3.5	8.8 ± 4.3	9.0 ± 4.5	8.5 ± 4.6
Number of Psychotropics	1.0 ± 1.1	1.4 ± 1.1	1.4± 1.2	0.8 ± 1.1
DRS-R98 total	22.0 ± 8.4†	18.9± 6.9§	14.0± 6.8*	6.1± 5.2
DRS-R98 severity	17.3 ± 7.4‡	15.1 ± 6.1§	11.8 ± 6.3*	4.7± 4.1
CTD total	14.6 ± 9.6	14.2± 7.7	18.1± 8.0*	24.6 ± 4.8
Short IQCODE	3.1 ± 0.3	4.2 ± 1.4¥	4.1 ±0.7ø	2.9 ± 0.6
NPI-Q Distress	8.4± 6.4	9.9 ± 7.2	6.7 ±6.1*	1.5 ± 2.1
NPI-Q Severity	11.9 ± 10.6	12.3 ± 10.6	10.2 ± 9.5*	1.6 ± 2.7

Note: †delirium > dementia at p<0.001.
‡delirium > dementia at p<0.005.
§comorbid delirium-dementia > dementia at p<0.05.
*all three neurocognitive groups greater than controls at p <0.001.
¥comorbid delirium-dementia> delirium and controls at p<0.001
øDementia> delirium and controls at p<0.001

Table 2.DRS-R98 item severities (mean scores ± SD) and frequencies (% scoring ≥1 and ≥2) for delirium, comorbid delirium-dementia, dementia alone, and control groups

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia	Dementia (n = 32)

			(n = 62)	
1. Sleep-wake cycle disturbance	0.5 ± 0.7 44% (9%)	2.0 ± 0.9†** 91% (73%)	1.5 ± 0.9* 79% (53%)	0.9 ± 0.8¶ 65% (22%)
2. Perceptual disturbances and hallucinations	0.2 ± 0.7 6% (6%)	1.0 ± 1.3† 41% (32%)	0.7 ± 1.1* 37% (23%)	0.2 ± 0.7¶ 14% (6%)
3. Delusions	0.1 ± 0.6 6% (3%)	0.6 ± 1.0 35% (21%)	0.4 ± 0.8 31% (10%)	0.3 ± 0.7¶ 15% (9%)
4. Lability of affect	0.2 ± 0.6 6% (3%)	1.4 ± 1.1‡ 75% (47%)	1.0 ± 0.9* 62% (33%)	0.5 ± 0.7 37% (9%)
5. Language	0.1 ± 0.4 6% (3%)	1.1 ± 1.1† 55% (39%)	0.8 ± 1.0* 43% (23%)	0.3 ± 0.7¶ 20% (10%)
6. Thought process abnormalities	0.6 ± 0.8 47% (13%)	2.5 ± 4.6*§ 88% (63%)	1.1 ± 1.1 62% (38%)	0.8 ± 0.9¶ 53% (22%)
7. Motor agitation	0.2 ± 0.5 11% (7%)	1.5 ± 1.1‡** 73% (55%)	0.9 ± 0.9 57% (25%)	0.6 ± 0.8 37% (16%)

	0.1 ± 0.4	0.6 ± 0.9	0.5 ± 0.8	0.3 ± 0.6¶
8. Motor retardation	6% (3%)	31% (20%)	37% (13%)	19% (3%)
	0.2 ± 0.4	1.2 ± 1.0	1.5 ± 0.7*	1.0 ± 0.8
9. Orientation	16% (16%)	74% (37%)	90% (52%)	70% (22%)
	0.6 ± 0.8	2.4 ± 1.4‡	2.0 ± 0.9*	1.6 ± 1.1
10. Attention	37% (15%)	98% (80%)	93% (72%)	70% (31%)
	0.9 ± 0.9	1.7 ± 1.2	2.1 ± 0.9	1.7 ± 1.0
11. Short term memory	56% (28%)	80% (60%)	97% (69%)	89% (60%)
	0.4 ± 0.6	1.4 ± 1.0	1.3 ± 0.9	1.1 ± 1.1
12. Long term memory	35% (11%)	80% (42%)	77% (42%)	59% (31%)
	0.6 ± 0.9	2.1 ± 1.1	1.8 ± 1.1	1.6 ± 1.2
13.Visuospatial ability	34% (22%)	89% (70%)	85% (60%)	73% (60%)
	0.4 ± 0.6	2.0 ± 0.6‡§	1.6 ± 0.9‡	0.6 ± 0.7
14. Temporal onset of symptoms	17% (13%)	100% (78%)	89% (54%)	41% (13%)
	0.2 ± 0.5	1.2 ± 0.6‡**	0.7 ± 0.7†	0.3 ± 0.4¶
15. Fluctuation in symptom severity	11% (6%)	91% (26%)	59% (11%)	27% (27%)

16. Physical disorder	0.8 ± 0.6 72% (10%)	1.9 ± 0.4‡ 98% (92%)	1.8 ± 0.4‡ 98% (84%)	1.2 ± 0.7 83% (33%)

* more impaired than dementia at p ≤ 0.05

† more impaired than dementia at p <0.01

‡ more impaired than dementia at p <0.001

** more impaired than delirium-dementia at p < 0.01

§ more impaired than delirium-dementia at p ≤ 0.05

¶ no difference between dementia and controls

Table 3. Cognitive Test for Delirium (CTD) section scores for neurocognitive disorder groups, delirium, comorbid delirium-dementia, dementia alone, and control. Controls performed in the normal range for each item.

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)

1. Orientation	5.8 ± 0.6	3.7 ± 2.4	3.2 ± 2.1	4.3 ± 2.1
2. Attention	4.7 ± 1.7	2.1 ± 2.1†*	3.1 ± 2.1	3.8 ± 2.1
3. Memory	5.2 ± 1.1	2.9 ± 2.3	2.3 ± 2.3†	3.6 ± 2.0
4. Comprehension	5.7 ± 0.5	3.8 ± 2.1*	4.1 ± 1.8	4.7 ± 1.7
5. Vigilance	4.3 ± 1.9	1.6 ± 2.2	1.4 ± 2.0*	2.5 ± 2.3

* more impaired than dementia at p ≤ 0.05

† more impaired than dementia at p < .01

‡ more impaired than dementia at p < .001

** more impaired than delirium-dementia at p < .01

§ more impaired than delirium-dementia at p ≤ 0.05

¶ no difference between dementia and controls

Table 4. Frequencies (%) for the 12 individual *severity* items of the Neuropsychiatric Inventory (NPI)fordelirium, comorbid delirium-dementia, dementia alone, and control groups.

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)	*p*
1. Delusions	1 (3%)	12 (24%)	17 (27%)	5 (15%)	≤.05

2. Hallucinations	0 (0%)	14 (28%)	21 (34%)	5 (15%)	<.01
3. Agitation / Aggression	1 (3%)	23 (46%)	35 (56%)	12 (38%)	<.001
4. Depression / Dysphoria	5 (16%)	14 (28%)	30 (48%)	14 (44%)	≤.05
5. Anxiety	6 (19%)	21 (42%)	31 (50%)	16 (50%)	≤.05
6. Elation / Euphoria	0 (0%)	1 (2%)	7 (11%)	2 (6%)	NS
7. Apathy / Indifference	2 (6%)	15 (30%)	30 (48%)	9 (28%)	<.001
8. Disinhibition	2 (6%)	8 (16%)	18 (29%)	1 (3%)	<.01
9. Irritability / Lability	4 (13%)	23 (46%)	36 (58%)	11 (34%)	<.001
10. Aberrant Motor Behaviour	2 (7%)	19 (38%)	25 (40%)	9 (28%)	<.01
11. Sleep and Nighttime Disturbances	3 (9%)	13 (26%)	32 (52%)	12 37%)	<.001
12. Appetite / Eating Disturbances	7 (22%)	16 (32%)	29 (47%)	10 (31%)	NS

Table 5.Frequencies (%) for the 12 individual *distress* items of the Neuropsychiatric Inventory (NPI) fordelirium, comorbid delirium-dementia, dementia alone, and control groups.

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)	*p*

1. Delusions	1 (3%)	12 (24%)	17 (27%)	5 (16%)	≤.05
2. Hallucinations	0 (0%)	15 (30%)	19 (31%)	4 (13%)	<.001
3. Agitation / Aggression	1 (3%)	23 (46%)	33 (53%)	12 (38%)	<.001
4. Depression / Dysphoria	3 (9%)	15 (30%)	28 (45%)	14 (44%)	<.01
5. Anxiety	5 (16%)	20 (40%)	28 (45%)	15 (47%)	≤.05
6. Elation / Euphoria	0 (0%)	1 (2%)	6 (10%)	2 (6%)	NS
7. Apathy / Indifference	2 (6%)	12 (24%)	27 (44%)	9 (28%)	<.01
8. Disinhibition	1 (3%)	8 (16%)	15 (24%)	1 (3%)	≤.05
9. Irritability / Lability	3 (9%)	21 (42%)	33 (53%)	11 (34%)	<.001
10. Aberrant Motor Behaviour	2 (6%)	19 (38%)	20 (32%)	9 (28%)	<.01
11. Sleep and Nighttime Disturbances	3 (9%)	13 (26%)	31 (50%)	12 (38%)	<.01
12. Appetite / Eating Disturbances	5 (16%)	16 (32%)	23 (37%)	9 (28%)	NS

Table 6.Comparison of NPI-Q subscale scores for delirium, comorbid delirium-dementia, dementia alone, and control groups

	Controls	**Delirium**	**Comorbid delirium-dementia**	***Dementia***
NPIQ4-Agitation Aggression	0.3± 0.6**	1.8±1.2	1.9 ± 1.4	1.2 ± 1.1*

NPIQ3-Mood	0.7 ±1.0ǂ	2.6 ± 2.1	3.0 ± 2.4	2.7 ± 2.2
NPIQ4-Frontal	0.4 ± 0.8†	2.3 ± 2.3	2.9 ± 2.5	1.6 ±2.2
NPIQ- Psychosis	0.0± 0.2	1.4 ± 1.7	1.5 ± 2.5	1.4 ±4.1

*Dementia < Comorbid delirium dementia <0.05;
**Controls< comorbid delirium and dementia; and delirium ≤ 0.05
ǂControls < all other neurocognitive groups ≤0.002
† Controls < Comorbid delirium and dementia; and delirium ≤0.005

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A Comparison of Cognitive and Neuropsychiatric Profiles in hospitalised elderly medical patients with Delirium, Dementia and Comorbid Delirium-Dementia

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ABSTRACT

Objectives: Differentiation of delirium and dementia is a key diagnostic challenge but there has been limited study of features that distinguish these conditions. We examined neuropsychiatric and neuropsychological symptoms in elderly medical inpatients to identify features that distinguish major neurocognitive disorders.

Setting: University teaching hospital in Ireland

Participants and measures: 176 Consecutive elderly medical inpatients [mean age 80.6 ± 7.0 (range 60-96); 85 males (48%)] referred to a psychiatry for later life consultation-liaison service with DSM-IV delirium, dementia, comorbid delirium-dementia, and cognitively intact controls. Subjects were assessed cross-sectionally with comparison of scores (including individual items) for the Revised Delirium Rating Scale (DRS-R98), Cognitive Test for Delirium (CTD) and Neuropsychiatric Inventory (NPI-Q).

Results: The frequency of neurocognitive diagnoses was delirium (n=50), dementia (n=32), comorbid delirium-dementia (n=62) and cognitively intact (n=32). Both delirium and comorbid delirium-dementia groups scored higher than the dementia group forDRS-R98 and CTD total scores, but all three neurocognitively impaired groups scored similarly in respect of total NPI-Q scores. For individual DRS-R98 items, delirium groups were distinguished from dementia by a range of non-cognitive symptoms, but only for impaired attention of the cognitive items. For the CTD, attention (p=0.002) and vigilance (p=0.01) distinguished delirium from dementia. No individual CTD item distinguished comorbid delirium-dementia from delirium. For the NPI-Q, there were no differences between the three neurocognitively impaired groups for any individual item severity.

Conclusions: The Neurocognitive profile of delirium is similar with or without comorbid dementia and differs from dementia without delirium. Simple tests of attention and vigilance can help to distinguish delirium from other presentations. The NPI-Q does not readily distinguish between neuropsychiatric disturbances in delirium versus dementia. Cases of suspected behavioural and psychological symptoms of dementia should be carefully assessed for possible delirium.

Article summary: strengths and Limitations of this study

● This study includes a detailed cross-sectional assessment comparing the phenomenological profile of common neurocognitive disorders in elderly medical patients within a general hospital setting

●The findings highlight that delirium and dementia are characterised by different neuropsychiatric and cognitive disturbances

● Performance on simple bedside tests of attention and vigilance is disproportionately impaired in patients with delirium compared to dementia and thus have distinguishing capacity

●The Neuropsychiatric Inventory (NPI) lacks specificity for the neuropsychiatric disturbances of dementia over delirium

●Further study should examine how these patterns are reflected for different dementia subtypes

Introduction

Delirium and dementia are major neurocognitive disorders that are both common and commonly misdiagnosed in hospitalized elderly. [1, 2] Improved management of these under-recognized neuropsychiatric presentations is a key target within healthcare services. Accurate and timely recognition of these disorders is important because delirium is linked to a variety of adverse outcomes and is frequently the principal presenting feature of urgent physical illness. Gonzalez et al, [3] for example, found that mortality was increased by 11% for each additional 48 hours of active delirium. Bellelli et al [4] found that patients with delirium superimposed upon dementia experience a two-fold risk of death within one year, emphasizing the need for clear delineation of this presentation. However, distinction is complicated by the considerable phenomenological overlap between these conditions and high comorbidity where the prevalence of delirium superimposed upon dementia in community and hospital settings ranges from 22-89%.[5]

Our understanding of the comparative phenomenological profile of major neurocognitive disorders is based upon studies conducted in a variety of populations.[6-16] These studies have applied different methods to the assessment of neuropsychiatric profile but have focused upon characterizing the neuropsychiatric features of comorbid illness rather than identifying distinguishing features of delirium versus dementia. Moreover, they have included limited account of the range of neuropsychological impairments that occur in these conditions.

We studied the cognitive and neuropsychiatric profiles of consecutive referrals of elderly medical inpatients toa psychiatry for later life consultation-liaison service. In particular, we aimed to address: (i) how does neuropsychiatric and cognitive profile in comorbid delirium-dementia compare to that of either disorder alone when analysed in conjunction with cognitively-intact control patients from the same setting, and (ii) which features best differentiate delirium and dementia, including comorbid cases.

METHODS

Subjects and Design

We conducted a cross-sectional study of neuropsychiatric symptoms and cognitive performance in consecutive referrals to a psychiatry for later life consultation-liaison service at University Hospital Limerick, a 400-bedded tertiary care centre in the Midwestern region of Ireland. Between October 2011 and July 2012 cases with altered mental state suggestive of neurocognitive disorder were identified on daily rounds by the medical team and referred for assessment and diagnosis by the research team. All patients were ≥60 years old. Patients were assessed and classified with delirium, dementia, comorbid delirium-dementia, or cognitively normal.

Assessments were conducted by raters (DM, ML, JMcF, SMcI) specifically trained in the use of the tools included herein (see below) and to further enhance inter-rater reliability, ratings associated with any uncertainty were discussed and agreed by consensus between raters.

Delirium was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria[17] based upon a full clinical assessment at the time of consultation and independent of the DRS-R98, CTD and NPI assessments. Dementia was defined as a clear history of documented DSM-IV dementia (based on all available information at the time of assessment including clinical case notes and collateral history from family and / or carers) *or*a short Informant Questionnaire on Cognitive Decline in the elderly (IQCODE) score of ≥ 3.5.[18-20] Comorbid delirium-dementia was defined as the presence of both disorders. Patients with normal cognition and no prior history of cognitive problems were also recruited for assessment.

Each case was then assessed by first completing the DRS-R98 followed by administration of the CTD. The DRS-R98 rated the preceding 24 hour period whereas the CTD measured cognition at the time of its administration. CTD responses were not used to rate DRS-R98 items. The NPI-Q and IQ-CODE were completed on the same day and after consultation with family and / or carers who were familiar with the day to day functioning of the patient over the recent past.

Informed Consent

The procedures and rationale for the study were explained to all patients but because many patients had cognitive impairment at entry into the study it was presumed that many might not be capable of giving informed written consent. Because of the non-invasive nature of the study, University Hospital Limerick Regional Ethics Committee approved an approach to establishing

consent by virtue of augmenting patient assent with proxy consent from next of kin (where possible) or a responsible caregiver for all participants in accordance with the Helsinki Guidelines for Medical research involving human subjects.[21]

Assessments

Demographic data and medication at the time of the assessment were recorded. All available information from medical records and collateral history was used. Nursing staff were interviewed to assist rating of symptoms over the previous 24 hours.

The Delirium Rating Scale-Revised-98 [DRS-R98][22] is designed for broad phenomenological assessment of delirium. It is a 16-item scale with 13 severity and 3 diagnostic items with high interrater reliability, sensitivity and specificity for detecting delirium in mixed neuropsychiatric and other hospital populations. Each item is rated 0 (absent/normal) to 3 (severe impairment) with descriptions anchoring each severity level. Severity scale scores range from 0-39 with higher scores indicating more severe delirium. Delirium typically involves scores above 15 points (Severity scale) or 18 points (Total scale) when dementia is in the differential diagnosis. For determination of item frequencies in this study, any item score $\geq$ 1 was considered as being "present".

The Cognitive Test for Delirium [CTD][23] was specifically designed to assess hospitalized patients with delirium, in particular those who are intubated or unable to speak or write. It assesses five

neuropsychological domains (orientation, attention, memory, comprehension, and vigilance) emphasizing nonverbal (visual and auditory) modalities. Each individual domain is scored from 0-6 in 2 point increments, except for comprehension (single point increments). Total scores range between 0-30 with higher scores indicating better cognitive function and scores of less than 19 consistent with delirium. It reliably differentiates delirium from other neuropsychiatric conditions including dementia, schizophrenia and depression.[23]

The Neuropsychiatric Inventory (NPI) [24,25]was developed for assessing neuropsychiatric symptoms in patients with Alzheimer's disease and other neurodegenerative disorders. Studies of cognitively intact older adults indicate extremely low scores suggesting that the NPI is relatively specific for dementia-related neuropsychiatric pathology.The NPI-Q is a short questionnaire version of the NPI[25]intended for use in everyday clinical practice. Neuropsychiatric symptom severity is assessed in the same way as the original NPI. The NPI-Q includes ten behavioural and two neurovegetative items that are assessed by an informed caregiver who is knowledgeable about the patient's daytime and night-time behaviours. Symptoms are rated over the past four weeks. Each of the 12 symptom domains is assessed by a screening question derived from the NPI-Q that covers symptom manifestations with anchor points for symptom severity rated on a three point scale and caregiver distress ratings rated on a five point scale. The questionnaire includes written instructions and the total NPI-Q severity score represents the sum of individual symptom scores and ranges from 0 to 36. [26] The NPI can be further divided into four subscales – Agitation/aggression, frontal, mood and psychosis. [27]

The Informant Questionnaire on Cognitive Decline in the Elderly-Short Form (IQCODE-SF) is a validated screening tool for detecting cognitive impairment.[19] The short version of the IQCODE includes 16 items that rate cognitive change over time, each of which are rated by an informant on a 5 point likert scale. The short-IQCODE takes approximately 10 minutes to administer. The total score divided by the number of questions provides a mean item score where ratings ≥ 3.5 are considered indicative of longstanding cognitive difficulties and dementia.

The Delirium Etiology Checklist (DEC)[28] was used to document etiological underpinnings of delirium. This standardised checklist captures delirium etiology according to twelve categories. The presence and suspected role of multiple potential causes were documented for each case of delirium, rated on a 5-point scale for degree of attribution to the delirium episode, ranging from 'ruled out/not present/not relevant' (0) to 'definite cause' (4).

Statistical Analyses

Statistical analysis was conducted using SPSS-19. Demographic and rating scale data are expressed as means plus standard deviation. Continuous variables (e.g. age, total DRS-R98 and CTD scores) were compared by one way ANOVA with independent t-tests used for post hoc comparisons. Although data regarding scores for individual items on the DRS-R98 and CTD are shown as means and standard deviations, these data are not normally distributed and as such statistical comparisons relate to non-parametric tests (e.g. Mann-Whitney U tests for between

group comparisons). Cohen's d was used to estimate the effect size for key differences (e.g. differences in CTD item scores).

RESULTS

A total of 176 patients [mean age 80.6 ± 7.0 (range 60-96); 85 males (48%)] were assessed of whom 50 had delirium without dementia, 62 had both delirium and dementia, 32 had dementia without delirium, and 32 were deemed cognitively intact. Demographic, medication and general clinical data for patients from these four groups are shown in Table 1. There were no statistically significant differences between the four groups in respect of age, gender distribution, number of medications received or use of psychotropic medications.

The principal underlying etiologies for delirium (n=112) as captured on the DEC were systemic infection (66), CNS infection (4), metabolic/ endocrine disturbance (39), drug intoxication (5), drug withdrawal (6) cerebrovascular (28), organ insufficiency (22), seizure-related (12), neoplasm (9), traumatic brain injury. (2)

Table 1 compares mean scores for the four groups for the DRS-R98 total and severity scales, CTD, IQ-CODE and NPI-Q. Both delirium groups were more impaired than the dementia group on total scores for the DRS-R98 and CTD. All three neurocognitively impaired groups scored similarly in respect of total NPI-Q scores. The mean short IQCODE scores distinguished the groups, with both

dementia groups scoring well in excess of the suggested cut-off score and significantly higher than both the delirium without dementia and control groups.[19]

Means and standard deviations for each individual item (1-16) on the DRS-R98 are described in Table 2. The three groups with cognitive impairment differed from cognitively intact controls across the majority of items, including both cognitive and non-cognitive symptoms. Delirium diagnostic items (symptom fluctuation, acute onset, and attributable physical disorder) significantly distinguished delirium groups from the other groups. In addition, both delirium groups were distinguished from the dementia-only group for sleep-wake cycle disturbances, perceptual disturbances, affective lability, and language abnormalities. Of note, the delirium and dementia alone groups were not distinguished by cognitive items (including either measures of memory) apart from impaired attention which was more severe in both delirium groups. Both delirium groups were very similar in disturbance levels for the majority of items but were distinguished by severity of sleep-wake cycle disturbance, thought process abnormalities and motor agitation.

Table 3 shows the comparison of individual CTD item scores between the four groups. There was a statistically significant difference overall between the four neurocognitive groups for each of the five individual sections ($p<0.001$). No item distinguished comorbid delirium-dementia from delirium. Both attention ($p=0.002$; $d=0.81$and vigilance ($p=0.01$; $d=0.4$) distinguished delirium from dementia, while only vigilance significantly distinguished delirium-dementia from dementia ($p<0.001$; $d=1.8$).

The frequencies for each of the 12 individual severity and distress items for the neurocognitive disorder groups (delirium alone, comorbid delirium-dementia, dementia, and control) are shown in tables 4 and 5. There was a significant difference overall between the four patient groups for 10 of the 12 individual distress items of the NPI-Q. All three neurocognitive groups scored more highly than controls for anxiety, while the two delirium groups (but not the dementia-only group) scored more highly than controls for agitation-aggression, irritability-lability and aberrant motor behaviour. Conversely, the dementia groups (but not delirium alone) scored more highly than controls for depression-dysphoria and sleep disturbances, while only the comorbid delirium-dementia group scored more highly than controls for apathy-indifference. Analysis of the NPI-Q subscale scores[27]showed significant differences between all three neurocognitive groups and controls and broadly replicated these findings (Table 6).

DISCUSSION

We compared the neuropsychiatric profile of elderly medical inpatients with a variety of neurocognitive presentations, including a cognitively-intact group. We used well-validated instruments for both delirium and dementia symptom severity – the DRS-R98, CTD and NPI-Q - which allow for detailed investigation of cognitive and neuropsychiatric profile in these complex syndromes. We found that patients with active delirium – both with and without comorbid dementia – could be distinguished from patients with dementia-alone in respect of a range of neuropsychiatric and cognitive disturbances identified with the DRS-R98 and CTD scales, but

less so with the NPI-Q. This suggests that the NPI-Q does not readily distinguish between the neuropsychiatric disturbances of delirium and the so-called Behavioural and Psychological Symptoms of Dementia (BPSD).

We found similar cognitive and neuropsychiatric profile in patients with delirium and comorbid delirium-dementia. However, delirium (both comorbid and without dementia) was distinguished from dementia without delirium by both a variety of neuropsychiatric symptoms and in terms of cognitive performance on tests of attention and vigilance.

The findings in respect of differences in cognitive profile between delirium and dementia extends previous work using similar instrumentation conducted in palliative care, where attention distinguished both delirium and comorbid delirium-dementia from dementia alone.[12] In addition, this study of elderly medical inpatients found that performance on vigilance distinguished delirium groups from dementia. Attentional disturbances in delirium are in respect of the ability to direct, focus, sustain and shift attention. Vigilance is a term that has many possible meanings, but is most commonly equated with the ability to sustain attention to a task and thus is often referred to as 'vigilant' attention.[29]The vigilance test of the CTD used herein involves a letter recognition test and thus explores the ability to sustain attentional performance. Previous work has highlighted how attention and vigilance are closely linked,including in patients with delirium [30] where there was high correlation between DRS-R98 attention (which emphasizes the months backwards test) and CTD attention (which uses combined performance on the digit span forwards and backwards) (r = -0.73), as well as

between DRS–R98 attention and CTD vigilance (r = -0.60). Similarly, Brown et al [31] compared performance among patients with delirium, dementia and unimpaired cognition on a series of tests of sustained visual attention and found that delirious patients could be distinguished across a range of tests, while performance among the patients with dementia was relatively preserved and equivalent to the unimpaired controls. These findings highlight how efforts to improve detection of delirium (e.g. developing screening tools) can be enhanced by emphasizing sustained attention/vigilance as key elements within the cognitive domain.

Neuropsychiatric profiles

Previous comparisons of delirium versus comorbid delirium-dementia in terms of neuropsychiatric profile measured on the Delirium Symptom Interview in elderly medical inpatients,[6,32] and DRS and BPRS in geropsychiatric patients[7]has found that these conditions are phenomenologically similar. However, other studies using the Organic Brain Scale (OBS) in mixed community-dwelling and hospitalized groups [11,14] found that delirious patients with comorbid dementia have more hyperactive features, more commonly experience psychotic symptoms, have more profound communication difficulties and are more prone to symptom worsening in the evening. Margiotta et al[10] compared DRS profiles in delirious elderly medical inpatients with and without comorbid dementia. They found that comorbid cases had higher overall DRS scores, with greater perceptual disturbances, symptom fluctuation and experienced more prolonged delirium episodes. Otherwise, these groups were similar in terms of other DRS symptoms and MMSE scores. We found that delirium and comorbid-delirium dementia groups

were very similar in disturbance levels for the majority of symptoms but were distinguished by severity of DRS-R98 thought process abnormalities and motor agitation.

Studies that have compared profiles in patients with dementia with and without comorbid delirium indicate considerable differences in terms of neuropsychiatric symptom burden. Landreville et al[15] studied long term care residents using the Behaviour Problem Scale and found that patients with comorbid delirium-dementia had greater sleep problems, wandering, irrational behaviour and aggression. They suggested that BPSD may be a risk factor for delirium. Holtta et al[13] used the NPI in demented patients from acute geriatric inpatient (n=195) and Nursing home settings (n=230) with and without delirium and found that the majority of patients with dementia had multiple neuropsychiatric symptoms (NPS) but, that comorbid delirium was associated with greater NPS and a poorer prognosis. In addition, one third of dementia patients with multiple NPS had comorbid delirium. Hasegawa et al[16] compared dementia to comorbid delirium-dementia in respect of NPI ratings in memory clinic attenders. They found significantly higher total NPI scoresfor comorbid delirium-dementia, with similar scores across the groups for most individual items except for greater agitation in comorbid delirium-dementia. They concluded that delirium 'exaggerates' BPSD in dementia. We found that in comparison to dementia patients without delirium, comorbid delirium-dementia patients had greater DRS-R98 sleep-wake cycle disturbances, perceptual disturbances, affective lability, and language abnormalities, as well as CTD impairment of vigilance. However, these two groups did not differ in respect of NPI-Q ratings.

Two previous studies [8,12]have compared phenomenological profile in patients with delirium, dementia, comorbid delirium-dementia and without neurocognitive disorder. Laurila et al[8] supplemented a detailed clinical assessment with the WAIS and digit span. Demented patients with and without delirium differed in respect of multiple symptoms including attention, disorganised thinking, perceptual disturbances, sleep difficulties, psychomotor abnormalities, acuity of onset and presence of etiology - all of which were more prominent in patients with comorbid illness. Specific comparison of delirious patients with and without underlying dementia was not reported. Meagher and colleagues [12] studied palliative care patients and found that delirium and comorbid delirium-dementia groups had comparable DRS-R98 and CTD total scores, which were greater than in dementia or control groups. On the DRS-R98, inattention, disorientation andmultiple non-cognitive symptoms(sleep-wake cycle, perceptual abnormality, affective lability, thought process abnormality, motor agitation and motor retardation) were more severe in delirium groups compared with dementia-alone. In this study, we found that both delirium groups were distinguished from the dementia-only group for attention, sleep-wake cycle disturbances, perceptual disturbances, affective lability, language abnormalities and all three diagnostic items (acuity of onset, symptom fluctuation and attributable physical disorder).

Trzepacz and colleagues [33] in a comparison of delirium and dementia without delirium found greater impairment in delirium for disturbances of attention, visuospatial ability, the sleep-wake cycle, perception, thought process, affective lability, motor agitation, comprehension, and acuity of onset and fluctuation of symptoms.

Overall, these findings highlight how delirium symptoms overshadow dementia when comorbid and, along with the greater diagnostic urgency for delirium, emphasise that elderly medical patients with neuropsychiatric symptoms should be presumed to have delirium until otherwise clarified.

Comparison of assessment tools

Although the neuropsychiatric profile of patients varied according to delirium and dementia status, these patterns differed across the assessment tools employed. The instruments that we used differ both in their content and timeframes covered – the CTD exclusively focuses on cognitive performance at the time of testing, the DRS-R98 includes cognitive and neurobehavioural elements over the previous 24 hours, while the NPI-Q focuses on neuropsychiatric disturbances over the previous month. Our findings suggest that although patients with delirium and dementia experience a similar range of neurobehavioural disturbances (e.g. over a month as measured with the NPI-Q), the relative acuity of delirium is associated with greater symptom burden in the previous twenty four hours (as captured on the DRS-R98). In addition, although the DRS-R98 and NPI-Q both assess for psychosis, sleep-wake cycle disturbance, motor behaviour and affective alterations, the emphasis for some features is different whereby NPI-Q explores specifically for apathy and sustained affective changes, while in the DRS-R98 the focus is upon lability of affective expression.

In particular, the differences between delirium groups and dementia in respect of DRS-R98 items for sleep, affective lability and perceptual disturbances were not mirrored with the NPI-Q. In addition to the contrasting time frames covered by these tools, their emphasis within these domains is different; the DRS-R98 focuses upon alterations to the sleep-wake cycle over the previous twenty-four hours and emphasizes fragmentation and cycle reversal in severity rating. The NPI-Q emphasizes sleep at night, with the range and duration of night-time behaviours central to rating of severity. Moreover, the NPI-Q is rated by an informant rather than a psychiatrist. As such, our findings suggest that the character of sleep disturbances differs across neurocognitive disorders and that delirium is particularly characterized by altered sleep-wake cycle. This echoes previous work which has emphasised that more severe disturbances involving altered sleep-wake cycle such as fragmentation and cycle reversal are relatively specific to delirium and occur in 75% or more of patients with active delirium.[30,34,35]

Similarly, we found different patterns in respect of altered affective functioning. Classically, delirium is associated with affective lability while dementia is often complicated by more sustained disturbances of mood, apathy and indifference. We found that delirium groups had higher scores for the DRS-R98 item for affective lability, while only the dementia groups scored higher than controls for depression-dysphoria on the NPI-Q. Affective disturbances are thus common elements of both delirium and dementia, and are increasingly recognized as risk factors for both conditions.[36,37] More detailed study of affective symptoms and how they differ across neurocognitive disorders is warranted.

Study limitations

Cross-sectional studies cannot fully capture the phenomenological profile of conditions such as delirium where symptom fluctuation is prominent, though the DRS-R98 utilizes a 24-hour reporting period and the NPI-Q captures symptom profile over the previous month. Our control group derives from referrals to a psychiatry for later life service and as such are not necessarily representative of elderly medical inpatients in general. However, they do provide an appropriate comparison group who reflect the population in which accurate diagnosis of neuropsychiatric problems is most challenging. We could not specify the stage or primary cause of dementia but evidence indicates that the frequency of different neuropsychiatric disturbances varies across dementia types.[38,39] The observations regarding sleep and affective changes can be better explored with tools that have these domains as their primary focus and that explore different aspects of each in greater detail in order to ascertain the different character of disturbances across neurocognitive syndromes. Finally, the syndromal concept of delirium remains primarily defined by phenomenological elements rather than by particular pathophysiological disturbances which could define a disease state. The gathering evidence for biomarkers of delirium can be integrated with our knowledge from phenomenological studies to add further precision to the concept of delirium.[40]

Implications

Guidance regarding differentiating symptoms between delirium and dementia is relatively lacking in the definition of delirium in DSM-5[41]or ICD-10[42], suggesting that these diagnostic systems would be advanced by criteria to guide efforts to distinguish these common conditions. This work suggests that particular neuropsychiatric symptoms and the methods by which these symptoms are assessed, including their character and timeframe are key to accurately distinguishing neurocognitive disorders. This is especially relevant in the assessment of suspected BPSD or major neurocognitive disorder with behavioural disturbance as described in DSM-5.[40] As a general rule, neuropsychiatric disturbances captured on the DRS-R98 are relatively specific for delirium, while disturbances captured on tools such as the NPI are less discerning between these major neurocognitive disorders. Given the diagnostic urgency of delirium, our findings favour use of the DRS-R98 as the primary symptom assessment tool. Although delirium and dementia are both characterised by generalised disturbance of cognitive function, this work emphasises how delirium can be distinguished from dementia by virtue of the disproportionate impairment of attention and vigilance. These cognitive functions should be emphasised in efforts to identify delirium, including in populations where there are high rates of dementia.

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Contributorship statement

Study design was conducted by Maeve Leonard, Shane McInerney, John McFarland, Margaret O'Connor, Paul Reynolds, Anna Maria Meaney, Paula T. Trzepacz, David J. Meagher.

Data collection was conducted by Maeve Leonard, Shane McInerney, John McFarland, David J. Meagher.

Data analysis was performed by Maeve Leonard, Candice Condon, Dimitrios Adamis, Paula T. Trzepacz, David J. Meagher.

Manuscript preparation was performed by Maeve Leonard, Shane McInerney, John McFarland, Candice Condon, Fahad Awan, Margaret O'Connor, Paul Reynolds, Anna Maria Meaney, DimitriosAdamis, Colum Dunne, Walter Cullen, Paula T. Trzepacz, David J. Meagher.

Data Sharing Statement

No additional data available.

Competing Interests

The authors have no competing interests to declare

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Table 1. Demographic and medication data for the four patient groups (mean ± SD)

	Delirium (n=50)	Comorbid delirium-dementia (n=62)	Dementia (n=32)	Control (n=32)
Male (%)	55	43	53	41
Age	78.9 ± 9.8	81.1 ± 7.3	80.9 ± 5.0	81.7 ± 7.5
Total number of medications	8.7 ± 3.5	8.8 ± 4.3	9.0 ± 4.5	8.5 ± 4.6
Number of Psychotropics	1.0 ± 1.1	1.4 ± 1.1	1.4± 1.2	0.8 ± 1.1
DRS-R98 total	22.0 ± 8.4†	18.9± 6.9§	14.0± 6.8*	6.1± 5.2
DRS-R98 severity	17.3 ± 7.4‡	15.1 ± 6.1§	11.8 ± 6.3*	4.7± 4.1
CTD total	14.6 ± 9.6	14.2± 7.7	18.1± 8.0*	24.6 ± 4.8
Short IQCODE	3.1 ± 0.3	4.2 ± 1.4¥	4.1 ±0.7ø	2.9 ± 0.6
NPI-Q Distress	8.4± 6.4	9.9 ± 7.2	6.7 ±6.1*	1.5 ± 2.1

NPI-Q Severity	11.9 ± 10.6	12.3 ± 10.6	10.2 ± 9.5*	1.6 ± 2.7

Note: †delirium > dementia at p<0.001.
‡delirium > dementia at p<0.005.
§comorbid delirium-dementia > dementia at p<0.05.
*all three neurocognitive groups greater than controls at p <0.001.
¥comorbid delirium-dementia> delirium and controls at p<0.001
ødementia> delirium and controls at p<0.001

Table 2.DRS-R98 item severities (mean scores ± SD) and frequencies (% scoring ≥1 and ≥2) for delirium, comorbid delirium-dementia, dementia alone, and control groups

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)
1. Sleep-wake cycle disturbance	0.5 ± 0.7 44% (9%)	2.0 ± 0.9†** 91% (73%)	1.5 ± 0.9* 79% (53%)	0.9 ± 0.8¶ 65% (22%)
2. Perceptual disturbances and hallucinations	0.2 ± 0.7 6% (6%)	1.0 ± 1.3† 41% (32%)	0.7 ± 1.1* 37% (23%)	0.2 ± 0.7¶ 14% (6%)
3. Delusions	0.1 ± 0.6	0.6 ± 1.0 35% (21%)	0.4 ± 0.8 31% (10%)	0.3 ± 0.7¶ 15% (9%)

	6% (3%)			
4. Lability of affect	0.2 ± 0.6 6% (3%)	1.4 ± 1.1‡ 75% (47%)	1.0 ± 0.9* 62% (33%)	0.5 ± 0.7 37% (9%)
5. Language	0.1 ± 0.4 6% (3%)	1.1 ± 1.1† 55% (39%)	0.8 ± 1.0* 43% (23%)	0.3 ± 0.7¶ 20% (10%)
6. Thought process abnormalities	0.6 ± 0.8 47% (13%)	2.5 ± 4.6*§ 88% (63%)	1.1 ± 1.1 62% (38%)	0.8 ± 0.9¶ 53% (22%)
7. Motor agitation	0.2 ± 0.5 11% (7%)	1.5 ± 1.1‡** 73% (55%)	0.9 ± 0.9 57% (25%)	0.6 ± 0.8 37% (16%)
8. Motor retardation	0.1 ± 0.4 6% (3%)	0.6 ± 0.9 31% (20%)	0.5 ± 0.8 37% (13%)	0.3 ± 0.6¶ 19% (3%)
9. Orientation	0.2 ± 0.4 16% (16%)	1.2 ± 1.0 74% (37%)	1.5 ± 0.7* 90% (52%)	1.0 ± 0.8 70% (22%)
10. Attention	0.6 ± 0.8	2.4 ± 1.4‡ 98% (80%)	2.0 ± 0.9* 93% (72%)	1.6 ± 1.1

	37% (15%)			70% (31%)
11. Short term memory	0.9 ± 0.9 56% (28%)	1.7 ± 1.2 80% (60%)	2.1 ± 0.9 97% (69%)	1.7 ± 1.0 89% (60%)
12. Long term memory	0.4 ± 0.6 35% (11%)	1.4 ± 1.0 80% (42%)	1.3 ± 0.9 77% (42%)	1.1 ± 1.1 59% (31%)
13.Visuospatial ability	0.6 ± 0.9 34% (22%)	2.1 ± 1.1 89% (70%)	1.8 ± 1.1 85% (60%)	1.6 ± 1.2 73% (60%)
14. Temporal onset of symptoms	0.4 ± 0.6 17% (13%)	2.0 ± 0.6‡§ 100% (78%)	1.6 ± 0.9‡ 89% (54%)	0.6 ± 0.7 41% (13%)
15. Fluctuation in symptom severity	0.2 ± 0.5 11% (6%)	1.2 ± 0.6‡** 91% (26%)	0.7 ± 0.7† 59% (11%)	0.3 ± 0.4¶ 27% (27%)
16. Physical disorder	0.8 ± 0.6 72% (10%)	1.9 ± 0.4‡ 98% (92%)	1.8 ± 0.4‡ 98% (84%)	1.2 ± 0.7 83% (33%)

* more impaired than dementia at p ≤ 0.05

† more impaired than dementia at p <0.01

‡ more impaired than dementia at p <0.001

** more impaired than delirium-dementia at p < 0.01

§ more impaired than delirium-dementia at p ≤ 0.05

¶ no difference between dementia and controls

Table 3. Cognitive Test for Delirium (CTD) section scores for neurocognitive disorder groups, delirium, comorbid delirium-dementia, dementia alone, and control. Controls performed in the normal range for each item.

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)
1. Orientation	5.8 ± 0.6	3.7 ± 2.4	3.2 ± 2.1	4.3 ± 2.1
2. Attention	4.7 ± 1.7	2.1 ± 2.1†*	3.1 ± 2.1	3.8 ± 2.1
3. Memory	5.2 ± 1.1	2.9 ± 2.3	2.3 ± 2.3†	3.6 ± 2.0
4. Comprehension	5.7 ± 0.5	3.8 ± 2.1*	4.1 ± 1.8	4.7 ± 1.7
5. Vigilance	4.3 ± 1.9	1.6 ± 2.2	1.4 ± 2.0*	2.5 ± 2.3

* more impaired than dementia at $p \leq 0.05$

† more impaired than dementia at $p < .01$

‡ more impaired than dementia at $p < .001$

** more impaired than delirium-dementia at $p < .01$

§ more impaired than delirium-dementia at $p \leq 0.05$

¶ no difference between dementia and controls

Table 4. Frequencies (%) for the 12 individual *severity* items of the Neuropsychiatric Inventory (NPI)fordelirium, comorbid delirium-dementia, dementia alone, and control groups.

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)	*p*
1. Delusions	1 (3%)	12 (24%)	17 (27%)	5 (15%)	≤.05
2. Hallucinations	0 (0%)	14 (28%)	21 (34%)	5 (15%)	<.01
3. Agitation / Aggression	1 (3%)	23 (46%)	35 (56%)	12 (38%)	<.001
4. Depression / Dysphoria	5 (16%)	14 (28%)	30 (48%)	14 (44%)	≤.05
5. Anxiety	6 (19%)	21 (42%)	31 (50%)	16 (50%)	≤.05
6. Elation / Euphoria	0 (0%)	1 (2%)	7 (11%)	2 (6%)	NS
7. Apathy / Indifference	2 (6%)	15 (30%)	30 (48%)	9 (28%)	<.001
8. Disinhibition	2 (6%)	8 (16%)	18 (29%)	1 (3%)	<.01
9. Irritability / Lability	4 (13%)	23 (46%)	36 (58%)	11 (34%)	<.001
10. Aberrant Motor Behaviour	2 (7%)	19 (38%)	25 (40%)	9 (28%)	<.01
11. Sleep and Nighttime Disturbances	3 (9%)	13 (26%)	32 (52%)	12 37%	<.001

12. Appetite / Eating Disturbances	7 (22%)	16 (32%)	29 (47%)	10 (31%)	NS

Table 5.Frequencies (%) for the 12 individual *distress* items of the Neuropsychiatric Inventory (NPI) fordelirium, comorbid delirium-dementia, dementia alone, and control groups.

	Controls (n = 32)	Delirium (n = 50)	Comorbid delirium-dementia (n = 62)	Dementia (n = 32)	*p*
1. Delusions	1 (3%)	12 (24%)	17 (27%)	5 (16%)	≤.05
2. Hallucinations	0 (0%)	15 (30%)	19 (31%)	4 (13%)	<.001
3. Agitation / Aggression	1 (3%)	23 (46%)	33 (53%)	12 (38%)	<.001
4. Depression / Dysphoria	3 (9%)	15 (30%)	28 (45%)	14 (44%)	<.01
5. Anxiety	5 (16%)	20 (40%)	28 (45%)	15 (47%)	≤.05
6. Elation / Euphoria	0 (0%)	1 (2%)	6 (10%)	2 (6%)	NS
7. Apathy / Indifference	2 (6%)	12 (24%)	27 (44%)	9 (28%)	<.01
8. Disinhibition	1 (3%)	8 (16%)	15 (24%)	1 (3%)	≤.05
9. Irritability / Lability	3 (9%)	21 (42%)	33 (53%)	11 (34%)	<.001
10. Aberrant Motor Behaviour	2 (6%)	19 (38%)	20 (32%)	9 (28%)	<.01

11. Sleep and Nighttime Disturbances	3 (9%)	13 (26%)	31 (50%)	12 (38%)	<.01
12. Appetite / Eating Disturbances	5 (16%)	16 (32%)	23 (37%)	9 (28%)	NS

Table 6.Comparison of NPI-Q subscale scores for delirium, comorbid delirium-dementia, dementia alone, and control groups

	Controls	Delirium	Comorbid delirium-dementia	*Dementia*
NPIQ4-Agitation Aggression	0.3± 0.6**	1.8±1.2	1.9 ± 1.4	1.2 ± 1.1*
NPIQ3-Mood	0.7 ±1.0ǂ	2.6 ± 2.1	3.0 ± 2.4	2.7 ± 2.2
NPIQ4-Frontal	0.4 ± 0.8†	2.3 ± 2.3	2.9 ± 2.5	1.6 ±2.2
NPIQ- Psychosis	0.0± 0.2	1.4 ± 1.7	1.5 ± 2.5	1.4 ±4.1

*Dementia < Comorbid delirium dementia <0.05;
**Controls< comorbid delirium and dementia; and delirium ≤ 0.05
ǂControls < all other neurocognitive groups ≤0.002
† Controls < Comorbid delirium and dementia; and delirium ≤0.005