Phenotype of subsyndromal delirium using pooled multicultural Delirium Rating Scale—Revised-98 data

Paula T. Trzepacz a,b,* , Jose G. Franco c,d , David J. Meagher e , Yanghyun Lee f , Jeong-Lan Kim g , Yasuhiro Kish i b , Leticia M. Furlanetto f , Daniel Negreiros i , Ming-Chyi Huang j , Chun-Hsin Chen k , Jacob Kean l , Maeve Leonard e

a Lilly Research Laboratories, Indianapolis, IN, USA
b Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA
c Faculty of Medicine, Universidad Pontificia Bolivariana, Medellín, Colombia
d Hospital Psiquiatric Universitari Institut Pere Mata, ISPV, Universitat Rovira i Virgili, Reus (Tarragona), Spain
e Department of Psychiatry, University of Limerick School of Medicine, Limerick, Ireland
f Department of Psychiatry, Mungyeong Jeil General Hospital, Mungyeong, South Korea
g Department of Psychiatry, College of Medicine, Chungnam National University, Daejeon, South Korea
h Department of Psychiatry, Nippon Medical School Musashikosugi Hospital, Kawasaki-city, Kanagawa, Japan
i Department of Internal Medicine, Federal University of Santa Catarina, Brazil
j Department of Psychiatry, Taipei Medical University–Wan Fang Hospital, Taipei, Taiwan
k Department of Psychiatry, Taipei City Psychiatric Center, Taipei City Hospital, Taipei, Taiwan
l Department of Rehabilitation Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

ARTICLE INFO

Article history:
Received 8 December 2011
Received in revised form 23 April 2012
Accepted 24 April 2012

Keywords:
Delirium
Delirium Rating Scale—Revised-98
Phenotype
Subsyndromal

ABSTRACT

Objective: There is no consensus definition for the phenotype of subsyndromal delirium (SSD), a subthreshold state to full delirium. Without an a priori definition we applied advanced analytic techniques to discern SSD.

Method: We pooled Delirium Rating Scale—Revised-98 (DRS-R98) data from 859 DSM-IV diagnosed nondemented delirious adults and nondelirious controls collected by investigators in 7 countries. Discriminant analyses defined an SSD group that was then compared to Nondelirium and Delirium groups.

Results: SSD (n=138) had intermediate DRS-R98 item severities between Delirium (n=497) and Nondelirium (n=224) groups, where groups significantly differed on all DRS-R98 items (ANOVA p<.001) except delusions. Discriminant analysis found SSD phenomenologically closer to Delirium than Nondelirium. Using full multinomial logistical regression, SSD was distinguished from Nondelirium by temporal onset, sleep–wake cycle, perceptual disturbances, motor retardation, delusion, affective lability, and all cognitive items; SSD was similar to Delirium in thought process, language, motor agitation or retardation, sleep–wake cycle, all cognitive items, fluctuation and physical disorder. The multivariate model correctly classified 94.2% of Nondelirium, 75.4% of SSD and 97.2% of Delirium subjects. Binary logistic regression of six core domain symptoms (sleep–wake cycle, thought process, language, attention, orientation, and visuospatial ability) together were found as highly differentiating of SSD from Nondelirium, which correctly classified almost 80% of SSD.

Conclusions: SSD is intermediate in severity between nondelirious controls and full syndromal delirium, but its phenotype is more like delirium. Core domain delirium symptoms present at milder severity in SSD should be evaluated further for utility in detecting and managing SSD, preventing delirium, and possible inclusion in DSM-V.

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Introduction

Delirium is an acute neuropsychiatric disorder impairing consciousness and affecting many higher cortical functions. Application of standardized instruments has increased our understanding of delirium phenomenology. Phenomenological research supports three core domains of symptoms comprised of abnormalities of attention and other cognition (memory, visuospatial, orientation), circadian rhythm (sleep–wake) and higher order thinking (comprehension and thought...
Delirium symptoms persist at essentially comparable severity throughout an episode while Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria are met [2].

Subsyndromal delirium (SSD) is not well characterized. It is a subthreshold for full delirium by virtue of the number, type and/or severity of symptoms and its occurrence may be during a prodromal or resolving delirium phase, or even be chronically persistent. However, there are only a few studies of SSD, where measurement methods varied. Prodromal symptoms during 1 to 4 days prior to a delirium episode have included sleep disturbance, changes in behavior, consciousness, motor activity, thinking and cognition, and EEG slowing [1, 3], supporting the notion of a transitional state.

Most studies focused on outcomes in elderly and used a priori symptom selection to define SSD. Nondelirious elderly with disorientation, clouding of consciousness and perceptual disturbances on the Delirium Symptom Interview had a longer term prognosis intermediate to that for Delirium or Nondelirium [4]. Compared to controls, nondelirious elderly with SSD defined as at least two symptoms of clouding of consciousness, inattention, disorientation or perceptual disturbances had longer length of stay, reduced cognitive and functional status, and increased institutionalization and mortality rates that correlated with the number of SSD symptoms [5]. Compared to nondelirious at 6 months follow up, those with SSD defined as the median Memorial Delirium Assessment Scale (MDAS) score in nondelirious elderly hip fracture surgery admissions had higher mortality and decline in activities of daily living [6]. Defined as partially fulfilling the Confusion Assessment Method (CAM) algorithm in elderly care geriatric admissions, SSD was an independent predictor of post-discharge institutionalization [7].

Several reports used mixed age range adult samples and well-validated severity rating scales without a priori symptom selection for SSD. Combining Delirium Rating Scale (DRS) and MDAS items for daily ratings of prodromal and syndromal deliriums in adult bone marrow transplantation patients, cognitive deficits, psychomotor behavior changes, emotional lability and perceptual and thought disturbances were present during several days prior to delirium diagnosis [8]. Previous researchers defined SSD as 8 to 13 points on the Delirium Rating Scale—Revised-98 (DRS-R98) [9] or used a cutoff score of 15 on the DRS-R98 among DSM-IV delirious cases [10]. These reports found comparable severity of SSD to delirium for sleep–wake cycle and perceptual disturbances, motor activity changes, acute onset, and affective lability, but intermediate severity between delirious and control groups for most cognitive items, language, thought process and delusions.

The inadequate research database on SSD phenomenology contrasts with its clinical relevance and possible consideration by the DSM-V Neurocognitive Disorders Work Group as to whether SSD criteria could be added in the proposed version of the manual. Diagnostic criteria in DSM-IV are less restrictive than International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) or DSM-III-R [11, 12] and, therefore, allow more cases to be diagnosed as delirious even if they are subsyndromal using more rigorous definitions. SSD may represent its own risk factors, outcomes and management. Identification of those with SSD offers opportunity for prophylactic interventions.

This report analyzed a large pooled research dataset of nondemented delirious and nondelirious adults from investigative sites in countries in the Americas, Europe and Asia in order to delineate the phenomenology of SSD and used advanced statistical methods without a priori assumptions as to which DRS-R98 items defined SSD.

Methods

Dataset selection and inclusion criteria

De-identified cross-sectional data for adult patients from 14 studies (11 of them published) conducted by expert delirium researchers in 7 countries (United States, Brazil, Colombia, Ireland, Taiwan, Korea and Japan) from 4 continents comprised the pooled database (see Supplemental Table 1S). Investigators were invited by Dr. Trzepacz, the developer of the DRS-R98, to participate in this study because they had previously received permission to use the scale for work related to its validation. Their work, published or not yet published, needed to meet the following criteria: 1) all site investigators were delirium experts and well-trained in the use of the DRS-R98; 2) delirium and other psychiatric diagnoses in the original projects were made according to DSM-IV/DSM-IVTR using all sources of clinical information; 3) DRS-R98 ratings were independent (blinded) from DSM-IV diagnosis and covered the previous 24 hour period; and 4) all subjects (delirium and controls) were evaluated cross-sectionally using DSM-IV criteria and the DRS-R98.

All studies were approved by the appropriate human ethics committees at participating sites and informed or proxy consent was obtained as required.

Patient populations

Patients were consecutively assessed adults (n = 859) from a variety of inpatient and outpatient clinical settings, where 516 had delirium and 343 were nondelirious controls according to DSM-IV criteria. Controls were drawn from the same samples as the delirious cases. Demographic data and comorbid psychiatric diagnoses according to DSM-IV were collected and demented cases were excluded from the study in order to avoid contamination from overlapping symptoms. Active medical–surgical diagnoses from the original datasets were categorized according to the Delirium Etiology Checklist (DEC) that allows classification of diverse medical–surgical diagnoses into 13 categories [1].

Procedures

The DRS-R98 is a widely used, well-validated, specific and sensitive rating scale with phenomenological descriptive anchors for rating the severity levels for each item (0 is normal to a maximum of 3) with a maximum scale score of 46 points. It is designed to evaluate the breadth and severity of delirium symptoms for phenomenological and treatment studies, in addition to diagnosing deliriums [13]. The DRS-R98 is not derived from any particular diagnostic system and instead was developed based on known delirium characteristics. Its 16 items include 3 diagnostic items for the Total score where 13 items constitute the Severity scale score. It was originally validated using raters blind to diagnoses and results were compared against four other diagnostic groups of inpatients. It has been subsequently translated and revalidated in countries outside of the U.S. Translations were used, as appropriate, and raters had been trained as part of individual projects. The DRS-R98 versions used had very high inter-rater reliability (intraclass correlation coefficient > 0.9), and excellent validity as shown by the area under the curve > 0.9 (Receiver–Operator Characteristic analyses) when comparing DSM Delirium vs. Non-delirium patients for all DRS-R98 versions utilized in this study [13,14,16,17,19,21,22]. The DRS-R98 broadly measures delirium phenomenology using anchored item descriptors and has been validated against other neuropsychiatric disorders making it an ideal instrument to assess phenomenology.

The DEC is a standardized tool that categorizes medical–surgical etiologies of delirium (for example: drug intoxication, traumatic brain injury or metabolic/endocrine disturbance). We used the DEC category table with the only purpose of grouping for description in a standardized way medical surgical diagnoses across all studies [1].

Statistical analysis

Comparability of DRS-R98 scores across samples

In order to evaluate the consistency of DRS-R98 across studies included in this study Cronbach’s alpha was performed for its Total, Severity, and Diagnostic item scores, and then alpha was calculated for the same item scores when removing each study. Finally, Cronbach’s
Fig. 1. Boxplots of DRS-R98 Total scores to illustrate the effects of the step-wise method used to define the SSD group. Part A shows the two DSM-IV-defined groups for Delirium and Nondelirium. Note the overlapping tail distributions that may reflect SSD cases. Part B shows DRS-R98 Total scores for DSM-IV Nondelirium cases after being subjected to cluster analysis to delineate the SSD cases. Part C shows the DRS-R98 Total scores for the resultant SSD group after applying the DRS-R98 full syndromal cutoff [≥13 points on Total score] to the Delirium group. Parts C and D show DRS-R98 Total and Severity scores for the three study groups used for analyses of phenomenology in this report. (Median scores are denoted by a solid line within the boxes, boxes represent the middle 50% of scores, and the tails denote the 25th percentiles.).
alpha was calculated for the same groups of item scores by comparing among all published and all unpublished studies.

Delineation of the SSD group

Boxplot distributions of DRS-R98 Total scores for pooled DSM-IV-defined Delirium cases and nondelirious controls are shown in Fig. 1 (part A). To delineate an SSD group from the DSM-IV defined delirious and nondelirious groups, we analyzed DRS-R98 data in two steps.

Step 1. In order to obtain an initial group of SSD cases from DSM-IV Nondelirium defined subjects, we analyzed DRS-R98 items from the nondelirious cases using hierarchical cluster analysis with Ward’s method to cluster the subjects, and squared Euclidean distance (Σ of the squares from differences between variable values) as a measure of dissimilarity between all DRS-R98 item scores from all subjects in the DSM-IV nondelirious defined group. This is a technique for exploratory data analysis designed to reveal natural groupings within a collection of data. In short, data observations close together should fall into the same cluster while observations far apart should be in different cluster groups. There are several methods available for performing clustering and calculating distances of elements [24]. Ward’s method was utilized for clustering in order to minimize loss of information that occurs in the element grouping process. The DRS-R98 item characteristics (scored almost the same interval) made them candidate for squared Euclidean distance as a measure of distance (first assumption for this distance measure), so, we accounted for possible colinearity or presence of latent groups with different numbers of correlated variables or items (unbalanced groups) in cluster analysis (second assumption). Even though we knew by previous factor analysis that DRS-R98 items are distributed in a balanced way [9], we performed a principal component analysis before performing the cluster analysis and evaluated the Eigenvalues (i.e., variance indices that measure the part of the total variance induced by a factor) of the components (factors) to determine whether collinearity was an issue (Eigenvalues close to zero suggest a collinearity problem). We used the square root of the ratio between the higher Eigenvalue and the lowest one (following the Belsley criteria: values between 5 and 10 for the square root of the ratio indicate a weak colinearity problem and values between 30 and 100 indicate a moderate to strong collinearity problem). We did not find a collinearity problem because the higher Eigenvalue was 3.833 and the lower was 0.268 (square root of the ratio = 3.78). The best 2-cluster solution was selected from the resulting dendrogram plot to separate Nondelirium and SSD cases.

Cluster analysis obtained groups may depend on method of clustering and dataset used. So, we divided the DSM-IV defined nondelirious group according to age in two groups (>65 and all others) and performed cluster analysis with a totally different method (K-means clustering, a non-hierarchical, iterative method for calculation of Euclidean distances) in both age groups. This second analysis was performed in order to evaluate in two different subsets with a different clustering method, the reliability of the hierarchical cluster analysis solution [24]. Percentage of subjects correctly classified in the hierarchical clusters by the K-means method is reported.

Step 2. Boxplots of DRS-R98 Total scores were made for the 3 groups (the two cluster-defined groups and the DSM-IV Delirium group) (Fig. 1, part B). We then determined which cases in the Delirium group belonged to the SSD group by applying a DRS-R98 Total cutoff score (<13) that represented cases who were below the 75th percentile of the SSD group in order to correct for the broad range of milder cases that DSM-IV criteria captures. This 2-step method allowed us to differentiate three groups from the original two, including a Delirium group that is more restrictive than the DSM-IV criteria (Fig. 1, part C).

Comparison of groups

Age and DRS-R98 score differences among groups were compared using one-way ANOVA. Between group comparisons were done using the post hoc Games–Howell test set at <0.001 significance. Sex and other psychiatric diagnosis differences between groups were compared with chi-square.

To estimate the ability of DRS-R98 items to discriminate among groups we performed two types of analysis. First, we dichotomized the items as being absent or present at any severity (score = 0 and score ≥1) and evaluated two subsamples (Nondelirium vs. SSD patients or SSD vs. Delirium) to obtain sensitivity, specificity and percent correctly classified subjects as SSD using 2×2 tables in a univariate discriminant analysis. Second, we used full factorial multinomial logistic regression in the whole sample with SSD as the reference category to discriminate which DRS-R98 dichotomized items (absence or presence) were the most differentiating of the SSD group from the Nondelirium and Delirium groups (i.e., which items had an exponentiated value of the β coefficients, Exp(β), significantly >1), and which items were the most similar between SSD group and the other two groups (i.e., which items had an Exp(β) significantly <1) when controlling for all items’ impact. In addition to Exp(β) values for comparisons between SSD and the other two groups, the percentage of correctly classified subjects by the multivariate model is reported for all three groups.

Three core domains were evaluated using six DRS-R98 items (sleep-wake cycle, language, thought process, attention, orientation and visuospatial ability). We performed a binary logistic regression analysis with those items’ scores dichotomized (absent/present) in the subsample of those with Nondelirium or SSD, with Nondelirium as the reference category. Exp(β) is reported where significant values >1 differentiate between groups when controlling for all items in the model.

Homser and Lemeshow goodness of fit statistics and other literature recommendations were followed for logistic models construction [25].

Results

Comparability of DRS-R98 scores across samples

Cronbach’s alpha for the DRS-R98 Total items in the whole sample was 0.934 (range from 0.925 to 0.940 when removing each study from the sample), for its Severity items was 0.917 (range from 0.907 to 0.924 when removing each study), and for its Diagnostic items was 0.856 (range from 0.843 to 0.865 when removing each study). Cronbach’s alpha for the DRS-R98 Total items in the 11 published studies was 0.927, for Severity items was 0.910, and for Diagnostic items, 0.847. Cronbach’s alpha for DRS-R98 Total items in the 3 unpublished studies was 0.969, for Severity items was 0.961, and for Diagnostic items, 0.908.

Delineation of the SSD group

Fig. 1 shows boxplots of DRS-R98 Total scores to illustrate the effects of the step-wise method used to define the SSD group, starting with the DSM-IV-defined groups for Delirium and Nondelirium (part A) and then part B showing the effects of applying hierarchical cluster analysis to the Nondelirium cases (88.2% of those >65 years old and 81.5% of those ≤65 were classified into the same cluster by K-means method); and then applying the DRS-R98 syndromal cutoff (≥13 points on DRS-R98 Total) to the Delirium group (part C). Three groups resulted: Nondelirium (n = 224), SSD (n = 138) and Delirium (n = 497). Part D shows boxplot distributions of the DRS-R98 Severity scores for these three groups where the SSD group has an overall delirium symptom severity that is intermediate to the other two groups. The lower quartile distribution for the Delirium group overlaps with the SSD group and the upper quartile for the control group overlaps with the SSD lower quartile, though medians were different across the three groups (Median Tests p <0.001).

Description of groups

Mean ages of the whole sample (n = 859) was 62.90 ± 17.09 and for Nondelirium, 57.40 ± 17.83 (range 18–90), for SSD, 57.83 ± 19.63 (range 18–98), and Delirium 66.80 ± 14.81 (range 18–100), where the Delirium group was older than each of the other two groups (F = 32.96, df 2, p <0.001). The proportion of males was 47.8% in the Nondelirium group, 48.6% in SSD, and 65.0% in Delirium. There was a statistically higher proportion of males in the Delirium as compared to both the Nondelirium (χ² = 19.026, df 1, p <0.001) and SSD groups (χ² = 12.318, df 1, p <0.001).

The most frequent medical–surgical diagnoses across all patients as grouped by the DEC were systemic neoplasm in 108 (12.6%), metabolic/endocrine disturbance in 89 (10.4%), systemic infection in 89 (10.4%), organ insufficiency in 72 (8.4%), cerebrovascular disorder in 47 (5.5%), traumatic brain injury in 38 (4.4%), and intracranial neoplasm in 25 (2.9%).

Two hundred sixty-seven (30.1%) subjects had at least one comorbid psychiatric disorder besides delirium. The three most frequent comorbid disorders were...
Depressive disorders, Schizophrenia or other psychotic disorder, and Alcohol use disorder (abuse or dependence): 25 (11.2%) in the Nondelirium group, 24 (17.4%) in the SSD group and 59 (11.9%) in the Delirium group had Alcohol Use disorder. Only the Schizophrenia or other Psychotic disorder diagnosis frequency was statistically different among the groups (p < .001 for all chi²).

Sensitivity, specificity and the percent of subjects correctly classified as SSD by individual (dichotomized) DRS-R98 items (using univariate discriminant analysis) are listed in Table 2. The percent correctly classified as SSD as compared to Nondelirium was at least 65% for every item indicating very good differentiation of SSD from Nondelirium, whereas the percent correctly classified as SSD as compared to Delirium was much lower with the lowest at 10.1% and only three items were above 30% though less than 45% (motor retardation, perceptual disturbances and delusion) indicating much similarity to Delirium.

Comparison for individual delirium symptoms

Mean scores for the DRS-R98 and its items are shown by group in Table 1. Using ANOVA, all item scores were significantly different across groups (p < .001) such that the SSD group’s symptoms were intermediate in severity between Nondelirium and Delirium groups, except for delusions that were different from Nondelirium but similar for SSD and Delirium groups. DRS-R98 item mean score distributions for the three groups are visually represented in a radar graph in Fig. 2, where patterns of symptoms are generally more similar between SSD and Delirium than SSD and Nondelirium, except that language appears less impaired in SSD than in Delirium.

Full multinomial logistic model

The full multinomial logistic regression model using the DRS-R98 items and dichotomized scale scores comparing SSD to the other two groups is shown in Table 3. Given that comorbid schizophrenia or other psychotic disorders were more frequent in the SSD group, we conducted the analysis using those as a covariate. We also ran the model without including this covariate. Both models identified essentially the same DRS-R98 items as being significant in the comparisons except that sleep–wake cycle was not similar between SSD and Delirium in the model not accounting for psychotic disorder comorbidity even though its Exp(β) value was only slightly lower (3.669 vs. 4.069).

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### Table 1

<table>
<thead>
<tr>
<th>DRS-R98</th>
<th>Nondelirium</th>
<th>SSD</th>
<th>Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
</tr>
<tr>
<td>Sleep–wake cycle</td>
<td>0.53</td>
<td>0.02</td>
<td>0–2</td>
</tr>
<tr>
<td>Perceptual disturbances</td>
<td>0.35</td>
<td>0.02</td>
<td>0–2</td>
</tr>
<tr>
<td>Delusion</td>
<td>0.38</td>
<td>0.03</td>
<td>0–3</td>
</tr>
<tr>
<td>Affective lability</td>
<td>0.70</td>
<td>0.04</td>
<td>0–3</td>
</tr>
<tr>
<td>Language</td>
<td>0.22</td>
<td>0.01</td>
<td>0–1</td>
</tr>
<tr>
<td>Thought process</td>
<td>0.21</td>
<td>0.01</td>
<td>0–1</td>
</tr>
<tr>
<td>Motor agitation</td>
<td>0.30</td>
<td>0.02</td>
<td>0–1</td>
</tr>
<tr>
<td>Motor retardation</td>
<td>0.30</td>
<td>0.02</td>
<td>0–1</td>
</tr>
<tr>
<td>Orientation</td>
<td>0.38</td>
<td>0.02</td>
<td>0–2</td>
</tr>
<tr>
<td>Attention</td>
<td>0.47</td>
<td>0.02</td>
<td>0–2</td>
</tr>
<tr>
<td>Short-term memory</td>
<td>0.47</td>
<td>0.02</td>
<td>0–2</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>0.41</td>
<td>0.02</td>
<td>0–3</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>0.25</td>
<td>0.01</td>
<td>0–2</td>
</tr>
<tr>
<td>Temporal onset</td>
<td>0.54</td>
<td>0.03</td>
<td>0–3</td>
</tr>
<tr>
<td>Fluctuation</td>
<td>0.09</td>
<td>0.01</td>
<td>0–1</td>
</tr>
<tr>
<td>Physical disorder</td>
<td>0.47</td>
<td>0.02</td>
<td>0–2</td>
</tr>
<tr>
<td>Severity score</td>
<td>1.67</td>
<td>0.05</td>
<td>0–6</td>
</tr>
</tbody>
</table>

All item means between groups were significantly different at p < .001 using a post hoc Games-Howell test comparison for all 3 groups, except for bold and italicized values (delusion).
For the SSD and Nondelirium analysis, sleep–wake cycle, perceptual disturbances, delusion, affective lability, motor retardation, all cognitive items and temporal onset were worse in SSD as compared to Nondelirium controls. The other 5 items were similar between SSD group and controls. Exp(β) values for 11 items were significantly > 1 and perceptual disturbances and visuospatial ability had the lowest Exp(β) value among symptom items and temporal onset had the lowest Exp(β) value among diagnostic characteristic items.

For the SSD and Delirium analysis sleep–wake cycle, language, thought process, motor agitation and retardation, all cognitive items, fluctuation and physical disorder were similar between SSD and Delirium groups and only perceptual disturbances, delusions and affective lability were different. Attention had the highest Exp(β) value among symptom items, and fluctuation and physical disorder had the highest Exp(β) values among diagnostic characteristic items. Moreover, sleep–wake cycle, motor retardation, and all cognitive items differentiated SSD from Nondelirium but not from Delirium.

The multivariate model correctly classified 94.2% of the Nondelirium subjects, 75.4% of the SSD and 97.2% of the Delirium subjects.

Core domains of delirium

Binary logistic regression analysis of six DRS-R98 items representing core domains correctly classified 87.1% of Nondelirium and 79.7% of SSD subjects (n = 362) (Nagelkerke R² = 0.60). Exp(β) values that were significantly > 1 were found for almost all these items (except for language) and separated the two groups as follows (with 95%CI): sleep–wake cycle = 5.85 (3.04–11.23), language = 1.65 (0.62–4.37), thought process = 7.06 (2.71–18.37), orientation = 3.43 (1.68–6.99), attention = 3.73 (1.74–6.53), and visuospatial ability = 8.05 (3.62–17.88). Each item except language individually differentiated SSD from Nondelirium (Wald statistics significant at ≤0.05).

Discussion

We describe an SSD phenotype using pooled DRS-R98 data from 859 nondemented adults in 14 studies from 7 countries, comprising the largest SSD phenomenology report to date. Rather than making a priori assumptions about what constitutes the SSD phenotype, we applied hierarchical cluster analysis to delineate the SSD group. In general, SSD was found to be intermediate in symptom severity from the two other groups, though Exp(β) values in regression models suggested more similarity between SSD and Delirium than Nondelirium. Further, five of six core domain symptoms of delirium significantly distinguished SSD from nondelirious controls. Our data suggest that SSD is a valid clinical state linked to delirium as a unique neuropsychiatric syndrome. Though our findings are consistent with prior descriptions of SSD, they offer more clarity and focus for the SSD phenotype because of our analytic methods and use of the DRS-R98 which is specific to SSD and Delirium than Nondelirium. Further, five of the six core domain symptoms of delirium significantly distinguished SSD from nondelirious controls. Our data suggest that SSD is a valid clinical state linked to delirium as a unique neuropsychiatric syndrome. Though our findings are consistent with prior descriptions of SSD, they offer more clarity and focus for the SSD phenotype because of our analytic methods and use of the DRS-R98 which is specifically designed for detailed phenomenological research.

Symptoms that distinguished SSD from Nondelirium were acute onset, psychosis, and alterations in cognition, sleep–wake cycle, motor retardation and affective lability. Psychosis was less common than other symptoms but when present it is linked to SSD. These are consistent with naturalistic literature that found cognitive deficits in SSD or prodromal delirium [8]. Our finding of affective lability reflects reports of mood and behavioral changes in SSD [26,27]. Attentional deficits and circadian abnormalities have been described as two of the three core domains of delirium [10,15], and we found these to be present in SSD and differentiating from Nondelirium. Inattention measured by computerized testing differentiated SSD from controls in orthopedic surgery inpatients, supporting the cardinal symptom status of inattention in SSD as well as in delirium [28]. We found that core domain symptoms of delirium were comparable between SSD and Delirium and correctly classified 79.7% of the SSD subjects compared to the Nondelirium group, and recommend that future studies of SSD include these three core domains.

Extrapolating from our results and the phenomenological descriptions for DRS-R98 items for milder severities, we propose that clinicians interested in detecting SSD should search for an acute change from baseline for a combination of the following:

Table 2

Discriminant analysis of individual DRS-R98 items for differentiating SSD from Nondelirium (n = 362) and from Delirium (n = 635).

<table>
<thead>
<tr>
<th>DRS-R98 item</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>% Correctly classified as SSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep–wake cycle</td>
<td>72.5</td>
<td>69.2</td>
<td>70.4</td>
</tr>
<tr>
<td>Perceptual</td>
<td>39.1</td>
<td>97.8</td>
<td>75.4</td>
</tr>
<tr>
<td>Delusion</td>
<td>33.3</td>
<td>95.1</td>
<td>71.5</td>
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<tr>
<td>Affective lability</td>
<td>46.0</td>
<td>90.6</td>
<td>71.5</td>
</tr>
<tr>
<td>Language</td>
<td>21.0</td>
<td>95.1</td>
<td>66.8</td>
</tr>
<tr>
<td>Thought process</td>
<td>32.6</td>
<td>95.5</td>
<td>71.5</td>
</tr>
<tr>
<td>Motor agitation</td>
<td>26.1</td>
<td>90.2</td>
<td>65.7</td>
</tr>
<tr>
<td>Motor retardation</td>
<td>25.4</td>
<td>92.9</td>
<td>67.1</td>
</tr>
<tr>
<td>Orientation</td>
<td>46.1</td>
<td>89.7</td>
<td>73.5</td>
</tr>
<tr>
<td>Attention</td>
<td>57.2</td>
<td>87.5</td>
<td>76.0</td>
</tr>
<tr>
<td>Short-term memory</td>
<td>56.5</td>
<td>84.8</td>
<td>74.0</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>55.8</td>
<td>90.1</td>
<td>77.1</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>47.8</td>
<td>95.1</td>
<td>77.1</td>
</tr>
<tr>
<td>Temporal onset</td>
<td>63.8</td>
<td>85.3</td>
<td>77.1</td>
</tr>
<tr>
<td>Fluctuation</td>
<td>31.2</td>
<td>99.1</td>
<td>73.2</td>
</tr>
<tr>
<td>Physical disorder</td>
<td>52.2</td>
<td>85.3</td>
<td>72.6</td>
</tr>
</tbody>
</table>

Table 3

Full factorial multinomial logistic regression analysis was performed with the SSD group as reference category for DRS-R98 items in 859 patients with Delirium, SSD, or Nondelirium. DRS-R98 items in bold denote that which distinguished the SSD group from Nondelirium (Exp(β) significantly < 1) and those that made SSD similar to Delirium (Exp(β) significantly > 1) (p < .05 for the Wald statistic and with 95% confidence intervals within the range). The model takes into account a contribution from primary psychotic disorder as a covariate.

Multivariate modela

<table>
<thead>
<tr>
<th>DRS-R98 item</th>
<th>Exp(β) for comparison between SSD and Nondelirium groups</th>
<th>Exp(β) for comparison between SSD and Delirium groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep–wake cycle</td>
<td>0.147</td>
<td>4.092</td>
</tr>
<tr>
<td>Perceptual</td>
<td>0.002</td>
<td>2.158</td>
</tr>
<tr>
<td>Delusion</td>
<td>0.230</td>
<td>1.591</td>
</tr>
<tr>
<td>Affective lability</td>
<td>0.088</td>
<td>1.323</td>
</tr>
<tr>
<td>Language</td>
<td>2.093</td>
<td>4.124</td>
</tr>
<tr>
<td>Thought process</td>
<td>0.494</td>
<td>4.688</td>
</tr>
<tr>
<td>Motor agitation</td>
<td>0.885</td>
<td>3.741</td>
</tr>
<tr>
<td>Motor retardation</td>
<td>0.127</td>
<td>4.088</td>
</tr>
<tr>
<td>Orientation</td>
<td>0.126</td>
<td>4.558</td>
</tr>
<tr>
<td>Attention</td>
<td>0.124</td>
<td>6.767</td>
</tr>
<tr>
<td>Short-term memory</td>
<td>0.076</td>
<td>4.025</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>0.025</td>
<td>3.946</td>
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<tr>
<td>Visuospatial ability</td>
<td>0.019</td>
<td>5.186</td>
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<tr>
<td>Temporal onset</td>
<td>0.076</td>
<td>3.518</td>
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<tr>
<td>Fluctuation</td>
<td>0.160</td>
<td>8.221</td>
</tr>
<tr>
<td>Physical disorder</td>
<td>1.375</td>
<td>14.657</td>
</tr>
</tbody>
</table>

R² = 0.60. Exp(β) values that were significantly > 1 were found for almost all these items (except for language) and separated the two groups as follows (with 95%CI): sleep–wake cycle = 5.85 (3.04–11.23), language = 1.65 (0.62–4.37), thought process = 7.06 (2.71–18.37), orientation = 3.43 (1.68–6.99), attention = 3.73 (1.74–6.53), and visuospatial ability = 8.05 (3.62–17.88). Each item except language individually differentiated SSD from Nondelirium (Wald statistics significant at ≤0.05).

a R² for the likelihood ratio test = 1394.944, df = 34, p < .001, Cox and Snell Pseudo R² = 0.803.
1. Mild sleep continuity disturbances at night or occasional drowsiness during the day
2. Tangential or circumstantial thought processes
3. Disorientation to time or place
4. Mild distractibility or difficulty sustaining attention, but ability to refocus with cueing
5. Mild difficulty navigating in one's surroundings.

This can be accomplished through routine cognitive bedside testing that includes an attention task plus observations of acute changes in thinking ability, emotional control and sleep–wake cycle. Unfortunately these symptoms are not captured by two commonly used tools, the Mini–Mental State Examination (MMSE) and the CAM [29] so we cannot recommend their use to detect SSD. A test of simple visual attention span may be the best single cognitive test for delirium detection [15,30] and measures two of the five domains in the above list. The 3-item Delirium Diagnostic Tool–Provisional (DDT-Pro), which quantitates only the core domains, highly distinguished delirious from nondelirious post-traumatic brain injury patients [20] and might be evaluated as a possible tool for SSD.

In summary, we delineated a plausible set of symptoms that describe SSD and have face validity with what is known about the core domains of delirium. As seen in Fig. 2, the SSD group separated nicely from the other two groups and its phenomenological pattern mirrors that of the Delirium group. We also advocate for inclusion of SSD as a condition in DSM-V and ICD-11 coded within the Delirium category. Inclusion of an SSD coding will prompt clinicians to become more cognizant of it and also encourage more research in this important area by standardizing its definition. Our findings contribute meaningfully to the emerging literature about the importance of recognizing a subthreshold state of delirium and we advocate provisional clinical use of the five proposed symptoms to raise awareness of SSD and possibly improve patient care through detection, management and prevention of full delirium.

Limitations of our report include that our pooled analysis across conditions did not allow for a single DRS–R98 interrater reliability assessment across all raters, although all were trained on the DRS–R98 as part of other delirium research. Further, the consistency of items was high (≥84%) according to Cronbach’s alpha, with little variation (≤6.1%) when scores for DRS–R98 Total, Severity, and Diagnostic items were evaluated for either whole sample, samples when excluding each study, published or unpublished studies. Dementia was excluded clinically and not with an instrument, though many of our subjects were not elderly. Validation studies of DRS–R98 translations report slightly different full syndromal delirium cutoff values that could make pooling data difficult, but we used statistical methods to first discern differences based on phenomenology between SSD and Non-delirium before applying a cutoff (<13 points) for SSD vs. Delirium. The latter cutoff may have excluded some cases in countries where the cutoff value is higher and whose scores were in the SSD range but attributed to the Delirium group in our report. Although our K-means cluster analysis in different subsets of patients performed to evaluate reliability of hierarchical method showed that almost 9/10 of those >65 years old and that more than 8/10 of those ≤65 were correctly classified in its hierarchical clusters, the data-dependence of cluster analysis warrants further studies in diverse populations in order to replicate our findings. Another limitation is the cross-sectional nature of our data so we cannot comment on relationships in temporal onset among individual key distinguishing features of SSD. However, our data suggest that evaluation for an acute change from baseline for the presence of a cluster of symptoms that define SSD, even though their severity is still a subthreshold for syndromal delirium, is a reasonable approach and that whenever these appear together the threshold for reaching an SSD state is achieved and is relevant. This cluster represents the same core phenotype as delirium and thereby reduces the likelihood of nonspecific isolated neuropsychiatric symptoms being erroneously attributed to SSD as can occur using previously reported a priori definitions.

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jspychores.2012.04.010.

Disclosure statement

Dr. Trzepacz is a full-time salaried employee and minor shareholder at Eli Lilly and Company. Dr. Trzepacz holds the copyright for the Delirium Rating Scale—Revised-98 but does not charge a fee for a not-for-profit use. No other coauthors have conflicts of interest to disclose.

Role of funding source

There was no formal funding for this study.

Competing interest statement

All authors will complete the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf upon notification of acceptance. All relevant author disclosures and/or competing interests have been declared in the previous section, “Disclosure statement.”

References