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The neuropsychological profile of delirium vulnerability: A systematic review and meta-analysis

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Abstract

Delirium is a common neurocognitive disorder in hospitalised older adults with substantial negative consequences. Impaired global cognition is a well-established delirium risk factor. However, poor performance on attention tests and higher intra-subject variability may be more sensitive delirium risk factors, given the disorder is characterised by a fluctuating course and attentional deficits. We systematically searched databases (Embase, PsycINFO, MEDLINE) and 44 studies satisfied inclusion criteria. Random-effects meta-analysis models showed poor performance in all cognitive domains except perception was significantly associated with incident delirium. Largest effects were for orientation (g=-1.20) and construction and motor performance (g=-0.60). These effects were no longer significant in the subgroup without pre-existing cognitive impairment, where executive functions and verbal functions and language skills were associated with incident delirium. A small, non-significant association between intra-subject variability and incident delirium was found (g=0.42). Cognitive domain specific tests may be quicker and more sensitive predictors of incident delirium. This pattern of neuropsychological findings supports the proposition that vulnerability for delirium manifests as a dysfunction of whole-brain information integration.

Keywords: delirium; neuropsychology; cognition; cognitive domains; attention; intra-subject variability; risk prediction; systematic review; meta-analysis; brain; ageing

1. Introduction

Delirium is an acute and fluctuating neurocognitive disorder characterised by inattention, disorganised thinking and an altered level of consciousness (1, 2). Delirium can occur across the lifespan but is most common in late-life (3). Delirium is prevalent across settings, seen in 20-70% of hospitalised older adults in general medical and geriatric wards (4-8). Incident delirium is also commonly seen following precipitating events such as surgery, procedures, and transplantations (4). In surgical populations, an incidence of 11-50% is observed (4, 8). Increased mortality, risk of institutionalisation, cognitive decline, dementia, and declines in overall function and quality of life have been observed following delirium (4, 9-13). Despite these adverse outcomes, compared with other psychiatric disorders common in late-life such as dementia and depression, delirium has received little attention and is still under-diagnosed or misdiagnosed.

There is evidence that delirium is preventable in up to 30-40% of cases (4, 14, 15). A Cochrane review reported strong evidence (30% reduction in delirium risk) for the use of multicomponent interventions to prevent delirium in hospitalised patients (14). Overall, better outcomes are evident for preventative strategies rather than management or treatment (16). To ensure the success of such preventative interventions and allow for targeted intervention in vulnerable patients, those at risk for developing delirium must be readily and accurately identified. Previous attempts have sought to identify those at increased risk of delirium, including a recent review of 23 delirium prediction models (17). Overall, these models were limited in terms of predictive ability. Refinement of factors included within these prediction models will optimise their overall performance.

Pre-existing cognitive impairment is a well-established risk factor for delirium (4, 18, 19), consistently included across risk prediction models identified by Lindroth and colleagues (17). Generally cognitive impairment is defined in these models as an impairment in global cognitive function (e.g., Mini-Mental State Examination [MMSE], or composite scores across multiple cognitive tests) (18). This global approach to cognitive assessment can be contrasted with domain-based testing, whereby specific cognitive domains (e.g., memory, attention, executive functions) are targeted. Clinical presentations of impairments in individual cognitive domains differ; attentional deficits often result in slowed processing of stimuli while deficits in executive functions may lead to loss of independence due to impaired ability to plan or carry out cognitive tasks (20). While delirium is a disorder of cognition, it is

primarily characterised by an impairment in the cognitive domain of attention (1, 2). Vulnerability or risk profiles for other psychiatric disorders show neuropsychological profiles which mirror their clinical characterisations. For example, memory impairments are most strongly associated with incident Alzheimer disease (21, 22), and impairments in processing speed, verbal learning and memory are most strongly associated with vulnerability for psychosis and schizophrenia (23). Similarly, in the context of predictive tools for incident delirium, poor attentional performance may be a more accurate predictor than poor performance within other cognitive domains (e.g., language or memory) (24). This would be an important finding, and the inclusion of domain-specific cognitive tests (rather than global cognitive measures) may increase the sensitivity of current delirium risk prediction tools.

Cognitive function can be indexed relative to domain (e.g., attention, executive function, language), but also to measurement type. A critical measure in the context of delirium vulnerability is intra-subject variability, given that delirium tends to have a fluctuating course (1). It is possible that such fluctuations may be captured before delirium onset and reflected in measurements of intra-subject variability in cognition. Lowery and colleagues (25) reported a greater preoperative intra-trial reaction time variability on a test of attention in those who went on to develop delirium as compared to those who did not.

Theories on the neurobiological basis of delirium vulnerability can also be refined through investigations of the neuropsychology of incident delirium. Vulnerability for delirium is currently thought to be characterised by functional brain disintegration, whereby neurotransmitter dysfunction leads to a breakdown in functional brain connectivity, resulting in abnormal sensory and motor-related neural processing (3). Sanders (26) theorised that those at high risk of incident delirium have reduced baseline functional connectivity and that modifiable risk factors such as inflammation can further compromise functional connectivity. Impairments in global cognition are captured by neurobiological theories of delirium vulnerability (3, 17, 26). However, we can likely improve the precision of these theoretical understandings and their clinical applications. Identifying the neuropsychological profile of delirium vulnerability will ultimately improve the neurobiological understanding of delirium and associated prevention and intervention strategies (3, 26).

Previous approaches to delirium risk prediction have focused on global cognitive impairments (17), however, the cognitive profile of delirium, as opposed to the risk for

delirium itself, may be specific to cognitive domains. This systematic review and meta-analysis will synthesise available literature reporting cognition (by performance within cognitive domains or intra-subject variability) and incident delirium. We focus on incident delirium (following a precipitating event) to capture observational study designs whereby cognition is measured prior to the occurrence of both a precipitating event and delirium. We aim to understand the neuropsychological profile of delirium vulnerability. Improving this understanding will allow refinement of delirium risk prediction tools and neurobiological theories. We hypothesise that poor performance on tests of attention will be more strongly associated with incident delirium than poor performance within other cognitive domains. Further, that increased intra-subject variability in cognition will be associated with incident delirium.

2. Methods

This work adhered to the PRISMA 2020 statement (27) and was registered prior to data extraction with the Open Science Framework (OSF) (osf.io/g95ce).

2.1 Information sources and study selection

Medline, PsycINFO and Embase databases were searched through Ovid from inception to 27 August 2020. The complete search strategy was: deliri* AND cognit* AND (post-op* OR postop* OR surgical OR surgery OR procedure* OR operat* OR transplant*). We applied no database limits. Screening for initial eligibility (based on title and abstract) and full-text eligibility for each article was completed by two independent reviewers (ESG, TJR, RS, JT or TT). We resolved disagreements through discussion and consensus between reviewers.

2.2 Eligibility criteria

Original empirical research papers (no reviews, opinion pieces, theses, or conference abstracts) published in English-language were included. Studies comprising adult participants (>18 years old) of any sex were included. Case studies or studies with N=1 in either outcome group were excluded. Included studies must have measured incident delirium (using any method, validated or unvalidated) and cognition (assessed prior, and not concurrently to, delirium). Incident delirium was defined as delirium following some surgical, procedural or operative precipitant (including transplantations). The cognitive measure needed to represent intra-subject variability (e.g., intra-trial standard deviation) or an individual cognitive domain (e.g., attention or memory). Studies reporting only global or composite cognitive measures

(e.g., total MMSE score) were excluded. An association between an appropriate cognitive measure and incident delirium (from which we can calculate an effect size) must have been reported for inclusion. Study authors were contacted in cases of unclear reporting. Duplicate samples were excluded.

2.3 Data collection and coding

Data extracted included: country of publication, study design, time-points of measures (cognition and delirium), study setting, sample size, participant demographics (age, sex, exclusion criteria), details of precipitant or condition of the sample (pre-cursor to delirium), cognitive test, delirium measure, and statistics representing the association between the cognitive measure and delirium. Data were extracted independently for each article by two reviewers (ESG, TJR, or RS), and a third reviewer resolved any discrepancies. Univariate statistics were extracted. Descriptive data (e.g., means and standard deviations by group) were extracted in preference of analysed data (e.g., t-test, correlation coefficient) if both were reported.

Coding of outcomes into eight cognitive domains (attention, concept formation, construction and motor performance, executive functions, memory, orientation, perception, verbal functions and language skills) and cognitive test effect direction was completed independently for each cognitive test by two reviewers (ESG, TJR, or RS) according to the neuropsychological categorisation outlined by Lezak and colleagues (20). We resolved any disagreements through discussion and consensus.

2.4 Risk of bias in individual studies

Risk of bias within included studies was assessed using the Risk of Bias for Non-randomised studies (RoBANS) (28) tool for cohort studies, following the recommendation of Wang et al. (29). Two independent reviewers (ESG, TJR, or RS) assessed risk of bias for each study with disagreements resolved through discussion and consensus. Evaluation of risk of bias was not used to determine study eligibility or inclusion.

2.5 Data analysis

All analyses were performed in R version 4.0.1 using the *metafor* (30) package. The data and code associated with this analysis are publicly available (github.com/ericaghezzi/neuropsychology_delirium_metaanalysis). We converted any

medians to means and standard deviations using the quantile estimation method within the *estmeansd* (31) package. We decided to transform rather than analyse median data separately due to the relatively small (approximately 10%) proportion of data represented by medians.

Effect sizes for differences in continuous cognitive outcomes (e.g., scores on cognitive tests) between delirium and no delirium groups were calculated as Hedges' *g*. Dichotomous cognitive outcomes (e.g., impairment vs no impairment groups based on score cut-off) were also summarised as standardised mean differences using a transformed odds ratio (30, 32). This allowed pooling of all data (continuous and dichotomous). Small, medium, and large effect sizes were classified using the Hedges and Olkin (33) method, as .20, .50, and .80 respectively. No meaningful differences were found through sensitivity analyses where dichotomous data were summarised as logistic odds ratio and pooled separately to continuous data. In all cases, a positive effect size indicates better cognitive performance in the incident delirium group (as compared to the no incident delirium group), regardless of the direction of the original cognitive test.

Effect sizes were pooled across studies using random-effects meta-analysis due to heterogeneity across study populations and characteristics. Individual random-effects models were run for the intra-subject variability data and each cognitive domain where $k>2$. Individual models were estimated for cognitive domains to allow for different between-study variance components (tau^2) within each domain. A fixed-effects model was used for between cognitive domains (as subgroups) comparisons. Following the recommendation of Langan and colleagues (34), we used the Paule and Mandel (35) method to estimate between-study variance. Sensitivity analyses revealed no meaningful difference in outcomes when common between-groups estimators (DerSimonian and Laird, restricted maximum likelihood) were used (36, 37). We used the Knapp and Hartung (38) method to calculate the confidence intervals. Statistical dependency in analysis was present due to several studies reporting more than one outcome for a particular cognitive domain in the same or largely overlapping participant samples. This was accounted for by averaging effect sizes and variances within these studies to produce a single study-level estimate, which we then entered into meta-analysis. Between-study variance was quantified using tau^2. The proportion of between-study heterogeneity out of total variance was assessed using the I^2 statistic. Values of I^2 were classified as low (25%), moderate (50%), or high (75%) (39). A result was considered statistically significant if $p < 0.05$.

We investigated heterogeneity (between-study variance) within these primary analyses through subgroup analyses where mixed-effects models were used to explore the effect of potential moderators. Pre-specified subgroup analyses of the following study-level variables were undertaken: specified training or no mention of training of delirium assessors; presence or absence of an exclusion for delirium before the precipitant; and type of precipitant (cardiac surgery, non-cardiac surgery, procedure). We did not conduct the pre-specified analysis stratified by type of delirium tool as all studies used validated delirium assessment tools. Further, a pre-specified meta-regression investigating the impact of age on outcomes was not conducted as age did not vary substantially across most included studies. We covered an investigation of the effect of different age groups within the subgroup analysis stratified by precipitant, as the procedure subgroup contained most of the younger participant samples. We investigated an additional study-level variable of presence or absence of an exclusion for pre-existing cognitive impairment or dementia. This analysis was not pre-specified in our registration, as we did not think there would have been sufficient data to do so.

Funnel plots of effect size versus standard error were visually examined for symmetry to assess for bias across studies in primary analyses due to the small-study effect (40). In analyses with at least 10 studies, the small-study effect was formally tested using Egger's intercept test (41). If we found evidence of asymmetry (one-tailed $p < 0.1$ on the Egger's test), Duval and Tweedie's (42) trim and fill method was used to quantify the magnitude of potential bias.

Certainty in the body of evidence was assessed using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) (43). Overall certainty was categorised as high, moderate, low, or very low according to assessments of the eight GRADE criteria: risk of bias, inconsistency of results, indirectness of evidence, imprecision, publication bias, magnitude of effect, dose-response gradient, and influence of residual plausible confounding.

3. Results

3.1 Summary of studies

The database search identified 5423 articles. Following removal of duplicates, 3695 studies were screened by title and abstract by two authors. Full-text screening of 1209 articles was

undertaken, with reasons for exclusion outlined in Figure 1. 87 studies measured both an appropriate cognitive measure and incident delirium but did not report a measure of association between the two (or descriptive statistics to calculate an association). Two studies reported statistics that were unable to be used to calculate an effect size (44, 45). Three studies reported summary statistics that were unable to be synthesised with other statistics, so were excluded (46-48). The final review and meta-analysis included 43 studies (see Table 1 for overview of included studies). All included data involved observational measures of delirium (cohort, case-control, or control group data from RCTs with intervention effects on delirium). Detailed information including specific cognitive tests administered and condition of the sample for included studies is shown in Supplementary Table 1. The cognitive domain each individual cognitive test was assigned to according to Lezak and colleagues (20) is outlined in Supplementary Table 2. All studies used validated methods or tools to assess delirium (see Table 1 for specific methods). The weighted mean age of participants across included studies was 69 years, and the total number of participants across all included studies was $N = 8790$.

3.2 Cognitive domain analysis

Studies within each individual cognitive domain meta-analysis ranged from 4 to 31. One cognitive domain (concept formation) was unable to be meta-analysed as only one study reported data (49). One study (50) reporting on the construction and motor performance domain was excluded as it was an extreme outlier. The pooled effect sizes of the difference in baseline cognition between incident delirium and no incident delirium groups for all remaining cognitive domains ranged from small to large in effect size (see Table 2 and Figure 3 for model results). A large effect was found for orientation ($k = 5$, $g = -1.20$, 95%CI = -2.19 to -0.21, $p = .028$), and medium effects for construction and motor performance ($k = 10$, $g = -0.60$, 95%CI = -0.88 to -0.31, $p = .001$) and perception ($k = 4$, $g = -0.64$, 95%CI = -1.43 to 0.15, $p = .083$), although perception was not statistically significant. Moderate or high heterogeneity was found between studies in all but one (memory) cognitive domain analyses. There was insufficient evidence for differences in estimates across cognitive domains ($Q = 8.52$, $p = .203$). The pooled effect size of the difference in baseline global cognition (averaged across domains, including concept formation) between incident delirium and no incident delirium groups was medium in size and significant ($k = 42$, $g = -0.48$, 95%CI = -0.60 to -0.36, $p < .001$) with moderate heterogeneity between studies ($tau^2 = 0.09$, $I^2 = 68.38\%$).

As planned, subgroup analyses were performed to investigate the identified heterogeneity (See Supplementary Tables 3 – 6 for all subgroup results). Reduced or unchanged heterogeneity was generally seen across subgroup analyses, although lowered heterogeneity was especially evident in two subgroup analyses: studies that excluded participants with delirium at baseline (before a precipitant); studies that stated delirium assessors were trained. Notably, performance on tests of construction and motor performance (g = -0.64, 95%CI = -0.99 to -0.29, p = .003) was significantly associated with incident delirium in studies which included those with pre-existing cognitive impairment (i.e., did not exclude for cognitive impairment) and not in studies which excluded participants with cognitive impairment (See Supplementary Table 5). The reverse was found for executive function and verbal functions and language skills, which were associated with incident delirium within the subgroup without cognitive impairment (g = -0.56, 95%CI = -0.95 to -0.16, p = .012 and g = -0.39, 95%CI = -0.63 to -0.14, p = .006, respectively), but not the subgroup which included those with impaired cognition (no exclusion for cognitive impairment) (See Supplementary Table 5). In the subgroup analysis by precipitant type, there were no notable differences between surgical populations (cardiac vs non-cardiac), however there were no significant associations between cognitive domains and incident delirium in the procedure-only subgroup (consisting exclusively of hematopoietic stem cell transplantation patients).

3.3 Intra-subject variability analysis

The pooled effect size of the difference in baseline intra-subject variability in cognition between delirium and non-delirium groups was small and non-significant (g = 0.42, 95%CI = -3.09 to 3.93, p = .371) with moderate heterogeneity between studies (tau^2 = 0.09, I^2 = 56.45%).

3.5 Risk of bias in studies

Figure 2 displays a summary of risk of bias evaluations. Risk of bias assessments for individual studies are presented in Supplementary Table 8. Considerable selection bias was found across studies, with very few confirming and adjusting for all major confounding variables (dementia/mild cognitive impairment, preoperative delirium, stroke, age, existing neurological disorder/comorbidities [e.g., head injury, multiple sclerosis, epilepsy, spinal cord injury]) within analyses. Additionally, over half did not confirm the absence of the outcome (delirium) at the starting point of the study, demonstrating potential bias in selecting

participants. Performance bias was indicated across studies that failed to specify the training of the assessors of neuropsychological performance. A large proportion of studies also showed potential detection bias, with no mention of blinding of delirium assessors. Overall, there was low attrition and reporting bias. Attrition bias was reflected in missing follow-up data without explanation.

3.6 Reporting biases

We found no evidence of asymmetry in the analyses. See Supplementary Table 9 for funnel plots and results of Egger's intercept test for the intra-subject variability and all cognitive domain analyses.

3.7 Certainty of evidence

Utilising the GRADE approach, the overall level of certainty (or confidence) in the body of evidence presented in this meta-analysis was deemed to be moderate. As such, we are moderately confident in the effect estimates reported; the true effect is likely to be close to the reported estimates but may be considerably different. We identified serious limitations for both risk of bias within included studies and inconsistency across studies. While we identified a high risk of selection and detection bias across studies, we deemed that these risks were unlikely to impact our effect estimates very seriously. Additionally, we identified large inconsistency (heterogeneity) in the main analyses. We identified reasons for this through subgroup analyses where we replicated results with less heterogeneity.

4. Discussion

We have extended previous approaches by investigating the associations between individual cognitive domains (measured before a precipitant) and incident delirium. However, against our hypothesis, the cognitive domain of attention did not show the largest effect. Interestingly, effect sizes for orientation (g >1) along with construction and motor performance (g = 0.7) were larger than global cognitive function, even with a smaller number of contributing studies. We also replicated the well-known finding of global cognitive impairment (i.e., poor performance across all cognitive domains) relating to incident delirium (g = 0.5).

We found lower heterogeneity across subgroup analyses, especially within subgroups where studies (1) excluded participants with delirium before a precipitant and (2) in those which

specified that delirium assessors were trained. It is essential that future studies measure delirium at baseline (in conjunction with cognitive measures) and either adjust for this or separately investigate these effects. Training of delirium assessors is also key to ensure consistency and accuracy in the screening for/diagnosis of delirium. We found no significant associations between performance across cognitive domains and incident delirium following hematopoietic stem cell transplantation (procedure subgroup analysis). This result may be due to the population undergoing these procedures, who were younger (mean age = 44 years) compared to the average age of surgical (cardiac or non-cardiac) populations (mean age = 69 years) included in the meta-analysis.

Contradictory to our hypothesis, we did not find an association between intra-subject variability in cognition and incident delirium (small but non-significant effect). There was limited literature assessing this; only two studies were identified and pooled through meta-analysis. Intra-subject variability in cognition appears to be associated with incident mild cognitive impairment and Alzheimer disease (51). Variability in cognition may not be specific to delirium vulnerability but rather more broadly applicable to cognitive impairment and neurodegeneration. Yet, a fluctuating course and variability are defining features of delirium (1, 2). Variability which represents the risk of incident delirium may be better captured before a precipitant through measures other than cognition (e.g., brain activity, gait, or heart rate). A direction for future research may be in exploring the use of functional neuroimaging and other physiological measures to capture this variability.

4.1 Disentangling delirium vulnerability from dementia

The subgroup findings are important. They suggest that executive function and verbal function and language tests may be sensitive measures of delirium vulnerability in older adults without pre-existing cognitive impairment (with medium and large effects). In contrast, construction and motor performance tests may be best for those with existing impairment (with medium and large effects).

The clock-drawing test (included in 5 of 10 studies within the construction and motor performance domain) demonstrates good sensitivity in the detection of existing dementia (50), with lower sensitivity in early and mild cases of dementia (51). Whether poor construction and motor performance is capturing the effects of dementia (rather than delirium risk per se) or is a signal of delirium in those with dementia, is unknown. Our subgroup

analyses are limited, with few studies in each analysis and no distinct cognitive impairment participant sample (only no cognitive impairment vs mixed group). It will also be important for future studies to consider depression, which is a risk factor for both delirium and dementia (52, 53), and could be contributing to these results.

4.2 Features of delirium

With diagnostic criteria primarily characterising delirium by inattention (1, 2) it is surprising we did not find that deficits in attention had the strongest association with incident delirium. Measures of attention included within assessments of delirium varied greatly and few studies have directly assessed their reliability and validity (54). Commonly employed measures of attention for delirium (e.g., months of the year backwards, digit span) reflect multiple cognitive domains while others (vigilance tests) are considered 'purer' measures of attention (55). Further, poor performance on measures of delirium is also associated with other conditions, such as mild cognitive impairment or dementia. While sensitive to delirium, the months of the year backward test is not specific to delirium as poor performance is also seen in those with cognitive impairment (56). Previous studies have explored the degree to which items on a common test for delirium (the revised delirium rating scale [DRS-R98]) are present in those with delirium, compared to subsyndromal delirium and dementia (57, 58). In both, inattention is a more prominent feature in delirium (compared to subsyndromal delirium or dementia) yet impairments in orientation are seen to a similar extent across diagnoses, as are non-cognitive features such as motor symptoms.

Physical and motor function is worse in those with, as compared to without, delirium (66). Meagher and colleagues (56) propose that motor disturbances are a core feature of delirium. While motor disturbances are currently used to categorise delirium subtypes, they are not reflected in the diagnostic criteria for delirium (2). Our results demonstrating significant effects for the association between construction and motor performance and incident delirium suggest that motor impairments warrant further investigation as both a predictor and characteristic of delirium. Importantly, these motor performance measures may be more relevant to those with cognitive impairments such as dementia.

Delirium varies in its presentation or subtype, severity, and duration. A growing body of literature demonstrates differences in detection rates, pathophysiology, and clinical outcomes between delirium subtypes (59-62). It follows that vulnerability for these different

presentations of delirium may differ. One included study investigated differences between motor subtypes of delirium in the association with baseline cognitive performance across cognitive domains and found lower scores on a test of orientation for the mixed delirium group compared to hypoactive or hyperactive subtypes (24). Another included paper reported negative associations between executive function performance at baseline and delirium severity at follow-up (63). Investigating differences in vulnerability for delirium according to presentation and severity is a useful avenue for future research, given the subtypes attract different care and prognosis.

4.3 Clinical and theoretical applications

While cognition is identified as a major risk factor for delirium, tests of global cognition are often difficult to implement in practice (even as part of a risk prediction tool) due to time requirements, mental burden on patients, and the need for specialised staff. Understanding which cognitive domains are most strongly related to incident delirium allows for direct assessment of these domains within delirium risk models. Our findings suggest that poor performance on executive function tests may be the best predictor of incident delirium in those without cognitive impairment. It also may be that construction and motor performance is the best predictor in those with cognitive impairment or dementia. Orientation may also hold promise, displaying a large effect size although the effect was not statistically significant due to large variability.

In included studies, the most common test of orientation was verbal questions relating to time and place (e.g. “What is the date today?”) and the most common test of construction and motor performance was the clock drawing test (64). Both typically take less than a few minutes to implement and score and require minimal training, making them simple to integrate within delirium risk prediction models and routine preoperative investigations (65). Replacing global cognitive function with these more sensitive domain-specific assessments (tailored to presence or absence of existing cognitive impairment) may improve the sensitivity of delirium prediction models. Better risk prediction models can inform decision making aids for elective procedures, allow for targeted preventative interventions within preoperative care, as well as identifying those requiring post-operative delirium screening. Future research should consider the effects of education on cognitive test results to minimise biases.

At a neural level, performance on construction and motor tasks, such as the clock drawing test, have been shown to positively relate to activity within motor and supplementary motor regions along with bilateral occipital, parietal, frontal, and inferior temporal lobes (66). Orientation to time, place, and person is a key cognitive function, a fundamental aspect of examining mental status and consciousness. Structural neuroimaging studies have reported that brain regions related to orientation across domains (orientation to space, time and person) overlaps with the default mode network but are separated into domain-specific sub-systems (67). The default mode network which includes the inferior parietal cortex, posterior cingulate cortex, precuneus, and medial prefrontal cortex, is one of multiple brain networks that play a role in maintenance and modulation of consciousness and attention (68). It is notable that brain networks underlying cognitive domains most strongly associated with incident delirium - construction and motor performance along with orientation - are broadly distributed. This observation fits with current neurobiological theories of delirium relating to broad functional brain disintegration (3, 17, 26).

In a recent systematic review reporting electroencephalography associations with delirium relative to time (i.e., before, during, and after delirium), we reported increased slow wave activity and reductions in functional connectivity in delirium in late-life, reflective of advanced cognitive ageing (69). Although more prospective data are required, delirium vulnerability is associated with less connected functional networks, and less connected and efficient structural networks (70). Together, findings suggest that delirium vulnerability may represent an extensive failure of normal brain function. The association between poor global cognition and incident delirium align with this proposition, as integrated functional networks are required for optimal cognition function. The application of recent theoretical advances in adaptive brain dynamical systems will aid the progress of delirium neurophysiological theories (71-73). The inclusion of neurophysiological data in future work will also enable delirium researchers to index arousal, a core deficit in delirium, which is difficult to do at a behavioural level, especially in the context of differentiating from cognitive impairments. Arousal has been traditionally conceptualised by psychology as a unitary and homogenous concept, a diffuse modulator of cortical activity. However, arousal is a multidimensional construct, which can shape patterns of neural processing differently across cortical areas (72, 74). Understanding how the ascending arousal system modulates brain dynamics, though subcortical (thalamus and basal ganglia being key structures) and cortical (including

cerebellum (72)) connections, in the context of delirium and delirium vulnerability is needed and will advance our neuropsychological and neurophysiological understandings of delirium.

4.4 Limitations

There are important limitations of this meta-analysis. Non-English language studies were outside the scope of the current review and so were excluded, which may have resulted in the exclusion of relevant studies. Moderate to high heterogeneity was found generally across analyses. This was investigated through subgroup analyses and, while attenuated in most cases, moderate heterogeneity was still present in some cases. As such, results should be interpreted with caution. Univariate statistics were exclusively extracted and, as such, effects are unadjusted for other factors. While multivariate statistics were reported in some papers, the factors adjusted for were too heterogeneous across studies to be pooled through meta-analysis.

As stated in the Introduction, cognitive function can be indexed relative to both domain (e.g., attention, executive function, language) and measurement type. We only assessed one measurement type: intra-subject variability. There are many other ways to index cognitive performance and it is likely that patterns and types of errors across cognitive tasks would be good measures of delirium and delirium vulnerability. For example, Libon and colleagues (75) demonstrated that mild cognitive impairment subtypes were associated with distinct patterns of errors on a verbal learning task (e.g., intrusions, recognition of word foils), and cautioned against single test performance measures. Recently, Hasemann and colleagues (76) reported response patterns on the month of the year backwards task differentiated delirium from dementia in hospitalised patients. More sensitive measures within cognitive tasks (opposed to one total performance score) are likely an important avenue for future delirium research.

4.5 Conclusion

There is a substantial cost associated with delirium, both directly to the healthcare system due to increased length of stay and higher rates of adverse events and indirectly through loss of independence and well-being (77). Recent estimates place the direct cost of delirium in Australia at AUD 4.2 billion per year and, including the impact from attributed dementia cases (estimated 11% of all cases), this total rises to an annual burden of AUD 8.8 billion which equates to Euro 5.4 billion and USD 5.9 billion (78). Knowing who is more vulnerable

to developing delirium will permit interventions to be targeted that may mitigate the negative consequences of delirium. It would also enable the design of interventions targeted at identified neural mechanisms (e.g., brain stimulation, pharmacological or behavioural)

This meta-analysis provides a detailed assessment of the neuropsychological profile of incident delirium risk. Our results highlight orientation and construction and motor performance as the best predictors for delirium (above global cognition). The finding of similar, or stronger, associations with tests of individual domains may allow easier assessment of those at risk within clinical practice. Theoretically, our findings tie into functional disintegration theories of delirium vulnerability with impairments across all cognitive domains (except perception) found to relate to incident delirium.

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7. Supplementary Materials

Supplementary Table 1. Details of the condition of the sample and cognitive tests used within each included study.

Lead author, year	Condition of sample	Cognitive tests
Beglinger, 2006	HSCT	TMT-A; TMT-B
Beglinger, 2011	Hemopoietic stem cell/bone marrow transplantation	TMT-A; TMT-B; RBANS
Benoit, 2005	Elective abdominal aortic aneurysm surgery	TMT-A; TMT-B; ROCF: Copy; ROCF: Recall; MOTYB; Time to print Alphabet; Animal Naming - category fluency; Wechsler Logical Memory (Immediate); Wechsler Logical Memory (Delayed)
Brown, 2018	Cardiac surgery	RAVLT; RCFT; COWAT; SDMT; TMT-A; TMT-B; Grooved Pegboard
Brown, 2011	Cardiac surgery	NART; Digit Span; Fluency Score; Stroop Tests
Cinar, 2014	CABG surgery	CDT
Cizginer, 2017	Elective surgery	WTAR
Cunningham, 2017	Primary elective hip or knee arthroplasty	CLOX-1; CLOX-2: Letter Fluency; Category Fluency; Stroop Task; TMT-1, TMT-2; New York Paragraph Recall Test; MOTYB; MMSE
Fann, 2007	First myeloablative allogeneic, autologous marrow or peripheral-blood HSCT	BDS
Fann, 2002	HSCT	HVLT; Digit Symbol (WAIS-R); TMT-A; TMT-B; COWAT
Fisher, 1995	Elective hip or knee replacement surgery	CDT
Fong, 2015	Elective surgery	TMT-A; TMT-B; Phonemic F-A-S Fluency Tasks; Category Fluency; VSAT; HVLT-R; Digit Span Forward; Digit Span Backward; BNT; RBANS DSST; WTAR
Greene, 2009	Major noncardiac surgery	WAIS-III
Hshieh, 2016	Elective surgery	HVLT-R; VSAT; TMT-A, TMT-B; Phonemic Fluency; Category fluency; Digit Span Forward; Digit Span Backward; BNT; DSST; WTAR
Jankowski, 2011	Elective hip or knee arthroplasty	AMNART; AVLT; Stroop Test; COWAT
Jones, 2016	Elective major noncardiac surgery	WTAR
Kagansky, 2004	Orthopaedic surgery	MMSE
Kat, 2008	Hip surgery	Digit Span Forward; Digit Span Backward
Kazmierski, 2014	Elective CABG surgery with CPB	TMT-B
Lindroth, 2019	Noncardiac Surgery	TMT-A; TMT-B
Long, 2015	Hip, knee or spine surgery and requiring a postoperative stay > 24 hours	Animal Fluency Test

Lead author, year	Condition of sample	Cognitive tests
Lou, 2003	Urological surgery	MMSE
Lowery, 2007	Hip or knee replacement surgery	Simple Reaction Time; Choice Reaction Time; Digit Vigilance Time
Morimoto, 2009	Elective abdominal surgery	Kana-Hiroi test
Neufeld, 2013	Elective or emergency surgery with general anaesthesia	Verbal Fluency Test; Digit Span Forward; Digit Span Backward
Oldham, 2015	Elective CABG surgery	WMS-IV; HVLT; DSST; Digit Sequencing; Word Fluency Tests; TMT-A; TMT-B; NAB Mazes; WRAT Reading Test
Oliveira, 2018	Aneurysm repair	Verbal Fluency Tests
Otomo, 2013	Elective isolated CABG surgery	Digit Span Forward; Digit Span Backward; DSST; Kana Pick-up Test
Pan, 2019	Elective hip or knee arthroplasty	Colour Trails 2
Papadopoulos, 2014	Femoral or hip fracture rehabilitation surgery	TMT; Three Words – Three Shapes Test; COWAT
Price, 2017	Elective cardiac surgery	MMSE
Racine, 2020	Extremity arterial bypass; open abdominal aortic aneurysm repair; open or laparoscopic colectomy	HVLT; TMT-B
Rudolph, 2007	Anticipated general anaesthesia and an inpatient stay	VVLT; Memory Scanning Test; Stroop Colour-Word Test; CST; Letter Digit Substitution; Four Boxes Test
Sauer, 2017	Cardiac surgery	Corsi Block-Tapping Task; RAVLT; Grooved Pegboard; TMT-A, TMT-B, WAIS Digit Span
Smith, 2009	Inpatient for a minimum of two days after major noncardiac surgery	CST; Letter Digit Coding Task; Stroop Task
Smith, 2015	Lung transplant	RBANS; TMT-A; TMT-B
Styra, 2019	Elective vascular surgery	MoCA
Tai, 2015	Transurethral prostatectomy for benign prostatic hyperplasia	CDT
Tognoni, 2011	Major (open) and minor (endoscopic) surgery	CDT
Tow, 2016	Elective orthopaedic surgery	AMNART
van Zuylen, 2020	Elective major surgery	Visual Vigilance Test
Vasilian, 2018	Hip repair surgery	MoCA; CDT-4
Witlox, 2013	Hip fracture surgery	Expanded Digit Span Forward; Expanded Digit Span Backward

Note: AMNART: American National Adult Reading Test; AVLT: Auditory Verbal Learning Test; BDS: Behavioral Dyscontrol Scale; BNT: Boston Naming Test; CABG: Coronary Artery Bypass Grafting; CDT: Clock Drawing Test; CLOX: Clock Drawing Task; COWAT: Controlled Oral Word Association Test; CPB: Cardiopulmonary Bypass; CST: Concept Shifting Test; DSST: Digit Symbol Substitution Test; HSCT: Hematopoietic Stem Cell Transplantation; HVLT: Hopkins Verbal Learning Test; HVLT-R: Hopkins Verbal Learning Test – Revised; MMSE: Mini-Mental State Evaluation; MoCA: Montreal Cognitive Assessment; MOTYB: Months of The Year Backward; NAB: Neuropsychological Assessment Battery; NART: National Adult Reading Test; RASS: Richmond Agitation – Sedation Scale; RAVLT: Rey Auditory Verbal Learning Test; RBANS: Repeatable

Battery for the Assessment of Neuropsychological Status; RCFT: Rey Complex Figure Test; ROCF: Rey-Osterrieth Complex Figure; SDMT: Symbol Digit Modalities Test; TMT-A: Trail Making Test – Group A; TMT-B: Trail Making Test – Group B; VSAT: Visual Search and Attention Test; VVLT: Visual Verbal Learning Test; WAIS-III: Weschler Adult Intelligence Scale 3rd Edition; WAIS: Weschler Adult Intelligence Scale; WAIS-R: Wechsler Adult Intelligence Scale Revised; WMS-IV: Weschler Memory Scale 4th Edition; WRAT: Wide Range Achievement Test; WTAR: Wechsler Test of Adult Reading

Supplementary Table 2. Cognitive tests from included studies according to cognitive domain categorisation.

Cognitive domain	Cognitive tests across included studies
Attention	Choice Reaction Time; Colour Trails 2; Corsi Block-Tapping Task; CST; Digit Sequencing; Digit Span Backward; Digit Span Forward; Digit Symbol; DSST; Four Boxes Test; Kana Pick-up Test; Letter Digit Coding Task; Letter Digit Substitution; Memory Scanning Test; MMSE (Attention/Calculation); MMSE (Registration); MoCA (Attention); MOTYB; RBANS (Attention); RBANS (Coding); RBANS (DSST); SDMT; Simple Reaction Time; Stroop Test; TMT-A; TMT-B; Visual Vigilance Test; WAIS (Digit Span)
Concept formation	MoCA (Abstraction)
Construction and motor performance	CDT; CDT-4; CLOX; Grooved Pegboard; MMSE (Copying); RCFT (Copy); ROCF (Copy); Time to print alphabet
Executive functions	Animal Fluency Test; Animal Naming – category fluency; BDS; Category Fluency; COWAT; Letter Fluency; NAB Mazes; Phonemic Fluency Tasks; RBANS (Semantic fluency); Verbal Fluency
Memory	AVLT (Delayed recall); AVLT (Learning efficiency); AVLT (Percent retention); HVLT (Delayed recall); HVLT (Discrimination); HVLT (Immediate recall); HVLT (Total recall); MMSE (Delayed recall); MoCA (Memory); New York Paragraph Recall Test (Delayed recall); New York Paragraph Recall Test (Immediate recall); RAVLT (Attention); RAVLT (Delayed recall); RAVLT (Immediate recall); RAVLT (Memory); RBANS (Delayed memory); RBANS (Immediate memory); RBANS (List learning); RBANS (List recall); RBANS (List recognition); ROCF (Recall); Three Words – Three Shapes Test; VVLT (Learning score); VVLT (Memory percent); Wechsler Logical Memory (Delayed); Wechsler Logical Memory (Immediate); WMS-IV (Delayed recall); WMS-IV (Immediate recall)
Orientation	MMSE (Orientation); MoCA (Orientation); Orientation to place
Perception	Kana-Hiroi Test; WAIS-III (Symbol Search); VSAT
Verbal functions and language skills	AMNART; BNT; MMSE (Language); MoCA (Naming); NART; WRAT Reading Test; WTAR

Note: Cognitive tests categorised according to Lezak and colleagues (1). AMNART: American National Adult Reading Test; AVLT: Auditory Verbal Learning Test; BDS: Behavioral Dyscontrol Scale; BNT: Boston Naming Test; CDT: Clock Drawing Test; COWAT: Controlled Oral Word Association Test; CST: Concept Shifting Test; DSST: Digit Symbol Substitution Test; HVLT: Hopkins Verbal Learning Test; MMSE: Mini-Mental State Evaluation; MoCA: Montreal Cognitive Assessment; MOTYB: Months of The Year Backward; NAB: Neuropsychological Assessment Battery; NART: National Adult Reading Test; RAVLT: Rey Auditory Verbal Learning Test; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RCFT: Rey Complex Figure Test; ROCF: Rey-Osterrieth Complex Figure; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; VSAT: Visual Search and Attention Test; VVLT: Visual Verbal Learning Test;

WAIS: Weschler Adult Intelligence Scale; WAIS-III: Weschler Adult Intelligence Scale 3rd Edition; WMS-IV: Weschler Memory Scale 4th Edition; WRAT: Wide Range Achievement Test; WTAR: Wechsler Test of Adult Reading

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Supplementary Table 3. Pooled estimates and heterogeneity for meta-analysis of the association between individual cognitive domains and incident delirium stratified by presence or absence of exclusion criteria for baseline delirium within studies.

	Pooled estimate				Heterogeneity	
Cognitive domain	***k***	***g***	***95% CI***	***p***	***tau²***	***I²***
Subgroup: Studies with exclusion criteria for baseline delirium						
Attention	7	-0.49	-0.79 - -0.20	.007	0.06	62.95
Executive Functions	4	-0.35	-0.50 - -0.20	.005	0.00	0.00
Memory	5	-0.48	-0.72 - -0.25	.005	0.03	7.77
Perception	2	-0.36	-0.71 - 0.00	.050	0.00	0.00
Verbal Functions & Language Skills	7	-0.39	-0.67 - -0.10	.016	0.07	78.30
Subgroup: Studies with no exclusion criteria for baseline delirium						
Attention	24	-0.41	-0.56 - -0.27	<.001	0.05	49.75
Construction & Motor Performance	9	-0.56	-0.88 - -0.25	.003	0.11	71.06
Executive Functions	11	-0.38	-0.78 - 0.03	.065	0.30	84.19
Memory	14	-0.35	-0.46 - -0.23	<.001	0.00	0.00
Orientation	4	-1.28	-2.72 - 0.16	.066	0.74	92.79
Perception	2	-1.10	-6.25 - 4.06	.226	0.17	44.58
Verbal Functions & Language Skills	6	-0.67	-1.20 - -0.14	.023	0.16	71.41

574 **Supplementary Table 4.** Pooled estimates and heterogeneity for meta-analysis of the association
575 between individual cognitive domains and incident delirium stratified by studies which did and did
576 not specify that delirium assessors were trained.

	Pooled estimate				Heterogeneity	
Cognitive domain	***k***	***g***	***95% CI***	***p***	***tau²***	***I²***
Subgroup: Training of delirium assessors specified						
Attention	20	-0.38	-0.52 - -0.24	<.001	0.04	43.67
Construction & Motor Performance	5	-0.55	-1.09 - -0.01	.048	0.15	77.46
Executive Functions	11	-0.25	-0.41 - -0.08	.007	0.02	31.72
Memory	13	-0.41	-0.55 - -0.28	<.001	0.01	12.82
Orientation	2	-0.91	-1.51 - -0.30	.033	0.00	0.00
Perception	3	-0.44	-0.96 - 0.09	.069	0.01	20.79
Verbal Functions & Language Skills	9	-0.37	-0.60 - -0.14	.006	0.05	66.43
Subgroup: Training of delirium assessors not specified						
Attention	11	-0.55	-0.80 - -0.30	.001	0.07	58.50
Construction & Motor Performance	5	-0.65	-1.12 - -0.18	.019	0.07	54.54
Executive Functions	4	-0.88	-2.00 - 0.25	.089	0.43	87.06
Memory	6	-0.34	-0.54 - -0.15	.006	0.00	0.00
Orientation	3	-1.43	-4.00 - 1.15	.140	1.01	95.58
Verbal Functions & Language Skills	4	-0.77	-1.616 - 0.07	.061	0.22	82.98

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Supplementary Table 5. Pooled estimates and heterogeneity for meta-analysis of the association between individual cognitive domains and incident delirium stratified by presence or absence of exclusion criteria for baseline cognitive impairment or dementia within studies.

	Pooled estimate				Heterogeneity	
Cognitive domain	***k***	***g***	***95% CI***	***p***	***tau²***	***I²***
Subgroup: Studies with exclusion criteria for baseline cognitive impairment/dementia						
Attention	17	-0.40	-0.50 - -0.30	<.001	0.00	0.00
Construction & Motor Performance	2	-0.40	-3.52 - 2.72	.353	0.05	37.39
Executive Functions	9	-0.56	-0.95 - -0.16	.012	0.21	83.75
Memory	9	-0.46	-0.58 - -0.34	<.001	0.00	0.00
Orientation	2	-1.64	-11.98 - 8.69	.293	1.18	89.11
Perception	3	-0.65	-2.28 - 0.99	.230	0.34	86.96
Verbal Functions & Language Skills	10	-0.39	-0.63 - -0.14	.006	0.07	70.85
Subgroup: Studies with no exclusion criteria for baseline cognitive impairment/dementia						
Attention	14	-0.46	-0.73 - -0.19	.002	0.15	77.31
Construction & Motor Performance	8	-0.64	-0.99 - -0.29	.003	0.12	74.11
Executive Functions	6	-0.12	-0.46 - 0.21	.387	0.05	51.15
Memory	10	-0.32	-0.49 - -0.14	.003	0.02	30.16
Orientation	3	-0.93	-2.41 - 0.54	.112	0.32	90.87
Verbal Functions & Language Skills	3	-0.78	-1.92 - 0.36	.098	0.18	85.18

582 **Supplementary Table 6.** Pooled estimates and heterogeneity for meta-analysis of the association
583 between individual cognitive domains and incident delirium stratified by type of precipitant.

	Pooled estimate				**Heterogeneity**	
Cognitive domain	***k***	***g***	***95% CI***	***p***	***tau²***	***I²***
Subgroup: Cardiac surgery						
Attention	7	-0.40	-0.73 - -0.06	.027	0.08	66.11
Construction & Motor Performance	4	-0.49	-1.22 - 0.24	.124	0.17	83.24
Executive Functions	4	-0.37	-0.53 - -0.21	.005	0.00	0.00
Memory	4	-0.37	-0.70 - -0.05	.036	0.01	28.15
Verbal Functions & Language Skills	3	-0.31	-0.47 - -0.15	.014	0.00	0.00
Subgroup: Non-cardiac surgery						
Attention	20	-0.51	-0.66 - -0.36	<.001	0.04	44.45
Construction & Motor Performance	6	-0.68	-1.06 - -0.29	.006	0.07	51.24
Executive Functions	8	-0.53	-1.02 - -0.05	.034	0.28	87.93
Memory	13	-0.42	-0.55 - -0.29	<.001	0.00	1.49
Orientation	4	-1.43	-2.60 - -0.27	.029	0.44	84.45
Perception	4	-0.64	-1.44 - 0.15	.083	0.17	76.32
Verbal Functions & Language Skills	10	-0.56	-0.87 - -0.24	.003	0.15	84.67
Subgroup: Procedure only (hematopoietic stem cell transplantation)						
Attention	3	0.00	-0.25 - 0.25	.998	0.00	0.00
Executive Functions	3	0.00	-1.13 - 1.14	.991	0.15	72.81
Memory	2	-0.16	-2.17 - 1.86	.503	0.00	0.00

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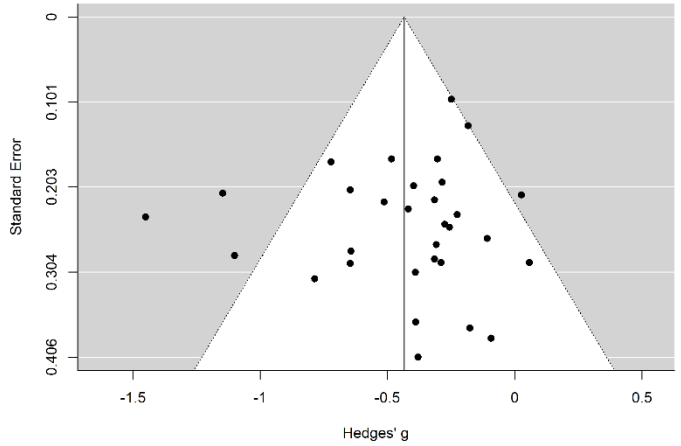
587 **Supplementary Table 8**. Individual risk of bias assessment for each included study using the Risk of
588 Bias for Non-randomised studies (RoBANS) checklist.

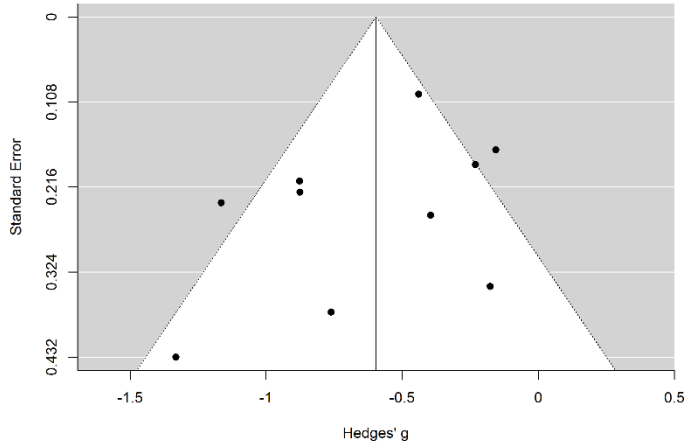
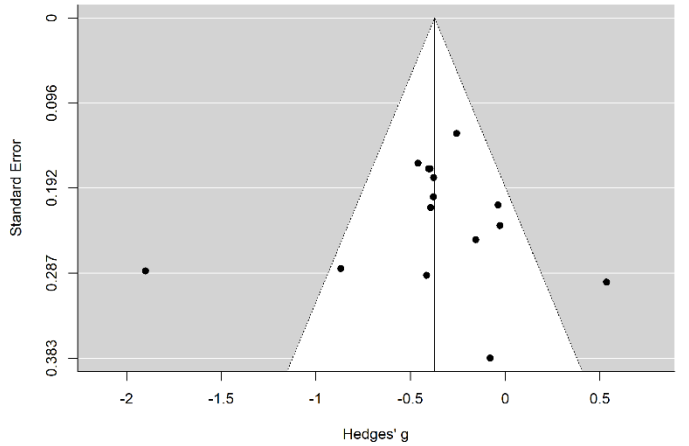
	RoBANS Item					
Lead author, year	The selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Beglinger, 2006	High	High	High	High	Low	Low
Beglinger, 2011	High	High	Low	High	High	Low
Benoit, 2005	High	High	Low	High	High	Low
Brown, 2018	High	High	High	Unclear	Low	Low
Brown, 2011	Unclear	High	Low	Low	Low	Low
Cinar, 2014	High	High	High	High	Unclear	Low
Cizginer, 2017	Low	Unclear	Low	High	Low	Low
Cunningham, 2017	High	High	Low	High	Low	Low
Fann, 2007	Unclear	High	Low	Unclear	Low	High
Fann, 2002	Unclear	High	High	High	Low	Low
Fisher, 1995	High	High	Low	Low	High	Low
Fong, 2015	Low	High	Low	High	Low	Low
Greene, 2009	Unclear	High	Low	High	Low	Low
Hshieh, 2016	Low	High	Low	High	High	Low
Jankowski, 2011	Low	High	Low	High	High	Low
Jones, 2016	Low	High	High	Low	Low	Low
Kagansky, 2004	High	High	High	High	Low	High
Kat, 2008	Low	High	Low	High	Low	Low
Kazmierski, 2014	Unclear	High	Low	High	Low	Low
Lindroth, 2019	Unclear	High	Low	High	Unclear	Low
Long, 2015	High	High	Low	Low	Low	Unclear
Lou, 2003	Low	High	Low	High	High	Low
Lowery, 2007	High	High	High	High	Unclear	Low
Morimoto, 2009	High	High	High	High	Low	Low
Neufeld, 2013	High	High	Low	Low	Low	Low
Oldham, 2015	Unclear	High	Low	High	High	Low
Oliveira, 2018	Low	High	High	High	Low	Low
Otomo, 2013	High	High	Unclear	High	Low	High
Pan, 2019	High	High	High	High	Unclear	Low

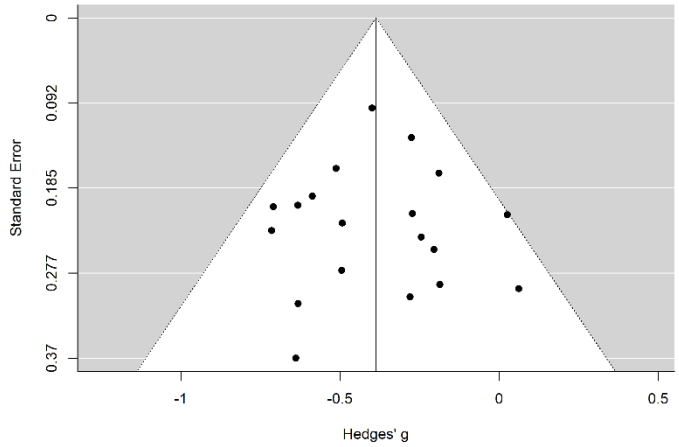
Papadopoulos, 2014	High	High	High	Unclear	Low	Low
Price, 2017	High	High	High	High	Low	High
Racine, 2020	Low	High	Low	High	Low	Low
Rudolph, 2007	High	High	Low	High	High	Low
Sauer, 2017	High	High	Unclear	Unclear	Low	Low
Smith, 2009	High	High	High	High	Low	Low
Smith, 2015	High	High	Low	High	Low	Low
Styra, 2019	High	High	Low	High	Low	Low
Tai, 2015	High	High	Low	High	Low	Low
Tognoni, 2011	High	High	Low	High	Low	Low
Tow, 2016	Low	High	Low	Low	Low	Low
vanZuylen, 2020	High	High	High	Low	Low	Low
Vasilian, 2018	High	High	Unclear	High	Low	Unclear
Witlox, 2013	High	High	High	High	Low	Low

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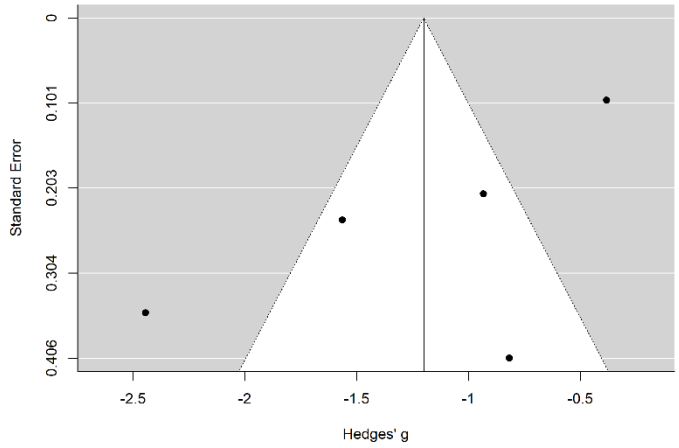
Supplementary Table 9. Funnel plots for intra-subject variability and cognitive domain meta-analyses, and results of publication bias/small-study effect investigation when at least 10 studies were available.

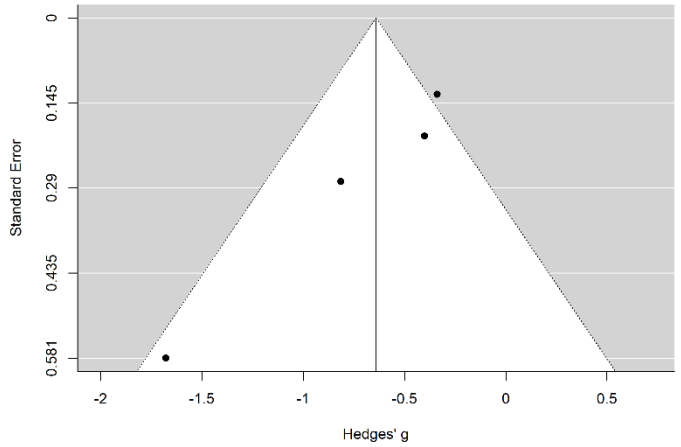
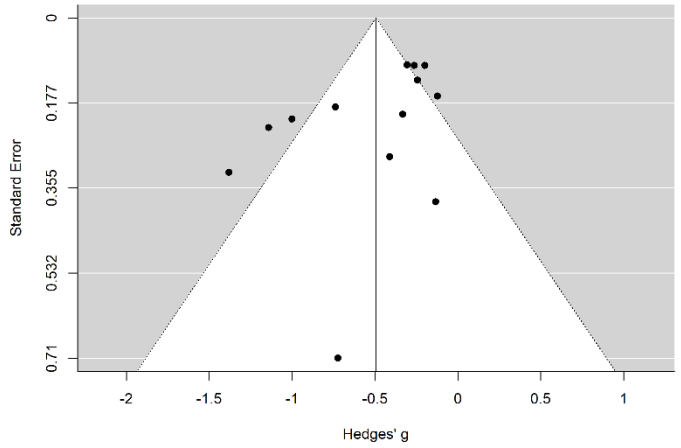
		Egger's Test	
Meta-analysis	Funnel plot	Test statistic	p-value (1-tailed)
Cognitive domain: Attention		-0.15	.880

Cognitive domain: Construction & Motor Performance		-1.26	.245
Cognitive domain: Executive Functions		-0.15	.889
Cognitive domain: Memory		-0.06	.953

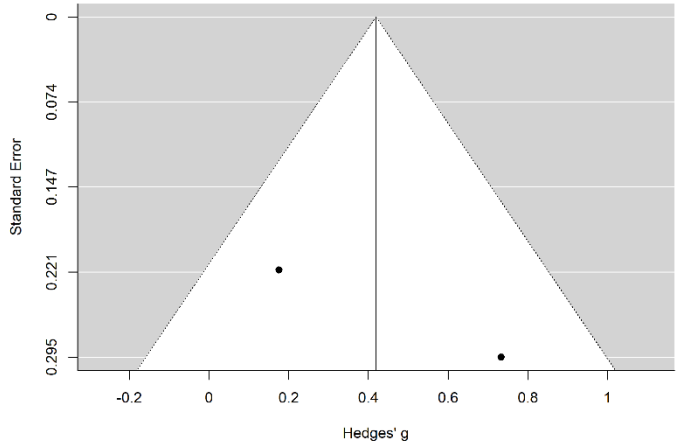


Cognitive domain: Orientation



Cognitive domain: Perception			
Cognitive domain: Verbal Functions & Language Skills		-1.48	.168

Intra-subject variability



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9. Figure captions

Figure 1. PRISMA flow diagram (27).

Figure 2. Percentage of studies with high risk (black), low risk (white), or unclear (grey) risk of bias ratings for each Risk of Bias for Non-randomised studies (RoBANS) (28) item as assessed by authors.

Figure 3. Forest plot of individual cognitive domain random effects meta-analyses and overall pooled cognition estimate.

962 **10. Tables**

963 **Table 1.** Overview of included studies.

Lead author, year	Country (2-digit ISO)	Sample size, N*	Male/ female, N	Mean age (SD)†	Precipitant	Cognitive domains assessed	Training of delirium assessors specified	Delirium assessment method(s)	Exclusion for pre-existing:	
									Delirium	Cognitive impairment/ Dementia
Beglinger, 2006 (79)	US	30	20/10	47.6 (11.1)	Procedure (HSCT)	Attention	No	DRS; MDAS	No	Yes
Beglinger, 2011 (80)	US	52	34/18	53.0 (11.0)	Procedure (HSCT)	Attention; Executive function; Memory	Yes	DRS; DRS-R; MDAS	No	No
Benoit, 2005 (81)	CA	76	79/23‡	70.8 (8.2)	Non-cardiac surgery	Attention; Construction & motor performance; Executive function; Memory	Yes	DSM-IV; Delirium Index	No	No
Brown, 2018 (82)	US	142	107/35	70.0 (8.0)	Cardiac surgery	Attention; Construction & motor performance; Executive function; Memory	Yes	CAM; CAM-ICU; Chart review	No	No
Brown, 2011 (83)	GB	37	26/11	70.5 (7.3)	Cardiac surgery	Attention; Executive function; Verbal functions & language skills	Yes	CAM	No	No
Cinar, 2014 (84)	TR	35	27/8	64.2 (10.3)	Cardiac surgery	Construction & motor performance	No	DRS-98-T; DSM-IV-TR	No	Yes
Cizginer, 2017 (85)	US	556	NR	77.0 (5.0)	Non-cardiac surgery	Verbal functions & language skills	Yes	CAM	Yes	No

Lead author, year	Country (2-digit ISO)	Sample size, N*	Male/ female, N	Mean age (SD)†	Precipitant	Cognitive domains assessed	Training of delirium assessors specified	Delirium assessment method(s)	Exclusion for pre-existing:	
									Delirium	Cognitive impairment/ Dementia
Cunningham, 2017 (86)	GB	315	136/179	74.4 (5.8)	Non-cardiac surgery	Attention; Construction & motor performance; Executive function; Memory Orientation; Verbal functions & language skills	Yes	MMSE; CAM; DSM-IV	No	Yes
Fann, 2007§ (87)	US	90	54/36	41.4 (9.9)	Procedure (HSCT)	Executive function	Yes	DRS	No	Yes
Fann, 2002§ (88)	US	90	54/36	41.4 (9.9)	Procedure (HSCT)	Attention; Executive function; Memory	Yes	DRS; MDAS	No	No
Fisher, 1995 (89)	CA	80	43/37	71.2 (NR)	Non-cardiac surgery	Construction & motor performance	No	CAM	No	No
Fong, 2015 (90)	US	300	135/165	76.9 (5.0)	Non-cardiac surgery	Attention; Executive function; Memory; Perception; Verbal functions & language skills	Yes	Digit span; DSI; CAM; Chart review	Yes	No
Greene, 2009 (91)	US	100	91/9	64.6 (7.7)	Non-cardiac surgery	Attention; Perception	Yes	CAM	No	Yes
Hshieh, 2016 (92)	US	146	59/87	76.0 (4.0)	Non-cardiac surgery	Attention; Executive function; Memory; Perception; Verbal functions & language skills	Yes	CAM; CAM-S	Yes	No

Lead author, year	Country (2-digit ISO)	Sample size, N*	Male/ female, N	Mean age (SD)†	Precipitant	Cognitive domains assessed	Training of delirium assessors specified	Delirium assessment method(s)	Exclusion for pre-existing:	
									Delirium	Cognitive impairment/ Dementia
Jankowski, 2011 (93)	US	418	206/212	72.9 (5.4)	Non-cardiac surgery	Attention; Executive function; Memory; Verbal functions & language skills	Yes	CAM	Yes	Yes
Jones, 2016 (18)	US	566	236/330	76.7 (5.2)	Non-cardiac surgery	Verbal functions & language skills	Yes	DSI; CAM; Chart review	Yes	Yes
Kagansky, 2004 (94)	IL	102	26/76	82.5 (5.3)	Non-cardiac surgery	Attention; Memory; Orientation; Verbal functions & language skills	No	CAM; DRS	No	Yes
Kat, 2008 (95)	NL	112	30/82	82.7 (6.6)	Non-cardiac surgery	Attention	Yes	DSM-IV; CAM; DRS-R-98; MMSE; Digit span	Yes	Yes
Kazmierski, 2014 (96)	PL	113	90/23	65.1 (9.0)	Cardiac surgery	Attention	Yes	CAM-ICU	No**	No
Lindroth, 2019 (63)	US	97	55/42	71.7 (4.6)	Non-cardiac surgery	Attention	Yes	CAM; 3D-CAM; DRS	No	Yes
Long, 2015 (97)	US	199	93/106	73.4 (5.5)	Non-cardiac surgery	Executive function	No	Validated chart-based tool	No	Yes
Lou, 2003 (98)	TW	106	54/52	73.9 (6.5)	Non-cardiac surgery	Attention; Construction & motor performance; Memory; Orientation; Verbal functions & language skills	Yes	DSM-IV; Consensus meeting with neurologist	Yes	No

Lead author, year	Country (2-digit ISO)	Sample size, N*	Male/ female, N	Mean age (SD)†	Precipitant	Cognitive domains assessed	Training of delirium assessors specified	Delirium assessment method(s)	Exclusion for pre-existing:	
									Delirium	Cognitive impairment/ Dementia
Lowery, 2007 (25)	GB	94	41/53	76.5 (4.5)	Non-cardiac surgery	Attention	No	CAM	No	Yes
Morimoto, 2009 (99)	JP	20	14/6	66.3 (6.6)	Non-cardiac surgery	Perception	No	DSM-IV; DRS	No	Yes
Neufeld, 2013 (100)	US	74	38/53‡	79.0 (6.0)	Non-cardiac surgery	Attention; Executive function	Yes	DSM-IV	No	No
Oldham, 2015 (101)	US	102	76/26	65.1 (9.0)	Cardiac surgery	Attention; Executive function; Memory; Verbal functions & language skills	No	MMSE; aDST; CAM; Delirium Index	No	Yes
Oliveira, 2018 (102)	BR	173	106/67	69.5 (5.8)	Cardiac surgery	Executive function	No	CAM-ICU; DSM-IV	Yes	Yes
Otomo, 2013 (103)	JP	153	109/44	72.0 (6.9)	Cardiac surgery	Attention	Yes	DRS; DSM-IV; Chart review	No	No
Pan, 2019 (104)	IE	54	25/29	76.1 (5.4)	Non-cardiac surgery	Attention	No	CAM; Chart review; DSM-IV	No	Yes
Papadopoulos, 2014†† (105)	GR	55	NR	70.7 (13.3)	Non-cardiac surgery	Attention; Executive function; Memory	No	CAM	No	Yes

Lead author, year	Country (2-digit ISO)	Sample size, N*	Male/ female, N	Mean age (SD)†	Precipitant	Cognitive domains assessed	Training of delirium assessors specified	Delirium assessment method(s)	Exclusion for pre-existing:	
									Delirium	Cognitive impairment/ Dementia
Price, 2017 (24)	US	594	413/181	65.6 (12.2)	Cardiac surgery	Attention; Construction & motor performance; Memory; Orientation; Verbal functions & language skills	No	CAM-ICU; RASS	No	No
Racine, 2020 (106)	US	140	55/85	76.1 (4.5)	Non-cardiac surgery	Attention; Memory	Yes	CAM; Chart review	Yes	Yes
Rudolph, 2007 (107)	DK, FR, DE, GB, GR, NL, ES, US	1161	618/543	68.9 (5.9)	Non-cardiac surgery	Attention; Memory	Yes	CAM; CAM-ICU	No	Yes
Sauer, 2017 (108)	NL	176	127/49	66.1 (11.8)	Cardiac surgery	Attention; Construction & motor performance; Memory	Yes	CAM; CAM-ICU; Chart review	No	No
Smith, 2009 (109)	US	996	365/631	51.0 (17.0)	Non-cardiac surgery	Attention	No	CAM; Chart review	No	Yes
Smith, 2015 (110)	US	48	23/40‡	52.7 (16.8)	Non-cardiac surgery	Attention; Memory	No	CAM; DRS	No	No
Styra, 2019 (111)	CA	173	127/46	69.9 (11.0)	Non-cardiac surgery	Memory	Yes	CAM; CAM-ICU	No	No
Tai, 2015 (50)	CN	485	485/0	71.3 (2.4)	Non-cardiac surgery	Construction & motor performance	No	CAM; DSM-IV	No	No

Lead author, year	Country (2-digit ISO)	Sample size, N*	Male/ female, N	Mean age (SD)†	Precipitant	Cognitive domains assessed	Training of delirium assessors specified	Delirium assessment method(s)	Exclusion for pre-existing:	
									Delirium	Cognitive impairment/ Dementia
Tognoni, 2011 (112)	IT	90	81/9	74.3 (0.4)	Non-cardiac surgery	Construction & motor performance	No	CAM; DSM-IV	No	Yes
Tow, 2016 (113)	US	142	50/92	71.3 (7.5)	Non-cardiac surgery	Verbal functions & language skills	Yes	CAM; Chart review; MDAS	Yes	Yes
van Zuylen, 2020 (114)	NL	152	87/65	75.8 (4.5)	Mixed surgery (cardiac and non-cardiac included)	Attention	Yes	CAM	No	Yes
Vasilian, 2018 (49)	RO	98	24/74	81.8 (6.3)	Non-cardiac surgery	Attention; Concept formation; Construction & motor performance; Memory; Orientation; Verbal functions & language skills	No	CAM	No	No
Witlox, 2013 (115)	NL	48	12/36	83.2 (5.6)	Non-cardiac surgery	Attention	No	CAM	No	Yes

Note: *Refers to sample size within included analysis; †Transformed from median/IQR to mean/SD if appropriate using R package *estmeansd* (31); ‡Male/female reported by N at baseline, not N for included analysis; §Duplicate sample, only one test included from Fann 2007 (not reported in Fann 2002). **No specific exclusion for baseline delirium, but no participants had delirium at baseline so included in 'Exclusion for baseline delirium' analysis. ††Data for control group only extracted. aDST: abbreviated Digit Span Test; CAM: Confusion Assessment Method; CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; CAM-S: Confusion Assessment Method for Severity; DRS: Dementia Rating Scale; DRS-98-T: Delirium Rating Scale 98 Turkish version; DRS-R: Delirium Rating Scale-Revised; DSM: Diagnostic and Statistical Manual of Mental Disorders; DSI: Delirium Symptom Interview; HSCT: Hematopoietic Stem Cell Transplantation; MDAS: Memorial Delirium Assessment Scale; MMSE: Mini-Mental State Examination; NR: Not reported; RASS: Richmond Agitation–Sedation Scale.

Table 2. Pooled estimates and heterogeneity for random-effects meta-analyses on the association between individual cognitive domains and incident delirium.

	Pooled estimate				Heterogeneity	
Cognitive domain	*k*	*g*	95% CI	*p*	tau^2	I^2
Attention	31	-0.43	-0.56 - -0.31	<.001	0.05	52.63
Construction & Motor Performance	10	-0.60	-0.88 - -0.31	.001	0.10	69.74
Executive Functions	15	-0.37	-0.65 - -0.10	.011	0.19	81.47
Memory	19	-0.39	-0.49 - -0.29	<.001	0.00	5.92
Orientation	5	-1.20	-2.19 - -0.21	.028	0.56	92.09
Perception	4	-0.64	-1.44 - 0.15	.083	0.17	76.32
Verbal Functions & Language Skills	13	-0.49	-0.74 - -0.25	.001	0.11	80.92