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Abstract

Patients with delirium (acute confusional state) show extensive cognitive deficits. These deficits have typically been measured using tests of fluid cognition, which involve the active processing of mental representations. However, the effects of delirium on stored, crystallized dimensions of cognition, such as well-learned word pronunciation knowledge, are not known. In this study 37 patients (aged 60-85 years) without delirium were recruited before undergoing cardiac surgery. Cognitive assessments were performed 0-8 days before surgery and again 2-9 days after surgery in order to determine the effects of post-operative delirium on fluid and crystallized aspects of cognition. Crystallized cognition was tested with the National Adult Reading Test (NART). Fluid cognition was tested with digit span, verbal fluency and Stroop tests. Nine patients (24%) developed delirium post-operatively. Patients with delirium showed significant post-operative deficits on most tests of fluid cognition, but no change in the NART measure of crystallized cognition ($p = 0.95$). These results parallel recent findings in Alzheimer's dementia and suggest that, despite showing extensive deficits of fluid cognitive processing, crystallized cognition is preserved in delirium. The results also suggest that the NART may be a useful tool for assessing pre-morbid ability in patients with delirium.

Keywords: Delirium; Dementia; Cognition; Attention; Reading; Psychogeriatrics; Neuropsychological tests

1. Introduction

Delirium (or “acute confusional state”) is an acute neuropsychiatric disorder characterized by impaired attention, disturbed consciousness and disorganized thinking. It is highly prevalent in the elderly hospitalized population (Siddiqi et al. 2008), and is particularly common following hip fracture (Edlund et al., 2001) or cardiac surgery (Rudolph et al., 2009). Delirium is independently associated with increased mortality, and is a strong risk factor for long-term cognitive decline (Rockwood et al., 1999).

Cognitive impairment is one of the core diagnostic features of delirium (American Psychiatric Association, 1994), although detailed characterization of this impairment is lacking (Bhat and Rockwood, 2007). What is known is that patients show marked attentional deficits (O’Keeffe and Gosney, 1997), and so are impaired on tasks that require ‘fluid’ cognitive processing; that is, tasks that involve active, flexible processing of neural information, such as retrieving, maintaining, or manipulating mental representations (Horn and Cattell, 1966; Craik and Bialystok, 2006). For instance, patients with delirium are impaired at remembering arrays of objects (Hart et al, 1996) or words (Brown et al., 2009); responding to repeated presentations of a given target (Hart et al, 1996; O’Keeffe and Gosney, 1997; Lowery et al., 2008); and repeating or reversing oral sequences of numbers or words (Christensen et al., 1994; O’Keeffe and Gosney, 1997; Simon et al., 2006).

Fluid cognition can be contrasted with crystallized cognition, which reflects the stores of knowledge that have been accumulated through the product of learning and experience, and which is not concerned with the dynamic processing of this content (Horn and Cattell, 1966; Craik and Bialystok, 2006). Crystallized cognition includes ‘well-learned’ knowledge, such as vocabulary, grammar, procedural skills and general knowledge. Crystallized cognition is typically measured by assessing participants’ ability to accurately pronounce irregularly spelt words, or to recognize pieces of information that have been learnt throughout the lifetime (Scott et al., 2006).

Fluid and crystallized dimensions of cognition are believed to utilize separate resources in the brain, and can be differentially affected by particular neural events. For example, patients with mild to moderate Alzheimer’s dementia show a sparing of crystallized cognition despite having marked deficits in fluid cognitive processing (McGurn et al., 2004). Preserved crystallized cognition has also been shown in patients with depression (Crawford et al., 1987) and schizophrenia (O’Carroll et al., 1992), who also have known deficits in fluid cognition. Furthermore, these two dimensions of cognition show different developmental trajectories over time: fluid cognition develops rapidly until early adulthood and subsequently shows a

steady decline, whereas crystallized cognition shows a more gradual pattern of growth but is then maintained or increases throughout older adulthood (Horn and Cattell, 1967; Craik and Bialystok, 2006). This stability of crystallized cognition in the face of declines in fluid processing abilities means that patients' performance on tests of crystallized cognition can be used to reliably estimate their premorbid levels of functioning (Crawford et al., 2001). Such estimates of prior ability are particularly useful when trying to assess the extent of decline in individuals presenting with cognitive difficulties.

Whilst delirium is known to have pervasive effects on fluid cognition, its effect on crystallized cognition is not known. This is important as a better understanding of the cognitive domains that are affected in delirium could provide insights into the pathophysiological mechanisms that underlie it. Furthermore, if crystallized cognition is found to be unaffected by delirium, then patients' performance on these tasks might be useful for estimating their premorbid level of functioning. We therefore addressed this issue by measuring aspects of fluid and crystallized cognition in older patients before and after they underwent cardiac surgery, and then comparing the degree of pre- to post-operative changes in cognition between patients who did and did not develop delirium post-operatively. We hypothesized that crystallized cognition would be preserved in delirium, as it is in Alzheimer's dementia, and that this would contrast with substantial deterioration in fluid cognition.

2. Subjects and methods

2.1. Participants

Thirty seven patients of mean age = 70.5 ± 7.3 years ($\pm$ S.D) years; 26 males, completed the study. All patients were aged over 60 years, and were recruited on an opportunistic basis prior to undergoing coronary artery bypass graft (CABG), aortic valve replacement (AVR) or combined CABG and AVR surgery. This population was selected due to the high incidence of post-operative delirium that occurs in patients of this age group undergoing cardiac surgery (Rudolph et al., 2009). Patients with evidence of dyslexia, dementia, or severe visual or auditory impairment, or who did not speak English as a first language, were not recruited. Forty eight patients initially provided written informed consent to take part in the study. However, eleven of these patients did not complete the study (five patients were discharged before being able to undergo both testing sessions, five patients withdrew from the study, and one patient experienced prolonged post-operative complications that prevented her from completing the study), resulting in the final sample size of 37.

2.2. Procedure

Patients' cognition and delirium status were assessed both pre- and post-operatively. Pre-operative assessments were conducted on hospital wards, 0-8 days (mean = 1.5 ± 1.6) before surgery. Post-operative assessments were carried out in hospital, 2 – 9 days (mean = 4.1 ± 1.7) after surgery. All cognitive and delirium assessments were conducted by two researchers (HF and JR) who had been fully trained by a senior geriatrician (AM) and a psychologist (LB). The study was approved by the Scotland A Research Ethics Committee.

2.2.1. Cognitive tests

The cognitive tests were administered in the same, fixed order for each patient and in each session. Crystallized cognition was assessed using the NART (Nelson, 1982). In this test, patients are asked to read aloud 50 English words with irregular grapheme-phoneme or stress patterns. The NART provides an estimate of crystallized verbal knowledge (Scott et al., 2006), and is relatively independent of fluid cognition (Crawford et al., 1989). Before beginning the test, patients were given a brief practice task to ensure comprehension of instructions. For this, patients were asked to read aloud five common, regularly spelled words (bag, car, shop, paper, toast) that were printed in black, 24 point, 'Times New Roman' font. All patients successfully completed this practice task in both sessions. The 50 words of the NART test, printed in a 26 point font, were then presented to the patient. The patient was asked to read each word aloud, making his/her best guess for any words they were unsure of. The patient was prompted by the experimenter to continue with the task, and to attempt each word, when necessary. The NART score was defined as the number of words correctly pronounced by the patient.

Fluid cognition was measured using tests of verbal fluency, Stroop and digit span. Verbal fluency was assessed by asking patients to produce as many words as possible (excluding proper nouns, numbers and derivatives of a previously given word) beginning with a target letter specified by the experimenter. Different target letters were used in the pre ("T") and post ("S") operative test sessions in order to minimize practice effects. Fluency scores were defined as the number of permissible words produced in one minute. The test was preceded in both sessions by a non-scored 30 second practice session using the target letter "R".

Stroop performance was then assessed using the Victoria version of the Stroop test, which is particularly appropriate for older age groups with potential cognitive impairment

(Spreen and Strauss, 1998). This test consists of three consecutive tasks: D, W and C. In task D, patients are asked to name aloud the colors of 24 dots (six each printed in red, blue, green and yellow ink), presented in a 4 x 6 array. Next, in task W, patients are asked to name the colors in which 24 words (six each of “hard”, “when”, “and”, and “over”, printed in the same colors as for task D) are printed. Finally, in task C, patients are asked to name the colors in which 24 further words (this time the words “blue”, “green”, “red” and “yellow”) are printed. These words are also printed in the same colors as for task D, with the color of each word always being incongruous to the printed color name. Patients were instructed to name the colors as quickly as possible for each task. They were prompted to continue if they stopped or lost their place on any of the three tasks, and any errors made by the patient were corrected during the task by the experimenter, as per the standard test instructions. The time taken to complete each task was used to measure patients’ performance. The times that each patient took to complete tasks D and C were also used to calculate a Stroop “interference” score using the formula $C-D/D$ (where C is the number of seconds taken to complete task C, and D is the number of seconds taken to complete task D).

Digit span was assessed using the forward and backward digit span tasks of the Wechsler Memory Scale III (Wechsler, 1998). The experimenter read a string of digits to the patient, who was then required to repeat the string back in either the same or the reverse order. The lengths of the strings started at two digits in each task, and were gradually increased to a maximum of nine digits in the forwards task and eight digits in the backwards task. Two trials of each span length were presented in each task, and the task was discontinued if a patient responded incorrectly to both trials of any given length. Performance was determined by the total number of correct strings produced in both tasks, out of maximum of 30.

2.2.2. Delirium assessment

Delirium assessments were conducted by the researcher who did not administer the cognitive tests, as soon as possible (and no more than eight hours) after completion of the cognitive tests. The presence of delirium was assessed using the confusion assessment method (CAM) (Inouye et al., 1990). This diagnostic algorithm requires the examiner to determine the presence or absence of the four core features of delirium. For a diagnosis of delirium to be made the patient must show evidence of having: 1) inattention and either, 2) disorganized thinking or, 3) an altered state of consciousness, which must have 4) either had an acute onset or show fluctuation over time. To aid assessment of these features the experimenter administered a battery of instruments validated for this purpose (Simon et al., 2006). This

comprised the mini-mental state examination (MMSE) to measure general cognitive function (Folstein et al., 1975); digit span forwards (3-5 digits) and backwards (3-4 digits) and reciting the days of the week and months of the year backwards to measure attention; and the delirium symptom interview (Albert et al., 1992) to determine patients' behavior and experiences over the preceding 24 hours. Medical and nursing staff and patients' clinical notes were also consulted to aid with diagnosis.

2.3. Statistical analysis

As the distributions of some cognitive test data were non-normal, and variances were not always homogeneous between groups, non-parametric statistics were used for all statistical comparisons. Mann-Whitney U tests were used for the between group comparisons and Wilcoxon Signed Ranks tests were used for the repeated measures comparisons. Statistical significance was taken as a two-sided $p < 0.05$.

3. Results

3.1. Patient characteristics

None of the thirty-seven patients had delirium during the pre-operative test session. Nine patients (mean age = 75.7 ± 8.5 years; 5 males) had delirium at the time of the post-operative test session, and 28 (mean age = 68.9 ± 6.2 years; 21 males) did not. Demographic and clinical characteristics of the two groups are presented in Table 1. Patients who developed post-operative delirium (POD) were older and more likely to be undergoing valve replacement in addition to coronary artery bypass grafting, and had longer periods on cardiopulmonary bypass than patients who did not develop post-operative delirium (non-POD). POD patients also had hospital stays that were more than twice the length of non-POD patients.

3.2. Cognitive data

All patients were able to complete the NART in both test sessions. However, a small amount of the other cognitive data is missing. Digit span data are complete. Verbal fluency data are missing for one non-POD patient who felt too unwell to complete this task during the post-operative test session. Stroop test data are absent for three patients: one from each group who were color-blind, and one POD patient whose glasses were lost during the peri-operative period. Stroop W and C data are missing for one other POD patient who was deemed by medical staff to be too unwell to continue with the tests in the post-operative testing session,

and Stroop C data are missing from one further POD patient who was unable to complete this task.

3.2.1. Pre-operative comparisons between groups

POD patients showed a tendency to score lower than non-POD patients in all of the pre-operative cognitive tests (Fig 1), although this difference was only significant for the digit span task ($U = 68.00$; $p = 0.040$). This pattern is consistent with previous reports showing that prior cognitive impairment is a risk factor for developing post-operative delirium (Freter et al., 2005).

3.2.2. Pre- to post-operative comparisons within each group

POD patients also showed the expected pre- to post-operative reduction in performance in all of the fluid cognitive tests (Fig 1). These deficits were significant for the Digit Span ($z = -2.53$, $p = 0.011$), Stroop W ($z = -2.20$, $p = 0.028$) and Stroop C ($z = -2.02$, $p = 0.043$) tasks, and showed trends toward significance in the Stroop D ($z = -1.95$, $p = 0.051$) and Verbal Fluency ($z = -1.72$, $p = 0.085$) tasks. POD patients also showed a significantly greater post-operative interference effect on the Stroop task ($z = -2.02$, $p = 0.043$) and a significant pre to post-operative reduction in MMSE score ($z = -2.55$, $p = 0.011$). In marked contrast to these fluid processing deficits, POD patients showed no pre- to post-operative reduction in NART score (median pre-operative score = 24.0, median post-operative score = 28.0; $z = -0.06$, $p = 0.95$).

As expected, non-POD patients showed no consistent pre- to post-operative change in fluid cognition performance (Figure 1). Only performance on the Stroop D task deteriorated significantly ($z = -2.16$, $p = 0.031$). They also showed improved post-operative performance in Stroop Interference ($z = -2.04$, $p = 0.041$), indicated by a reduction in the size of the interference score. They also showed no pre- to post-operative change in NART score (median pre-operative score = 30.5, median post-operative score = 33.0; $z = -1.10$, $p = 0.27$).

3.2.3. Between group comparisons of magnitude of changes

In order to compare the magnitude of cognitive change between the two groups, the difference between the pre- and post-operative scores of each participant were calculated for each variable and then compared between the groups (Table 2). As expected, POD patients showed pre- to post-operative changes in score that were significantly greater than the non-POD patients for the MMSE ($U = 32.50$; $p < 0.001$), Digit Span ($U = 45.50$; $p = 0.003$),

Stroop W ($U = 18.00$; $p = 0.002$), Stroop C ($U = 3.00$; $p < 0.001$) and Stroop Interference ($U = 2.00$; $p < 0.001$) measures. They also showed trends towards greater changes in performance on the

Stroop D ($U = 55.00$; $p = 0.097$) and Verbal Fluency ($U = 72.00$; $p = 0.073$) tasks. In contrast, the magnitude of pre to post-operative change in NART scores did not differ between the two groups ($U = 115.00$; $p = 0.715$).

4. Discussion

The main new finding in this prospective study is that patients who developed post-operative delirium (POD) showed preserved crystallized cognition, as measured by performance on the NART, despite showing extensive impairment of fluid cognitive ability. These results provide an intriguing parallel with studies that have indicated preserved crystallized cognition during normal aging (Horn and Cattell, 1967; Crawford et al., 2001; Craik and Bialystok, 2006), in Alzheimer's dementia (McGurn et al., 2004), depression (Crawford et al., 1987) and schizophrenia (O'Carroll et al., 1992), and suggest that performance on tests of crystallized cognition might be useful for estimating levels of premorbid cognitive ability in delirium. These findings also suggest that different cognitive domains may not be equally affected in delirium, and contribute new information to the under-researched field of the neuropsychology of delirium.

Previous studies of delirium have shown widespread patterns of cognitive impairment (Christensen et al., 1994; Hart et al., 1996; O'Keeffe and Gosney, 1997; Simon et al., 2006; Lowery et al., 2008; Brown et al., 2009), leading some researchers to suggest that these patients have global deficits in cognitive functioning (Lipowski, 1990). However, such research has typically involved tasks of fluid cognitive function, which require active processing of mental representations (Horn and Cattell, 1966; Craik and Bialystok, 2006), and so are highly dependent on attentional resources (Gray et al., 2003). As attentional impairment is one of the defining features of delirium (American Psychiatric Association, 1994), it is perhaps unsurprising that these patients perform poorly in tasks that place high demands on fluid cognition. The NART provides a measure of crystallized cognition that is relatively independent of fluid cognitive function (Crawford et al., 1989). Our finding of preserved NART performance in delirium indicates that some aspects of cognitive function are actually preserved, and that the extent of cognitive impairment associated with delirium might be less than previously believed. For instance, assessments of memory or stored knowledge that do not place high demands on the active processing of this content might

reveal a much lesser extent of impairment than when more traditional methods of explicit recall are used (Brown et al., 2009).

This novel finding of preserved NART performance in delirium also indicates that the test may be useful when assessing the presence of cognitive change for delirium assessment. NART scores have been shown to provide reliable indicators of pre-morbid ability in several populations who show deficits in fluid cognition (Crawford et al., 1987, 2001; O'Carroll et al., 1992; McGurn et al., 2004), allowing the extent of an individual's cognitive decline to be determined. As NART scores also seem to be resistant to the acute cognitive changes that occur in delirium, they could also allow the extent of cognitive decline to be estimated in these patients. Accurate estimates of cognitive decline are particularly useful for delirium assessments, for which evidence of an acute change in the patient's cognitive status is a requisite for diagnosis (American Psychiatric Association, 1994), but for which data on premorbid functioning is often not available.

Some limitations of this study should be mentioned. Firstly, the number of participants was relatively small, and some of the cognitive data for the fluid tests are missing, therefore limiting the statistical power of the study. Secondly, it is difficult to determine how representative patients in the POD group were in terms of the severity and characteristics of their symptoms. However, the size of the POD group, and the severity of their symptoms, were sufficient to enable clear declines in fluid test performance to be observed. Thus, even if these patients do represent only the milder cases of delirium, they still show a striking dissociation between impaired fluid cognition and intact crystallized cognition. Furthermore, it is notable that the POD group actually showed an overall tendency to make more correct NART responses in the post-operative test session, making it highly unlikely that the lack of a significant reduction in NART performance was simply due to statistical power.

In summary, these results provide novel preliminary evidence for the preservation of crystallized cognition in delirium. Further work is now required to determine whether there are additional facets of cognition that are preserved during delirium, and whether this finding of preserved NART performance holds true even for the most severe cases of delirium.

Conflict of interest statement: None

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Figure caption

Figure 1: Median Pre-operative and Post-operative Test Scores of each Group. The upper four panels show median numbers of correct responses made in the National Adult Reading Test (NART) (A), Mini-Mental State Examination (MMSE) (B), Digit Span (C) and Verbal Fluency (D) tasks. In each of these tasks a higher score is indicative of better task performance. The lower four panels show median numbers of seconds taken to complete the Stroop D (E), Stroop W (F) and Stroop C (G) tasks, and median Stroop Interference scores (H). In each of these tasks a higher value is indicative of poorer task performance. Data from patients who developed post-operative delirium (POD) are shown with filled symbols and solid lines. Data from patients who did not develop post-operative delirium (non-POD) are shown with unfilled symbols and broken lines. Error bars show the interquartile range of each data point.

Table 1. Demographic and clinical characteristics of patients who did (POD) and did not (Non-POD) develop post-operative delirium. Data are median (range), unless stated. Comparisons are POD vs. Non-POD.

	POD (n=9)	Non-POD (n=28)	p value
Age (years):	79.0 (63 – 85)	66.5 (60 – 79)	0.028 [†]
Sex: % male	56	71	0.43 [‡]
Co morbidities: %			
Ischemic heart disease	44	82	0.041 [‡]
Cerebrovascular disease	33	7	0.081 [‡]
Hypertension	89	75	0.65 [‡]
Diabetes mellitus	22	25	1.00 [‡]
Hyperlipidaemia	67	79	0.66 [‡]
Smoking History: %			
Current smokers	11	11	1.00 [‡]
Ex-smokers	56	43	0.39 [‡]
Non-smokers	33	46	0.39 [‡]
Admission: % elective/urgent	89/11	68/32	0.39 [‡]
Surgery Type: %			
CABG*	22	79	0.004 [‡]
AVR*	44	18	0.12 [‡]
CABG* & AVR*	33	4	0.038 [‡]
Bypass Time (mins):	120 (0 – 279)	67 (0 – 260)	0.038 [†]
Total Hospital Stay (hours):	359 (138 – 858)	142 (92 – 1058)	0.003 [†]

* CABG = coronary artery bypass grafting; AVR = aortic valve replacement

Comparison by [†] = Mann-Whitney U test; [‡] = Fisher's Exact Test:

Table 2: Median Changes in Cognitive Test Performance for each Group. The difference between the pre-operative and post-operative test score was calculated for each participant and then compared between groups. Tests marked with a * symbol showed a significant between-group difference at $p < 0.05$. Tests marked with a † symbol showed a trend towards a significant between group difference ($p = 0.05 - 0.10$).

Measure	POD			Non-POD		
	N	median score change (interquartile range)		N	median score change (interquartile range)	
NART score	9	-1	(-3.5 - +4.5)	28	0	(-1 - +2)
MMSE score *	9	-5	(-9.0 - -2.5)	28	-1	(-1.8 - +1.0)
Digit Span score *	9	-2	(-4.5 - -1.0)	28	0	(-1.8 - +1.0)
Fluency score †	9	-2	(-6.5 - 0.0)	27	0	(-2.0 - +3.0)
Stroop D time (s) †	7	+6.6	(+0.1 - +26.3)	27	+1.2	(-0.2 - +3.0)
Stroop W time (s) *	6	+17.4	(+8.6 - +27.4)	27	+1.9	(-1.4 - +3.5)
Stroop C time (s) *	5	+73.9	(+19.0 - +92.3)	27	+0.2	(-7.0 - +3.4)
Stroop Interference *	5	+1.08	(+0.75 - +1.99)	27	-0.3	(-0.79 - +0.22)

Figure 1 (continued on next page)

Figure 1 (continued from next page)