Long Term Post-Operative Cognitive Dysfunction;

A 12 month longitudinal cohort study of elderly non-cardiac patients.

Nathan Gauge

Abstract

Post-operative cognitive dysfunction (POCD) in elderly non-cardiac patients has recently been identified as a significant risk factor for increased mortality, welfare dependence and premature withdrawal from work over a follow up of 8.5 years. The single most important risk factor for the development of POCD is advancing age. In the UK population ageing, coupled with an increase in the age of patients undergoing surgery will make POCD and increasingly important condition.

Despite the significant long term impact of POCD, previous studies in the elderly have failed to identify significant levels of POCD at one year post operatively. This essay will present the first longitudinal cohort study to demonstrate a significantly greater level of global cognitive impairment in surgical patients compared to controls 1 year post-operatively. The discussion will identify why previous trials have failed to show a significant level of POCD at 1 year post operatively and has substantial implications for future research into reducing the impact of POCD.

1 Nathan Gauge is a KCL final year medical student
He was involved in all aspects of the study including design, data collection and was solely responsible for the statistical analysis and authorship of this essay. This work has been submitted for the Amulree prize with the permission of the other authors involved in the study.
Epidemiology of POCD

POCD has been identified in medical literature for over 50 years[4] when Bedford noted that "He’s never been the same since his operation” is often heard in geriatric practice” and conducted a retrospective study identifying POCD for the first time. Despite this it took a further 40 years before the landmark study into non-cardiac POCD was conducted by the ISPOCD study group - published in 1998 demonstrating that amongst major non-cardiac surgical patients greater than 60 years old POCD was present in 25.8% of patients at one week and 9.9% at 3 months post operatively[31].

It is important to distinguish POCD from postoperative delirium which is a temporary change in mental status characterized by a reduced awareness of the environment and a disturbance in attention occurring shortly after surgery[13]. Post operative delirium is associated with delayed recovery and increased mortality[30]. POCD in contrast is a more persistent condition identified by neuropsychological testing which demonstrate a decline in cognitive function without an alteration in mental status or awareness[13].

Estimates of the prevalence of POCD have varied widely from no reported change up to 71% of patients showing POCD between one week and 6 months after surgery[34]. There are two principle reasons for the wide range of incidence; firstly variation in type of surgery and anaesthesia and secondly variation in the definition of POCD itself. The problem of defining POCD has been addressed by several authors[28, 34, 40] and a consensus has yet to be reached. There are several barriers to establishing a definition of POCD.

1. POCD is currently defined on the basis of a randomly assigned statistical cut off point. Different authors have a variety of opinions on where this cut off point should be placed. Important consideration needs to be given to previously established definitions of cognitive decline in the elderly and both the clinical and personal impact of any given level of decline.

2. POCD is a binary definition of cognitive decline. It is plausible that POCD is present to a greater or lesser extent in the majority of patients and therefore represents a continuum of cognitive dysfunction. Reduction of the continuous data produced by neuropsychological tests to binary data may therefore be inappropriate.

3. There is little data on whether different areas of cognition are preferentially affected in POCD. Neuropsychological testing allows isolation of several areas of cognitive function. Authors disagree on the number and type of tests as well as which cognitive aspects should be focussed on.

The approach taken in this study is based on evidence that individual cognitive domains have different effects on patients’ activities of daily living and capacity to function independently. Price et al. demonstrated that POCD patients suffering from executive function deficits either alone or in combination with memory deficits have the greatest functional impairment[36]. Previous studies have demonstrated that deficits in attentional function have a particularly significant impact on patients’ activities of daily living[8].

Computerised neuropsychometric testing and in particular the Cognitive Drug Research (CDR) computerised assessment system has been shown to reduce the learning effect caused by repeated assessments used in the study of POCD[47]. For these reasons we have employed a computerised test
battery which focuses on attention and executive function. We have followed the ISPOCD study group Z score method for calculating global cognitive decline as well as including analysis of individual neuropsychometric tests.
Impact of POCD

POCD has been shown to have severe long-term consequences for patients including increased mortality in both the short term - between three months and one year post operatively [32] - and long-term with one study demonstrating an increased mortality over a median follow-up of 8.5 years post operatively[44]. POCD has also been associated with increased duration of hospital stay[32], premature withdrawal from the labour market and increased duration of welfare payments[44]. Following cardiac surgery Newman et al. have shown that cognitive decline is significantly associated with significantly reduced quality of life and a less productive working status [33].

Despite the long-term implications of POCD both for the patient and the health service very few studies have assessed POCD one year post operatively. A literature search of the Medline database\(^2\) identified only six papers that assessed POCD over six months post operatively and incorporated a control group for comparison [1, 3, 5, 19, 20, 22]. The papers are summarised in table 3 in the appendix. Only one paper found a significant difference in cognitive function between patients and controls. Ancelin et al. identified a decline in cognitive function in visuo-spatial tests whilst also noting a simultaneous improvement in patients compared to controls in the language tests[3]. This study failed to control for the learning effect caused by repeated psychometric testing of patients and did not include a measure of global decline.

The failure of previous trials to identify a significant difference in global cognitive decline between patients and controls may represent either 1) evidence that POCD is a temporary impairment that resolves completely within one year or 2) previous trials have failed to use a sufficiently sensitive neuropsychological test battery to detect long-term changes in cognitive function without succumbing to the difficulties of either the ceiling effect or the learning effect. The epidemiological evidence demonstrating long-term health and welfare consequences to POCD suggest that there are lingering cognitive deficits that have remained undetected.

Whilst POCD is believed to be a condition that is – at least in some patients - reversible many authors have considered a link between POCD and the development of dementia in later life. The difference in definitions between POCD and measures of early dementia such as Mild Cognitive Impairment (MCI) and Age Associated Cognitive Decline (AACG) is only the presence of a surgical history. MCI and AACD have been used extensively throughout the psychiatric literature and are well documented as predictors of future dementia including Alzheimer’s disease amongst elderly patients [27].

Xie and Tanzi [50] have argued that there is some experimental evidence to support a link between general anaesthesia, surgery and permanent cognitive damage. They point to studies that show ischemic brain injury is associated with the development of dementia, and - at least in experimental

\(^2\) The literature search was based on the systematic review by Newman et al.[34] Updated using the same search terms to cover the period 2005 to 2010.
models - exposure to anaesthetic substances including isoflurane and propofol has induced neuronal cell death and altered the formation of Aβ peptides associated with Alzheimer’s disease. However, case-control studies linking Alzheimer’s disease with exposure to general anaesthetic, although limited by design, have been inconclusive [6, 7]. Further research is clearly needed before a link can be satisfactorily established.
Aetiology, Pathogenesis and Prevention

Several studies have identified risk factors associated with POCD. As with many diseases age is the strongest predictor of POCD risk. In the ISPOCD1 study at three months POCD was found in 7% of patients aged 60-69 and in 14% of patients over 69. In addition; duration of anaesthesia, respiratory complications, infection and further operations were found to be independent risk factors for POCD [31]. A connection has also been found between lower levels of education, depression and POCD [2]. It is suggested that these risk factors are explained by deficiencies in the test as individuals with high level of intelligence are able to compensate for some levels of cognitive decline with their so called ‘cognitive reserve’ [16] and it is well recognised that depression can lead to a reduction in neuropsychological test scores[42]. POCD has been associated with lower alcohol consumption in middle aged patients – thought to be a result of increased sensitivity to CNS active substances [25]. Conversely in male cardiac surgical patients a history of alcohol dependence has been associated with increased cognitive decline [24].

A plethora of theories explaining the underlying pathogenesis of POCD have been put forward but none have yet been satisfactorily proven. It is useful when considering an area where there are so many possible mechanisms to construct a simple set of categories from which to explore potential mechanisms. Assuming that POCD is genuine and is caused by part of the process of surgery there are at least three major areas that should be considered:
Surgical Insult

The potential for microemboli to cause cognitive decline has been explored previously [15, 26]. Koch et al. used transcranial Doppler to assess the number of microemboli in either of the middle cerebral arteries during hip or knee replacements. Whilst microemboli were detected in both patients with and without a venous-arterial shunt the authors were unable to correlate the number of emboli detected with POCD. It is worth noting however that this study may have been underpowered to detect an effect involving just 22 patients and size as well as number of emboli may play an important role.

The possibility of systemic inflammation causing POCD in cardiac surgery has been explored by randomising the use of intra-venous ketamine during anaesthetic induction. The authors found a significant improvement in the intervention arm in one specific cognitive domain and a significant reduction in the levels of C-Reactive Protein postoperatively[23]. Experimentally the exposure of rats to anaesthesia and splenectomy resulted in increased levels of CNS inflammation and cognitive impairment [46] – interestingly in rats exposed only to anaesthesia no cognitive deficit was found.

Cerebral oxygen de-saturation has been a significant area of study in cardiac and carotid artery surgery and has been correlated with POCD[11, 43]. In non-cardiac surgery it is a more complex picture. Significant cerebral oxygen desaturation only occurs in a minority of patients during non-cardiac surgery [11], but amongst these individuals preliminary evidence indicates that monitoring to enable intervention improves outcome [10]. Cerebral oxygen de-saturation has been shown to be significantly correlated with blood loss in abdominal patients and a percentage fall in haemoglobin [21]. Treatment of anaemia and vitamin B12 deficiency in patients with cognitive impairment has been shown to significantly improve cognition [14] postoperative anaemia represents a plausible cause of POCD.

General Anaesthetics on CNS

The possibility of General Anaesthetic (GA) agents causing long term cognitive impairment is a controversial one and provokes strong responses amongst anaesthetists. Neurotoxicity of general anaesthetics has been investigated both in the laboratory and the clinical context.

In a recent review article [35] considered the laboratory evidence for neurotoxicity of general anaesthetics. In some animal models a paradoxical improvement in memory has been shown amongst rats exposed to GA – however refinement of the model showed a consistent impairment in learning for 2-3 weeks following exposure [12]. Experiments on cells in vitro have exposed some potential pathways for neurotoxicity of GA agents – notably in the oligomerisation of Aβ peptides linked with Alzheimer’s disease [49]. The applicability of the laboratory work to clinical practice is not yet clear.
Clinical assessment of the impact of GA on neurotoxicity has been addressed by studies comparing regional anaesthesia (RA) with GA. A number of trials have looked at this with the majority finding no significant difference between the two suggesting that GA plays only a small role in POCD, however, methodological limitations complicates their results [38]. It is worth noting that the largest study so far found – when using per protocol analysis – that there was a significant reduction in POCD amongst patients with RA (12.7%) compared to patients receiving GA (21.2%) at one week postoperatively [39]. Evidence from these trials is therefore still somewhat inconclusive.

An alternative assessment of the impact of GA can be achieved through the monitoring of the depth of anaesthesia. However, this method is likely to pick up additional systemic effects of sedation as well as any direct neurotoxicity from GA. Depth of anaesthesia monitoring using electroencephalography has been attempted in four papers.

Three randomised control trials were reported [17, 18, 48]. Gaba et al. have not reported full analysis of their data, however, they found no correlation between BiS values and postoperative delirium. Wong et al randomised patients to either titration of isoflurane to Bispectral Index Scores (BiS) of 50-60 or standard treatment. In the intervention group they showed a 30% reduction in use of isoflurane (p <0.05), a reduction in time to orientation (p < 0.01) and no difference in POCD. However the analysis of POCD was done without reference to baseline values and by repeating the neuropsychological tests 7 times within the first 72 hours postoperatively[18]. Without a control group for learning effect and conducting all psychometric tests within 3 days postoperatively these results are more applicable to postoperative delirium than POCD.

Farag et al randomised patients to two different anaesthetic depths and found a significant reduction in cognitive decline in the group randomised to deeper levels of anaesthesia (p = 0.006) in one of their three neuropsychological tests – the processing speed index – at 4-6 weeks postoperatively. Unfortunately the two anaesthetic depths were similar and both overlapped with the ideal level of sedation (a BiS score of between 40-60 [37]). It has also been noted that there was poor compliance with the target BiS values – patients in the low BiS group were within or below the range only 54% of the time and in the high BiS group were within or above the range for only 57% of the time[45].

Steinmetz et al. conducted an excellent correlation study using intraoperative cerebral state index (CSI) – a very similar measure to BiS - with POCD. They found no statistical difference in mean CSI, deep hypnotic time (CSI<40) and light hypnotic time (CSI>60) between patients with POCD and those without at 1 week postoperatively. They also found no significant correlation between the Z scores for the 7 neuropsychological tests and mean CSI [45].

Given the mixed results found using depth of anaesthesia monitoring and issues with study design further research is urgently needed. Any role for GA in the development of POCD is far from clear.
Postoperative Recovery

A number of routine postoperative medications are known to have significant effects on patients’ cognitive response especially in attention and reaction speed tasks. This effect has been monitored only sporadically in POCD studies and has been found to be significant in some trials (see for example opioid medication in [45]). However, a study addressing the effect of benzodiazepines in elderly patients found no significant relationship between blood concentrations of the drug and POCD [41]. Despite this finding the use of neurologically active drugs in studies of POCD is a potentially important confounder. Postoperative complications including infection and respiratory difficulties have been shown to be associated with increased risk of POCD [31]. Careful consideration of these potential confounders is therefore essential.

Prevention

No modifiable cause of POCD in non cardiac surgery has yet been identified[38]. Several trials have considered possible mechanisms (reviewed in (Newman et al., 2007). These include normotensive and hypotensive anaesthesia, intravenous versus inhalation Anaesthesia, pulse oximetry monitoring, hypocapnia and vitamin supplementation. None have found significant effects with respect to POCD[34].

As identified previously, several trials in cardiac surgery have shown some promise in preventing POCD[23, 43]. In non-cardiac surgery to date only one trial has shown a reduction in a sub test of POCD[17]. This trial has been heavily criticised in the literature[45] and the results therefore need cautious interpretation.
Methods

The study protocol was approved by the local research ethics committees and all patients gave written informed consent. Patients were taken from two UK regional teaching hospitals and were matched based on age, gender and baseline mini mental state exam (MMSE) to control subjects taken from the local regions. The full selection protocol for surgical patients has been published previously [29]. Patients were included if they were scheduled to undertake elective major abdominal or orthopaedic surgery under general anaesthesia at either centre. Exclusion criteria included age under 60 years, inability to complete or unwillingness to comply with any of the protocol or procedures and pre-existing dementia (defined as a MMSE score of 23 or less).

Assessments

Patients were assessed using a combination of the MMSE and the standard computerised drug research (CDR) battery. Assessments were carried out at baseline (preoperatively for surgical patients) and as a minimum at 12 months following the baseline assessment.

In line with previous studies cognitive decline was classified at three levels; mild, moderate and severe[36]. These levels correspond to measures commonly used to describe cognitive decline in elderly subjects, specifically; age associated cognitive decline (AACD), mild cognitive impairment (MCI) and post-operative cognitive dysfunction (POCD). The scores were calculated using the ISPOCD Z score method described previously [31]. The change for individual subjects from baseline was calculated and the control group was used to remove any learning effect and to provide the values for standard deviation. The following seven cognitive tests were used; MMSE, simple reaction time, digit vigilance accuracy, digit vigilance reaction time mean, choice reaction time accuracy, choice reaction time mean and cognitive reaction time mean. The level of cognitive decline was defined as follows;

Mild (AACD) = greater than 1 SD decline in at least one of the seven cognitive domains.

Moderate (MCI) = greater than 1.5 SD decline in at least one of the seven cognitive domains.

Severe (POCD) = greater than 1.96 SD decline in at least two of the seven cognitive domains.

Analysis

A sample size of 250 patients provides a 99% power to detect a difference of 25% between the two groups with a 0.05 risk of type 1 error. Assuming a patient loss to follow up at one year of 25% this requires an initial study population of 313. The 25% difference in proportions of decline was based on the 3 month difference in mild cognitive decline reported previously from the London cohort 1.

Analysis was conducted using SPSS software, version 17.0 (SPSS, Chicago, IL, USA). Significance was determined as two-sided p values <0.05. No correction was made for multiple comparisons.
Comparison of the baseline MMSE, age and gender of the control and surgical groups was made using the \( \chi^2 \) test, Student’s \( t \) test and Mann–Whitney \( U \) test as appropriate. The Kolmogorov-Smirnov test was used to establish deviation from a normal distribution.

The primary outcome measure was predetermined as the difference in the prevalence of mild, moderate and severe cognitive decline between surgical patients and controls assessed using the \( \chi^2 \) test. Continuous analysis was also conducted on the individual cognitive domains using Student’s \( t \) test, the Mann–Whitney \( U \) test as appropriate.
Results
Cohort Analysis

Population Characteristics

330 subjects were assessed at baseline including 192 surgical patients and 138 controls. The baseline characteristics are reported in table 1. There was no significant difference in Age (p = 0.498), baseline MMSE (p= 0.252) or Gender (p = 0.563) between the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Median (IQR)</th>
<th>Test</th>
<th>Asymp. Sig. (2-tailed)</th>
</tr>
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<tbody>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>patient</td>
<td>192</td>
<td>75 (9)</td>
<td>M-W</td>
<td>0.498</td>
</tr>
<tr>
<td>control</td>
<td>138</td>
<td>76 (7)</td>
<td></td>
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<td>MMSE</td>
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<td>192</td>
<td>28 (2)</td>
<td>M-W</td>
<td>0.252</td>
</tr>
<tr>
<td>control</td>
<td>138</td>
<td>28 (2)</td>
<td></td>
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<tr>
<td>Male Gender</td>
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<tr>
<td>patient</td>
<td>192</td>
<td>40%</td>
<td></td>
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<tr>
<td>control</td>
<td>138</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1

A total of 256 (78%) subjects completed all of the 1 year assessments. There were no significant differences with respect to Age (p = 0.910), baseline MMSE (p = 0.313) or Gender (p= 0.372) between subjects who completed the 1 year assessment and those who did not.

Global Decline

At one year post operatively there was a significant difference between patients and controls in all three levels of cognitive decline. Mild POCD was found in 76% of surgical patients compared to 50.4% of nonsurgical controls (Pearson $\chi^2$ p <0.001). Moderate POCD was found in 48% of surgical patients compared to 27.5% of nonsurgical controls (Pearson $\chi^2$ p = 0.001). Severe POCD was identified in 11.2% of surgical patients compared to just 3.8% of nonsurgical controls (Pearson $\chi^2$ p = 0.024). These results are displayed in figure 1.

![Percentage of Subjects with POCD at 1 year](image)
Individual Domains

Significant differences were found between surgical patients and controls with respect to simple reaction times - median(IQR) 25.57(73.80) v 9.52(49.75) \( p = 0.025 \), cognitive reaction times - median(IQR) -25.69(120.96) v -3.42(65.35) \( p = 0.006 \) and digit vigilance mean accuracy (median (IQR) 0.00 (4.44) v 0.00 (0.00) \( p = 0.05 \)). The full results of the continuous analysis are presented in table 2.

<table>
<thead>
<tr>
<th></th>
<th>Z</th>
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<td>.614</td>
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<td>9.25 (59.26)</td>
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<td>control</td>
<td>-3.42 (65.35)</td>
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Table 2
Discussion

This is the first longitudinal cohort study of POCD to demonstrate a significant difference in the level of global cognitive decline between surgical patients and controls at 12 months post operatively. It identifies attentional and executive function as particularly sensitive neurocognitive domains in POCD.

It is important to address the reasons why our trial has successfully identified significant differences in the level of cognitive decline where previous trials have not. I have highlighted three possible mechanisms for this:

- The reduction of ceiling and learning effects using the CDR system
- The use of multiple levels of POCD
- The focus on attention and executive function

Our emphasis on computerised neuropsychometric analysis and reaction speeds substantially reduces the learning effect observed with many other studies[47]. It is worth noting that the only other 12 month trial to demonstrate any difference between surgical patients and controls also employed a computerised test battery[3]. Previous studies into POCD including the work of the ISPOCD study group is substantially hampered by learning effect. Despite attempts to account for the effect using a control group this analysis method exposes trials to 2 primary flaws.

Firstly the trial is not truly assessing cognitive decline but rather a failure to recall the neuropsychometric tests and to demonstrate cognitive improvement. It has been previously noted that memory function appears less significant in POCD than executive function and has a lower impact on patients functional impairment[36].

Secondly the fixed and invariable nature of paper-based neuropsychometric tests exposes them to a potential retest ceiling effect. This is distinct from an initial ceiling effect which will tend to overestimate the levels of POCD[9]. Instead during repeated retesting over a short time period subjects can achieve extremely high scores from which further improvement becomes exponentially difficult. The normal subjects reach the test ceiling early and subsequent retesting provides impaired subjects an opportunity to catch up. POCD studies focusing on differences in the learning effect will therefore tend to produce a gradual convergence in test scores between impaired and non-impaired subjects despite continued cognitive deficits within the impaired group – demonstrated graphically in figure 2.

This pattern has been observed in previous studies of POCD and has been presented as a reduction in the level of cognitive dysfunction with time [31]. The retest ceiling effect is substantially reduced, though not completely eliminated, with the CDR system employed in our study as a result of the variability of the
target, the emphasis on reaction times and the use of practice sessions prior to each test to standardise familiarity with the tasks and equipment and has been demonstrated empirically[47].

Whilst our definition of three levels of POCD has been used previously[36] it is not widely employed in POCD research. However, in our opinion it carries a number of advantages. Firstly it allows for the detection of more subtle changes in cognitive function – sacrificing specificity for increased sensitivity to cognitive decline. Improving the sensitivity for decline has identified a greater percentage difference between surgical and control populations, substantially increasing the statistical power to detect a variation in the proportions of two populations. This method also allows for comparison with the extensive literature on cognitive decline in the elderly – with the definitions corresponding to age associated cognitive decline and mild cognitive impairment. Finally we have also included the classic definition of severe POCD allowing for comparison with previous literature within this field.

Very few earlier papers assessing POCD over six months post operatively (table 4 appendix) have incorporated measures of attention and executive function. Our emphasis on these two cognitive domains was based on the evidence demonstrating their significance for functional impairment associated with cognitive decline in the elderly [8, 36]. The results from this study demonstrate that both attention and executive function are significantly affected in elderly surgical patients one year post operatively. Given the significant impact on functional impairment caused by these specific cognitive domains our findings may help to explain the substantial evidence demonstrating the continued impact of POCD on patients’ mortality and their capacity to function within society well beyond the 3 month cut off point previously identified[44].

As the first trial to identify significant levels of POCD a full twelve months post operatively our findings represent an important step in bridging the gap that has emerged between the impact of POCD on patients’ lives and our capacity to identify cognitive impairment beyond 3 months post operatively. Given the recent evidence demonstrating the mortality and morbidity associated with POCD as well as increased costs to the health service the identification of modifiable causes of POCD is an important research challenge. This trial establishes the combination of computerised neuropsychometric testing, a focus on attention and executive function and a multilevel approach to scoring cognitive decline as a powerful new method for identifying the long term effects of POCD. Our methods substantially reduce the experimental problems faced by previous trials and provide a greater sensitivity for differences in cognitive decline with a longer duration of effect. It is our hope that our findings will pave the way for future intervention trials.
### Table 3

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<th>visual and spatial</th>
<th>Visuo-motor</th>
<th>numerical</th>
<th>executive function</th>
<th>composite screening tools</th>
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<td>x</td>
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<td>N</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>up language</td>
<td>visuospatial</td>
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**Note:** A blank cell indicates results of no interest.
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