Neuroscience and Biobehavioral Reviews 36 (2012) 2118–2129

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

A meta-analysis of cognitive outcome following coronary artery bypass graft surgery

Francesca Cormack[a], Alex Shipolini[b], Wael I. Awad[b], Cassandra Richardson[c], David J. McCormack[b], Luciano Colleoni[b], Malcolm Underwood[d], Torsten Baldeweg[e], Alexandra M. Hogan[b,e,f,*]

[a] MRC Cognition & Brain Sciences Unit, 15 Chaucer Road, Cambridge, UK
[b] Barts and The London, NHS Trust/Queen Mary University of London, UK
[c] Brighton & Sussex Medical School, University of Sussex, Brighton, UK
[d] Prince of Wales Hospital, Shatin, New Territories, Hong Kong
[e] UCL Institute of Child Health, Guildford Street, London, UK
[f] University College London Hospital, NHS Trust, Euston Road, London, UK

ARTICLE INFO

Article history:
Received 7 March 2012
Received in revised form 16 May 2012
Accepted 12 June 2012

Keywords:
Coronary artery bypass graft surgery
Cognition
Meta-analysis

ABSTRACT

Coronary artery bypass graft (CABG) surgery is an established treatment for complex coronary artery disease. There is a widely held belief that cognitive decline presents post-operatively. A consensus statement of core neuropsychological tests was published in 1995 with the intention of guiding investigation into this issue. We conducted a meta-analysis evaluating the evidence for cognitive decline post-CABG surgery. Twenty-eight published studies, accumulating data from up to 2043 patients undergoing CABG surgery, were included. Results were examined at 'very early' (<2 weeks), 'early' (3 months) and 'late' (6–12 months) time periods post-operatively. Two of the four tests suggested an initial very early decrease in psychomotor speed that was not present at subsequent testing. Rather, the omnibus data indicated subtle improvement in function relative to pre-operative baseline testing. Our findings suggest improvement in cognitive function in the first year following CABG surgery. This is contrary to the more negative interpretation of results of some individual publications included in our review, which may reflect poor outcomes in a few patients and/or methodological issues.

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* Corresponding author at: UCL Institute of Child Health, 30 Guildford Street, London, WC1E 6BT, UK. Tel.: +44 20 7905 2746; fax: +44 20 7905 2616.
E-mail addresses: francesca.cormack@mrc-cbu.cam.ac.uk (F. Cormack), alex.shipolini@bartsandthelondon.nhs.uk (A. Shipolini), Wael.Awad@bartsandthelondon.nhs.uk (W.I. Awad), C.Richardson2@bsms.ac.uk (C. Richardson), djmccormack@doctors.org.uk (D.J. McCormack), lucianocolleoni@googlemail.com (L. Colleoni), mjunderwood@surgery.cuhk.edu.hk (M. Underwood), t.baldeweg@ucl.ac.uk (T. Baldeweg), a.hogan@ucl.ac.uk (A.M. Hogan).

0149-7634
http://dx.doi.org/10.1016/j.neubiorev.2012.06.002

1. Introduction

The neurological consequences of CABG have been well documented (Newman et al., 2006; Selnes et al., 2012) but there remains uncertainty about the severity and timing of post-operative cognitive decline, and its relationship with any underlying damage to the brain. There is a continuum of decline from mild, transient cognitive impairment without evidence of brain insult, to the more devastating occurrence of clinical stroke and perhaps even onset of dementia at the other extreme. A recently published study described a total overall stroke incidence of 1.6% in 45,432 patients presenting for CABG surgery between 1982 and 2010 (Tarakji et al., 2011). Estimates of the risk of milder impairments are much more variable, ranging from an early 3% estimate (Roach et al., 1996), to considerably higher when clinically silent brain lesions are taken into account (e.g. 45% by magnetic resonance imaging (MRI) diffusion weighted imaging) (Knipp et al., 2004).

The potential for post-operative cognitive decline has resulted in the greatest uncertainty in this literature. Post-operative cognitive decline has been described in approximately half of patients at time of discharge from hospital (Knipp et al., 2008; Newman et al., 2001; Norkiené et al., 2011; Slater et al., 2009), with subsequent decrease in incidence to around one-fifth to one-third of patients only a few weeks later (Knipp et al., 2008; Newman et al., 2001; Van Dijk et al., 2002), and then a late rise in incidence at one to five years post-operatively (Knipp et al., 2004; Newman et al., 2006; Van Dijk et al., 2002, 2007). Other studies (McKhann et al., 2005; Selnes et al., 2003; Van den Goor et al., 2008) have reported improvement in cognition in the early period post-CABG, with some going so far as to argue that "there are no detrimental effects of uncomplicated cardiac surgery assisted by cardio-pulmonary bypass on cognitive function, irrespective of the type of cardiac surgery." (Van den Goor et al., 2008). Notwithstanding this divergence of opinion, an understanding of the magnitude, time course and profile of any cognitive decline following CABG surgery is necessary for risk assessment and possible implementation of neuroprotective strategies (Selnes et al., 2012). The present study aims to add to a few but increasing number of well-controlled studies (Keizer et al., 2005; Selnes et al., 2009) and systematic reviews (Alston, 2011; Rudolph et al., 2010) that seek to address this issue.

The majority of studies have dichotomized cognitive outcome after surgery, classifying patients as "impaired" or "unimpaired" on the basis of their baseline cognitive performance. Whilst this approach has the advantage of delivering a headline rate of cognitive impairment in the population of interest, it has several limitations, not least of which is a lack of consensus for defining impairment (Rudolph et al., 2010). One comparison of the different criteria used in studies of post-operative cognitive function found that there were at least nine different statistical definitions of cognitive decline (Rasmussen et al., 2001). The authors applied these different definitions to a control sample of 176 non-hospitalized elderly control participants and found that the estimates of cognitive decline differed dramatically depending on the criterion used, ranging from 0 to 39% of cases. Others have recommended that the quantification of the decline observed in each patient is provided as a proportion of the change seen in a control group over a similar interval, thereby controlling for background levels of change and for practice effects (Silbert et al., 2004); however, this approach has not been widely adopted. The variable criteria for 'decline' may explain some of the discrepancy in prevalence of post-operative cognitive decline and limits our ability to make inferences across different studies in different centres. Furthermore, the reduction of continuous variables into binary variables limits the sensitivity to relative severity of impairment across individuals and domains, and over time. Consequently, analysis of the raw (mean) scores and standard deviations of these studies is required for any meaningful conclusions to be made (Selnes et al., 2012).

A further factor which complicates interpretation of the literature is the variability in timing of cognitive assessment. The follow-up period used by different studies ranges from up to one week after surgery (pre-discharge from hospital), to three or more years at the other extreme (Newman et al., 2001; Selnes et al., 2009; Van Dijk et al., 2008). As outlined above, the highest rates of post-operative cognitive decline (approximately 50% of patients) have been observed in the early weeks following surgery, followed by a significant reduction in incidence over the first 6 months (Knipp et al., 2008; Newman et al., 2001; Van Dijk et al., 2002). In addition to the severity of the observed impairment, its likely duration and persistence has clear clinical implications, but this has rarely been systematically addressed in this population using case-controlled longitudinal studies with similar criteria for determining decline.

There is no reason to predict that all regions of the brain will be uniformly affected during CABG surgery. For example, the relative vulnerability of the hippocampus to hypoperfusion (Román, 2004), such as may be encountered during CABG surgery, and its association with memory would lead cognitive neuroscientists to predict that this domain of function will be particularly susceptible to decline. However, other processes, such as the release of micro-emboli during cardio-pulmonary bypass, may affect the brain differently, for example, focusing any insult on deep white matter at arterial borderzones (Moody et al., 1990) and hence reduce speed of psychomotor processing amongst other domains of function. In part to reflect this heterogeneity of the possible neural consequences of CABG surgery, a wide variety of pencil and paper, and computerized (Van den Goor et al., 2008) cognitive tests have been employed. Comparison across these different tests is problematic, as they vary in their psychometric properties, particularly their susceptibility to practice effects and their sensitivity to subtle impairment and longitudinal change, as well as in their specificity to the brain insults thought to be associated with CABG (Lewis et al., 2004; Polunina, 2008; Rasmussen et al., 2001). In an attempt to provide some coherence to the field, Murkin and colleagues came together in 1995 (Murkin et al., 1995) to draft a consensus statement on the assessment of cognitive function after cardiac surgery. This included a small battery of tests with parallel forms and established data on test-retest reliability which they recommended formed the core assessment of cognition in the CABG-surgery population. Since publication, a large number of authors have at least partially adopted the recommendations of the consensus statement enabling us now, approximately fifteen years later, to examine the profile of cognitive outcome following CABG surgery.

With the above issues in mind, we performed a meta-analysis to evaluate trends in neuropsychological results across studies of patients undergoing CABG surgery. Results were examined parametrically (from means and standard deviations) rather than dichotomously (e.g. 'impaired or not'). We also considered the effect of post-operative interval, and conducted a regression analysis to explore potential associations. By combining data from studies that have used the same neuropsychological tests recommended by the consensus statement, we hope to get a fuller picture of the severity and duration of any cognitive dysfunction. This may offer an important insight for wider efforts to understand and quantify post-operative cognitive decline after CABG surgery.

2. Methods

2.1. Search strategy

Published studies assessing neuropsychological performance after CABG were considered. Studies were identified from

Table 1
Study and patient characteristics for the included studies.

	CPB	*N*	Age	(SD)	Male (%)	Diabetes (%)	HBP (%)	Stroke (%)	Dropout (*n*)	Follow up	Neuropsychological tests
Ahlgren et al. (2003)	On	23	65.7	3.3	91	17	39		0	4–6 wk	RAVLT, Trails A, Trails B
Baker et al. (2001)	On	14	65.9	8.3	71	30	70	0	4	1 wk, 6 mo	Trails A, Trails B
	Off	12	61.7	11.7	92	11	56	0			
Djaiani et al. (2007)	On	95	67.5	6	89	38	71		0	6 wks	GPB
Dupuis et al. (2006)	On	364	–	–	60.7	22.6		2.7	0	5–11 mo	Digit Symbol
Ernest et al. (2006)	On	61	63.7	10.7	81	31	79	3.6	15	2 mo, 6 mo	Digit Symbol, GPB, RAVLT, Trains A, Trails B
	Off	46	63.2	9	78	27	79	7.1			
Grigore et al. (2002)	On	100	62.1	10.6	70	18	63	3	0	6 wks	Digit Symbol, Trails B
Heyer et al. (2002)	On	35	62.5	11.3	89	36.1	52.7		6	5 d, 6 wk	GPB, Trails A, Trails B
Kadoi and Goto (2006)	On	88	62.4	10.5	80	22	55.7		0	6 mo	GPB, Trails A, Trails B
Khosravi et al. (2005)	On	20	65.2	9.3	80				0	1 wk, 4–6 mo	Digit Symbol, RAVLT
Knipp et al. (2004)	On	20	67.6	8.7	83	35	76	0	6	3 mo	Trails A, Trails B
Lee et al. (2003)	On	30	66	11.2	73	37	87	3	1	2 wks, 1 yr	Digit Symbol, GPB, RAVLT, Trains A, Trails B
	Off	30	65.5	9.1	80	20	70	7			
Lund et al. (2005)	On	52	65.2	8.4	72		43	6.6	8	3 mo, 1 yr	Digit Symbol, RAVLT
	Off	49	64.8	7.8	85		42	8.3	6		
Müllges et al. (2002)	On	52	63	7	84.6	31	68	0	0	9 d, 3–5 yrs	Trails A, Trails B
Newman et al. (2001)	Off	261	61	10.4	71.6	13.2	51.8	4.8		< 2ks, 6 wks, 6 mo	RAVLT, GPB
Rankin et al. (2003)	Both	43	61.1	9.8	77				9	2–3 mo	GPB, Trails A, Trails B
Robson et al. (2000)	On	102	59	9	88.2				0	3 mo	Digit Symbol, GPB, RAVLT, Trails A, Trails B
Rubens et al. (2007)	On	125	58.7	9.3	90	32	70		12	1 wk, 3 mo	GPB, RAVLT, Trails A, Trails B
Selnes et al. (2009)	On	152	63.6	9.4	76	30	64	5	30	1 yr, 72 mo	GPB, RAVLT, Trails A, Trails B
	Off	75	66	10.5	72	37	68	3			
Silbert et al. (2004)	On	50	66.3		82	30	30	0	0	6 d	Digit Symbol, GPB, Trails A, Trails B
Silbert et al. (2008)	On	281	68.4	7.8	75.5	24	81			3 mo, 12 mo	Digit Symbol, GPB, Trails A, Trails B
Stroobant et al. (2008)	Both	53	59	7.5	88.9	28.8	53.9		0–11	6 d, 6 mo, 3–5 yrs	GPB, RAVLT, Trails B
Stygall et al. (2003)	On	107	60.5	8.1	86.9				8	3–5 d	GPB, RAVLT, Trails A, Trails B
Sugiyama et al. (2002)	On	65	63	9	83	32	35		0	10–14 d	Digit symbol
Szalma et al. (2006)	On	47	56.2	5.5	78			0	1	6 wks	Digit Symbol
Van Dijk et al. (2002)	On	139	60.8	8.8	71	17	44	3	0–20	3 mo, 12 mo	Digit Symbol, GPB, RAVLT, Trails B
	Off	142	61.7	9.2	66	9	40	4	14		
Vedin et al. (2006)	On	37	65	9.1	84	19	46	0	0–37	1 wk, 1 mo, 6 mo	Digit Symbol, Trails A, Trails B
	Off	33	65	9.1	78	18	52				
Wang et al. (2002)	On	45	59.3	9.4	97.8	20	53.3	0	0	1 wk	Digit Symbol, GPB
Zamvar et al. (2002)	On	30	61.6	10	90			0	0–15	1 wk, 10 wk	Digit Symbol, GPB, RAVLT, Trails A, Trails B
	Off	30	63.5	9.1	83						
Zimpfer et al. (2004)	On	104	64.1	9.8	89.1	40.2	82.5	0	16	1 wk, 36 mo	Trails A

CPB – Cardiopulmonary bypass; HBP – High Blood Pressure; GPB - Grooved Pegboard Test.

systematic literature searches of databases including Cochrane (reviews and registry of controlled trials), Medline and PsycINFO. Searches were limited to the past 10 years in order to provide a picture of outcome following current practice. This also allowed time for the recommendations of the consensus statement, which was published in 1995, to impact on the wider literature.

The search strategy included the terms 'coronary revascularisation', 'coronary artery bypass', 'neurocognitive', 'cognitive', 'neuropsych*' and 'brain function'. All studies were then reviewed to determine if they had included neuropsychological outcomes as an endpoint. A search of other reviews of CABG was also conducted, checking the reference lists of these articles for further relevant studies.

2.2. Inclusion and exclusion criteria

Trials and observational studies evaluating cognitive function before and after CABG surgery in the years 2000–2010 were included. Neuropsychological testing as a study endpoint was a prerequisite. Studies were selected for inclusion if they included patients with first time CABG as their only surgical intervention. Both on and off pump CABG were included; whilst some earlier studies have suggested worse outcome when cardio-pulmonary bypass is used ("on-pump") (Stroobant et al., 2005), others have shown that there is no significant difference in outcome (Selnes et al., 2009); this variable was nonetheless explored in subanalyses. Studies were excluded where there was no assessment of neuropsychological function, the assessment did not include any measures included in the consensus statement, or means and standard deviations were not reported in the paper. Studies were excluded if they did not report preoperative performance.

2.3. Overview of consensus statement neuropsychological tests

Grooved Pegboard: this assesses fine motor speed as the individual simply has to place pegs in holes as quickly as possible. *Digit Symbol Test*: requires the individual to draw the correct symbols to match numbers as quickly as possible according to a 'key' that is left in front of them – assesses psychomotor speed. *Trails A/B Test*: is also a test of psychomotor speed that additionally requires a greater degree of planning and working memory (executive functions). It requires the individual to draw lines to connect letters and numbers in a pre-specified sequence. *RAVLT – Rey Auditory Verbal Learning Test*: assesses short-term memory for supraspan word lists.

2.4. Statistical analysis

The outcomes were analyzed as continuous variables based on the mean and standard deviation. The weighted mean difference was calculated for each outcome. The meta-analysis was performed using Review Manager (RevMan) Version 5 for Windows. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Further analysis was carried out using PASW18 (SPSS). Heterogeneity across trials was quantified using the I^2 statistic. Random effects (Der-Simonian and Laird) model was chosen for all analyses, as a large number of comparisons showed significant heterogeneity. Statistical significance was defined as two-sided $p < 0.05$.

3. Results

Initial search yielded 435 papers, of which 220 were selected for preliminary review as potentially meeting the criteria. From these, 28 met the inclusion criteria and were included in the final analysis (see Table 1 for overview). The main reasons for study exclusion were lack of consensus statement neuropsychological tests (23.6%),

Table 2
Summary of RAVLT meta-analysis results.

Study	CPB	Baseline			Very early					Early				Late				
		Mean	SD	*n*	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI
Ahlgren et al. (2003)	On	36.40	9.80	23						44.20	11.60	23	0.71	[0.12, 1.31]					
Ernest et al. (2006)	On	37.85	10.30	46						37.48	9.10	31	−0.04	[−0.49, 0.42]	40.59	12.06	32	0.33	[−0.12, 0.79]
	Off	37.20	9.63	61						37.90	9.00	44	0.07	[−0.31, 0.46]	40.25	10.00	47	0.23	[−0.15, 0.62]
Lee et al. (2003)	On	39.20	16.10	29	44.40	15.20	29	0.33	[−0.19, 0.85]						42.70	12.00	26	0.52	[−0.02, 1.06]
	Off	36.10	13.10	29	42.20	13.60	29	0.45	[−0.07, 0.97]						43.70	14.80	27	0.29	[−0.24, 0.81]
Lund et al. (2005)	On	35.70	7.90	60						41.20	8.70	52	0.66	[0.28, 1.04]	37.40	10.70	52	0.39	[0.01, 0.76]
	Off	33.60	8.90	60						37.90	9.00	54	0.48	[0.10, 0.85]	41.80	7.90	54	0.77	[0.39, 1.15]
Robson et al. (2000)	On	50.50	8.90	102						54.00	8.40	102	0.40	[0.13, 0.68]					
Rubens et al. (2007)	On	40.93	9.10	125	39.33	7.31	118	−0.19	[−0.44,0.06]	41.89	7.54	113	0.11	[−0.14, 0.37]					
Selnes et al. (2009)	On	39.10	8.80	152											44.60	10.60	124	0.57	[0.33, 0.81]
	Off	38.50	9.20	72											42.30	10.30	55	0.39	[0.04, 0.74]
Stroobant et al. (2008)	Both	45.10	9.60	54	43.60	9.60	54	−0.16	[−0.53, 0.22]						49.60	9.70	43	0.46	[0.06, 0.87]
Stygall et al. (2003)	On	42.68	9.53	107	41.73	11.14	107	−0.09	[−0.36, 0.18]	44.23	9.89	107	0.16	[−0.11, 0.43]					
Van Dijk et al. (2002)	On	36.00	8.58	139						37.00	10.92	120	0.10	[−0.14, 0.35]	41.00	10.14	122	0.52	[0.28, 0.77]
	Off	36.00	8.97	142						38.00	9.75	128	0.21	[−0.03, 0.45]	37.00	9.75	130	0.11	[−0.13, 0.35]
Zamvar et al. (2002)	On	35.20	8.99	30	34.00	4.10	30	−0.17	[−0.68, 0.34]	36.53	8.00	30	−0.15	[−0.35, 0.66]					
	Off	36.00	8.38	30	33.42	10.00	29	−0.28	[−0.79, 0.24]	38.00	9.20	30	−0.22	[−0.22, 0.73]					
Total					N1 = 404; N2 = 396			−0.07	[−0.23, 0.10]	N1 = 925; N3 = 834			0.24***	[0.13, 0.36]	N1 = 844; N4 = 712			0.41**	[0.29, 0.53]

CPB – cardio pulmonary bypass status; ES – effect size estimate (standardized mean difference).
** Significant $p < 0.001$.
*** Significant $p < 0.0001$.

Table 3
Summary of Digit Symbol meta-analysis results.

Study	CPB	Baseline			Very early					Early					Late				
		Mean	SD	*n*	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI
Dupuis et al. (2006)	On	39.00	11.90	364											41.60	11.80	546	0.22	[0.09, 0.35]
Ernest et al. (2006)	On	45.93	12.82	46						48.71	14.10	31	0.21	[−0.25, 0.66]	49.94	12.46	32	0.31	[−0.14, 0.77]
	Off	49.03	12.28	61						51.58	13.43	44	0.20	[−0.19, 0.59]	52.30	13.96	32	0.25	[−0.18, 0.68]
Grigore et al. (2002)	On	39.55	12.87	100						43.06	13.90	100	0.26	[−0.02, 0.54]					
Khosravi et al. (2005)	On	38.09	9.50	20	41.39	11.50	20	0.31	[−0.32, 0.93]						40.49	11.90	20	0.22	[−0.40, 0.84]
Lee et al. (2003)	On	52.50	17.00	29	35.50	19.50	29	−0.92	[−1.46, −0.37]						53.80	22.10	30	0.06	[−0.45, 0.58]
	Off	45.30	17.00	29	42.90	12.00	29	−0.16	[−0.68, 0.35]						43.70	14.50	30	−0.10	[−0.61, 0.41]
Lund et al. (2005)	On	36.40	9.60	60						38.80	9.70	52	0.25	[−0.13, 0.62]	39.10	10.10	52	0.27	[−0.10, 0.65]
	Off	36.60	8.90	60						38.90	10.40	54	0.24	[−0.13, 0.61]	38.50	10.20	52	0.20	[−0.17, 0.57]
Newman et al. (2001)	On	38.78	13.71	261	33.44	13.60	252	−0.39	[−0.57, −0.22]	45.28	14.24	222	0.47	[0.28, 0.65]	46.46	14.02	210	0.55	[0.37, 0.74]
Robson et al. (2000)	On	42.60	9.00	102						44.10	10.50	102	0.15	[−0.12, 0.43]					
Silbert et al. (2004)	On	33.80	13.80	50	27.70	12.50	50	−0.46	[−0.86, −0.06]	38.20	10.70	280	0.40	[0.23, 0.57]	38.50	11.20	280	0.42	[0.25, 0.59]
Sugiyama et al. (2002)	On	39.00	11.00	65	39.00	13.00	65	0.00	[−0.34, 0.34]										
Szalma et al. (2006)	On	27.56	11.94	46						29.57	11.10	47	0.17	[−0.23, 0.58]					
Van Dijk et al. (2002)	On	39.00	7.96	139						42.00	7.10	120	0.39	[0.15, 0.64]	41.00	8.28	122	0.25	[0.00, 0.49]
	Off	41.00	8.90	142						45.00	9.00	128	0.45	[0.20, 0.69]	42.00	9.40	122	0.11	[−0.13, 0.35]
Vedin et al. (2006)	On	36.00	10.64	37						41.00	4.37	34	0.60	[0.12, 1.08]	39.00	7.07	32	0.32	[−0.15, 0.80]
	Off	40.00	10.05	33						42.00	6.95	31	0.23	[−0.26, 0.72]	42.00	4.10	32	0.26	[−0.23, 0.74]
Wang et al. (2002)	On	30.00	10.00	45						27.60	11.10	45	−0.23	[−0.64, 0.19]					
Zamvar et al. (2002)	On	42.80	18.19	30	35.46	9.60	29	−0.50	[−1.01, 0.02]	38.74	8.10	30	−0.28	[−0.79, 0.22]					
	Off	42.47	10.23	30	40.97	8.10	30	−0.16	[−0.67, 0.35]	45.30	6.70	30	0.32	[−0.19, 0.83]					
Total					*N* = 514, 504			−0.30*	[−0.5, 0.09]	*N* = 1472, 1350			0.29**	[0.20, 0.39]	*N* = 1561, 1592			0.29**	[0.20, 0.38]

CPB – cardio pulmonary bypass status; ES – effect size estimate (standardized mean difference).

* Significant $p < 0.05$.

** Significant $p < 0.001$.

Table 4
Summary of Grooved Pegboard meta-analysis results.

Study	CPB	Baseline			Very early					Early				Late				
		Mean	SD	*n*	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI
Djiani et al. (2007)	On	90.81	21.79	95						87.43	20.38	95	0.16	[−0.13, 0.44]					
Ernest et al. (2006)	On	91.30	20.11	61						87.53	21.30	44	0.18	[−0.21, 0.57]	81.84	16.23	47	0.51	[0.12, 0.89]
	Off	99.76	49.65	46						87.38	24.61	31	0.30	[−0.16, 0.75]	88.23	24.50	32	0.28	[−0.18, 0.73]
Heyer et al. (2002)	On	98.42	24.48	35	120.43	50.22	34	−0.55	[−1.03, −0.07]	98.97	29.15	29	−0.02	[−0.51, 0.47]					
Lee et al. (2003)	On	96.80	46.90	29	105.80	67.10	29	−0.15	[−0.67, 0.36]						91.50	26.00	26	0.14	[−0.39, 0.67]
	Off	97.80	30.70	29	92.30	29.10	29	0.18	[−0.33, 0.70]						91.50	26.00	27	0.22	[−0.31, 0.74]
Rankin et al. (2003)	Both	106.05	49.09	41						89.55	24.55	34	0.41	[−0.05, 0.87]					
Robson et al. (2000)	On	80.30	17.10	102						79.70	18.10	102	0.03	[−0.24, 0.31]					
Rubens et al. (2007)	On	80.84	14.84	125	88.89	14.61	118	−0.54	[−0.80, −0.29]	76.71	16.38	113	0.26	[0.01, 0.52]					
Selnes et al. (2009)	On	107.50	53.70	152											95.60	29.90	122	0.27	[0.03, 0.50]
	Off	99.60	30.90	67											94.20	32.10	54	0.17	[−0.19, 0.53]
Silbert et al. (2004)	On	97.30	32.50	50	114.40	28.70	50	−0.55	[−0.95, −0.15]	91.60	30.60	277	0.32	[0.15, 0.48]					
Stroobant et al. (2008)	Both	182.50	36.80	54	203.10	48.90	54	−0.47	[−0.86, −0.09]						177.40	34.90	43	0.14	[−0.26, 0.54]
Van Dijk et al. (2002)	On	104.00	19.50	139						102.00	14.04	120	0.12	[−0.13, 0.36]	102.00	17.55	122	0.11	[−0.14, 0.35]
	Off	106.00	19.11	142						100.00	18.72	128	0.32	[0.08, 0.56]	99.00	17.55	130	0.38	[0.14, 0.62]
Wang et al. (2002)	On	125.80	32.60	45						140.50	39.20	45	−0.40	[−0.82, 0.01]					
Zamvar et al. (2002)	On	91.20	38.05	30	85.87	37.20	29	0.14	[−0.37, 0.65]	111.90	22.90	30	−0.65	[−1.17, −0.13]					
	Off	99.93	48.52	30	94.60	32.50	30	0.13	[−0.38, 0.63]	95.73	14.10	30	0.12	[−0.39, 0.62]					
Total					*N* = 382, 373			−0.27*	[−0.50, −0.04]	*N* = 1168, 1078			0.13*	[0.00, 0.26]	*N* = 719, 603			0.25**	[0.14, 0.36]

CPB – cardio pulmonary bypass status; ES – effect size estimate (standardized mean difference).
* Significant $p < 0.05$.
** Significant $p < 0.001$.

no report of means and standard deviations (27.9%), patient groups that did not meet inclusion criteria (e.g. mix of first time and re-do operations, or concomitant valve surgery: 6.4%). The details of the studies included in the meta-analysis, including demographics and study design are presented in Table 1; funnel plots showed no publication bias. The results of the meta-analysis are summarized in Tables 2–6.

At the earliest post-operative time point (<2 weeks post-surgery: 'very early') data were available from 1003 participants in total, across all studies and sub-groups. A statistically significant slowing in the Digit Symbol ($Z = -2.82$; $p = 0.005$) and Grooved Pegboard tests ($Z = -2.33$, $p = 0.02$) was observed. However the other measures showed no significant difference from baseline (RAVLT: $Z = -0.76$, $p = 0.45$; Trails A: $Z = 1.37$, $p = 0.17$/Trails B: $Z = 0.01$, $p = 1.00$). Thus, at this earliest time point post-surgery (often pre-discharge from hospital), two measures indicated that speed of psychomotor performance was reduced but higher forms of cognitive function (memory, executive function) remained stable.

Three months post-operative ('Early') follow-up data were available from a total of 1933 participants. At this time a significant improvement is seen all measures (RAVLT: $Z = 4.22$ $p < 0.001$; Trails A: $Z = 4.91$, $p < 0.001$/Trails B: $Z = 3.15$, $p = 0.002$; Digit Symbol test: $Z = 5.98$, $p < 0.001$); Grooved Pegboard test: $Z = 1.99$, $p = 0.05$). This shows that by three months post-CABG, psychomotor speed had normalized and that in fact all measures showed improvement relative to baseline.

At the late (6–12 months: 'Late') time point, data were available from 2043 participants and once again significant improvements were seen in the majority of measures (RAVLT: $Z = 6.69$, $p < 0.001$; Trails A: $Z = 4.80$, $p < 0.001$; Digit Symbol test: $Z = 6.30$, $p < 0.001$; Grooved Pegboard test: $Z = 4.53$, $p < 0.001$). Trails B was not significantly different to baseline ($Z = 1.81$, $p = 0.07$). However, when data from one study with very long completion times both pre and post operatively were excluded (Kadoi and Goto, 2006), this comparison became significant ($Z = 4.74$, $p < 0.001$), and the heterogeneity was reduced to non-significant levels (I^2 82% vs. 44%).

In summary, across all four measures there was a trend towards improvement in cognitive function following CABG surgery, not decline. This is demonstrated in Fig. 1.

3.1. Cardio-pulmonary bypass

A number of the studies reported the comparison of on- and off-pump CABG. The effect of bypass on cognition was not the focus of the present meta-analysis and our selection criteria were not designed to compare these different interventions in a systematic way. However, our findings are broadly consistent with those of another recent meta-analysis (Marasco et al., 2008) in demonstrating only very limited differences between on and off pump groups. On-pump CABG patients were slower on the Digit Symbol subtest at the earliest time point (<2 weeks; $X^2 = 7.1$, df = 2, $p = 0.03$). Conversely, the on-pump group performed better at late follow up (6–12 months; $X^2 = 3.74$, df = 1, $p = 0.05$).

3.2. Meta-regression

Random-effects inverse variance weighted regression was carried out to investigate the impact of age, gender balance, incidence of hypertension, diabetes and drop-out rate on post-operative outcome at each time point. Study data were collapsed across sub-group and outcome measure at each time point, yielding one index of effect size per study for each time point. The predictors were entered separately and together. The only significant predictor was drop-out rate at time 1 ('very early' assessment),

Table 5
Summary of Trails A meta-analysis results.

Study	CPB	Baseline			Very early					Early					Late				
		Mean	SD	*n*	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI
Ahlgren et al. (2003)	On	47.30	17.80	23						49.50	23.70	23	−0.10	[−0.68, 0.48]					
Baker et al. (2001)	On	41.71	13.30	14	40.71	19.40	14	0.06	[−0.68, 0.80]						40.90	11.41	10	0.06	[−0.75, 0.87]
	Off	38.83	13.55	12	31.75	8.96	12	0.60	[−0.23, 1.42]						30.75	6.50	8	0.68	[−0.24, 1.61]
Ernest et al. (2006)	On	41.13	14.82	46						39.00	17.58	41	0.13	[−0.29, 0.55]	41.69	15.42	32	−0.04	[−0.49, 0.41]
	Off	42.64	14.96	61						39.39	11.49	44	0.24	[−0.15, 0.63]	37.45	11.33	47	0.38	[0.00, 0.77]
Heyer et al. (2002)	On	39.39	17.28	35	44.66	24.15	34	−0.25	[−0.72, 0.23]	40.60	15.52	29	−0.07	[−0.56, 0.42]					
Lee et al. (2003)	On	43.70	32.60	26	42.80	33.10	26	0.03	[−0.52, 0.57]						43.40	34.40	26	0.01	[−0.53, 0.55]
	Off	47.40	22.20	27	41.60	16.50	27	0.29	[−0.24, 0.83]						45.70	15.20	27	0.09	[−0.45, 0.62]
Kadoi and Goto (2006)	On	46.90	5.10	88											45.90	5.90	88	0.18	[−0.12, 0.48]
Knipp et al. (2004)	On	46.40	12.70	35						44.90	15.10	29	0.11	[−0.39, 0.60]					
Müllges et al. (2002)	On	22.50	7.30	52	18.90	7.10	52	0.50	[0.11, 0.89]										
Rankin et al. (2003)	Both	40.75	19.83	41						38.85	19.69	34	0.10	[−0.36, 0.55]					
Robson et al. (2000)	On	33.30	11.40	102						33.10	10.90	102	0.02	[−0.26, 0.29]					
Rubens et al. (2007)	On	34.78	13.35	125	35.70	10.63	118	−0.08	[−0.33, 0.18]	31.98	10.42	113	0.23	[−0.02, 0.49]					
Selnes et al. (2009)	On	47.10	24.20	151											40.80	16.80	123	0.30	[0.06, 0.54]
	Off	48.00	23.00	69											43.40	17.50	55	0.22	[−0.14, 0.58]
Silbert et al. (2004)	On	52.00	23.00	50	60.90	38.70	50	−0.28	[−0.67, 0.12]	49.60	20.00	282	0.24	[0.08, 0.41]	48.60	20.00	282	0.29	[0.12, 0.45]
Stygall et al. (2003)	On	40.34	13.32	107	36.83	11.19	107	0.28	[0.01, 0.55]	33.98	9.96	107	0.54	[0.27, 0.81]	38.78	14.14	107	0.11	[−0.16, 0.38]
Vedin et al. (2006)	On	37.00	16.72	37						32.00	7.28	34	0.38	[−0.09, 0.85]	34.00	7.07	32	0.23	[−0.25, 0.70]
	Off	34.00	11.48	33						29.00	5.56	31	0.54	[0.04, 1.04]	32.00	8.21	30	0.20	[−0.30, 0.69]
Zamvar et al. (2002)	On	40.37	14.22	30	26.82	15.50	29	0.90	[0.36, 1.44]	38.74	13.00	30	0.12	[−0.39, 0.62]					
	Off	43.57	15.41	30	37.37	17.80	30	0.37	[−0.14, 0.88]	40.57	8.60	30	0.24	[−0.27, 0.75]					
Zimpfer et al. (2004)	On	34.70	9.10	104	36.80	9.20	104	−0.23	[−0.50, 0.04]										
Total					*N* = 612, 603			0.14	[−0.06, 0.34]	*N* = 987, 929			0.23**	[0.14, 0.32]	*N* = 953, 867			0.23**	[0.13, 0.32]

CPB – cardio pulmonary bypass status; ES – effect size estimate (standardized mean difference).

Table 6
Summary of Trails B meta-analysis results.

Study	CPB	Baseline			Very early					Early					Late				
		Mean	SD	*n*	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI	Mean	SD	*n*	ES	95% CI
Ahlgren et al. (2003)	On	129.20	56.70	23						125.80	60.10	23	0.06	[−0.52, 0.64]					
Baker et al. (2001)	On	115.50	44.98	14	123.64	66.76	14	−0.14	[−0.88, 0.60]						107.30	70.58	10	0.14	[−0.67, 0.95]
	Off	86.17	24.79	12	85.25	24.68	12	0.04	[−0.76, 0.84]						84.75	24.04	8	0.06	[−0.84, 0.95]
Ernest et al. (2006)	On	111.64	45.01	46						100.97	33.22	31	0.26	[−0.20, 0.72]	102.77	38.00	32	0.21	[−0.24, 0.66]
	Off	144.22	56.87	61						97.26	41.78	44	0.91	[0.50, 1.32]	100.24	45.42	47	0.84	[0.44, 1.23]
Grigore et al. (2002)	On	184.98	226.30	100						160.42	159.72	100	0.12	[−0.15, 0.40]					
Heyer et al. (2002)	On	88.19	41.50	35	103.43	49.14	34	−0.33	[−0.81, 0.14]	85.90	36.10	29	0.06	[−0.43, 0.55]					
Kadoi and Goto (2006)	On	167.90	29.70	88											198.80	35.80	88	−0.94	[−1.25, −0.62]
Knipp et al. (2004)	On	114.60	36.80	35						104.90	33.80	29	0.27	[−0.22, 0.76]					
Lee et al. (2003)	On	114.90	87.60	29	117.20	104.50	29	−0.02	[−0.54, 0.49]						104.40	92.10	26	0.12	[−0.41, 0.65]
	Off	126.00	86.70	29	115.60	52.30	29	0.14	[−0.37, 0.66]						117.30	63.40	27	0.11	[−0.41, 0.64]
Müllges et al. (2002)	On	52.40	22.00	52	46.80	19.30	52	0.27	[−0.12, 0.65]										
Newman et al. (2001)	On	142.24	73.56	261	158.77	81.81	252	−0.21	[−0.39, −0.04]	109.93	62.64	222	0.47	[0.29, 0.65]	106.77	64.27	210	0.51	[0.32, 0.69]
Rankin et al. (2003)	Both	111.25	60.39	41						104.85	67.04	34	0.10	[−0.36, 0.55]					
Robson et al. (2000)	On	90.40	46.40	102						89.80	48.70	102	0.01	[−0.26, 0.29]					
Rubens et al. (2007)	On	82.60	45.57	125	93.87	31.28	118	−0.29	[−0.54, −0.03]	76.95	24.66	113	0.15	[−0.10, 0.41]					
Selnes et al. (2009)	On	105.20	59.00	147											95.40	48.20	122	0.18	[−0.06, 0.42]
	Off	96.90	34.70	68											97.20	48.40	55	−0.01	[−0.36, 0.35]
Silbert et al. (2004)	On	125.40	74.50	50	158.50	138.60	50	−0.30	[−0.69, 0.10]	113.20	59.30	281	0.21	[0.04, 0.37]	110.70	58.70	281	0.25	[0.09, 0.42]
Stroobant et al. (2008)	Both	123.70	77.50	50	127.40	58.00	49	−0.05	[−0.45, 0.34]						108.00	55.50	40	0.23	[−0.19, 0.64]
Stygall et al. (2003)	On	87.67	36.59	107						76.31	31.80	107	0.33	[0.06, 0.60]					
Van Dijk et al. (2002)	On	94.00	39.78	139						79.00	33.93	120	0.40	[0.16, 0.65]	76.00	32.76	122	0.49	[0.24, 0.74]
	Off	83.00	40.56	142						75.00	33.93	128	0.21	[−0.03, 0.45]	77.00	35.88	130	0.16	[−0.08, 0.39]
Vedin et al. (2006)	On	104.00	54.74	37						81.00	14.57	37	0.57	[0.10, 1.03]	83.00	11.31	37	0.53	[0.06, 0.99]
	Off	82.00	28.72	33						88.00	16.70	33	−0.25	[−0.74, 0.23]	84.00	9.58	33	−0.09	[−0.58, 0.39]
Zamvar et al. (2002)	On	94.93	34.99	30	61.52	34.40	29	0.95	[0.41, 1.49]	122.17	31.00	30	−0.81	[−1.34, −0.29]					
	Off	98.30	36.09	30	80.34	53.10	30	0.39	[−0.12, 0.90]	98.56	19.90	30	−0.01	[−0.51, 0.50]					
Total						*N* = 717, 698		0.00	[−0.19, 0.19]		*N* = 1628, 1493		0.20*	[0.08, 0.33]		*N* = 1437, 1268		0.18	[−0.01, 0.38]

CPB – cardio pulmonary bypass status; ES – effect size estimate (standardized mean difference).
* Significant $p < 0.05$.

Table 7
Summary of meta-regression analyses.

Time point	Predictor	*N*	Nps	Mean ES	*β*	95% CI	*B*	SE	R^2	*Z*	*p*
Very early											
	Age	12	743	−0.067	0.112	[−0.051, 0.073]	0.011	0.032	0.012	0.35	0.73
	Gender (% m)	12	743	−0.072	−0.417	[−0.063, 0.009]	−0.027	0.018	0.174	−1.45	0.15
	Hypertension	9	556	−0.135	0.19	[−0.007, 0.012]	0.003	0.005	0.036	0.55	0.61
	Drop-out	13	1004	−0.114	−0.513	[−0.118, −0.001]	−0.06	0.03	0.263	−1.99	0.046*
	Diabetes	9	556	−0.137	−0.323	[−0.054, 0.02]	−0.017	0.019	0.104	−0.89	0.37
Early											
	Age	17	1672	0.211	0.335	[−0.008, 0.032]	0.012	0.01	0.112	1.19	0.23
	Gender (% m)	17	1672	0.211	−0.534	[−0.019, 0]	−0.009	0.005	0.285	−1.89	0.06
	Hypertension	12	1316	0.219	0.078	[−0.005, 0.007]	0.001	0.003	0.006	0.24	0.81
	Drop-out	18	1933	0.24	0.239	[−0.003, 0.008]	0.003	0.003	0.057	0.97	0.33
	Diabetes	11	1196	0.208	−0.19	[−0.015, 0.008]	−0.003	0.006	0.036	−0.55	0.58
Late											
	Age	12	1418	0.196	0.314	[−0.023, 0.069]	0.023	0.024	0.098	0.986	0.32
	Gender (% m)	13	1782	0.2	−0.175	[−0.018, 0.01]	−0.004	0.007	0.031	−0.569	0.57
	Hypertension	10	1291	0.205	0.09	[−0.01, 0.013]	0.001	0.006	0.008	0.232	0.82
	Drop-out	14	2043	0.235	0.227	[−0.003, 0.007]	0.002	0.003	0.051	0.746	0.46
	Diabetes	10	1535	0.191	0.116	[−0.02, 0.028]	0.004	0.012	0.013	0.336	0.74

N = number of studies in the meta-regression; Nps – number of patients; mean ES – mean effect size (standardized mean difference).
* Significant $p < 0.05$.

where a higher drop-out rate was associated with worse outcome ($\beta = -.513$, $p = .0457$) (Table 7).

4. Discussion

This meta-analysis shows evidence for very early post-operative decline in two of the four main consensus statement tests, specifically in two measures that are sensitive to speeded psychomotor function. These deficits were reversed by three months with significant improvement relative to baseline in all four measures.

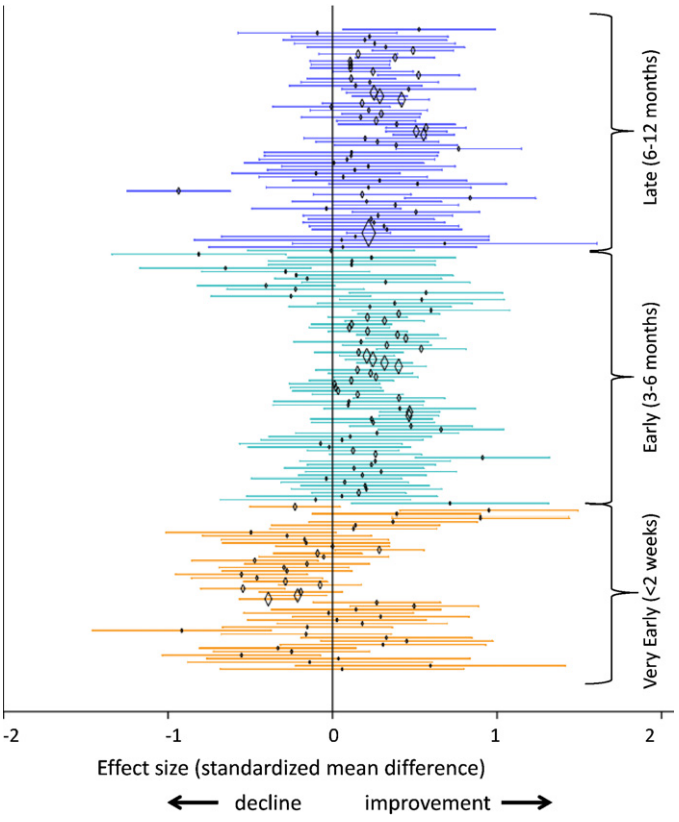

Fig. 1. Forest Plot across all time points and studies, showing effect size and 95% Confidence Interval for each comparison (separate lines for each measure and subgroup) at each follow up time. Size of markers indicates study weighting.

Improvement was sustained at the latest assessment time, up to one year post-CABG surgery. It is important to bear in mind that these findings are based on group level statistics, and may thus obscure individual patients' trajectories of postoperative cognitive change. Nevertheless, a tendency towards preservation of pre-operative function (even improvement), rather cognitive decline, is seen in the first year following CABG surgery, supporting earlier case-series (McKhann et al., 2005; Selnes et al., 2003; Van den Goor et al., 2008) which show that post-operative cognitive decline in the first year after CABG surgery is not inevitable.

There are a number of issues which must be considered when interpreting these data. Firstly, repeated neuropsychological testing would be expected to result in improvement due to practice effects (Selnes et al., 2009). However, this confound is mitigated by the use of parallel test versions (Van den Goor et al., 2008), so that, for example, different word lists are used pre and post operatively. Importantly, parallel forms are a key feature of the consensus statement tests, the use of which was a main inclusion criterion of this meta-analysis. If this recommendation was diligently implemented in the studies reported, it would serve to substantially reduce this confound. Practice effects are strongest over short test–retest intervals, making it difficult to reconcile this interpretation with the temporal pattern of short term decline in two of the measures followed by the improvement months later which we observed. Test performance would also be expected to improve with additional repetitions of the same test, but our effect size estimates at the late time point were similar irrespective of whether it was the first, second or third post-operative assessment the patients had received ($F = 0.93$; $p = 0.39$). Finally, the ability to benefit from practice is likely to be positively related to the level of baseline cognitive functioning (Wilson et al., 2002), suggesting that not all of the patients would have benefitted from practice effects equally. Thus, although we acknowledge that this is a potential confound in repeated neuropsychological assessment, we do not feel it can adequately explain the pattern of results observed. A further possibility is that patient drop-out from longitudinal assessment leads to a bias in outcome data, with only the most well patients willing and able to participate. This could artificially elevate scores on tests of cognitive function. However, the converse could also be true, in that the least well patients may commit to longitudinal studies as they are motivated by concern that something is wrong. Whilst not a definitive answer to this potential confound, our meta-regression indicates that higher 'very early' drop-out rate is associated with less favourable outcome at this time point, which is not consistent

with selective drop out spuriously elevating scores. Nevertheless, future studies should provide further detail of the neuropsychological profile of those patients who drop-out of follow-up compared to those who remain in longitudinal studies. In summary, we consider that improvement in performance during the first post-operative year is unlikely to be solely due to practice effects, nor to be overly influenced by patient drop-out rates.

There is a great deal of variability in cognitive function in these patients prior to CABG surgery. This consists not only of between-subjects variability at a single time point, but also of fluctuation and decline within individuals across time. As many as 46% of patients show significant impairments in cognitive function pre-operatively, compared to 29% of controls (Rosengart et al., 2005). These deficits have been associated with comorbidities such as diabetes and hypertension, and also with stroke which may affect up to 6% of patients before surgery (Glance et al., 2007; Tarakji et al., 2011). In our current analysis, the rate was between 2.7% and 7.1%, consistent with these earlier reports. We were unable to include pre-operative stroke rate in our meta-regression, but neither diabetes nor hypertension were significant predictors of cognitive outcome. Vascular disease in general is associated with both subtle cognitive decline and increased risk of dementia (Desmond, 2004; Knopman et al., 2001; Popovic et al., 2011; Selnes et al., 2009). Indeed, in CABG surgery patients, asymptomatic carotid artery stenosis independently accounts for 50% of the variance in post-operative cognitive decline (Norkiené et al., 2011). Thus, cognition is not stable in an ageing population with underlying cardiovascular disease, and test performance can be expected to decline over the course of a year (McKhann et al., 2005; Okonkwo et al., 2010; Wilson et al., 2002) even without surgery. Studies of CABG-surgery patients that have utilized appropriate control groups, such as non-surgical patients with cardiovascular disease, support this conclusion (McKhann et al., 2005; Selnes et al., 2003; Van Dijk et al., 2008). Taken together, this suggests that cognitive outcome should be considered against the rate of change in an age matched control group with similar cardiovascular risk factors (Abildstrom et al., 2000; McKhann et al., 2005; Mutch et al., 2011; Selnes et al., 2012), rather than simply relative to baseline. Such an approach would also enable the elimination of artefacts related to practice effects.

In addition to the global increase in cognitive scores reported in this meta-analysis, an early transient decline was found in two measures of speeded psychomotor function (Grooved Pegboard and Digit Symbol). Although 'Trials A' also requires psychomotor speed (Sanchez-Cubillo et al., 2009) we did not find a decline in this test. However, this test requires a greater working memory and motor planning contribution than the other two tests, perhaps making it a less specific measure of psychomotor speed. Slowing of psychomotor speed, assessed both behaviourally and using event related potentials (Fowler and Lindeis, 1992; Havashi et al., 2005), has been consistently observed in conditions of hypoxia. This leads us to speculate that brain vulnerability to transient hypoxia might help to explain certain findings in this population, such as the association of early post-operative cognitive decline with intra-operative mean arterial pressure (Gottesman et al., 2007), cerebral oximetry (Slater et al., 2009), and the short-term decline in speeded psychomotor function demonstrated herein. However, simple measures to improve intra-operative brain oxygenation have not been found to improve early cognitive outcome (Slater et al., 2009). This may be due to pre-operative exposure of the CABG-surgery patient to chronic-intermittent hypoxia owing to respiratory disease, smoking or sleep apnoea. Animal models suggest that chronic-intermittent hypoxia may result in up-regulation of protective factors (e.g. hypoxia inducible factor) thereby paradoxically offering protection to the brain (Chavez and LaManna, 2002). Another possible mechanism for cognitive decline is systemic inflammation induced by surgery, although there are few data to support this (Kálmán et al., 2006; Newman et al., 2006). It should also be borne in mind that at the earliest post-operative period, patients are receiving medication to control pain which may also have an impact on cognitive performance. In summary, whilst this meta-analysis may challenge the prevailing assumption that *most* patients are affected negatively by surgery, in order to address the issue more definitively, we may need to update the methods of assessing cognitive function by considering what is known regarding the pathophysiological events following and preceding CABG surgery.

The majority of the studies included in this analysis compared groups of patients undergoing CABG surgery with or without cardio-pulmonary bypass. Cerebral vasculature may be obstructed by emboli released into the circulation during cardio-pulmonary bypass-associated manipulation of the aorta (Brown et al., 2009), resulting in microvascular pathology, particularly in deep white matter (Moody et al., 1990). Such pathology may increase the risk of future cognitive decline in the elderly (Jokinen et al., 2011; Prins et al., 2005). However, a linear relationship between the number of emboli recorded from the middle cerebral artery intra-operatively and post operative decline has not been established (Van Dijk and Kalkman, 2009), and both our data and that from other studies reveal few consistent differences in outcome between on and off pump CABG (Alston, 2011; Marasco et al., 2008; Selnes et al., 2012), despite the lower burden of micro-emboli in the latter. This could be due to the complex interdependent relationship between emboli release during surgery, artherosclerosis, ageing (Boivie et al., 2010) and the severity of vascular disease, all factors which can independently impact cognitive function.

There are several potential explanations for the improved cognitive function observed. Most straightforwardly patients simply feel healthier (less angina) and thus are more motivated following CABG surgery, enabling them to perform better on neuropsychological tests. Cognition and quality of life could well be linked in patients following CABG surgery (Bute et al., 2006). Whilst the presence of depression at six months post-operatively (Goyal et al., 2005) suggests that improved mood may be an unlikely explanation for cognitive improvement in the present study there is also evidence for return to baseline mental health by one year post-surgery (Mathisen et al., 2010; Rothenhäusler et al., 2005), suggesting that emotional status might improve alongside cognitive function, just at a slower pace. Physiologically, a further potential mechanism for improvement is better cardiac output following CABG surgery in the immediate post-operative period. Indeed, impaired cardiac output has been highlighted in the Framingham cohort as a potential cause of abnormal ageing of the brain (Jefferson, 2010; Jefferson et al., 2011) suggesting the opposite, namely that its improvement might offer some benefit. Nevertheless, an important caveat when considering the improvements in cognitive function observed over the course of a year is that these do not preclude later cognitive decline in subsequent years. There are currently few data and little consensus regarding the long-term consequences of CABG (Mutch et al., 2011; Selnes et al., 2009, 2012; Van Dijk et al., 2007). More work is needed to evaluate the long-term impact of cardiovascular disease and CABG surgery on cognitive function.

For a few patients, CABG surgery may provide the catalyst for cognitive deficit that was not present pre-operatively. In others, it may be an added burden on a neurocognitive system that is already showing decline. In these cases it is of utmost importance to explore potentially modifiable peri-operative risk factors that may be associated with further brain insult (Selnes et al., 2012). For example EEG, transcranial Doppler sonography (embolus detection) and cerebral oximetry indicate acute deficits in brain perfusion and oxygenation during surgery; in fact the simple presence of such neuromonitoring can reduce the incidence of brain

injury by half (6.1% vs. 3% in non-monitored compared to neuromonitored patients) (Edmonds, 2005). In the majority of patients, however, CABG surgery may have a transient positive impact on a trajectory of cognitive change that is already set in motion with the ageing process and perhaps influenced by underlying vascular disease. In a few fortunate patients, we cannot discount the possibility that it may boost neurocognitive function more permanently. Genetic studies have already identified candidate markers of brain vulnerability to CABG surgery (Newman et al., 2006), and we have mooted the possibility that mechanisms underlying cognitive change reflect also expression of, for example, hypoxia protective genes. Thus research into those patients who make a *good recovery* might paradoxically explain why other patients develop cognitive decline. The only way to fully address these hypotheses is through longitudinal studies that include controls with non-surgical treatment of coronary artery disease, and bring to bear the cognitive neuroscience techniques which have developed since the consensus statement was initially formulated.

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