Systematic Review

Neurocognitive Function Following Out-of-Hospital Cardiac Arrest: A systematic review

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Abstract:

Objectives: The primary aim of this review was to investigate neurocognitive outcomes following out-of-hospital cardiac arrest (OHCA). Specifically, the focus was on identifying the different neurocognitive domains that are assessed, the measures used, and the level of, and criteria for, impairment.

Design and review methods: A systematic review of the literature from 2006 to 2021 was completed using Medline, Cinahl and Psychinfo. Criteria for inclusion were studies with participants over the age of 18, OHCA and at least one neurocognitive function measure. Qualitative and case studies were excluded. Reviewers assessed criteria and risk of bias using a modified version of Downs and Black.

Results: Forty-three studies were identified. Most studies had a low risk of bias (n=31) or moderate risk of bias (n=11) and one had a high risk; however, only six reported effect sizes or power analyses. Multiple measures of neurocognitive outcomes were used (>50) and level of impairment criteria varied considerably. Memory impairments were frequently found and were also more likely to be impaired followed by executive function and processing speed.

Discussion: This review highlights the heterogeneity of measures and approaches used to assess neurocognitive outcomes following OHCA as well as the need to improve risk of bias concerning generalizability. Improved understanding of the approaches used for assessment and the subsequent findings will facilitate a standardized evaluation of neurocognitive outcomes following OHCA.

Keywords: out-of-hospital cardiac arrest, neurocognitive outcomes, memory, executive functions

1. Introduction

Outcomes from out of hospital cardiac arrest (OHCA) are poor with high mortality; survival rates at hospital discharge are on average 8%, varying from 0% to 18%[1]. For those who survive, neurocognitive impairment is often a concern; however, understanding of the type and level of impairment is limited. A systematic review by Moulaert et al[2] found that the frequency of impairments reported after OHCA varied considerably, from 6% to 100%. The authors note the paucity of high-quality studies assessing neurocognitive outcomes. Specific weaknesses included: concerns with the patient populations used, the small sample size, the heterogeneity of assessments, and the lack of consideration of factors such as age, sex, and treatment. A more recent review over a seven-year period also notes the difficulty of generalizing findings across cardiac arrest studies[3].

Deficits in neuropsychological domains (e.g., attention, memory, executive function) are likely associated with damage to areas that are particularly vulnerable to the effects of

hypoxia, associated with out-of-hospital cardiac arrest. This is supported by studies showing specific decreases in the volume of areas of the brain such as the hippocampus, the anterior cingulate cortex, the dorsolateral prefrontal cortex, and the striatum [4,5]. These areas are associated with core deficits identified following OHCA in the neuropsychological domains of memory, attention and executive functions. Deficits in these areas for patients classified as having a 'good outcome' may be overlooked or underestimated, particularly when measures are used that are not sensitive to minor or subtle changes in neurocognitive function are used, creating a "ceiling effect" [6]. The patient may therefore be discharged without appropriate rehabilitation, or inadequately prepared to deal with the challenges that will follow in carrying out daily activities.

This systematic review of recent studies extends findings from the previous review by considering recent studies specifically focused on OHCA. The primary aims of this review were to identify: (1) the areas of neurocognitive function assessed following OHCA; (2) the specific measures used; (3) the timing of the assessment; (4) the prevalence and degree of impairment identified, and the criteria used to identify impairment. Studies were also reviewed for risk of bias in order to determine the strength of the evidence.

2. Methods

2.1 Search Strategy

Using Medline, Cinahl and PsycInfo a systematic literature review was completed (Prospero CRD42019149075). This included articles from January 2006 to August 2021. Additional searches were conducted over this time period using reference lists from papers selected and Google scholar (NZ). No additional papers were identified through these searches. The search terms included both cardiac arrest population terms and neurocognitive outcomes (**Appendix 1**). Articles were selected if they included at least one neurocognitive assessment in OHCA survivors over the age of 18 years and were either written in English or there was a translation available. Studies including both in- and out-of-hospital cardiac arrest were excluded if it was not possible to identify neurocognitive outcomes specific to the OHCA group. Functional outcome measures typically used at discharge -i.e., Cerebral Performance Category (CPC)[7], Glasgow Outcome Scale[8] (GOS) and modified Rankin Scale (mRS)[9] – were also excluded as the focus here was on measures of neurocognitive performance beyond discharge. Case studies and qualitative studies were also excluded.

Initially, articles were reviewed for inclusion and exclusion criteria using titles and abstracts (NZ). Following this, full texts were reviewed independently by two researchers (NZ, SV). Where consensus was not reached, input was sought from other reviewers (JB, SJB, EJ).

2.2 Quality appraisal

Quality was independently assessed using a modified version of a Downs and Black checklist for nonintervention studies[10,11] by two reviewers (NZ, EBN). A third reviewer (SV) assessed articles by EBN and co-authors. Quality was assessed using fifteen items scored as either 0 (absent or unable to determine) or 1 in the following categories: reporting (0-7), external validity (0-3), internal validity (0-4) and statistical power (0-1). Overall scores were used to identify the quality of the study in relation to the risk of bias. Those scoring 0-6 (40%) were considered low quality/high risk of bias, those scoring 7-9 (40-60%) being medium quality and over 10 as high quality/low risk for bias (60%). This quality appraisal was based specifically on the reporting of neurocognitive assessments rather than the overall focus of the study (e.g., other outcomes). Therefore, some studies with low ratings for the purposes of this review may be considered high quality when rated on other criteria for the study overall. Where quality appraisal differed, a third reviewer arbitrated (SV).

2.3 Data extraction

Data extracted from articles included the following: authors and date; study type; criteria for inclusion/exclusion; participant numbers and characteristics (age, sex, ethnicity, therapeutic hypothermia); functional outcome measures; follow-up times; objective and subjective neurocognitive outcome measures; other measures used; how impairment was defined; the type and degree of impairment found.

3. Results

The initial search yielded 5393 records which were imported for screening. Prior to review, 177 duplicates were removed leaving 5216 studies for title and abstract screening. From these, 517 studies were assessed for full-text eligibility; 474 studies were excluded leaving 44 studies for inclusion. Two articles[12,13] contained overlapping results and only one was included in the full review to give a total of 43 studies (see **Figure 1** for Prisma flowchart and **Table 1** for the included studies). The study designs varied and included prospective studies (32) and retrospective studies (11).

3.1 Quality Assessment

Quality assessment scores from the Modified Downs and Black were found to have quality (risk of bias) percentage ranges from 33% to 93% with higher scores indicating lower risk of bias. Papers were then rated as having either a high (<40%), moderate (40-60%) or low level (>60%) of risk of bias (see **Table 1**). There were twenty-eight studies rated as low risk of bias, ten as moderate, and one as high. Cohen's K was run to identify agreement between the rater's judgment; K= 0.89, p <0 .01. The mean score across the 15-items was 10.08 (SD=2.84). For the reporting subscale (7 questions), the mean was 5.45 (SD=1.77); for external validity subscale (3 questions) the mean was 1.52 (SD=0.90); for internal validity (4 questions) the mean was 2.95 (SD= 1.06). Only six studies reported a power calculation[14-19]. Proportions on the external validity scores (.51) were lower than those on the reporting (.77) and internal validity (.73) subscales.

3.2 Study population

The mean age of participants ranged from 50 (SD=15)[20] to 72[21]. The number of OHCA participants varied from 8[21] to 287 [22]. All the articles reviewed reported a higher percentage of males than females, ranging from 66[14, 16,23] to 100%.[21] Ethnicity was not reported in most studies. Most (n=29) studies reported that participants, or a subset of participants, had received some form of therapeutic hypothermia. The inclusion and exclusion criteria for OHCA patients varied between studies, with some restricting inclusion to a CPC of 1 or 2 (good outcome); however, others either did not specify criteria and likely included survivors with more severe outcomes.

3.3 Outcome measures and follow-up

Follow-up time for the neurocognitive measures varied from hospital discharge[24] to eighteen years[21]. Fifty-four different measures were used to assess neurocognitive function. The types of measures ranged both in relation to the method of administration (interview, self-report questionnaire, informant questionnaire, neuropsychological test) and the domain of function being measured (see **Table 1)**. The criteria used to identify impairment varied across studies making direct comparisons, even when using similar measures, difficult. Given the heterogeneity of studies reviewed, a narrative synthesis approach is used to summarise main findings.

When assessing overall and global cognitive function screening tools, the Mini-Mental Status Exam (MMSE)[25], the adapted version for use via telephone (MMSE-Adult Lifestyles and Function Interview, MMSE-ALFI)[26], and the Montreal Cognitive Assessment (MoCA)[27] were used. Where MMSE was reported, the percentage ranged from no participants showing impairment[28] (cut-off of 28) to 50% of participants (cut-off of 26) showing

impairment.[21] The MoCA impairment rate ranged from 54%[29] to 88%[21] using the standard cut-off criteria of 26. It should be noted that the higher rates of impairment reported by Andersson et al[21] need to be interpreted with caution due to the low sample size (n=8) and long follow-up time (15-18 years) compared with other studies.

When assessing specific domains of neurocognitive impairment, memory (23), executive function (17) and attention/information processing (10) were assessed most frequently. Studies also included measures of general neurocognitive ability, motor function, language, and visuo-perceptual measures. Memory measures varied and included both short- and long-term memory measures as well as working memory and visuospatial memory. Participants showing memory impairment ranged from 10% on the Rey CF[30] to 94%[31] using a memory composite variable (RAVLT, DSF, and BVRT). The most common memory measures were verbal learning tests (i.e., CVLT, RAVLT) which assess both episodic learning and memory and delayed recall. All of the studies reviewed identified some degree of impairment. Participants showing executive function impairment ranged from 8%[32] to 62%[31]. For attention and information processing, impairment levels ranged from 0%[31,20] to 57%[33]. Most studies used performance-based measures, though others used self-report measures (e.g., CFQ[34], DEX[19]) from survivors or informants (e.g., IQCODE[6,29,33,35], IQCODE-CA[36,37]) or questions relating to recovery (e.g., 2SQs[35], Perception of Recovery[38]). Again, there was a range of impairment reported; from 0% (DEX)[19] to 62% (IQCODE)[35].

Participant characteristics (age, sex) and treatment varied (therapeutic hypothermia, type of CPR, etc.), as did the time to follow-up (e.g., discharge[38] to 18 years[21]). Multiple studies included measures of depression, anxiety and quality of life.

Figure 1. Prisma flowchart of the literature search and selection process.

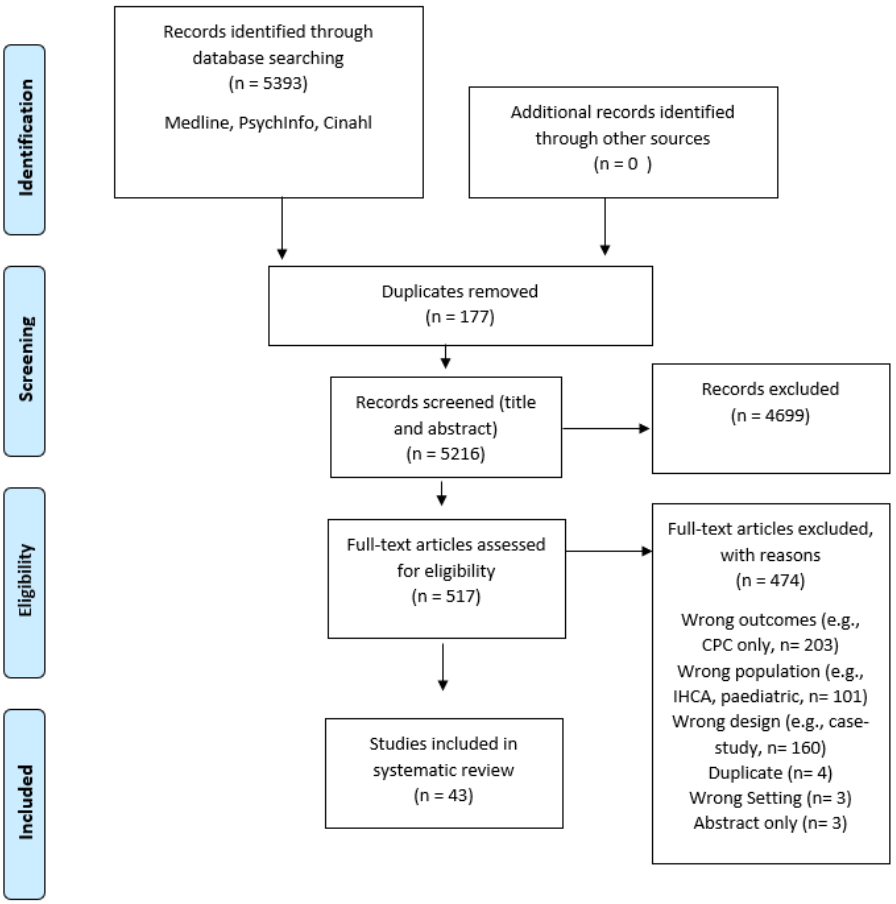

Table 1. Summary of studies and outcome measures, level of impairment and criteria used.

Reference (author & year)	Risk of Bias	study type	N (cog tests)	Follow-up (days/months)	Cognitive domain assessed (measure)[a]	Impairment and/or differences from other populations	Criteria Used
Alexander et al., 2011[39]	low	Pros	OHCA: 30, Controls:30	Ps: 113 days (26.5), Cs: 109 (17.5)	Premorbid function (NART) Memory (RAVLT, BVMT-R); EF (Trails B, VF, WCST); Semantic (BNT, PPV); Perceptual (JOL, Number location, Visual Discrimination); Psychomotor (Trails A, GP, Finger tapping)	OHCA composite scores lower than coronary controls on all domains; Memory 37%; Motor 27%; Semantic (21%), EF 13%	Norms; 2 SDs
Anderrson et al., 2015[21]	mod	Retro	8	15-18 years	Global cognitive function (MMSE, MoCA)	MMSE 50%; MoCA 88%	MMSE <27; MoCA < 26
Aufderheide et al., 2011[14]	mod	Pros	OHCA: 48 Controls: 74	90 days, 365 days	Global cognitive function (CASI)	NR, did not find a sig difference between treatment groups (CPR/Intervention)	Cut-off scores
Beesems et al., 2014[6]	low	Pros	220	6-13 mos, median 9	Global cognitive function (IQCODE or TICs)	IQCODE/TICS 18%	NR
Blennow Nordstrom et al., 2017[36]	low	Pros	268	180 days +/- 14	Global cognitive function (MMSE, IQCODE-CA), Memory (RBMT)	53%	MMSE <27 and RBMT profile score <17; IQCODE CA: >3.04
Bro-Jeppesen et al., 2009[15]	low	Pros	G1: 28; G2: 26	6 mos	Global cognitive function (MMSE)	<1%	MMSE < 24
Brønnick et al., 2021[40]	low	Retro	*see Evald et al., 2019		Premorbid function (Vocabulary, WAIS-IV);	22%	Norms; impaired = below cut-off ≥ 3 measures

					Memory (RAVLT, Rey CF); Attention (Trails A & B; DS WAIS-IV); EF (D-KEFs verbal fluency)		
Byron-Alhassan et al., 2020[41]	low	Pros	OHCA: 9, Controls: 12 MI: 19	OHCA: 13.78 (13.04), MI: 40.52 (21.96)	NAB Global Score	NR, mean scores did not show impairment	Norms
Byron-Alhassan et al., 2021[42]	mod	Pros			NAB (Attention, Memory, Language, Executive, Spatial)	Overall 42.9%; Attention 55.8%; Memory 45.5%; Language 41.6%; EF 29.9%; Spatial 16.9%	Norms
Caro-Codon et al., 2018[29]	low	Pros	79	3.1 yrs (1.7-4.4)	Global cognitive function (MoCA; Modified IQCODE); Executive function (Trails B)	MoCA 54.4%; Trails B: 24%; IQCODE 12%	Trails: Population Norms; MoCA <26;
Cronberg et al., 2015[35]	low	Pros	G1: 213; G2: 206	~6 mos (median: 186 days)	Global cognitive function (MMSE; MMSE ALFI, IQCODE, 2 Simple Questions, recovery)	MMSE 31%; IQCODE 62%; 2SQ 33.5%	MMSE <27; IQCODE >78
Davies et al., 2017[44]	low	Retro	41	~3 months, 4 at mos, 1 at 9 mos	Global cognitive function (MMSE); Visuo-spatial memory (DMS:Cantab)	MMSE M=27.5 (2.37); % under cutoff NR	NR
Evald et al, 2019[16]	low	Retro	79	G1: M=187 (181-204 days); G2; 188 (181-198)	Premorbid function (Vocabulary, WAIS-IV); Memory (RAVLT, Rey CF); Attention (Trails A & B; DS WAIS-IV); EF (D-KEFs verbal fluency)	G1: 33%; G2: 12%	Norms; impaired = below cut-off ≥ 3 measures
Evald et al., 2021[44]	low	Pros	79	187 (181-201)	Subjective Cognitive Function: CFQ	6.8%	CFQ raw scores
Fugate et al, 2013[23]	low	Pros	56	19.5 mos (14.3-24 mos)	Global cognitive function (TICs)	40%	TICs <32
Grand et al., 2019[37]	low	Retro	237	6 mos	MMSE; IQCODE-CA	MMSE 35%; IQCODE-CA 28%	MMSE <27; IQCODE >83

Grubb et al., 2007[38]	low	Pros	49	within 24-hrs of discharge, (5-26 days postarrest)	Premorbid function (NART); Memory (RBMT, WMS-R D-S)	RBMT:57%	RBMT Norms >21
Harve et al., 2007[20]	high	Retro	10	~15 yrs	Memory (Logical memory WMS), Visuo-constructive and visuomotor speed (Block design and Dig-Sym WAIS)	Memory 40%; Visuo-constructive 20%	Norms, 2 SDs
Heradstveit et al., 2011[28]	mod	Pros	9	MRIs at 2 h, 24 h and 96 h; M=22 (15-26) mos	MMSE	0%	MMSE <27
Ji et al., 2017[13]	mod	Pros	3 mos: G1:96, G2: 182 at 12 mos G1(mech): 89; G2:175	3 mos, 12 mos	MMSE	M=26.9 (3.7) & M=28 (2.3); % under cutoff NR	NR
Juan et al., 2018[45]	low	Pros	50 (42 complete)	6 mos	Subjective general function (Perception of recovery); Memory (CVLT, Doors and People, DSF WAIS-IV, block tapping WMS-3rd); Language (Naming subtest Lexis); Productivity (5 points test), Processing Speed (D-Sym WAIS-IV), Attention (Alert and Divided subtest,Test battery for attn performance), EF (verbal fluency, Trails, Stroop, FAB GREFEX)	Subj function: 30%; Neurocognitive tests: 26% overall; Processing speed 21%, Language 21%, LTM 19%, EF 19%, STM verbal 5%, attention 5-29%	Norms, SDs 1.65; Global Cognitive Impairment: # of domains impaired out of 13, >3 substantial cog impairment

Lilja, Nilsson, et al., 2015[33]	low	Pros	G1: 278; control STEMI: 119	180 days	Global cognitive function (MMSE, IQCODE, 2SQ); Memory (RBMT); EF (FAB); Processing Speed (SDMT)	NR; Sig correlations between neurocognitive performance and psychological distress (HADS)	NR
Lilja et al., 2018[22]	low	Pros	G1: 287; G2(control) 119	6 mos	Memory (RBMT); EF (FAB); Processing Speed (SDMT)	47%; specific details NR	RBMT < 22; FAB < 14; SDMT 1.5 SDs
Lilja, Nielsen et al., 2015[46]	low	Pros	as above	~6 mos	Memory (RBMT); EF (FAB); Processing Speed (SDMT)	RBMT 51-58%; FAB 20-23%; SDMT 52-57%	RBMT < 22; FAB < 14; SDMT 1.5 SDs
Lim et al., 2014[47]	mod	Pros	G1: 25; G2 (con, ACS): 27	3 mos, 12 mos	Premorbid function (ANART); Memory (RAVLT, BVMT-R); EF (Trails B, VF, WCST); Language (BNT, PPV); Visuo-perceptual (JOL, Number location, Visual discrimination); Psychomotor (Trails A, GP, Finger tapping)	T1: see Alexander et al., 2011; T2: Memory 64%; EF 32%; Semantic 24%; V-P 28%; Psychomotor 52%	Norms, Composite z-score
Longstreth et al., 2010[48]	mod	Pros	32	~3 mos	Global cognitive function (ALFI-MMSE; 2SQs)	2SQs 25%	Raw scores
Mateen et al., 2011[49]	low	Retro	47	7.8 yrs (median)	Global cognitive function (MMSE), General cognitive ability (WASI -MR, block design), Memory (RAVLT), Language (COWAT), EF (Stroop, Trails A & B)	MMSE 4%; WASI: 4%; AVLT: 24-38%; Trails 17%, Stroop 11%	Norms; 1 SD
Moulaert et al., 2010[34]	low	Retro	63	Mean: 60 mos (18.8); range 1-6 yrs	CFQ	Mean 29.8 (18.4), %NR	CFQ >43

Nichol et al., 2015[50]	low	Pros	644 (completed at least 1 assessment)	1, 3, 6 mos	ALFI MMSE	17.30%	<17
Orbo et al., 2014[51]	low	Pros	45	3 mos (114 days, range 80-131)	General cognitive ability (WASI); Memory (CVLT; Rey CF; WMS-3 DS); EF (D-Kefs Trail-making test, Color-Word, Verbal fluency); Psychomotor (GP)	Overall 44%; WASI 15.9%; CVLT 13.3%; Rey CF 30.8%; WMS -DS 9.8%; D-Kefs TMT 8.9%, color-word 15.4%, verbal fluency, 12.5%; grooved peg board 12.2%	Norms, 1.5 SDs
Orbo et al., 2016[30]	low	Pros	33	cog 3 & 12 mos, QoL 12 mos	General cognitive ability (WASI); Memory (CVLT; Rey CF; WMS-3 DS; EF (D-Kefs Trail-making test, Color-Word, Verbal fluency); Psychomotor (GP)	Composite scores: Visual memory T1: 21%, T2: 10%; Verbal memory T1: 18%, T2: 15%; Psychomotor T1:3%, T2: 0; EF T1: 12%, T2 10%; WASI T1 and T2 12%	Norms, 1.5 SDs
Orbo et al., 2015[32]	low	Pros	42	3 months	Memory (CVLT, Rey CF); Executive (D-KEFs TMT, Color-Word); Psychomotor (GP)	CVLT 10-33%; Rey CF 17%, D-KEFs TMT 5-8%, Color-word 10%; Grooved pegboard 7-10%	Norms, 1.5 SDs
Orbo et al., 2019[52]	low	Pros	13 ohca; 19 controls	3 months	Memory (CVLT, Rey CF); Executive (D-KEFs TMT); Psychomotor (GP)	Compared with healthy controls: significantly lower performance on verbal memory and psychomotor measures	NR
Orbo et al., 2018[17]	low	Pros	G1: 13, G2: 13; Controls: 19	3 months	Memory (CVLT)	Sig lower OHCA-unconsious arrival compared with conscious arrival/controls	NR
Polanowska et al., 2014[31]	mod	Pros	few days; 3 mos:21; 6 mos: 17; 12 mos: 14	OHCA, 3, 6, 12 mos	General cognitive ability (ACE-R) Memory (RAVLT, DSF, BentonVRT); Attention (Trails A); EF (WCST, Trails B);	Overall 57.2%; Memory 64-94%; Attention 0-48%; EF 21-62%; Visuo-spatial 14-33%; Language 14-48%	Norms

					Language (speech/naming); Visuo-spatial (Rey CF)		
Rosen et al., 2014[24]	mod	Pros	OHCA=21; control = 21	T1=2-4 days; T2=12-14 days; T3=45 days; T4=3 months; T5=1 year	MMSE	60%	<28
Stamenova et al., 2018[5]	mod	Pros	OHCA=9, 8 for neuropsych: MI = 7	5 mos, one at 20 days, average: 46 months for MI; 27 mos for OHCA	General cognitive ability (WAIS-III MR); Visual processing (Hooper, Rey CF); Memory (Rey CF, CVLT, CANTAB-Paired Associate Learning, Camden Memory Test, WMS-III Verbal Paired Associates and Logical Memory); EF (Trails, PASAT, COWAT, CANTAB Intra-Extra Dimensional Set Shift, WAIS-III DS)	Sig difference between groups (OHCA lower than MI) on memory	Norms
Sulzgruber et al., 2015[53]	low	Pros	OHCA: 33; controls (age/ed/sex matched): 33	4 weeks post	Memory (RAVLT, WAIS-R DSB, red-pencil-test, WMS logical memory)	Sig difference between groups (OHCA lower than healthy controls) on immediate and delayed recall, working memory, prospective memory	Raw scores by group
Tiainen et al., 2007[50]	low	Pros	hypothermia : 27; non: 18	MMSE: day 14; cog tests: 3 months	Global cognitive function (MMSE); Memory (WMS-R logical memory; AVLT, RBMT); EF (Stroop, Trails B, verbal fluency); Processing Speed (WAIS-R digit-symbol, Trails A, Stroop-congruent, GP)	Overall: 33-56%; Learning and memory 24%; EF: 33%, 19% speed	Norms, 1.5 SDs; patient's intact if 70% (6/8) scores above cut-off; specific cog functions impaired if 50% of tests below cut-off

Tiainen et al., 2015[54]	mod	Pros	n=41	6-8 mos, median 7 mos	General cognitive ability (WAIS-R: Similarities, Blocks, digit-symbol, visual search); Memory (WMS-R (logical passages, list learning); EF (Trails, Stroop, semantic fluency)	51%, specific area NR	Norms, 1 SD; Impaired if performance on >1 test was below norms
Torgersen et al., 2010[55]	low	Retro	26	13-28 mos (mean=20.4 mos)	Global cognitive function (MMSE); General cognitive ability (CANTAB motor screening test, delayed matching to sample, stockings, PAL)	52%; deficits in EF and episodic memory compared with norm data	MMSE <24; Norms, 1.5 SD on at least 3 measures or 2 SDs on 2 measures (out of 10)
Wachelder et al., 2009[56]	low	Retro	63	36 mos (18.8)	CFQ	21%	>/= 44
Wilson et al., 2014[19]	low	Retro	56	25.81 - 27.78 mos	DEX, EMQ-R	EMQ-R 9-16%	NR

Note: Norms=normative data; SD = standard deviation; Pros = prospective design; Retro = retrospective design; MI=Myocardial Infarction

Key for Measures: ACE-R, Addenbrooke's Cognitive Examination-Revised; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; BT, Block tapping, Weschler Memory Scale; BVMT, Brief Visual Memory Test; BVRT, Benton Visual Retention Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; CASI, Cognitive Abilities Screening Instrument; CFQ, Cognitive Failures Questionnaire; CMT, Camden Memory Test; CNB, Computerized Neurocognitive Battery; COWAT, Controlled oral word association test; CVLT, California Verbal Learning Test; DEX, Dysexecutive Questionnaire; D-KEFs, Delis-Kaplan Executive Function System; EMQ-R, Everyday Memory Questionnaire; FAB, Frontal Assessment Battery; HVOT, Hooper Visual Organisation Test; IQCODE/IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest; JOL, Judgement of Line Orientation; NAB, Neuropsychological Assessment Battery, NART/ANART, National Adult Reading Test; PAL, Paired Associates Learning; PASAT, Paced Auditory Serial Addition Test; PPV, Peabody Picture Vocabulary; RAVLT, Rey Auditory Verbal Learning Test; Rey CF, Rey-Osterrieth Complex Figure Test; RBMT, Rivermead Behavioural Memory Test; SDMT, Symbol digit modalities test; TICs, Telephone Interview for Cognitive Status; VF, Verbal Fluency; WAIS, Wechsler Adult Intelligence Scale: Dig-Sym, digit symbol, DS, Digit Span; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale.

4. Discussion

Forty-three articles were identified that included cognitive assessment after OHCA. Following on from the review of 28 articles by Moulaert et al. in 2009[2], this review sought to identify progress in this area since 2006. Moulaert identified key challenges when attempting to generalize findings across studies including studies having a high risk of bias, low sample size, lack of a standard protocol, and not accounting for possible confounding factors. There has been some progress in our understanding of neurocognitive outcomes; however, issues persist in all these areas.

Whilst most studies had a low risk of bias overall, there remain concerns over the generalizability of findings given the sampling approaches and sample sizes used as well as the lack of reporting of effect sizes and power analyses. Findings from papers with low sample sizes need to be interpreted with caution. In addition, there are also possible confounding factors such as age, premorbid status, comorbidities, and treatment differences that may also reduce generalizability of findings to the broader OHCA population. The timing of the assessments varied considerably, from days to years after the OHCA. Criteria for selection were similar to those used in the prior review; however, this review included assessments conducted from hospital discharge rather than starting from 3 months. When comparing findings, the time of the assessment needs to be considered and future work should focus on looking at change over time. The premorbid characteristics of those being studied (cognitive reserve, pre-existing conditions, etc.), and how these influences neurocognitive outcomes following OHCA, merits further consideration. Cognitive reserve estimates may help to understand differences in outcome between individuals. When classifying survivors into severe and mild groups based on composite cognitive tests, it has been found that those in the more severe groups also have lower reading score, which can be used as a proxy measure of premorbid function[e.g., 39, 43]. Therefore, deficits in high reserve individuals may be masked and underestimated when not accounting for this reserve.

Studies that included both in- and out of hospital cardiac arrest were excluded if it was not possible to identify cognitive outcomes specific to the OHCA group. Whilst this was necessary because those with IHCA may differ in a substantive way to patients with OHCA, it also likely means that high quality studies that could add to our knowledge base were excluded. In future studies it would be valuable to differentiate outcomes between these two populations.

It is also crucial to consider how representative survivors participating in research are of the entire population they represent. Studies are likely to report education level and gender; however, it is not standard to report variables such as race, ethnicity and socioeconomic background which makes it difficult to assess the inclusivity and generalizability of the findings. This risk of selection bias has been discussed in other work[e.g.,33,41]. Survivors with poorer outcome may be excluded or unable to perform the neurocognitive tests while survivors with good outcome may not be identified due to non-granular instruments used (e.g., ceiling effects) that were not designed to be sensitive to subtle impairment or decline participation due to not experiencing any perceived problems in their cognitive function. These issues should be addressed in future work.

There continues to be a heterogenous approach to the domains of cognitive function assessed and the measures used. Even studies using the same measures often have varying levels of impairment reported. It is difficult to tell if this is due to a range of cognitive impairment after OHCA or to other factors such as the population included in the study, the timing of the assessment, or the treatment protocol used. In addition, the threshold for classifying patients as impaired varies across studies depending on the cut-off criteria adopted. For example, some studies have a cut-off score for impairment based on established test norms whereas others compare performance to population or patient norma-

tive data. Even within this latter category, there are discrepancies with some studies identifying cut-off criteria as performance 1 SD below the mean and others at 2-3 SDs below the norm. A greater degree of standardization in cognitive assessment following OHCA would allow different studies and treatments to be assessed and compared more effectively.

Neurocognitive impairment following OHCA is associated with lower societal participation, fatigue and restricted mobility[22]. Studies also report associations between neurocognitive impairment and depression[19,22], while others do not[38,47]. Since the Moulaert et al (2009) review, the MoCA has been recommended by the European Resuscitation Council as a neurocognitive screening tool after CA[53]. The Core Outcome Set for Cardiac Arrest (COSCA) statement[54] recommends that core outcomes in CA effectiveness studies should include survival, neurological function, and health-related quality of life, with neurological function measured by the mRS[9] at hospital discharge, at 30 days, or both. Most studies included in this review were focused on neurocognitive function and performed after 30-days. The frequent neurocognitive problems identified in the studies of this review emphasise the need for a neurological screening at an early stage that could indicate neurocognitive impairment. Our findings are therefore in line with the COSCA[58] recommendations. Furthermore, using measures such as the CPC and the mRS, whilst useful, lack sensitivity and specificity in relation to identifying areas of potentially subtle cognitive impairment, increasing the risk of both Type I and Type II errors. Including multi-dimensional measures of function decreases Type-II errors though potentially increases Type I error, especially as additional measures are added to a battery of tests. Thus, future work should endeavour to cast a wide net initially and then identify specific measures across areas of function to appropriately balance Type I and Type II errors when identifying neurocognitive decline associated with OHCA.

Specific recommendations for further neurocognitive instruments with acceptable psychometric properties assessing specific neurocognitive domains do not currently exist and are needed for use in clinical trials and where indicated in clinical practice.

5. Conclusions

The need for neurocognitive assessment that is more sensitive to a wide range of OHCA outcomes is clear. A standardized framework for evaluation should incorporate inclusive approaches to recruitment, information on premorbid status and comorbidities, and specific factors related to the cardiac arrest. This should be combined with a consistent and efficient approach to the assessment of memory, executive functions, and attention/processing that is related to, and predictive of, quality of life and daily function. Improved understanding of the optimal approach to assessment and interpretation of the subsequent findings will facilitate the development of recommendations for the standardized evaluation of neurocognitive outcomes following OHCA.

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Appendix A: Search Approach and Terms:

Index Language Terms:

Medical Subject Headings (MesH); Embase subject headings (biomed/life science) and key words

Databases:

Medline, Cinahl, PsychInfo, follow-up with Google Scholar

Key words:

POPULATION	OUTCOMES
Heart arrest	Cognitive function
Asystole	Cognition disorders
Cardiac arrest	Cognitive impairment
Cardiopulmonary arrest	Neuropsychological assessment
Circulatory arrest	Neuropsychological evaluation
Cardiac sudden death	Neuropsychological test
Sudden cardiac death	Neuropsychological function
Resuscitation	Neurocognitive deficits
Cardiopulmonary resuscitation	Neurocognitive assessment
CPR	Executive function
Out-of-hospital cardiac arrest	Executive control
	Executive attention
	Working memory
	Memory disorders
	Attention
	Concentration

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