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Review

Contribution of brain or biological reserve and cognitive or neural reserve to outcome after TBI: A meta-analysis (prior to 2015)

Jane L. Mathias*, Patricia Wheaton

School of Psychology, University of Adelaide, Adelaide, South Australia, Australia

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ABSTRACT

Brain/biological (BR) and cognitive/neural reserve (CR) have increasingly been used to explain some of the variability that occurs as a consequence of normal ageing and neurological injuries or disease. However, research evaluating the impact of reserve on outcomes after adult traumatic brain injury (TBI) has yet to be quantitatively reviewed. This meta-analysis consolidated data from 90 studies (published prior to 2015) that either examined the relationship between measures of BR (genetics, age, sex) or CR (education, premorbid IQ) and outcomes after TBI or compared the outcomes of groups with high and low reserve. The evidence for genetic sources of reserve was limited and often contrary to prediction. APOE ∈4 status has been studied most, but did not have a consistent or sizeable impact on outcomes. The majority of studies found that younger age was associated with better outcomes, however most failed to adjust for normal age-related changes in cognitive performance that are independent of a TBI. This finding was reversed (older adults had better outcomes) in the small number of studies that provided age-adjusted scores; although it remains unclear whether differences in the cause and severity of injuries that are sustained by younger and older adults contributed to this finding. Despite being more likely to sustain a TBI, males have comparable outcomes to females. Overall, as is the case in the general population, higher levels of education and pre-morbid IQ are both associated with better outcomes.

Contents

* Corresponding author at: University of Adelaide, Adelaide, South Australia 5005, Australia. Tel.: +61 8 8313 5266; fax: +61 8 8313 3770.
E-mail address: jane.mathias@adelaide.edu.au (J.L. Mathias).

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1. Introduction

Traumatic brain injuries (TBI) often cause a variety of disabling cognitive and psychological sequelae, which can impact on all areas of a person's life. The number and seriousness of these problems is broadly related to the severity of the injury, as measured by the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) loss of consciousness (LOC) and/or post-traumatic amnesia (PTA). While injury severity is related both to the amount of brain damage that is sustained and to clinical outcomes, this relationship is imperfect (Lingsma et al., 2010; Nichol et al., 2011). Indeed, people who have been classified as having injuries of equivalent severity frequently have very different outcomes. Individual differences in the people who sustain the injury are therefore also likely to be important when predicting outcome; a more detailed consideration of which is needed in order to capture the heterogeneous nature of TBI and to improve our diagnostic and prognostic capabilities.

The contribution of individual differences to outcome has increasingly been acknowledged in a variety of settings (e.g., ageing, dementia), with the concept of 'reserve' providing a theoretical basis for some of this research. Reserve was originally proposed as a means by which to explain the functional variability that exists, both among those who are ageing normally and those who have a neurological injury or disease (Giogkaraki et al., 2013; Levi et al., 2013; Stern, 2002, 2003; Tucker-Drob et al., 2009). At a theoretical level, researchers have distinguished between 'passive' and 'active' models of reserve. Passive, or threshold, models assume that each person has a level (amount) of reserve (capacity), which determines how much age- or disease-related damage can be sustained before their functioning is compromised (Satz, 1993; Sole-Padulles et al., 2009; Staff et al., 2004; Stern, 2002, 2009; Tucker-Drob et al., 2009). High levels of reserve effectively provide a greater buffer against the effects of brain pathology because, having previously functioned at a higher level, more damage is needed before a person manifests problems in their day-to-day lives. In contrast, active models adopt a more dynamic view, with reserve referring more to the efficiency or *flexibility* with which a person's resources are used, rather than to the *quantity* of these resources (as is the case in passive models). Thus, people with high levels of reserve are able to complete tasks more efficiently, using fewer resources; better enabling them to adapt to (and compensate for) age-, injury- and disease-related changes (Sole-Padulles et al., 2009; Stern, 2009; Tucker-Drob et al., 2009). Regardless of the model that is adopted, higher levels of reserve are thought to lead to better functional outcomes by moderating or mediating the effects of normal ageing or injury/disease-related brain pathology. In the current context, differences in reserve may impact on both the extent of the initial injury/impairment and the extent to which a person recovers over time (Bigler and Stern, 2015; Green et al., 2008).

Also important, is the distinction between brain or biological, and cognitive or neural, reserve. These constructs have some broad parallels with computer 'hardware' and 'software', but are not as distinct due to the complex interplay between brain structure and function, and the many variables that affect either or both of these. Brain or biological reserve (BR) generally refers to individual differences in the underlying biological resources that are available to a person and are often discussed in the context of 'passive' models of reserve (Sole-Padulles et al., 2009; Stern, 2009). BR is generally assessed using anatomical measures of brain size, although indirect estimates – such as head circumference or total intracranial volume (TICV) – may be needed if any pathology is suspected because TICV is one of the few proxy measures of brain size that is invariant after childhood and, consequently, not affected by brain injury or disease (Bigler et al., 1999; Kesler et al., 2003; Ropacki and Elias, 2003). Brain size, structure and function – and potentially BR – are affected by genetics (Erickson et al., 2008; Lee, 2003; Thompson et al., 2001), age (Deary et al., 2009; Lindenberger et al., 2008; Schonberger et al., 2009; Witelson et al., 2006), and a person's sex (Im et al., 2008; Ingalhalikar et al., 2014; Ruigrok et al., 2014); suggesting that these may be additional candidate variables to consider in the context of BR. Moreover, the fact that sex differences in brain structure have been found to exist independently of sex differences in brain size (Luders et al., 2009) and that there are sex differences in the prevalence, onset and symptoms of a variety of neurological and neuropsychiatric disorders (Ruigrok et al., 2014), further supports the consideration of sex in this context. Age is also interesting in the context of injury and disease because differences in reserve are thought to explain some of the variability that occurs with normal ageing (functional outcomes), in the absence of any injury or disease. However, normal ageing may also affect the biological and cognitive resources (reserve) that are available to a person if they are injured or develop a disease, further complicating the picture.

Cognitive or neural reserve (CR), on the other hand, refers to individual differences in the cognitive or neural networks and processes that are employed by a person to complete a task (Dennis et al., 2000; Stern, 2002, 2003). CR is generally evaluated using measures of cognitive ability and flexibility that are resistant to the effects of normal ageing or acquired brain pathology, such as educational or occupational achievement and estimated premorbid IQ.

Evidence for the relationship between measures of BR and/or CR and the development of cognitive and functional problems as a consequence of brain pathology has increasingly been documented in a variety of clinical contexts, including Alzheimer's disease (Valenzuela and Sachdev, 2006), Parkinson's disease (Lewis et al., 2003; Vingerhoets et al., 2003), multiple sclerosis (Beatty et al., 1990; Sumowski et al., 2009, 2013b) and TBI (Bigler and Stern, 2015; Green et al., 2008; Kesler et al., 2003; Ropacki and Elias, 2003; Satz, 1993). In the case of TBI, much of the research that is relevant to this topic has not been explicitly undertaken for the purpose of examining the relationship between reserve and outcome after TBI. Rather, variables that may impact on reserve (e.g., age, sex, education) or mediate/moderate recovery have often been included in studies of TBI, but they may either be incidental to the main purpose of the study or may not have been considered within this theoretical framework. Consequently, existing research on the contribution of different aspects of BR and CR to outcome after TBI has not yet been adequately consolidated to enable an evaluation of the importance of these variables to patient outcomes.

The current study therefore undertook a meta-analysis of research that has examined the contribution of measures of BR and CR to outcome after TBI in order to improve our understanding of some of the individual differences that may add to the heterogeneity in outcomes after TBI. For the purposes of this study, BR was defined as any measure of brain anatomy that would be unaffected by a TBI (TICV), together with other biological variables that may impact on brain size and brain function (genetics, age, sex). CR was indexed by measures of cognitive ability/flexibility that are

unaffected by, or relatively resistant to, a TBI (educational level, estimated premorbid IQ).

2. Method

2.1. Literature search and inclusion criteria

A comprehensive search of the research literature published before January 2015 was conducted using the PubMed and PsycINFO electronic databases (see Appendix A, Supplementary materials for detailed search strategies). For a study to be included in this meta-analysis, it had to meet the following criteria: (1) participants were adults who had sustained a non-penetrating TBI; (2) one or more measures of BR (e.g., brain volumetric measures not affected by TBI [TICV], genetic measures [e.g., apolipoprotein – APOE], age, sex) and/or CR (e.g., education, estimated pre-morbid IQ/cognitive ability) were used; (3) one or more measures of post-injury outcome were administered (e.g., cognitive tests, measures of global outcome or functional status); (4) participants were not reported to have a history indicating a previous TBI, psychiatric illness, substance abuse, or other neurological disorder that could independently affect outcome; (5) it was published in a journal in English, and (6) data that could be converted into effect sizes were provided. More specifically, data could either be in the form of correlations between the measures of reserve and outcome (r or exact p values from which r could be calculated), or means and SDs (or exact p values) for groups that were dichotomised on the basis of a measure of reserve (outcomes for high reserve vs low reserve groups). Self-report scales, other than commonly-used measures that are administered by interview (e.g., Glasgow Outcome Scale), were excluded because problems with cognition and insight following TBI may render them less reliable (Fleming et al., 1996; Roessler-Gorecka et al., 2013; Schiehser et al., 2011; Spencer et al., 2010).

2.2. Data collection and preparation

Background information (injury severity [Glasgow Coma Scale: GCS; post traumatic amnesia: PTA; loss of consciousness: LOC; category of injury severity], time-since-injury, demographic data [age, education, sex]) and data relating to the measures of BR/CR and outcome were extracted from each study.

One of the challenges of a meta-analysis is to preserve the integrity of the original research data, which were often collected for other purposes and reported in a variety of different ways, in order to ensure that the analyses are accurate and informative. The data extracted from the primary studies for the current meta-analysis were in one of two forms: correlation coefficients (r) or means and standard deviations (or raw data). Correlations are themselves standardised effect sizes, measuring the relationship between measures of BR/CR and outcome. Alternatively, the data were in the form of means and SDs for two groups, which can be converted to Cohen's d effect sizes in order to measure the standardised mean difference between the outcomes of two groups. These groups could be defined on the basis of either an inherently dichotomous measure of reserve (e.g., males vs females) or a continuous variable that was treated dichotomously (e.g., younger vs older adults).

Given the variation in the data that was available for analysis and the potential for different effect sizes to be calculated (r or d), the option of choosing one effect size, to which the others would be converted, was considered. However, there are numerous complex statistical issues associated with combining data from continuous variables (e.g., age) that are also treated dichotomously (see Lipsey and Wilson, 2001 and McGrath and Meyer, 2006 for detailed discussion). Specifically, correlations are attenuated in size when they are calculated on the basis of an *artificially* dichotomized variable (e.g., age: maximum $r = .8$ for a 50:50 split in the samples) and this attenuation increases when the dichotomised groups are unequal in size (e.g., 90:10 sample split, the maximum $r = .59$), rendering the resultant effect sizes (r) numerically incomparable to those calculated from studies that measure the variable on a continuous scale (Lipsey, 2013). These same problems apply when Cohen's d is calculated from an artificially dichotomised variable and then converted to r; necessitating multiple complicated statistical corrections in order to deal with the unequal sample sizes and the attenuation caused by the artificial dichotomization of a variable (Hunter and Schmidt, 1990). Notably, these problems do *not* arise when calculating Cohen's d from artificially dichotomised variables (because the formula for d adjusts for unequal sample sizes) or with inherently dichotomous variables (e.g. males vs females).

Thus, in the absence of a clear choice between r and d, and the problems and complexities associated with converting them to a common statistic (McGrath and Meyer, 2006), it was thought that the most defensible option was to report the r and d effect sizes separately and to compare the findings obtained from both types of analyses. Thus, both r and d effect sizes are reported for the same BR/CR and outcome measures, based on how the data was reported in the original study.

2.3. Effect size calculation and interpretation

All analyses were performed using the Comprehensive Meta-Analysis software (random effects model) (CMA Version 2.0; ©2006, Biostat, Inc., Englewood, NJ, USA). For correlations, the effect sizes (r) obtained from all studies that used the same or comparable measures of BR or CR and outcome were averaged in order to combine the findings across studies. Given that the reliability of an individual effect is affected by the size of the sample from which it is derived, individual effects were weighted by their inverse variance before being averaged (mean r_w) (effect sizes from larger samples are more precise and have less variance and are, therefore, given higher weighting) (Hedges and Olkin, 1985; Lipsey and Wilson, 2001). Positive mean r_w values (or r where an outcome was assessed by one study and, consequently, not weighted or averaged) indicate that people with higher levels of reserve had better outcomes following TBI, with $r = .1$, .3, and .5 defining small, medium and large effects, respectively (Cohen, 1992).

Alternatively, Cohen's d statistics were calculated to quantify the differences in outcomes for those studies that assessed BR or CR in terms of a dichotomous variable (e.g., $APOE^+$ vs $APOE^-$, males vs females). Where multiple studies used the same outcome measure, the effect sizes from these studies were weighted and pooled to calculate a mean weighted effect (d_w). As with r, effect sizes were weighted by the inverse variance. A positive d_w (or d, where an outcome was assessed by one study) indicates that greater reserve (e.g., younger age), was associated with better outcomes, with $d = .2$, .5 and .8 equating to small, medium and large effects (Cohen, 1992).

Ninety-five percent confidence intervals (95% CIs) were calculated to provide the range within which the true population effect is likely to lie and p values were calculated to test the statistical significance of the effect size. A $p < .05$ indicates that, in the TBI population, the true relationship (r) between reserve (BR or CR) and outcome, or the true difference between those with high and low reserve (d), differs from zero. In addition, Fail Safe N (N_{fs}) statistics were calculated to address the potential for publication bias, which refers to the fact that statistically significant findings are more likely to be published and, therefore, included in a meta-analysis (Rosenthal, 1979). The N_{fs} statistic provides an estimate of the number of unpublished studies with non-significant results that,

in theory, would need to exist (in file-drawers) to reduce the current finding to a small effect (defined here as $r = .1$ and $d = .2$). Thus, the larger N_{fs}, the more confidence we have in a finding. Effects sizes whose associated N_{fs} statistics were greater than $N_{studies}$ (i.e., the number of studies that contributed data to an effect) were, in general, thought to be less vulnerable to the potential effects of publication bias. Importantly, unlike some meta-analyses (e.g., Zakzanis et al., 1999), the N_{fs} calculations were based on the number of studies that contributed to each effect size (Orwin, 1983), rather than the total number of studies that were meta-analysed (which yields higher N_{fs} statistics), because measures of BR/CR and specific outcomes have not been examined with equal frequency. This enabled a more informative comparison between the actual number of studies that have been analysed and the hypothetical N_{fs}.

3. Results

3.1. Participants

The literature searches yielded a total of 15611 potentially relevant papers. Initial screening of the titles and abstracts of these papers reduced the number to 409, after which re-application of the inclusion criteria to the full-text versions reduced the number of eligible studies to 94. A further 7 papers (comprising one set of three studies and two sets of two studies) provided data for non-independent samples; the data for these were combined and treated as 3 studies in order to ensure that all analyses were based on independent data. This reduced the final number of studies to 90 (see Supplementary Materials, Figure A for full details).

The 90 studies that were included within this analysis provided data for a total of 8856 participants who had sustained a TBI. Table 1 summarises descriptive demographic data for these studies, where it can be seen that the sample sizes varied between 8 and 1069 (mean = 98, median = 62). The majority of participants were young (mean age = 34, SD = 6) males (72%) who had completed high school (mean = 12 years education). Time-since-injury was reported by 62 studies (69%), averaging just under 1½ years, although this varied considerably (median = 8 months). GCS scores were only reported by 39% of all studies ($N = 35$), with the mean and median falling in the severe TBI category, however most (89%) provided descriptive categorical information relating to injury severity (see Table 1). These data revealed that the majority of studies examined severe TBI ($N_{studies} = 25$) or mixed samples of mild/moderate/severe TBIs ($N_{studies} = 24$), followed by moderate to severe TBI ($N_{studies} = 20$). Data relating to PTA and LOC were only available for a small number of studies ($N_{studies} = 15$ and 10, respectively) and were not, therefore, informative for current purposes.

3.2. Measures of brain and cognitive reserve

Variables were classified as indices of BR if they assessed either brain size or were 'biological' variables that could affect brain size, structure and/or function, but were unaffected by brain injury or disease. Unfortunately, there are very few measures of brain size that are not affected by pathology (e.g., TICV, head circumference) and no study that used these measures met the aforementioned inclusion criteria. Thus, the relationship between BR and outcome could only be assessed using other biological variables, namely: genetic status, age and sex. The genetic markers that have been investigated in TBI samples (and met the study criteria) were APOE ∈4 status, which is associated with an increased risk of cognitive decline and Alzheimer's dementia (Sivanandam and Thakur, 2012; Van Den Heuvel et al., 2007; Zhou et al., 2008); KIBRA, which is implicated in memory (Makuch et al., 2011; Papassotiropoulos et al., 2006); COMT, which plays a role in the bioavailability of dopamine in the prefrontal cortex (Savitz et al., 2006); neuroglobin (NGB), which is involved in neuroprotection and oxygen transportation in the brain (Brittain et al., 2010; Burmester and Hankeln, 2009); Interleukin (IL-1 and IL-6), which mediates both pro- and anti-inflammatory responses (Gebhard et al., 2000; Hadjigeorgiou et al., 2005; Ley et al., 2011); and a number of mitochondrial polymorphisms/variants (A10398G, A4917G, T195C and T4216C), which are thought to be important because mitochondrial dysfunction plays a key role in the pathophysiological changes that occur after a TBI (Bulstrode et al., 2014; Gajavelli et al., 2015; Novgorodov et al., 2014). CR, on the other hand, was assessed using educational level and estimated pre-morbid IQ.

Mean effects, 95% CIs, p values and N_{fs} statistics were calculated for each of the BR (genetics, age, sex) and CR (education, premorbid IQ) variables to provide an overall measure of the extent to which these aspects of reserve moderate/mediate outcome. However, in

Table 1
Summary demographic and background data.

	$N_{studies}$ [a]	$N_{Patricipants}$ [a]	Mean	SD	Median	Min	Max
Sample size	90	8856	98	137	62	8	1069
Age	69	5553	34	6	34	21	51
Education (years)	33	2186	12	1	12	10	15
GCS	35	1900	7	2	7	4	13
LOC (days)	10	288	19	8	19	8	32
PTA (days)	15	1057	40	29	29	19	127
Time since injury (months)	62	5910	17	22	8	0.3	108

	$N_{studies}$ [a]	$N_{Participants}$ [a]	%
Sex			
Males	79	4467	72
Females	78	1740	28
Injury severity – category			
Mild	7	1678	8
Severe	25	2074	28
Mild/moderate	3	177	3
Mild/severe	1	146	1
Moderate/severe	20	1289	22
Mild/moderate/severe	24	2348	27
Not specified	10	1144	11

Note: $N_{studies}$ = number of studies; $N_{participants}$ = number of participants; SD = standard deviation; GCS = Glasgow Coma Scale; LOC = loss of consciousness; PTA = post-traumatic amnesia.

[a] Number varies within columns because not all studies reported this information.

the absence of a sound empirical and theoretical basis for predicting which aspects of outcome were most likely to be affected by reserve (e.g., fluid and/or crystallised cognitive abilities, immediate and/or delayed memory, etc.), and the strong likelihood that not all abilities would be equally affected, the data for specific outcomes were also individually evaluated, even where measures were used by only one study. While meta-analyses are designed to statistically pool data from multiple studies, it is not possible to determine how many studies have used a specific measure of reserve or outcome (and therefore how much data can be combined) until data collection has been completed. Given the diversity of cognitive tests that are available, it is not surprising that researchers have used a wide selection of outcome measures (see Lezak et al., 2012 for a compendium of tests). Nevertheless, the provision of effect sizes, 95% CIs, p values and N_{fs} statistics for all measures, regardless of the number of studies that used them, serves the useful purpose of standardising the data and enabled the findings to be directly compared and evaluated; which arguably represents an important advance in the research literature.

Consideration was given to: (1) the overall mean effect for each measure of reserve, (2) the general direction of the findings obtained for each measure of reserve (% positive vs % negative effects), and (3) the moderate to large ($r \geq .3$, $d \geq .5$) and significant ($p < .05$) effect sizes for outcomes that were assessed by multiple ($N_{studies} > 1$) and single studies. In addition, N_{fs} statistics were examined to assess whether the findings would be affected by additional unpublished non-significant findings.

3.3. Brain reserve

3.3.1. Genetic markers

A total of 14 studies examined the relationship between the APOE, KIBRA, COMT, NGB, IL-1, IL-6, and mitochondrial polymorphisms and outcome. All studies provided group comparisons ($APOE^{+ve}$ vs $^{-ve}$ genetic/polymorphism status), making Cohen's d the most appropriate effect size. The weighted mean effect sizes (d_w), and associated statistics (SD, 95%CI, p, N_{fs}) for each of the genetic variables are summarised in Table 2.

APOE has been investigated by eight studies that provided data for a total of 26 outcomes. The overall effect for APOE, based on all of the findings, was small and positive but non-significant (mean $d_w = .16$, $p > .05$), suggesting that APOE status has a negligible overall effect on outcome following TBI (see Table 2). Moreover, 11 (42%) of the effects were positive and 15 negative in direction, highlighting the disparate nature of the findings. A positive Cohen's d indicates that persons who had the APOE ∈4 allele (considered the less desirable genetic status) had poorer outcomes and a negative d indicates they had better outcomes. Of the seven outcomes that were examined by more than one study, only two showed moderate-to-large and significant differences between the outcomes of the $APOE^{+ve}$ and $APOE^{-ve}$ groups; one positive (Trails B) and one negative (PASAT). Both of these measures assess attention and speed of processing, further highlighting the conflicting nature of the findings. In addition, there were three effects (one positive d, two negative d) from individual studies that were moderate-to-large and significant with acceptable N_{fs} statistics (Functional Status Examination, Digit Symbol Test, Word List Learning short-delay cued-recall). Whereas the first of these results strongly favoured better functional status in persons who were $APOE^{-ve}$, the other two suggested that digit symbol and verbal memory performance (short-delayed cued-recall) were, unexpectedly, moderately worse in $APOE^{-ve}$ (i.e., moderately better in $APOE^{+ve}$) persons.

The KIBRA gene (rs17070145 polymorphism: presence vs absence T allele) was examined by one study of severe TBI, which assessed a variety of general and specific outcomes (Table 2). Consistent, with the study's predictions, all 17 effects were positive, indicating that non-carriers performed better following a severe TBI. However, the overall effect was small and non-significant (mean $d = .27$, $p > .05$) and only one outcome was associated with a moderate and significant effect (word list learning delayed cued-recall), although four other outcomes were associated with smaller, albeit significant, effects ($d = .38$ to $.44$) (word list learning: delayed free- and recognition-recall, Trails A, DRS). Nonetheless, the N_{fs} statistics were all very small, indicating that few unpublished studies with non-significant (or opposing results) would be needed to call these findings into question. Thus, any conclusions are, at best, tentative.

A single study that examined COMT (Val158Met polymorphism: Val/Val vs Met/Met alleles) in relation to 14 different outcomes following mild, moderate and severe TBI yielded a small non-significant overall effect (mean $d = .03$, $p > .05$). In all but one case, the individual measures showed small non-significant effects that were relatively evenly distributed between both positive (54%) and negative (46%) effects, with very low N_{fs} statistics (Table 2). The exception was for matrix reasoning, which showed a moderate negative and significant effect indicating that those with a Val/Val allele status performed better than those with the Met/Met allele.

The single study that examined two variants of the NGB gene (rs3783988 presence [CC/CT] vs absence [TT]; rs10133981 presence [TT/GT] vs absence [GG]) used the Glasgow Outcome Scale to assess outcome and found that people who were negative for the rs3783988 mutation (considered to be the better genetic outcome) had somewhat better outcomes (low-moderate and significant $d = .45$), albeit with a small N_{fs} ($N_{fs} = 1$) (refer to Table 2). The other mutation (rs10133981) did not have a sizeable or significant impact.

Single studies of IL-1 (carriers vs non-carriers IL-1RN & IL-1B) and IL-6 (GG vs CG/CC genotypes) revealed that there was a small but significant difference in global outcomes for the IL-1RN polymorphism, but small and non-significant difference in for the IL-1B and IL-6 −174C/G polymorphisms (see Table 2). In the case of IL-1RN, carriers had better overall outcomes than non-carriers 6 months after their injury.

Finally, a single study examining the A10398G (A vs G variant), A4917G (A vs G variant), T195C (C vs T variant) and T4216C (C vs T variant) mitochondrial polymorphisms found very limited evidence to suggest that they affect three measures of general outcome, with only the A10398G polymorphism being associated with significantly higher levels of disability. The latter finding was, however, associated with a very small N_{fs} ($N_{fs} = 1$), indicating that it is very vulnerable to publication bias.

3.3.2. Age

Most of the 56 studies that examined age reported data in the form of correlations between age and outcome ($N_{studies} = 47$; see Table 3), although a number dichotomised this variable and compared the mean outcomes of groups of young(er) and old(er) adults ($N_{studies} = 9$; see Table 4). The overall mean r_w, calculated across the 47 correlation studies and measures, was small but highly significant ($r_w = .18$, $p < .001$) with a N_{fs} of 38. While the N_{fs} statistic is lower than the $N_{studies}$, it is very large and indicates that a substantial number of unpublished studies with non-significant findings would need to be in existence to alter the current conclusion. Thus, there appears to be a modest positive overall effect, with younger adults having slightly better outcomes. In terms of the specific outcomes, 67% of the correlations were positive (see Table 3), indicating that younger age (greater reserve) was more frequently associated with better outcomes when only the direction ($^{+ve}$ vs $^{-ve}$) of the effect was considered, and not its size or significance. Age was significantly correlated with five of the 12 outcomes that were assessed by multiple studies (clock drawing, Trails B, Functional Independence, Community Integration, GOS).

Table 2
Genetic measures and outcome: Cohen's *d*.

Gene/outcome measure	$N_{studies}$	$N_{participants}$	Mean d_w	95% CIs		p	Severity	N_{fs}	Study references
APOE ($\in 4^{+ve}$ vs $\in 4^{-ve}$)									
Functional Status Examination	1	69	1.46	.91	.00	**	Not specified	6	Friedman et al. (1999)
Letter Fluency	2	129	−1.15	−4.06	.44		Mild, moderate	10	Crawford et al. (2002), Shadli et al. (2011)
Trail Making Test B (time)	2	97	.67	.17	.01	*	Mild, moderate	5	Han et al. (2007), Shadli et al. (2011)
Digit Symbol Test	1	78	−.59	−1.14	.04	*	Mild, moderate	2	Han et al. (2007)
Word List Learning (Trials 1–5)	3	211	−.59	−1.91	.38		Mild, moderate, severe	6	Han et al. (2007), Shadli et al. (2011), Noe et al. (2010)
Word List Learning (short delay cued recall)	1	78	−.57	−1.12	.04	*	Mild, moderate	2	Han et al. (2007)
PASAT	2	158	−.52	−.90	.01	*	Mild, moderate	3	Han et al. (2007), Liberman et al. (2002)
GOS/GOSE	1	79	−.46	−1.05	.13		Moderate, severe	1	Willemse-van Son et al. (2008)
Word List Learning (long delay cued recall)	1	78	−.44	−.99	.12		Mild, moderate	1	Han et al. (2007)
Word List Learning (recognition)	1	114	.44	−.03	.07		Moderate, severe	1	Noe et al. (2010)
Card Sorting (score)	2	97	−.43	−.92	.09		Mild, moderate	2	Han et al. (2007), Shadli et al. (2011)
Stroop	1	80	.42	−.11	.12		Mild, moderate	1	Liberman et al. (2002)
Working Memory Index	1	114	.41	−.04	.07		Moderate, severe	1	Noe et al. (2010)
Story Memory II	1	78	−.39	−.94	.16		Mild, moderate	1	Han et al. (2007)
Category Fluency	1	110	.36	−.07	.10		Not specified	1	Crawford et al. (2002)
Matrices	1	78	−.31	−.86	.27		Mild, moderate	1	Han et al. (2007)
Card Sorting (recognition)	1	78	−.26	−.81	.35		Mild, moderate	0	Han et al. (2007)
Verbal Fluency	1	78	−.24	−.79	.39		Mild, moderate	0	Han et al. (2007)
Functional Independence Measure	1	31	.22	−.62	.61		Severe	0	Lichtman et al. (2000)
Word List Learning (immediate delayed recall)	4	321	−.17	−.94	−.68		Mild, moderate, severe	0	Crawford et al. (2002), Han et al. (2007), Noe et al. (2010), Shadli et al. (2011)
Word List Learning (delayed recall)	4	321	.16	−.33	.52		Mild, moderate, severe	1	Crawford et al. (2002), Han et al. (2007), Noe et al. (2010), Shadli et al. (2011)
Stroop Interference (time)	1	78	.14	−.41	.62		Mild, moderate	0	Han et al. (2007)
Design Fluency	1	78	−.12	−.67	.67		Mild, moderate	0	Han et al. (2007)
Block Design	1	78	.04	−.51	.89		Mild, moderate	1	Han et al. (2007)
Digit Span	1	78	.03	−.52	.58		Mild, moderate	1	Han et al. (2007)
Story Memory I	1	78	−.02	−.57	.53		Mild, moderate	1	Han et al. (2007)
OVERALL APOE	8	580	.16	−.29	.62			2	
KIBRA rs17070145 polymorphism (presence vs absence T allele: CT/TT vs CC variant)									
SRT Word List Learning (delayed cued recall)	1	129	.62	.25	.99	**	Severe	2	Wagner et al. (2012)
CVLT Word List Learning (Trials 1–5)	1	129	.44	−.05	.93		Severe	1	Wagner et al. (2012)
SRT Word List Learning (delayed free recall)	1	129	.44	.07	.81	*	Severe	1	Wagner et al. (2012)
SRT Word List Learning (delayed recognition)	1	129	.42	.05	.79	*	Severe	1	Wagner et al. (2012)
Trail Making A	1	129	.42	.07	.77	*	Severe	1	Wagner et al. (2012)
CVLT Word List Learning (long delay recall)	1	129	.42	−.02	.85		Severe	1	Wagner et al. (2012)
CVLT Word List Learning (short delay recall)	1	129	.38	−.11	.87		Severe	1	Wagner et al. (2012)
CVLT Word List Learning (long delay cued recall)	1	129	.38	−.11	.87		Severe	1	Wagner et al. (2012)
Disability Rating Scale	1	129	.38	.03	.73	*	Severe	1	Wagner et al. (2012)
Complex Figure Test (immediate recall)	1	129	.36	.01	.71		Severe	1	Wagner et al. (2012)
CVLT Word List Learning (short delay cued recall)	1	129	.30	−.19	.79		Severe	1	Wagner et al. (2012)
Functional Independence Measure	1	129	.29	−.06	.64		Severe	1	Wagner et al. (2012)
Complex Figure Test (Copy)	1	129	.27	−.08	.62		Severe	0	Wagner et al. (2012)
Complex Figure Test (delayed recall)	1	129	.23	−.12	.58		Severe	0	Wagner et al. (2012)
Trail Making B	1	129	.20	−.15	.55		Severe	0	Wagner et al. (2012)
GOS/GOSE (6-months)	1	129	.12	−.23	.47		Severe	0	Wagner et al. (2012)

Table 2 (*Continued*)

Gene/outcome measure	$N_{studies}$	$N_{participants}$	Mean d_w	95% CIs		p	Severity	N_{fs}	Study references
Neurobehavioral Rating Scale	1	129	.01	−.34	.36		Severe	1	Wagner et al. (2012)
OVERALL KIBRA	1	129	.27	−.10	.63			0	
COMT Val158Met polymorphism (Val/Val vs Met/Met alleles)									
Matrices	1	107	−.58	−.97	−.19	**	Mild, moderate, severe	2	Willmott et al. (2014)[a]
Reaction Time	1	18	−.38	−1.34	.58		Moderate, severe	1	Willmott et al. (2014)
Ruffs 2 & 7 Selective Attention Test	1	18	−.29	−1.25	.67		Moderate, severe	1	Willmott et al. (2014)
Block Design	1	107	.26	−.13	.65		Mild, moderate, severe	0	Willmott et al. (2014)
Trail Making A (time)	1	107	.19	−.20	.58		Mild, moderate, severe	0	Willmott et al. (2014)
Arithmetic	1	107	.18	−.21	.57		Mild, moderate, severe	0	Willmott et al. (2014)
Complex Figure Test	1	107	.17	−.22	.56		Mild, moderate, severe	0	Willmott et al. (2014)
Digit Symbol Test	1	107	.15	−.24	.54		Mild, moderate, severe	0	Willmott et al. (2014)
Choice Reaction Time	1	18	−.09	−1.03	.85		Moderate, severe	1	Willmott et al. (2014)
Digit Span	1	107	−.05	−.44	.34		Mild, moderate, severe	1	Willmott et al. (2014)
Word List Learning (delayed recall)	1	107	.03	−.36	.42		Mild, moderate, severe	1	Willmott et al. (2014)
Letter Number Sequencing	1	18	−.02	−.96	.92		Moderate, severe	1	Willmott et al. (2014)
Trail Making B (time)	1	107	.01	−.38	.40		Mild, moderate, severe	1	Willmott et al. (2014)
Word List Learning (Trials 1–5)	1	107	.00	−.39	.39		Mild, moderate, severe	1	Willmott et al. (2014)
OVERALL COMT	1	107	.03	−.65	.59			1	
NGB (presence [CC/CT] vs absence [TT] rs 3783988; presence [TT/GT] vs absence [GG] rs 10133981)									
rs 3783988 polymorphism – GOS/GOSE	1	151	.45	.12	.78	*	Severe	1	Chuang et al. (2010)
rs 10133981 polymorphism – GOS/GOSE	1	148	.27	−.32	.86		Severe	0	Chuang et al. (2010)
IL-1 (carriers vs non-carriers IL-1RN; carriers vs non-carriers IL-1B)									
RN allele – GOS/GOSE (6-months)	1	151	−.35	−.68	−.02	*	Mild, moderate, severe	1	Hadjigeorgiou et al. (2005)
B allele – GOS/GOSE (6-months)	1	151	−.11	−.44	.22		Mild, moderate, severe	1	Hadjigeorgiou et al. (2005)
IL-6 −174C/G polymorphism (GG vs CG/CC genotypes)									
GOS/GOSE (acute: post-ICU)	1	77	.05	−.05	.15		Severe	1	Dalla Libera et al. (2011)
Mitochndrial polymorphisms (A10398G, A4917G, T195C, T4216C)									
A10398G (A vs G)									
DRS	1	255	.38	.05	.71	*	Severe	1	Conley et al. (2014)
GOS/GOSE (6-months)	1	255	.12	−.19	.43		Severe	0	Conley et al. (2014)
NRS	1	255	.03	−.28	.34		Severe	1	Conley et al. (2014)
OVERALL A10398G	1	255	.18	−.14	.50			0	
A4917G (A vs G)									
DRS	1	293	−.20	−.55	.15		Severe	0	Conley et al. (2014)
GOS/GOSE (6-months)	1	293	−.02	−.37	.33		Severe	1	Conley et al. (2014)
NRS	1	293	.01	−.34	.36		Severe	1	Conley et al. (2014)
OVERALL A4917G	1	293	−.07	−.42	.28			1	

Table 2 (*Continued*)

Gene/outcome measure	$N_{studies}$	$N_{participants}$	Mean d_w	95% CIs		p	Severity	N_{fs}	Study references
T195C (C vs T)									
GOS/GOSE (6-months)	1	272	−.22	−.53	.09		Severe	0	Conley et al. (2014)
NRS	1	272	.10	−.21	.41		Severe	1	Conley et al. (2014)
DRS	1	272	.08	−.23	.39		Severe	1	Conley et al. (2014)
OVERALL T195C	1	272	−.01	−.33	.30			1	
T4216C (C vs T)									
GOS/GOSE (6-months)	1	291	.04	−.23	.31		Severe	1	Conley et al. (2014)
DRS	1	291	.02	−.25	.29		Severe	1	Conley et al. (2014)
NRS	1	291	.01	−.26	.28		Severe	1	Conley et al. (2014)
OVERALL T4216C	1	291	.02	−.25	.30			1	

Note. $N_{studies}$ = number of studies contributing to an effect size; $N_{participants}$ = number of participants; Mean d_w = weighted mean Cohen's d; SD = standard deviation; 95% CI = 95% confidence interval; N_{fs} = Fail-safe N; PASAT = Paced Auditory Serial Addition Test; GOS/GOSE = Glasgow Outcome Scale/Glasgow Outcome Scale Extended; CVLT = California Verbal Learning Test; SRT = Buschke Selective Reminding Task; ICU = Intensive Care Unit; DRS = Disability Rating Scale; NRS = Neurobehavioral Rating Scale.
Positive Cohen's d = gene/polymorphism present had worse outcomes; Negative Cohen's d = gene/polymorphism present had better outcomes.

[a] Participant numbers and injury severity vary between rows because data was taken from 2 non-independent papers (Willmott et al., 2013, 2014).

* $p < .05$.

** $p < .001$.

These correlations were all positive (younger adults performed better; $r = .19–.42$), but only one was moderate-to-large in size ($\geq .3$). Age also correlated significantly with a number of other measures that were used by single studies, although these included both negative and positive correlations. Specifically, age showed moderate to large and significant positive correlations with performance on tests of reaction time (simple and choice), executive functioning (BADS Total and Zoo map performance), and the Mayo-Portland Adaptability Inventory (measure of post-TBI physical, cognitive, emotional, behavioural, social problems), indicating that younger adults performed better. In contrast, the moderate-large and significant negative ($\leq .3$) correlations with story memory (immediate recall) and MMSE suggest that older adults performed better on these measures.

Turning to the 9 studies that compared groups of younger and older TBI participants when examining the impact of age on outcome, it can be seen from Table 4 that 68% of the Cohen's d values were positive (i.e., better outcomes for younger adults), with the overall mean d_w being positive, small and significant ($d_w = .38$, $p < .05$). Thus, on the whole, younger age appears to be associated with significantly better outcomes. Of the three measures that were used by multiple studies, two yielded moderate and significant positive effects (GOS, Trail Making Test: younger adults performed better) and one low-moderate and significant negative effect (full-scale IQ: older adults performed better). In addition, there were moderate to large ($d \geq .5$) and significant group differences on 12 other outcomes that were assessed by single studies (all with acceptable N_{fs} statistics), 7 of which were positive in direction. These findings indicate that the younger groups performed better than older adults on Trail Making (Part B), Finger Tapping, reaction time, vocational independence, tracking, word list learning (short-delay cued-recall), and functional independence tests. In contrast, older adults performed markedly better on a variety of Wechsler Adult Intelligence Scale subtests (WAIS Information, Similarities, Picture Completion, Arithmetic, Object Assembly).

As age is known to affect cognitive performance in *healthy* adults, it is possible that some of the aforementioned results may have confounded normal age-related changes in cognition with the effect of sustaining a TBI at different ages. That is, the relationship between age and outcome (r; or differences in the outcomes of young and old, d) may exist independently of the TBI. Aged-scaled scores arguably provide a better test of whether the age at which a person sustains a TBI provides a source of biological reserve; potentially acting as a buffer against the effects of a TBI. However, age-scaled scores were only used by a limited number of studies, all of which compared groups of younger and older TBI participants (Table 4: WAIS Information, Similarities, Picture Completion, Arithmetic, Object Assembly, Comprehension, FSIQ, VIQ, PIQ; WMS Memory quotient, General Memory Index, Attention Index, Delayed Memory Index). The mean weighted effect for these 13 measures was −.27, but this was not significant. Interestingly, the Cohen's d effect for the one measure that was used by multiple studies (FSIQ; $d = -.33$, $p < .01$) was also relatively small, but negative and significant (older people had better outcomes), and all of the moderate-to-large and significant effects from individual studies were negative (Information, Similarities, Picture Completion, Arithmetic, Object Assembly). Thus, when normal age-related decline was statistically controlled using age-scaled scores, older age appears to be associated with significantly better outcomes after a TBI – reflecting modest to large differences – on a range of IQ subtests.

3.3.3. Sex

Data relating to sex differences in outcome following TBI were reported in the form of correlations for 18 studies, where the ratio of males to females was 2.8 to 1 (see Table 5), and group comparisons for 10 (see Table 6), where the ratio was 1.9 to 1. Taking the correlations first, although 64% of the 23 effect sizes were positive in direction (indicating that males performed better), the overall mean r_w was small negative and non-significant ($r_w = -.09$, $p > .05$), suggesting that, on balance, there are no sex differences in outcomes following a TBI (Table 5). Notably, most effects were non-significant, including those that were sizeable ($r \geq .3$), regardless of whether they were based on the results of single or multiple studies. The only exception was for Word List Learning (Trials 1–5) which, based on the findings of two studies, showed a moderate negative and significant effect, indicating that females performed better on this measure.

Although more suited to analysis as a dichotomous variable, fewer studies used group comparisons to compare the outcomes of males and females; albeit assessing a larger number of outcomes (10 studies, 45 measures) (see Table 6). Consistent with the aforementioned findings, these analyses also revealed a small and non-significant mean effect ($d_w = .10$, $p > .05$), with 55% of the Cohen's d effect sizes for individual measures being positive (i.e., males had better outcomes). However, unlike the previous analyses, there were seven moderate-to-large and significant effects (all based on single studies), with four being positive (males performed better: Stroop Interference, Family Pictures I & II, WMS Auditory Recognition Delayed Index) and three negative (females performed better: Word List Learning short- and long-delay cued-recall and recognition trials) in direction. Thus, while sex does not appear to

Table 3
Age and outcome: correlations.

Outcome measure	$N_{studies}$	$N_{participants}$	Mean r_w	95% CIs		p	Severity	N_{fs}	Study references
Story Memory I (immediate recall)	1	12	−.68	−.91	−.14	*	Severe	6	Bornhofen and McDonald (2008)
Reaction Time (time)	1	10	.68	.09	.92	*	Moderate, severe	6	Hetherington et al. (1996)
Category Fluency	1	12	.60	−.41	.95		Not specified	5	Barclay et al. (1985)
Story Memory II (delayed recall)	2	32	−.53	−.92	.37		Severe	4	Bornhofen and McDonald (2008), Carlesimo et al. (1998)
Facial Perception (recognition)	1	12	.49	−.16	.84		Severe	4	Bornhofen and McDonald (2008)
Picture Recall (short delay cued recall)	1	12	−.47	−.90	.44		Not specified	4	Barclay et al. (1985)
BADS Total	1	25	.46	.08	.72	*	Mild, moderate, severe	4	Rochat et al. (2009)
BADS Zoo Map	1	25	.42	.03	.70	*	Mild, moderate, severe	3	Rochat et al. (2009)
Clock-Drawing Task	2	207	.42	.30	.53	**	Mild, moderate, severe	6	Wagner et al. (2011), de Guise et al. (2011)
Choice Reaction Time (time)	1	27	.39	.01	.67	*	Mild, moderate, severe	3	Rieger and Gauggel (2002)
Mayo-Portland Adaptability Inventory	1	111	.39	.22	.54	**	Moderate, severe	3	Spitz et al. (2012)
Word List Learning (delayed recall)	1	20	−.35	−.69	.11		Severe	3	Carlesimo et al. (1998)
Mini-Mental State Exam	1	162	−.35	−.48	−.21	**	Mild, moderate, severe	3	de Guise et al. (2011)
Receptive Vocabulary	1	13	−.29	−.73	.31		Mild, moderate, severe	2	Kennedy (2004)
Cambridge Prospective Memory Test	1	60	.29	−.01	.54		Severe	2	Fleming et al. (2008)
Trail Making Test B (time)	2	103	.28	.09	.45	**	Mild, moderate, severe	4	Perianez et al. (2007), Kennedy (2004)
Cancellation Task (time)	1	12	−.27	−.85	.61		Not specified	2	Barclay et al. (1985)
Functional Status Examination	2	45	.24	−.07	.51		Mild, moderate, severe	3	Ding et al. (2008), Warner et al. (2010)
Functional Independence Measure	4	247	.23	.10	.34	**	Mild, moderate, severe	5	Jacobsson et al. (2009), Sidaros et al. (2009), Sommer et al. (2013), Bondanelli et al. (2002)
Letter Fluency	4	100	.23	−.02	.44		Mild, moderate, severe	5	Barclay et al. (1985), Cockburn (1995), Dowler et al. (2000), Turner and Levine (2008)
Community Integration Questionnaire	3	252	.21	.03	.38	*	Mild, moderate, severe	3	Corrigan and Deming (1995), Dowler et al. (2000), Jacobsson et al. (2009)
GOS/GOSE	22	2503	.19	.10	.28	**	Mild, moderate, severe	20	Abadal-Centellas et al. (2007), Ariza et al. (2006), Balestreri et al. (2004), Carlesimo et al. (1998), Chastain et al. (2009), Czosnyka et al. (2005), Hou et al. (2007), Huang et al. (2010), Jacobs et al. (2010), King et al. (2005), Marcoux et al. (2008), Meier et al. (2008), Newcombe et al. (2007), Salmond et al. (2005):2006, Sidaros et al. (2009), Siddique et al. (2002), Tateishi et al. (1998), Valente et al. (2002), Wang et al. (2008), Warner et al. (2010), Winter et al. (2004), Wu et al. (2004)
Trail Making Test B-A (time)	2	98	.18	−.02	.37		Mild, moderate, severe	2	Perianez et al. (2007), Turner and Levine (2008)
Immediate Auditory Memory (immediate recall)	1	13	.17	−.42	.66		Mild, moderate, severe	1	Kennedy (2004)
Block Design (time)	1	12	−.17	−.68	.45		Not specified	1	Barclay et al. (1985)
Disability Rating Scale	4	199	.16	−.07	.37		Mild, moderate, severe	2	Bergsneider et al. (2001), Dowler et al. (2000), Jacobsson et al. (2009), Kim et al. (2005)
Word List Learning (cued recall)	1	12	.16	−.61	.78		Not specified	1	Barclay et al. (1985)
Activities of Daily Living	1	100	.15	−.05	.34		Moderate, severe	1	Bottari et al. (2009)
Trail Making Test A (time)	1	90	.15	−.06	.35		Mild, moderate, severe	1	Perianez et al. (2007)
SF-36 Physical	1	358	.14	.04	.24	*	Moderate, severe	0	Hu et al. (2012)
Verbal Skills	1	30	−.14	−.48	.23		Severe	0	Hough (2008)

Table 3 (*Continued*)

Outcome measure	$N_{studies}$	$N_{participants}$	Mean r_w	95% CIs		p	Severity	N_{fs}	Study references
Block Design (score)	1	12	−.13	−.73	.58		Not specified	0	Barclay et al. (1985)
SCATBI	1	30	−.12	−.46	.25		Severe	0	Hough (2008)
Tower Test (score)	1	20	.12	−.34	.53		Severe	0	Cockburn (1995)
Category Test (subtests 3–7) (error)	1	146	.12	−.04	.28		Mild, severe	0	Donders (2001)
Tower Test (time)	1	20	−.10	−.52	.36		Severe	0	Cockburn (1995)
Card Sorting	1	20	.10	−.36	.52		Severe	0	Cockburn (1995)
VIQ	1	13	−.05	−.58	.52		Mild, moderate, severe	1	Kennedy (2004)
Matrices	2	32	.05	−.37	.46		Not specified, severe	1	Barclay et al. (1985), Carlesimo et al. (1998)
Word List Learning (Trials 1–5)	2	76	.05	−.19	.28		Mild, moderate, severe	1	Barclay et al. (1985), Callahan and Johnstone (1994)
Digit Symbol Test (score)	1	8	−.03	−.77	.74		Moderate, severe	1	Turner and Levine (2008)
Verbal Comprehension (error)	1	12	.02	−.62	.64		Not specified	1	Barclay et al. (1985)
OVERALL	47	4138	.18	.13	.24	**		38	

Note. $N_{studies}$ = number of studies contributing to an effect size; $N_{participants}$ = number of participants; Mean r_w = weighted mean correlation; SD = standard deviation; 95% CI = 95% confidence interval; N_{fs} = Fail-safe N; BADS = Behavioural Assessment of the Dysexecutive Syndrome; GOS/GOSE = Glasgow Outcome Scale/Glasgow Outcome Scale Extended; SF-36 = Short Form 36; SCATBI = Scales of Cognitive Ability for Traumatic Brain Injury; VIQ = Verbal Intelligence Quotient; CHART SF = Craig Handicap Assessment and Reporting Technique, Short Form.
Positive r = younger age was associated with better outcomes; negative r = younger age was associated with worse outcomes.
* $p < .05$.
** $p < .001$.

have a pervasive overall effect on outcomes after TBI, there were specific tests where either males or females who had sustained a TBI performed better.

3.4. Cognitive reserve

3.4.1. Education

Whether education plays a role in outcomes after TBI has been widely researched using a very diverse range of measures (refer to Table 7). All studies reported correlations ($N_{studies}$ = 26), which were largely positive (85%), demonstrating that greater education is associated with better outcomes. Moreover, although the overall mean was relatively small (mean r_w = .20, mid-way between a small/medium effect), it was highly significant and positive in direction ($p < .001$). In addition, three measures that were used by multiple studies (Verbal IQ, Word List Learning [Trials 1–5], Trails B), and nine that were used by single studies (Full Scale IQ, Card Sorting, general cognitive status, Verbal Comprehension Index, Functional Status Examination, Working memory Index [immediate recall], Word List Learning [Immediate delayed recall], Perceptual Organisation Index, MMSE) showed moderate-to-large and significant correlations with education; 89% of which were positive in direction, indicating that higher education was associated with better outcomes.

3.4.2. Pre-morbid IQ

Pre-morbid IQ was the only other measure of CR that has been investigated and was estimated using a variety of measures, namely the Wechlser and National Adult Reading Tests (WTAR, NART) (Nelson and Willison, 1991; Wechsler, 2001), the Vocabulary subtest of the Wechsler Adult Intelligence Sale (Wechsler, 1997) and the Shipley Vocabulary test (Shipley et al., 2009). All studies provided data in the form of correlations ($N_{studies}$ = 8; see Table 8), albeit with a large number of outcomes (20 scores/measures). The overall mean r_w was .24 ($p < .001$), which equates to a modest but significant positive relationship, indicating that higher pre-morbid ability is associated with slightly better outcomes. While most of the correlations (88%) for individual measures were positive, only two were moderate-to-large and significant (Paced Serial Addition Test/PASAT, Complex Figure Test: recognition trial), and both of these were based on the findings of single studies (Table 8).

4. Discussion

The current study analysed data from 90 studies that examined a total of 8856 participants in order to examine the extent to which variables thought to measure BR and CR may mediate or moderate differences in the cognitive and functional outcomes of people who have sustained a TBI. BR was assessed using a number of biological variables that may impact on brain size/structure/function and/or recovery; namely, genetics (APOE, KIBRA, COMT, NGB, IL-1, IL-6, mitochondrial polymorphisms), age and sex. CR, on the other hand, was assessed using two indices of pre-injury cognitive capacity: education and estimated premorbid IQ.

The inherent nature of the BR and CR variables (some continuous, others categorical), combined with study-specific differences in how these variables were analysed, meant that the resulting data-set was extremely complex. In particular, despite being inherently continuous and therefore suited to correlations examining the relationship between reserve and outcome, age was also artificially dichotomised in order to compare the outcomes of younger vs older adults, yielding different types of effect sizes for the same variable (r and Cohen's d, respectively). Similarly, sex – which is a categorical variable – was used both to examine sex differences in outcome following TBI (Cohen's d) and treated as a continuous variable for the purposes of examining the relationship between sex and outcome (r). Given the question under consideration – the extent to which measures of BR and CR may mediate or moderate outcomes after TBI – correlations seemed to be the most appropriate effect size.

Although it is possible to convert d to r for this purpose, correlations calculated from continuous variables that have been artificially dichotomised (e.g., age) are not numerically equivalent to correlations that are calculated when these same variables are treated as continuous variables or to those that are calculated from inherently dichotomous variables (e.g., sex) (Lipsey and Wilson, 2001). Artificially dichotomised variables result in attenuated

Table 4
Age and outcome: Cohen's *d*.

Outcome measure	$N_{studies}$	$N_{participants}$	Mean d_w	95% CIs		p	Severity	N_{fs}	Study references
Trail Making B (time)	1	22	2.46	1.36	3.56	**	Mild	11	Uzzell et al. (1987)
Finger Tapping	1	22	1.26	.36	2.16	*	Mild	5	Uzzell et al. (1987)
Information	1	148	−.85	−1.20	−.50	**	Mild	3	Raskin et al. (1998)
Similarities	1	148	−.72	−1.07	−.37	**	Mild	3	Raskin et al. (1998)
Reaction Time (time)	1	89	.71	.14	1.28	*	Severe	3	Keller (1998)
Picture Completion	1	148	−.64	−.99	−.29	**	Mild	2	Raskin et al. (1998)
Vocational Independence Scale	1	195	.64	.35	.93	**		2	Testa et al. (2005)
Visual Paired Associates I	1	22	.63	−.23	1.49		Mild	2	Uzzell et al. (1987)
Tracking Task	1	89	.60	.03	1.17	*	Severe	2	Keller (1998)
Digit Span	1	22	.59	−.27	1.45		Mild	2	Uzzell et al. (1987)
Arithmetic	1	148	−.58	−.93	−.23	**	Mild	2	Raskin et al. (1998)
Reaction Time (accuracy)	1	89	.56	−.01	1.13		Severe	2	Keller (1998)
GOS/GOSE	4	528	.55	.26	.83	**	Mild, moderate, severe,	7	Mosenthal et al. (2004), Resnick et al. (1997), Tan et al. (2004), Roe et al. (2013)
Trail Making A (time)	2	301	.55	.12	.97	*	Mild, Not specified	4	Johnstone et al. (1998), Uzzell et al. (1987)
Object Assembly	1	148	−.53	−.88	−.18	**	Mild	2	Raskin et al. (1998)
Word List Learning (short delay cued recall)	1	148	.52	.17	.87	**	Mild	2	Raskin et al. (1998)
Functional Independence Measure	1	182	.50	.15	.85	*	Mild	2	Mosenthal et al. (2004)
Comprehension	1	148	−.47	−.82	−.12	*	Mild	1	Raskin et al. (1998)
Independent Living Scale	1	195	.46	.17	.75	**	Mild, moderate, severe	1	Testa et al. (2005)
Disability Rating Scale	1	195	.36	.07	.65	*	Mild, moderate, severe	1	Testa et al. (2005)
FSIQ	2	301	−.33	−.57	−.09	*	Mild, Not specified	1	Johnstone et al. (1998), Uzzell et al. (1987)
VIQ	1	22	.23	−.61	1.07		Mild	0	Uzzell et al. (1987)
PIQ	1	22	.21	−.63	1.05		Mild	0	Uzzell et al. (1987)
Cancellation Task	1	22	.20	−.64	1.04		Mild	0	Uzzell et al. (1987)
Line Bisection	1	22	.15	−.69	.99		Mild	0	Uzzell et al. (1987)
Memory Quotient	1	22	.05	−.79	.89		Mild	1	Uzzell et al. (1987)
General Memory Index	1	279	−.04	−.29	.21		Not specified	1	Johnstone et al. (1998)
Attention Index	1	279	−.01	−.26	.24		Not specified	1	Johnstone et al. (1998)
Delayed Memory Index	1	279	.00	−.25	.25		Not specified	1	Johnstone et al. (1998)
OVERALL	9	1261	.38	.10	.66	*		8	

Note. $N_{studies}$ = number of studies contributing to the effect; $N_{participants}$ = number of participants; Mean d_w = weighted mean Cohen's *d*; SD = standard deviation; 95% CI = 95% confidence interval; N_{fs} = Fail-safe N; GOS/GOSE = Glasgow Outcome Scale/Glasgow Outcome Scale Extended; FSIQ = Full Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient.
Positive Cohen's *d* = younger age group had better outcomes than older age group, negative *d* = younger age group had poorer outcomes.
* $p < .05$.
** $p < .001$.

correlations; a problem that increases when the samples are not equal in size. Cohen's *d*, on the other hand, provides a standardised measure of the mean difference in outcomes that allows for unequal sample sizes and is not affected by whether a variable is intrinsically or artificially dichotomised. In light of the known risk factors for TBI (e.g., younger age, male sex) (Bruns and Hauser, 2003; Langlois et al., 2006), the sample was unlikely to be evenly divided when age was treated as a dichotomous variable. Thus, both *r* and *d* effect sizes were reported, reflecting the format of the data in the original study, in order to avoid this problem and preserve the integrity of the original data (McGrath and Meyer, 2006).

Given the range of outcome measures that have been used by these studies, it is perhaps not surprising that the results were highly variable. However, it is exactly this variability, and the fact that many of these findings have not previously been consolidated, that makes it difficult for clinicians to utilise the research that is available to inform their practice and for researchers to advance the work in this area; underscoring the importance of the current meta-analysis. For the purposes of this discussion, it is critical that multiple aspects of the findings be considered; namely the *overall* impact of a measure of reserve on outcome, the general direction of the results from *all* studies that examined a specific aspect of BR or CR ($+^{ve}$ vs $-^{ve}$ effect sizes), as well as those results that provide compelling evidence of the impact of reserve on specific outcomes (i.e., moderate-to-large/sizeable and significant effect sizes).

To date, most of the research that has examined genetic contributions to outcome following TBI has focused on APOE status, possibly reflecting the link between TBI and the development of dementia (Johnson et al., 2010; Mannix and Whalen, 2012). The findings in relation to APOE were very mixed and, although there

Table 5
Sex and outcome: correlations.

Outcome measure	$N_{studies}$	$N_{participants}$	Mean r_w	95% CIs		p	Severity	N_{fs}	Study references
Block Design (score)	1	12	.43	−.33	.85		Not specified	3	Barclay et al. (1985)
VIQ	1	13	.39	−.21	.77		Mild, moderate, severe	3	Kennedy (2004)
Word List Learning (Trials 1–5)	2	76	−.37	−.56	.14	*	Mild, moderate, severe	5	Barclay et al. (1985), Callahan and Johnstone (1994)
Block Design (time)	1	12	.35	−.36	.80		Not specified	3	Barclay et al. (1985)
Category Fluency	1	12	.32	−.66	.90		Not specified	2	Barclay et al. (1985)
Letter Fluency	1	12	.30	−.59	.86		Not specified	2	Barclay et al. (1985)
Story Memory II (delayed recall)	1	20	.26	−.21	.63		Severe	2	Carlesimo et al. (1998)
Picture Recall (short delay cued recall)	1	12	.22	−.64	.83		Not specified	1	Barclay et al. (1985)
Receptive Vocabulary	1	13	.21	−.39	.68		Mild, moderate, severe	1	Kennedy (2004)
Immediate Auditory Memory (immediate recall)	1	13	−.20	−.68	.39		Mild, moderate, severe	1	Kennedy (2004)
Verbal Comprehension (error)	1	12	.19	−.50	.73		Not specified	1	Barclay et al. (1985)
Disability Rating Scale	1	88	−.17	−.37	.04			1	Jacobsson et al. (2009)
Word List Learning (delayed recall)	1	20	.12	−.34	.53		Severe	0	Carlesimo et al. (1998)
Matrices	1	20	.11	−.35	.53		Severe	0	Carlesimo et al. (1998)
Cancellation Task (time)	1	12	−.10	−.79	.71		Not specified	0	Barclay et al. (1985)
Trail Making Test B (time)	1	13	.09	−.49	.61		Mild, moderate, severe	0	Kennedy (2004)
GOS/GOSE	11	272	−.08	−.20	.05		Mild, moderate, severe	9	Carlesimo et al. (1998), Chastain et al. (2009), Hou et al. (2007), Huang et al. (2010), Newcombe et al. (2007), Salmond et al. (2005):2006, Sidaros et al. (2009), Tateishi et al. (1998), Valente et al. (2002), Warner et al. (2010), Winter et al. (2004)
SCATBI	1	30	−.07	−.42	.30		Severe	0	Hough (2008)
Community Integration Questionnaire	2	192	−.07	−.33	.19		Mild, moderate, severe	1	Corrigan and Deming (1995), Jacobsson et al. (2009)
Functional Independence Measure	3	128	−.06	−.39	.28		Mild, moderate, severe	1	Jacobsson et al. (2009), Sidaros et al. (2009), Bondanelli et al. (2002)
Word List Learning (cued recall)	1	12	.04	−.68	.72		Not specified	1	Barclay et al. (1985)
Functional Status Examination	1	25	.04	−.36	.43		Mild, moderate, severe	1	Warner et al. (2010)
Verbal Skills	1	30	.00	−.36	.36		Severe	1	Hough (2008)
OVERALL	18	574	−.09	−.19	.00			2	

Note. $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants; Mean r_w = weighted mean correlation; SD = standard deviation; 95% CI = 95% confidence interval; N_{fs} = Fail-safe N; VIQ = Verbal Intelligence Quotient; SCATBI = Scales of Cognitive Ability for Traumatic Brain Injury; GOS/GOSE = Glasgow Outcome Scale/Glasgow Outcome Scale Extended.
Positive r = males had better outcomes, negative r = females had better outcomes/males had worse outcomes.
* $p < .001$.

were a reasonable number of studies ($N_{studies} = 8$), they measured a diverse range of outcomes. Overall, the small and non-significant mean effect size for APOE status suggests that it does not impact on outcomes after TBI. For the specific outcomes, there was a split in the number of positive and negative effects (42%:58%), suggesting that the findings are very contradictory. Moreover, there were only five moderate-to-large and significant effects (three from single studies): two indicating that $APOE^{-ve}$ genetic status, and three indicating that $APOE^{+ve}$, was associated with better outcomes. Importantly, many of the genetic studies had sample sizes below 100 (Friedman et al., 1999; Han et al., 2007; Liberman et al., 2002; Shadli et al., 2011), which falls below the numbers needed to reliably evaluate genetic associations (Gauderman, 2002; Hong and Park, 2012). These findings do not, therefore, provide clear or compelling evidence for the impact of APOE status on outcomes following TBI.

These findings are broadly consistent with those of an earlier meta-analysis by Zhou (Zhou et al., 2008), which examined the impact of APOE on injury severity (GCS) and Glasgow Outcome Scale scores (GOS/GOSE) in the first 6 months after a TBI. They, too, found that APOE was not associated with outcome in a small number of studies that treated the GOS as a continuous variable (negligible and non-significant d). Unlike the present study, they additionally examined studies that treated the GOS dichotomously and found that $APOE^{+ve}$ persons were at a greater risk of unfavourable outcomes; however this finding only equated to a small effect (Hopkins, 2002) and may be vulnerable to publication bias. They attributed their discrepant findings to the possibility that the GOS was more sensitive when scored dichotomously than continuously. However, their reasoning is unclear and is not supported by the current study, which examined a large number of sensitive cognitive tests but failed to find a sizeable or consistent effect.

The other genetic variables – KIBRA, COMT, NGB, IL-1 and IL-6 and various mitochondrial polymorphisms – were each examined by single studies, with some (COMT, IL-6) using samples that are considered to be unacceptably small for reliable genetic analysis (Gauderman, 2002; Hong and Park, 2012). Although preliminary, the findings suggest that there was a trend for non-carriers of the KIBRA rs17070145 polymorphism who sustained a severe TBI to have slightly better outcomes (primarily memory tests). Many

Table 6
Sex and outcome: Cohen's *d*.

Outcome measure	$N_{studies}$	$N_{participants}$	Mean d_w	95% CIs		p	Severity	N_{fs}	Study references
Stroop Interference	1	148	1.45	1.08	1.81	**	Mild	6	Raskin et al. (1998)
Word List Learning (short delay cued recall)	1	148	−1.06	−1.41	−.71	**	Mild	4	Raskin et al. (1998)
Word List Learning (long delay cued recall)	1	148	−1.03	−1.38	−.68	**	Mild	4	Raskin et al. (1998)
Family Pictures I	1	150	.80	.47	1.13	**	Mild, moderate, severe	3	Liossi and Wood (2009)
Family Pictures II	1	150	.71	.38	1.04	**	Mild, moderate, severe	3	Liossi and Wood (2009)
Word List Learning (recognition)	1	148	−.60	−.93	−.27	**	Mild	2	Raskin et al. (1998)
Word List Learning (Trials 1–5)	2	213	−.51	−1.47	.45		Mild, moderate, severe	3	Raskin et al. (1998), Tate et al. (2011)
WMS Auditory Recognition Delayed Index	1	150	.50	.17	.83	**	Mild, moderate, severe	2	Liossi and Wood (2009)
GOS/GOSE	3	426	.45	−.02	.93		Moderate, severe	4	Ponsford et al. (2008), Tan et al. (2004), King et al. (2005)
Hayling C	1	150	−.34	−.65	−.03	*	Mild, moderate, severe	1	Liossi and Wood (2009)
Symbol Search	1	150	.34	.03	.65	*	Mild, moderate, severe	1	Liossi and Wood (2009)
Letter Fluency	1	65	−.33	−.86	.20		Mild, moderate, severe	1	Tate et al. (2011)
SF-36 Mental	1	358	.32	.08	.56	*	Moderate, severe	1	Hu et al. (2012)
Hayling A	1	150	−.32	−.63	−.01	*	Mild, moderate, severe	1	Liossi and Wood (2009)
Hayling B	1	150	−.30	−.61	.01		Mild, moderate, severe	1	Liossi and Wood (2009)
Block Design	1	150	−.29	−.60	.02		Not specified	1	Liossi and Wood (2009)
Spatial Span	1	150	.25	−.06	.56		Mild, moderate, severe	0	Liossi and Wood (2009)
Complex Figure Test (delayed recall)	1	65	.21	−.32	.74		Mild, moderate, severe	0	Tate et al. (2011)
Story Memory II	2	215	.20	−.48	.88		Mild, moderate, severe	0	Liossi and Wood (2009), Tate et al. (2011)
Arithmetic	1	150	.18	−.13	.49		Mild, moderate, severe	0	Liossi and Wood (2009)
Picture Arrangement	1	150	−.18	−.49	.13		Mild, moderate, severe	0	Liossi and Wood (2009)
General Memory Index	1	402	−.18	−.38	.02		Mild, moderate, severe	0	Schopp et al. (2001)
Letter Number Sequencing	1	150	.17	−.14	.48		Mild, moderate, severe	0	Liossi and Wood (2009)
Brixton	1	150	−.16	−.47	.15		Mild, moderate, severe	0	Liossi and Wood (2009)
Word List Learning (immediate delayed recall)	1	65	−.15	−.68	.38		Mild, moderate, severe	6	Tate et al. (2011)
Comprehension	1	150	.14	−.17	.45		Mild, moderate, severe	0	Liossi and Wood (2009)
Verbal Paired Associates I	2	298	.14	−.91	1.18		Mild, moderate, severe	1	Liossi and Wood (2009), Raskin et al. (1998)
Verbal Paired Associates II	2	298	.13	−.99	1.26		Mild, moderate, severe	1	Liossi and Wood (2009), Raskin et al. (1998)
Finger Tapping	1	102	−.13	−.52	.26		Mild	0	Tsushima et al. (2009)
VIQ	2	552	.12	−.05	.28		Mild, moderate, severe	1	Liossi and Wood (2009), Schopp et al. (2001)
Digit Span	1	150	.12	−.19	.43		Mild, moderate, severe	0	Liossi and Wood (2009)
Digit Symbol Test	3	363	.10	−.35	.55		Mild, moderate, severe	2	Liossi and Wood (2009), Raskin et al. (1998), Tate et al. (2011)
BADS Zoo Map	1	150	.09	−.22	.40		Mild, moderate, severe	1	Liossi and Wood (2009)
Vocabulary	1	150	.07	−.24	.38		Mild, moderate, severe	1	Liossi and Wood (2009)
Similarities	1	150	−.07	−.38	.24		Mild, moderate, severe	1	Liossi and Wood (2009)
FSIQ	3	617	.07	−.09	.23		Mild, moderate, severe	2	Liossi and Wood (2009), Schopp et al. (2001), Tate et al. (2011)
Complex Figure Test (immediate recall)	1	65	−.06	−.59	.47		Mild, moderate, severe	1	Tate et al. (2011)
Functional Independence Measure	2	348	−.06	−.50	.38		Severe	1	Ponsford et al. (2008), Sommer et al. (2013)
Trail Making Test A (time)	4	719	.06	−.15	.27		Mild, moderate, severe	3	Liossi and Wood (2009), Schopp et al. (2001), Tate et al. (2011), Tsushima et al. (2009)
Attention Index	1	402	.04	−.16	.24		Mild, moderate, severe	1	Schopp et al. (2001)
Matrices	1	150	.04	−.27	.35		Mild, moderate, severe	1	Liossi and Wood (2009)
PIQ	2	552	−.02	−.19	.14		Mild, moderate, severe, Not specified	2	Liossi and Wood (2009), Schopp et al. (2001)
Visual Organisation	1	65	−.02	−.55	.51		Mild, moderate, severe	1	Tate et al. (2011)
Trail Making Test B (time)	4	719	−.01	−.35	.33		Mild, moderate, severe	1	Liossi and Wood (2009), Schopp et al. (2001), Tate et al. (2011), Tsushima et al. (2009)
Story Memory I	3	363	.00	−.67	.68		Mild, moderate, severe	3	Liossi and Wood (2009), Raskin et al. (1998), Tate et al. (2011)
OVERALL	10	1770	.10	−.07	.27			5	

Note. $N_{studies}$ = number of rating scales contributing to the effect size; $N_{participants}$ = number of participants; Mean d_w = weighted mean Cohen's *d*; SD = standard deviation of the effect size; 95% CI = 95% confidence interval; N_{fs} = Fail-safe N; SF-36 = Short Form-36; GOS/GOSE = Glasgow Outcome Scale/Glasgow Outcome Scale Extended; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; FSIQ = Full Scale Intelligence Quotient; BADS = Behavioural Assessment of the Dysexecutive Syndrome. Positive Cohen's *d* = males had better outcomes than females, negative Cohen's *d* = females had better outcome.

* $p < .05$.
** $p < .001$.

Table 7
Education and outcome: correlations.

Outcome measure	$N_{studies}$	$N_{participants}$	Mean r_w	95% CIs		p	Severity	N_{fs}	Study references
VIQ	3	55	.66	.46	.80	**	Mild, moderate, severe	17	Greiffenstein and Baker (2003), Kennedy (2004), Levin et al. (1979)
FSIQ	1	15	.55	.05	.83	*	Mild, moderate, severe	5	Greiffenstein and Baker (2003)
Card Sorting	1	20	.55	.14	.80	*	Severe	5	Cockburn (1995)
Cognitive Status	1	44	.54	.29	.72	**	Moderate, severe	4	Sumowski et al. (2013a)
Verbal Comprehension Index	1	100	.53	.37	.66	**	Moderate, severe	4	Walker et al. (2009)
Functional Status Examination	1	42	.44	.16	.66	**	Mild, moderate, severe	3	Mills et al. (1992)
Booklet Category Test	1	15	.43	−.11	.77		Mild, moderate, severe	3	Greiffenstein and Baker (2003)
Tower Test (score)	1	20	.40	−.05	.72		Severe	3	Cockburn (1995)
Working Memory Index (immediate recall)	1	100	.37	.19	.53	**	Moderate, severe	3	Walker et al. (2009)
Digit Symbol Test	1	8	.37	−.53	.88		Moderate, severe	3	Turner and Levine (2008)
Word List Learning (immediate delay recall)	1	48	.37	.10	.59	*	Mild		Waljas et al. (2014)
Perceptual Organisation Index	1	100	.35	.16	.51	**	Moderate, severe	3	Walker et al. (2009)
Letter Fluency	2	28	.34	−.07	.66		Moderate, severe	5	Cockburn (1995), Turner and Levine (2008)
Word List Learning (Trials 1–5)	3	127	.34	.17	.49	**	Mild, moderate, severe	3	Callahan and Johnstone (1994), Greiffenstein and Baker (2003), Waljas et al. (2014)
Trail Making B (time)	3	118	.32	.14	.48	**	Mild, moderate, severe	3	Greiffenstein and Baker (2003), Kennedy (2004), Perianez et al. (2007)
Mini-Mental State Exam	1	162	−.32	−.45	−.17	**	Mild, moderate, severe	2	de Guise et al. (2011)
Word List Learning (delayed recall)	2	35	.30	−.05	.59		Mild, moderate, severe	4	Carlesimo et al. (1998), Greiffenstein and Baker (2003)
Tower Test (time)	1	20	−.29	−.65	.17		Severe	2	Cockburn (1995)
SCATBI	1	30	.28	−.09	.58		Severe	2	Hough (2008)
Verbal Skills	1	30	.27	−.10	.57		Severe	2	Hough (2008)
Receptive Vocabulary	1	13	.26	−.34	.71		Mild, moderate, severe	2	Kennedy (2004)
Processing Speed Index (time)	1	100	−.25	−.43	−.06	*	Moderate, severe	2	Walker et al. (2009)
Delayed Auditory Memory Index (delayed recall)	1	100	.25	.06	.43	*	Moderate, severe	2	Walker et al. (2009)
Activities of Daily Living	1	100	.25	.05	.43	*	Moderate, severe	2	Bottari et al. (2009)
Visual Reproduction I (immediate recall)	1	15	.24	−.31	.67		Mild, moderate, severe	1	Greiffenstein and Baker (2003)
Choice Reaction Time (time)	1	27	−.24	−.57	.15		Mild, moderate, severe	1	Rieger and Gauggel (2002)
FSIQ change	1	74	.24	.01	.44	*	Not specified	1	Wood and Rutterford (2006)
Facial Perception (recognition)	1	12	.24	−.42	.73		Severe	1	Bornhofen and McDonald (2008)
Complex Figure Test	1	15	.22	−.33	.66		Mild, moderate, severe	1	Greiffenstein and Baker (2003)
GOS/GOSE	4	172	.22	.07	.36	**	Moderate, severe	0	Ariza et al. (2006), Carlesimo et al. (1998), Huang et al. (2010), Sigurdardottir et al. (2009)
Immediate Visual Memory Index (immediate recall)	1	100	.21	.01	.39	*	Moderate, severe	1	Walker et al. (2009)
Trail Making Test B-A (time)	2	98	.19	−.01	.38		Mild, moderate, severe	2	Perianez et al. (2007), Turner and Levine (2008)
Trail Making Test A (time)	2	105	.19	−.00	.37		Mild, moderate, severe	2	Greiffenstein and Baker (2003), Perianez et al. (2007)
Community Integration Questionnaire	1	151	.19	.03	.34	*	Mild, moderate, severe	1	Sander et al. (2009)
Matrices	1	20	.18	−.29	.58		Severe	1	Carlesimo et al. (1998)
BADS Total	1	25	.17	−.24	.53		Mild, moderate, severe	1	Rochat et al. (2009)
Cambridge Prospective Memory Test	1	44	.16	−.14	.44		Severe	1	Fleming et al. (2008)
Delayed Visual Memory Index (delayed recall)	1	100	.14	−.06	.33		Moderate, severe	0	Walker et al. (2009)
Complex Figure Test (delayed recall)	1	15	−.14	−.61	.40		Mild, moderate, severe	0	Greiffenstein and Baker (2003)
PIQ	2	42	.13	−.20	.43		Mild, moderate, severe	1	Greiffenstein and Baker (2003), Levin et al. (1979)
Category Test (subtest 3–7) (error)	1	146	.11	−.05	.27		Mild, severe	0	Donders (2001)
Clock Drawing Task	2	207	.11	−.16	.37		Mild, moderate, severe	0	Wagner et al. (2011), de Guise et al. (2011)
BADS Zoo Map	1	25	.10	−.31	.48		Mild, moderate, severe	0	Rochat et al. (2009)
Visual Reproduction II (delayed recall)	1	15	.08	−.45	.57		Mild, moderate, severe	0	Greiffenstein and Baker (2003)
Immediate Auditory Memory Index (immediate recall)	2	113	.08	−.43	.55		Mild, moderate, severe	0	Kennedy (2004), Walker et al. (2009)
Story Memory I (immediate recall)	2	27	−.06	−.46	.37		Mild, moderate, severe	1	Bornhofen and McDonald (2008), Greiffenstein and Baker (2003)
Story Memory II (delayed recall)	3	47	−.05	−.36	.27		Mild, moderate, severe	2	Bornhofen and McDonald (2008), Carlesimo et al. (1998), Greiffenstein and Baker (2003)
Finger Tapping	1	15	.03	−.49	.53		Mild, moderate, severe	1	Greiffenstein and Baker (2003)
OVERALL	26	1459	.20	.14	.27	**		26	

Note. $N_{studies}$ = number of studies contributing to an effect size; $N_{participants}$ = number of participants; Mean r_w = weighted mean correlation; SD = standard deviation; 95% CI = 95% confidence interval; N_{fs} = Fail-safe N; PIQ = Performance Intelligence Quotient; VIQ = Verbal Intelligence Quotient; FSIQ = Full Scale Intelligence Quotient; CHART SF = Craig Handicap Assessment and Reporting Technique, Short Form; SCATBI = Scales of Cognitive Ability for Traumatic Brain Injury; GOS/GOSE = Glasgow Outcome Scale/Glasgow Outcome Scale Extended; BADS = Behavioural Assessment of the Dysexecutive Syndrome.
Positive r = higher education associated with better outcomes; negative r = higher education associated with poorer outcomes.
* $p < .05$.
** $p < .001$.

Table 8
Premorbid IQ and outcome: correlations.

Outcome measure	$N_{studies}$	$N_{participants}$	Mean r_w	95% CIs		p	Severity	N_{fs}	Study references
Trail Making Test B-A (time)	1	8	.68	−.15	.95		Moderate, severe	6	Turner and Levine (2008)
Story Memory II (delayed recall)	1	12	.48	−.17	.84		Severe	4	Bornhofen and McDonald (2008)
Story Memory I (immediate recall)	1	12	.46	−.19	.83		Severe	4	Bornhofen and McDonald (2008)
PASAT (time)	1	22	.45	.04	.73	*	Moderate, severe	4	Madigan et al. (2000)
Facial Perception (recognition)	1	12	−.43	−.82	.23		Severe	3	Bornhofen and McDonald (2008)
Tower Test (score)	1	20	.40	−.05	.72		Severe	3	Cockburn (1995)
Card Sorting	2	98	.39	−.17	.76		Moderate, severe	6	Cockburn (1995), Schwarz et al. (2009)
Complex Figure Test (recognition)	1	78	.30	.08	.49	*	Moderate, severe	2	Schwarz et al. (2009)
Cognitive Estimation Test	1	30	.30	−.07	.60		Not specified	2	Freeman et al. (1995)
Gambling Test	1	71	.29	.06	.49	*	Mild, moderate, severe	2	Levine et al. (2005)
Complex Figure Test (immediate recall)	1	78	.25	.03	.45	*	Moderate, severe	2	Schwarz et al. (2009)
Tower Test (time)	1	20	−.23	−.61	.24		Severe	1	Cockburn (1995)
Complex Figure Test (delayed recall)	1	78	.22	.00	.42		Moderate, severe	1	Schwarz et al. (2009)
Rivermead Behavioural Memory Test	1	16	.22	−.31	.65		Not specified	1	Wills et al. (2000)
Complex Figure Test	1	78	.20	−.02	.40		Moderate, severe	1	Schwarz et al. (2009)
Pegboard Test	1	78	.10	−.13	.32		Moderate, severe	0	Schwarz et al. (2009)
Digit Symbol Test	2	86	.08	−.14	.29		Moderate, severe	0	Schwarz et al. (2009), Turner and Levine (2008)
Letter Fluency	3	106	.08	−.52	.63		Moderate, severe	1	Cockburn (1995), Schwarz et al. (2009), Turner and Levine (2008)
Trail Making B (time)	1	78	.02	−.20	.24		Moderate, severe	1	Schwarz et al. (2009)
Trail Making A (time)	1	78	.00	−.22	.22		Moderate, severe	1	Schwarz et al. (2009)
OVERALL	8	257	.24	.11	.36	**		11	

Note. $N_{studies}$ = number of studies contributing to the effect size; $N_{participants}$ = number of participants; Mean r_w = weighted mean correlation; SD = standard deviation of the effect size; 95% CI = 95% confidence interval; N_{fs} = Fail-safe N (@ criterion value = .1); PASAT = Paced Auditory Serial Addition Test.
Positive r = higher premorbid IQ associated with better outcomes; negative r = higher premorbid IQ associated with poorer outcomes.
* $p < .05$.
** $p < .001$.

of the differences for individual measures were small or non-significant and susceptible to publication bias, but the fact that the findings were all in the same direction suggests that this gene may warrant further research in TBI samples. Interestingly, however, whether carriers or non-carriers perform better on memory tasks has proven controversial in other clinical (e.g., Alzheimer's) and non-clinical samples (Wagner et al., 2012), highlighting the need for further research to examine the role that KIBRA plays in memory.

The findings for COMT were generally unremarkable, with a mixture of small non-significant effects that were both positive and negative in direction. Moreover, the single notable finding was contrary to prediction, with the Val/Val allele being associated with better performance on an abstract problem-solving task (WAIS Matrix Reasoning) following moderate-severe TBI than the Met/Met allele. Thus, this polymorphism does not appear to offer a source of biological reserve; although the sample size was extremely small, raising concerns about the veracity of these findings. In contrast, there may a slight advantage, in terms of broad outcomes following TBI, for people who are negative for the rs3783988 NGB mutation. However, as was the case for individual studies of APOE and COMT, the samples were very small (Gauderman, 2002; Hong and Park, 2012). Consequently, the results can only be considered tentative and further research is required to definitively establish a link. Similarly, the studies of IL-1 and IL-6 suggested that neither the IL-1B nor the IL-6-174C/G polymorphism provided a source of reserve following TBI. Moreover, although the IL-1-RN polymorphism was associated with significantly better GOSE outcomes 6 months after a TBI, this finding is counter-intuitive because IL-1-RN is pro-inflammatory – rather than anti-inflammatory – in its action. The main explanations given for this anomalous finding relate to limitations in the measures of injury severity and outcome, and to the fact that factors affecting the expression of IL-1-RN may vary in a time-dependent way which, in turn, impacts on pro- and anti-inflammatory responses (Hadjigeorgiou et al., 2005). Finally, there was very limited evidence to suggest that the four mitochondrial polymorphisms examined by Conley et al. (2014) sizeably or systematically affected outcomes after severe TBI. Indeed, the consistently low N_{fs} statistics highlight the precarious nature of these findings.

Age, on the other hand, has been examined by many more studies ($N_{studies}$ = 58), using a large number of outcome measures. The findings from studies that measured age on a continuous scale were generally similar to those that dichotomised this variable, with both overall mean effects being relatively small (mid-way between small and medium effect benchmarks) but significant; indicating that younger people have slightly better outcomes after a TBI. Similarly, the majority of the effects for individual outcomes were positive (r: 67%, d: 68%), as were most of the moderate to large and significant effects (r: 61%; d: 70%).

However, age-related changes in brain size/function and cognition are commonly observed in healthy adults (Ge et al., 2002; Myers, 2008; Steffener et al., 2012), possibly contributing to the aforementioned finding that younger persons had better outcomes after a TBI. These changes occur independently of a TBI and affect the biological and cognitive substrate on which a TBI is superimposed, making it important to additionally consider whether the aforementioned findings reflect normal age-related relationships/differences or something additional to this. A very small number of studies ($N_{studies}$ = 3) used age-scaled scores, which

control for the normal effects of ageing on cognition (i.e., WAIS Subtest, Index and IQ scores), enabling an examination of this issue. Interestingly, most of these effect sizes were negative (75%) and all effects that were moderate-to-large and significant were negative; suggesting that sustaining a TBI at a younger age may be associated with poorer cognitive outcomes, after controlling for normal age-related changes to cognition. While these largest effects were based on the findings of a single study (Raskin et al., 1998), it is worth noting that the sample had sustained mild TBIs – which are likely to cause relatively subtle deficits, making it harder to detect age-related differences in outcomes – adding weight to these findings. However, it also highlights the need for additional research that controls for normal age-related changes when examining the impact of age on outcome after TBIs.

Thus, consistent with reserve theory, the data suggest that being younger at the time of sustaining a TBI is associated with better performance on many commonly used measures of outcome. However, when normal levels of age-related decline are additionally taken into consideration in order to determine whether the age at which a person is injured has any independent effect on outcome, increasing age – or the greater experience that develops with age – appears to act as a source of reserve following a TBI, at least in terms of performance on standard IQ tasks. The former findings may reflect age-related changes to fluid intelligence – whereby the capacity to process information quickly and solve abstract problems declines with age – and the latter may reflect the changes to crystallised intelligence – which is more reliant on knowledge and experience, and continues to increase as people age (Flanagan et al., 2000).

The data for sex yielded very small non-significant effects ($r = -.09$; $d = .08$) when all outcomes were combined, suggesting that neither males nor females fare better, overall, after a TBI. Sixty-four percent of the correlations and 55% of the Cohen's *d* statistics for specific outcomes were positive (males performed better), but only eight were associated with moderate to large and significant effects, and these findings were equally split between those that indicated better outcomes for males and those that favoured females. It is also noteworthy that only one of these eight significant results came from studies that correlated sex with outcome, highlighting the fact that dichotomous variables are better suited to group comparisons. Based on the overall results, it appears that although males are more likely to sustain a TBI (Andelic, 2013; Bruns and Hauser, 2003; Feigin et al., 2013; Langlois et al., 2006), they appear to have broadly comparable outcomes to females. While sex differences are evident for some measures of outcome, it is possible that they may pre-date the injury, rather than reflecting differential responses to a TBI.

The findings for sex contrast with those of a previous smaller meta-analysis (Farace and Alves, 2000), which reported that females had slightly worse outcomes on 85% of their measures; although when all measures were combined, the difference equated to a small mean effect ($d = -.15$). However, this earlier meta-analysis was based on many fewer studies and evaluated a range of other outcomes (e.g., death, dizziness, fatigue, tinnitus, insomnia, hearing problems, double vision, headaches, anxiety, depression), possibly contributing to the different findings. Moreover, unlike the current study, it was largely based on self-reported symptoms, which have previously been documented to show sex differences (Covassin et al., 2006, 2007).

Education was one of two proxy measures of CR that were examined in this study. Overall, there was a small-to-medium positive and significant correlation between education and the outcome measures (mean $r_w = 20$), with the majority of individual measures also being positively correlated. With one exception (MMSE), the moderate to large and significant relationships were also positive. Thus, higher education appears to provide a source of reserve, leading to better outcomes after a TBI. However, as with age, education is correlated with many of the outcome measures in the general population. For example, the correlation between education and IQ is approximately .5 (Deary and Johnson, 2010; Neisser et al., 1996); which is comparable to the correlations reported here for VIQ (.66) and FSIQ (.55), but not PIQ (.13). Education-adjusted scores did not appear to be used by the current studies, precluding an analysis of the relationship between education and recovery after a TBI, independent of the relationship between education and cognition seen in healthy persons. Research examining the relationship between IQ and outcome after TBI, using both education-adjusted and unadjusted scores, is therefore needed to provide a more definitive assessment of the extent to which education contributes to building CR.

Finally, the relationship between premorbid IQ and outcome was evaluated. Overall, the findings suggest that higher premorbid ability is associated with better outcomes after TBI (mean $r_w = .24$). Most of the results for specific outcomes were positive and supported this conclusion, although only a few yielded moderate or large effects. Thus, once again, the effects are generally modest, but important nonetheless.

At a broader level, it is noteworthy that many of the significant findings – particularly those that reflected moderate to large effects – were for measures of attention/speed of information processing and memory. These cognitive domains are well known to be affected by TBI (Canty et al., 2014; Huang et al., 2014; Mathias and Wheaton, 2007; Upadhyay, 2008) and are commonly assessed by researchers in this field, but the fact that they feature prominently in the current context suggests that they warrant further attention in future research examining the relationship between reserve and outcomes after TBI.

4.1. Study limitations and research directions

The aforementioned findings must be tempered by the limitations of this study. First, as with most meta-analyses, numerous studies did not provide the data needed to calculate effect sizes. Corresponding authors were contacted in such instances, but this was often unsuccessful. Second, much of the research that is relevant to BR and CR in TBI samples has not been explicitly conducted with this in mind. Consequently, some relevant data (e.g., age, sex) are embedded in studies whose titles/abstracts/keywords may not indicate its existence, reducing the number of studies that were included. While it is likely that other studies exist, our searches were comprehensive and therefore should provide a representative sample of the data. Certainly, the analyses provided here represent a significant advance on the information that has hitherto been available when considering the impact of BR and CR on outcomes after TBI.

Third, few studies provided age-scaled scores for their outcome measures. Scaled scores are better suited to assessing the relationship between the age of the person who sustains the TBI and their outcome, independently of any normal age-related cognitive decline that may have predated their injury. However, it is also possible the cause and/or severity of a TBI may be confounded with age, as there are differences in the main causes of TBIs in younger (motor vehicle accidents, assaults) and older adults (falls), which can also impact on outcome (Faul et al., 2010). Once again, this highlights the need for research that examines the complex interplay between a range of moderating and mediating injury-related (e.g., cause and severity of TBI) and person-related (BR and CR) variables.

Fourth, due to limitations in the available data, it was not possible to additionally examine the impact of injury severity on the relationship between measures of BR/CR and outcome. This is, itself, an interesting question as it is possible that injury severity acts as a mediator; potentially increasing the importance of reserve

to outcome following more severe injuries – because pre-existing resources may be even more important – or decreasing its importance – because reserve may be less critical to outcome than other injury-related variables. Similarly, it was not possible to examine whether time-since-injury impacted on the variables under investigation. This is an important variable to consider because other injuries (e.g., orthopaedic or internal injuries) – and any associated pain/disability – are more likely to impact both on early assessments of outcome, when physical recovery is incomplete, and on those who sustain more severe TBIs.

Fifth, every attempt was made to exclude studies where there was a known history of a previous TBI, psychiatric disorder, substance abuse or other neurological disorder that could independently affect outcome. However, this information was not always provided, leaving open the possibility that these variables muddied the waters. Whether to include or exclude these cases in research remains a perennial problem because some of these variables (e.g., previous TBI, substance abuse) are risk factors for TBI and are common in people who are seen clinically (Bombardier et al., 2002; Chua et al., 2007; Harrison-Felix et al., 2004; Macmillan et al., 2002; Mayers, 2013; Olson-Madden et al., 2012). Their exclusion from research samples serves to improve research rigour, but may reduce the generalisability of the findings.

Sixth, numerous studies treated age as a dichotomous variable, but did so using different criteria. Thus, when young(er) versus old(er) participants were compared the cut-off varied between 30 and 65 years, although most were around 40.

Seventh, all estimates of pre-morbid IQ were obtained from commonly-used measures that are not suitable for use with people for whom English is a second language (e.g., NART, WTAR). Thus, research examining the relationship between pre-morbid IQ and outcomes is likely to exclude these individuals; possibly limiting the extent to which these findings can be generalised to the full range of individuals who sustain a TBI.

Finally, it was not possible to undertake multivariate analyses of the combined impact of multiple BR and CR variables on outcome. This is important because there is likely to be co-variation between some of the measures of reserve (e.g., education and premorbid IQ); a multivariate approach is therefore needed in order to examine the unique variance in outcomes accounted for by individual variables, as well as the total amount of variance that is accounted for by a larger number of BR and CR variables (e.g., age, sex, education, premorbid IQ). A multivariate approach would also enable a more detailed examination of some of the potential interactions between variables that are likely to impact on TBI. This could involve, for example, an examination of the interaction between age and specific causes of injury in order to determine whether, despite being more common in younger adults, motor vehicle accidents and assaults lead to poorer outcomes in older adults. Similarly, it could include an examination of the interaction between sex and age-related hormonal changes, as it has been suggested that the potentially neuroprotective effects of oestrogen and progesterone afforded to women declines with age (Niemeier et al., 2013; Petrone et al., 2015; Roof and Hall, 2000; Stein, 2008).

A large-scale study that examines multiple BR/CR variables and a range of outcomes across the full spectrum of injury severity (mild, moderate and severe) and at repeated intervals – while controlling for normal (and potentially confounding) age-related differences in ability, which exist at the time of the injury – is now needed to undertake a thorough analysis of the contribution of individual differences in reserve to outcome after TBI. By repeatedly assessing outcomes at critical post-injury intervals (e.g., 2, 6 and 12 months post-injury), it will be possible to examine the extent to which different BR/CR impact on both the level of impairment and the rate of recovery between these different time-points (Green et al., 2008). This work needs to be done in conjunction with research designed to improve our understanding of the biomechanical forces that occur at the time of an injury; the immediate and delayed pathophysiological changes that are set in motion; the resultant gross and microstructural disruption and damage; and the early and late cognitive, psychological and functional consequences of TBI. In doing so, it will improve our understanding of individual differences in 'the head/person' that is injured (BR and CR), the injury that is sustained, and the resulting brain damage; all of which contribute to the variability in patient outcomes that is seen in clinical settings.

4.2. Conclusion

In theory, the mechanisms by which BR and/or CR may mediate or moderate outcomes after TBI are numerous. For example, reserve may impact on the neural substrate and cognitive systems onto which the TBI is superimposed, affecting the amount and quality of resources that are available to a person following an injury and, consequently, whether an injury manifests as measurable problems. Reserve may also affect the flexibility with which the residual resources respond to alterations in functioning after an injury. Reserve may even affect who is most at risk of sustaining a TBI, such that those with lower levels of CR may show poorer judgement or problem solving, potentially placing them at greater risk of accidental injuries and assaults. Similarly, biological reserve may contribute to differences in the pathophysiological response at the time of injury.

The current meta-analysis highlights the need for additional well-designed research into BR and CR with TBI samples, as much as it served to consolidate the data. In terms of BR, the evidence relating to genetic contributors to outcome proved to be extremely mixed and, in many cases, was based on a very limited number of studies, which were also often under-powered. While this does not necessarily negate the importance of genetics to outcome, it suggests that larger studies are needed to more definitively evaluate their influence. Age may also provide a source of BR, albeit in competing ways. Younger adults performed slightly better than older adults, however this was not the case when the normal age-related decline seen in healthy persons was taken into consideration. Thus, age-adjusted scores are essential to an investigation of the impact of age on outcome after TBI. In contrast, the sex of the person who sustained the TBI did not provide an overall source of BR, although there were notable sex differences in specific outcomes. However, it remains unclear whether these differences pre-date the injury; consequently this needs to be evaluated in healthy controls. Lastly, higher levels of CR – as measured by years of education and estimated premorbid IQ – were associated with slightly better outcomes after TBI.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2015.06.001

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