Neuropsychology Review (2019) 29:288–312
https://doi.org/10.1007/s11065-019-09405-8

REVIEW

Corticosteroids and Cognition: A Meta-Analysis

Catherine E. Prado[1] · Simon F. Crowe[1]

Received: 11 May 2018 / Accepted: 10 April 2019 / Published online: 26 May 2019

Abstract

A thorough understanding of the cognitive effects of corticosteroids is essential given their frequency of use. This meta-analysis was conducted to investigate the effects of corticosteroids on the various domains of cognitive functioning, grouped by duration of use. An electronic search of PsycInfo, Medline and Google Scholar was conducted for all journal articles published between January 1990 and May 2018. Twenty six studies were included enabling calculation of standardised mean difference (SMD) using a random effects model for the cognitive domains of divided attention, executive function, expressive language, immediate memory, processing speed, recent memory, sustained attention, very long term memory and working memory. Results revealed that corticosteroids had a modest, negative effect on executive function for acute users, recent memory for short term and chronic users, and very long term memory for acute users. Corticosteroids had a small, significant, positive effect on expressive language for short term users.

Keywords Corticosteroids · Steroids · Cognition · Memory · Meta-analysis

Corticosteroids are synthetic analogues of the natural steroid hormones produced by the adrenal cortex. They are a commonly prescribed class of drug used to suppress the immune system and decrease inflammation (Judd et al., 2014), and include medications such as hydrocortisone, dexamethasone and prednisolone (Kusljic, Manias, & Gogos, 2016). Since their discovery in the 1940's, corticosteroids have become one of the most widely used and effective treatments for various inflammatory and autoimmune disorders (Liu et al., 2013), including respiratory, dermatologic, ophthalmologic, rheumatologic, pulmonary, haematologic, and gastrointestinal disorders (Ling, Perry, & Tsuang, 1981).

Despite their beneficial effects, use of corticosteroids has been associated with a range of behavioural and cognitive side effects including delirium, depression, mania, and psychosis (Bhangle, Kramer, & Rosenstein, 2013; Brown, Khan, & Nejtek, 1999). The terms 'steroid psychosis' (Freyne, 2005), and more recently corticosteroid- induced neuropsychiatric disturbances (CIPD, Bhangle et al., 2013) have been used to describe these diverse affective, behavioural, and cognitive syndromes.

Corticosteroids act via the low-affinity glucocorticoid (GR) and the high-affinity mineralocorticoid (MR) receptors (Schwabe, Schächinger, de Kloet, & Oitzl, 2010). These receptors are widely distributed throughout the brain (Belanoff, Gross, Yager, & Schatzberg, 2001), with the highest concentrations of receptors found in the hypothalamus, pituitary, and hippocampus (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998). There is some evidence to suggest that chronic exposure of these brain regions to corticosteroids is associated with a variety of neuroanatomical changes (Sapolsky, Krey, & McEwen, 1985; Sapolsky, Krey, & McEwen, 2002). Research using non-human primates, for example, suggests that exogenous corticosteroid administration is associated with changes in the hippocampus (Sapolsky, Uno, Rebert, & Finch, 1990; Uno et al., 1994; Uno, Tarara, Else, Suleman, & Sapolsky, 1989), however studies using human samples have generated conflicting results. Some researchers have found no change in hippocampal volume between short term corticosteroid users and controls (Scheel, Ströhle, & Bruhn, 2010; Tessner, Walker, Dhruv, Hochman, & Hamann, 2007). However, Brown et al. (2013) reported a trend toward a decrease in hippocampal activation, and an associated decline in memory with three days of hydrocortisone use. Brown et al. (2015) more recently reported a significant reduction in total

✉ Simon F. Crowe
s.crowe@latrobe.edu.au

[1] Department of Psychology and Public Health, La Trobe University, Bundoora, VIC 3086, Australia

hippocampal volume compared with placebo following brief hydrocortisone exposure.

Numerous case studies have also highlighted the deleterious effects of corticosteroids on cognition. Difficulties with concentration, memory, working memory, and executive functioning skills have been reported in both adult (Brown, 2009; Wolkowitz, Lupien, Bigler, Levin, & Canick, 2004) and paediatric populations (Barnes & Pedersen, 1993; Bender, Lerner, & Poland, 1991). In an early study using a clinical sample, Rome and Braceland (1952) investigated patients who were being treated with Cortisone, Hydrocortisone and related substances for various diseases. The authors reported that 'thinking disturbances' were a common symptom of corticosteroid therapy in these patients. Later research also reported associations between corticosteroid use and cognitive deficits across a range of cognitive functions (Hall, Popkin, Stickney, & Gardner, 1979; Keenan, Jacobson, Soleymani, & Newcomer, 1995; Lupien, Gillin, & Hauger, 1999), with a frequent finding being impairment of declarative memory. Studies have also highlighted the cognitive effects of corticosteroids in healthy subjects, with memory difficulties often being cited (Newcomer et al., 1999; Wolkowitz, Reus, Weingartner, Thompson, & Breier, 1990).

However, the finding of cognitive impairment as a result of corticosteroid use is not unequivocal. Some studies, including animal studies, have failed to find significant effects of corticosteroids on cognition (Lupien et al., 1999), while others have actually found evidence of corticosteroid-induced memory enhancement (Buchanan & Lovallo, 2001; Cottrell & Nakajima, 1977; Lupien et al., 2002; Sandi, Loscertales, & Guaza, 1997; Sandi & Rose, 1994).

Research has indicated that the duration of corticosteroid use may influence the presence or degree of associated cognitive impairment in a time dependent manner (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006). Evidence from a range of studies demonstrates the detrimental effects of corticosteroids on cognitive function across multiple time frames, including acute (Beckwith, Petros, Scaglione, & Nelson, 1986; Fehm-Wolfsdorf et al., 1993; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Lupien et al., 1999), short term (Brown, 2009; Liu et al., 2013; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Wolkowitz et al., 1990; Young, Sahakian, Robbins, & Cowen, 1999), and chronic use (Keenan, Jacobson, Soleymani, Mayes, & Yaldoo, 1996). These disturbances appear to be dose-dependent (Warrington & Bostwick, 2006), and cumulative exposure to high levels of corticosteroids has been suggested to detrimentally effect cognition (Lupien et al., 2002). Positively, when cognitive deficits have been observed, they have been reported to be reversible with discontinuation of corticosteroids (Brown & Chandler, 2001; Wolkowitz, Reus, Canick, Levin, & Lupien, 1997). However, other researchers have also reported non-significant effects, or even positive effects, across similar time frames (Denburg, Carbotte, & Denburg, 1994; Henckens, van Wingen, Joëls, & Fernández, 2011). As such, while time-dependent actions of corticosteroids may be an important predictor of potential cognitive side effects, this relationship is yet to be clearly determined in the literature.

One attempt to summarise the disparate findings in the literature was made by Het, Ramlow, and Wolf (2005) who conducted a meta-analysis on the effects of cortisol treatment. The researchers examined drug effects on memory for acute users only. Their results revealed a variable pattern of effects with significantly heterogeneous effect sizes. Understanding the way in which corticosteroids may affect memory is clearly clinically useful. However, given the potential for these drugs to act on a range of brain regions, including the prefrontal cortex (de Kloet, 1991), a comprehensive examination of the potential effects of corticosteroids on a range of cognitive domains is important.

The Current Study

Given the frequency with which corticosteroids are used, it is important to provide a synthesis of the current evidence in order to better enable clinicians and patients to make informed decisions regarding the possible impact of these drugs on cognitive functioning. While the data generated from Randomised Controlled Trials (RCTs) is regarded as one of the strongest levels of evidence, many researchers agree that non-randomised studies (e.g., non-randomised trials, longitudinal and cohort studies, and controlled before and after designs, etc.), are also important sources of evidence and should be an integral part of assessing health care interventions (for a review see Peinemann, Tushabe, & Kleijnen, 2013). Although methodological heterogeneity certainly exists in the literature, the systematic exploration of this heterogeneity presents opportunities to increase the relevance of conclusions drawn from included studies, and to enhance understanding of the evidence as a whole (Lau, Ioannidis, & Schmid, 1998). As such, in order to examine a wide evidence base, the current meta-analysis included appropriate studies of various methodologies. The primary objective of this meta-analysis was to investigate the effects of corticosteroids on cognition by examining their effects across a range of cognitive domains. Given that corticosteroids may differentially affect cognition as a function of duration of use, the analysis compared and contrasted the effects of corticosteroids on cognition, based on duration of use.

Method

Inclusion Criteria

Studies were included that examined the effect of corticosteroids on cognitive function in adults 18 years of age or older. We included studies that examined healthy participants, or those with other illnesses that required treatment with corticosteroid medication (e.g., asthma, ophthalmic diseases, rheumatic diseases etc.). Participants with psychiatric illnesses such as PTSD or Major Depressive Disorder were excluded given the range of cognitive deficits associated with these disorders (Gil et al. 1990; Rock et al. 2014; Wagner et al. 2015).

Because the aim of the current review was to examine the impact of corticosteroids on specific domains of cognitive functioning, only studies that reported results for one or more cognitive domain were included. Studies reporting only a single global cognitive score or screening measure (e.g. MMSE score) were excluded. Only those studies which employed objective, standardised measures of cognitive function that are widely used and referred to in either Lezak, Howieson, Bigler, and Tranel (2012) or Strauss, Sherman, and Spreen (2006) were included. Modified versions of tests were included if they were reasonably comparable to the standardised test.

A range of study methodologies were included to ensure that a breadth of information was available for interrogation and possible inclusion in the meta-analysis. As noted by Shrier et al. (2007), including a variety of study methodologies (both observational and randomised) in a meta-analysis is advantageous in many situations and is becoming more commonplace, particularly with regard to intervention studies (Cameron et al., 2015; Faber, Ravaud, Riveros, Perrodeau, & Dechartres, 2016; Harvey & Taylor, 2010; Prado, Watt, & Crowe, 2018). The inclusion of a range of methodologies also allowed for investigation of potential moderator variables when examining heterogeneous findings in the literature, and sensitivity analyses were conducted to investigate potentially disparate findings dependent on study design. As such, randomised controlled trials, controlled before and after trials, case controlled, and cohort studies were each eligible for inclusion.

Search Strategy

An electronic search was conducted for all journal articles published between January 1990 and May 2018 (last date of search was the 15th of May 2018). We elected to exclude studies published prior to 1990 in order to narrow the focus of the analysis to reasonably contemporary works, while still facilitating adequate breadth of potential studies for inclusion. We searched for studies that reported findings from a study or studies which investigated the effect of corticosteroid drugs on cognitive function published in PsycInfo, Medline and Google Scholar using the following search terms: beclomethasone, betamethasone, budesonide, corticosteroid, cortisone, deflazacort, dexamethasone, fludrocortisone, glucocorticoids, hydrocortisone, methylprednisolone, mineralocorticoids, prednisolone, prednisone, steroid, triamcinolone combined with cogniti*, neuropsych*, psychomotor, learning, memory, language, executive function, attention and social cognition. The asterisk (i.e., the truncation symbol) allowed for the inclusion of alternate word endings of the search term (e.g., cogniti* yielded articles containing cognition or cognitive). Searches were limited to human studies and English language. The reference lists of previously conducted systematic reviews and meta-analyses examining corticosteroids and cognitive function were also searched for relevant studies, as were the reference lists of studies identified from the initial electronic search.

Data Extraction and Statistical Analysis

Titles and abstracts of each of the articles identified in the search process were screened based on the inclusion/exclusion criteria outlined above. Full-text articles that passed the screening process were assessed for eligibility for inclusion in the quantitative analyses. Where there was uncertainty regarding inclusion, consensus was reached via consultation with the senior researcher (SC). Data, as outlined below, were extracted using a standardised form. The following data were extracted from each included study using a standardised form: publication details (including, author(s), title, year, journal name), study characteristics (study design, number of participants), participant characteristics (health status of participants and control group, mean age, age range), drug characteristics (drug type, dose, length of use), outcome measures (cognitive tests used, cognitive domain assessed) and cognitive test results required for calculation of effect size (usually means and standard deviations).

The primary outcome measure was the standardised mean difference (SMD). Depending on study design, the effect size indicated the difference between corticosteroid users and controls, or the difference between pre-treatment and post-treatment scores. When participants were assessed at several time points, the longest time point from baseline (i.e. end point) was used in the analysis. For RCTs, an effect size was calculated using final cognitive scores for treated compared to placebo (Higgins & Green, 2011). When large pre-treatment differences in cognitive scores were identified, or if the treatment and control groups were not comparable (e.g., treatment group with potentially confounding illness compared to a healthy control group), an effect size was calculated based on change from baseline. For controlled before and after studies, uncontrolled pre post studies and cross over designs where

participants acted as their own controls, the effect size was calculated as change from baseline.

None of the included studies reported data on the variance of pre and post test data. As recommended by the Cochrane Handbook for Systematic Review of Interventions and others (Follmann, Elliott, Suh, & Cutler, 1992), imputed correlation coefficients of 0.50 were used to impute the change-from-baseline standard deviation required to calculate an effect size. Sensitivity analyses revealed that the imputation of marginally lower (e.g., 0.2) or higher (e.g., 0.8) values did not significantly alter the effect size or confidence intervals for these outcomes. If mean and/or standard deviation values were not reported, these were calculated based on reported confidence intervals (CI) or *p*-values. If standard error was reported, this was converted to standard deviation. Where insufficient data was provided in the article to calculate an effect size, the authors were contacted with a request to obtain the required data. We contacted 17 authors for further information and of these, two responded with data that could be used in the analysis (Buchanan & Lovallo, 2001; Otte et al., 2015).

In line with previous research (Het et al., 2005; Waljee et al., 2017), studies were grouped according to duration of drug use, with up to one day denoted as acute use, two to 30 days denoted as short term use, and greater that 31 days use deemed chronic use. Each outcome (i.e., cognitive test score) was allocated to one of the following cognitive domains: immediate memory (i.e., learning), recent memory (i.e., free recall, cued recall and recognition), very long term memory (i.e., semantic and autobiographical), expressive language (i.e. naming, word finding, fluency, grammar and syntax), receptive language, sustained attention, divided attention, selective attention, processing speed, visual perception, visuospatial/constructional skills, perceptual motor, working memory or executive function. These cognitive domains are based on the DSM-5 neurocognitive domains (APA,2013). Cognitive tests were allocated to each cognitive domain based on the primary cognitive function it was designed to measure, or the domain that it is commonly used to measure in neuropsychological practice. Strauss et al. (2006) and Lezak et al. (2012) were used as guides, and test allocation also conforms to evidence-based practice guidelines developed by Daffner et al. (2015). Final test allocation decisions were reviewed by and agreed to by consensus of both authors.

To ensure that each study did not contribute more than one effect size to the pooled effect, only one effect size per cognitive domain was entered into the analysis. An exception to this occurred if a single study examined more than one subgroup or drug, in which case one effect size per subgroup was included in the analysis. Because multiplicity of outcome data was expected to occur in some studies, as recommended by Tendal et al. (2009), a hierarchy of measurement instruments was developed a priori that gave preference to neuropsychological tests most commonly in use. For studies that presented data for more than one test per cognitive domain, a single test per cognitive domain was selected based on this hierarchy. Care was taken to ensure that the scores for a given test provided independent measures of performance. Thus, sub scores and total scores from a test could not both be used in the calculation of an effect size.

Effect sizes were calculated in a multi-stage process. The first stage involved calculating effect sizes for each test that was included from each individual study. In most cases, higher cognitive test scores indicated better performance by the treatment group (i.e., corticosteroid group) compared to the control group (i.e., placebo group), or better performance after the administration of corticosteroids in pre post studies. Therefore, a positive effect size indicates that corticosteroid drug users performed better than controls, or participant's scores improved following drug administration. In cases where a higher score indicated poorer test performance than a lower score (e.g., number of errors, timed tasks), the direction of the effect sizes for these scores were transformed so that a positive effect size still indicated better performance in the corticosteroid users.

The calculation of effect size for each outcome, pooling of effect sizes and tests of heterogeneity were conducted using the Comprehensive Meta-Analysis Software (CMA). Given that the studies included in the meta-analyses differed in terms of several variables (e.g., drug type, length of use, participant characteristic etc.), a random effects model was used to calculate the pooled effect for each cognitive domain. As noted by Borenstein, Hedges, Higgins, and Rothstein (2010), the random effects model is often the most appropriate model to use in a quantitative synthesis of existing literature because the fixed-effect model is based on the assumption that all studies in the meta-analysis share a common (true) effect size. Conversely, the random-effects model allows that the true effect size may vary from study to study. Pooled effect sizes were calculated separately for each cognitive domain, for which there were two or more effect sizes. Homogeneity in effect sizes was tested using the Q statistic (Chi^2) for each cognitive domain. Heterogeneity was quantified using the I^2 statistic, where 25% = low, 50% = moderate, and 75% = high heterogeneity (Higgin, Thompson, Deeks, & Altman, 2003). To explore heterogeneity, the effects of several moderator variables were investigated including study design, length of drug use, participant age and drug dose.

Risk of Bias

Risk of bias was assessed for all studies included in the meta-analysis. The risk of bias tool used was developed by the Cochrane Effective Practice and Organisation of Care group (EPOC, 2015) and was selected as it is designed to assess a range of study methodologies including RCTs, non-randomised controlled trials (NRCTs) and controlled

before and after (CBA) studies. The following nine standard criteria were used to assess the risk of bias for all included studies: allocation sequence generation and concealment, measurement and comparability of baseline characteristics, incomplete (missing) data, blinding, contamination and selective outcome reporting. Studies were designated low risk for a given category if the authors described protocols to protect against the risk of bias, or if appropriate methods were used to mitigate the noted risk (e.g., if the groups were found to be imbalanced at baseline, but appropriate adjusted analysis was performed to control for this, the studies were denoted low risk). Studies were designated to be of high risk if the described protocols were concerning for bias in a given domain. If insufficient information was provided in the paper to determine the risk of bias, the studies were denoted as unclear risk. Note that all NRCTs were denoted as not applicable (NA) for allocation sequence generation and concealment. As recommended by the *Cochrane Review Handbook*, a funnel plot was created to assess for publication bias, sometimes referred to as small sample bias, for all included studies. An Egger's test was used to quantitatively assess for plot asymmetry.

Results

The literature search of electronic databases yielded a total of 4619 potentially relevant articles (Fig. 1). An additional 64 records were identified through additional sources. Titles and abstracts were screened, yielding a total of 163 articles for full text review. Of these, 26 articles were included in the meta-analysis.

The relevant demographic information for each study, including the cognitive domains studied and the neuropsychological tests used to examine these domains, is presented in Table 1. Overall, the analysis included 17 RCTs, four controlled before and after studies, two cohort studies, and three case controlled studies. The 26 studies included a total of 1991 treatment participants. The mean age across all included studies was 36.92 years.

As previously stated, pooled effect sizes were calculated when two or more studies contributed an effect size to that particular domain. Thus, pooled effect sizes were calculated for the cognitive domains of divided attention, executive function, expressive language, immediate memory, processing speed, recent memory, sustained attention, very long term

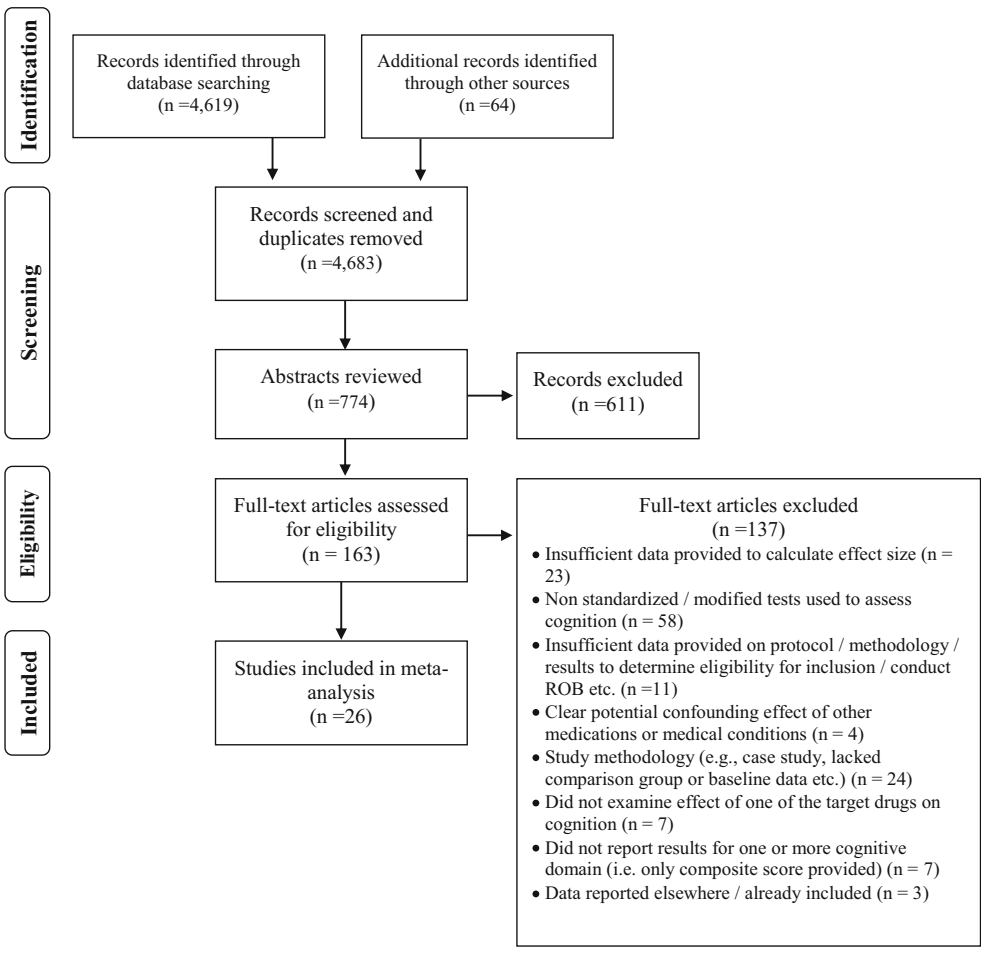

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection

Table 1 Demographic information of studies included in the meta-analysis

Study Name	Treatment Group n	Subgroup with Study (if Applicable)	Drug	Length of Drug Use (Days)	Length of Use (Classification)	Dose (mg per day)	Cognitive Domain	Cognitive Test	Participant Health Status	Mean Age	Age Range	Study Design
Abercrombie et al., 2003	29	Low Dose	Hydrocortisone	0.03	Acute	20	Immediate Memory	Word List	Healthy	NA	18–33	RCT
	30	High Dose				40	Immediate Memory	Word List				
Ancelin et al., 2012	352	Men / Inhaled	Corticosteroids	2445.50	Chronic	Various	Divided Attention Expressive Language Global Immediate Memory Sustained Attention	TMT B Isaacs MMSE Benton TMT A	Healthy	73.7	>65	Cohort
	352	Men / Oral					Divided Attention Expressive Language Global Immediate Memory Sustained Attention	TMT B Isaacs MMSE Benton TMT A				
	352	Women / Inhaled					Divided Attention Expressive Language Global Immediate Memory Sustained Attention	TMT B Isaacs MMSE Benton TMT A				
	352	Women / Oral					Divided Attention Expressive Language Global Immediate Memory Sustained Attention	TMT B Isaacs MMSE Benton TMT A				
Breitberg et al., 2013	22	High Dose	Hydrocortisone	0.05	Acute	0.45 mg/kg	Sustained Attention Working Memory	RVIP SS	Healthy	29.8	18–50	RCT
	22	Low Dose				0.15 mg/kg	Sustained Attention Working Memory	RVIP SS		28.65		
Bremner et al., 2004	13	NA	Dexamethasone	3.00	Short Term	1	Immediate Memory Recent Memory	LM I LM II	Healthy	42	NA	
Brown et al., 2004	17	NA	Prednisone	>182.5	Chronic	>10	Divided Attention Immediate Memory Recent Memory Sustained Attention	TMT B RAVLT T RAVLT D TMT A	Asthma / Rheumatic	46.8	18–65	Case Control
Brown et al., 2006	30	NA	Prednisone	3.00	Short Term	60	Immediate Memory Recent Memory	RAVLT T RAVLT D	Healthy	33.1	18–55	CBA
Brown et al., 2007	6	NA	Corticosteroids	4544.26	Chronic	8.3	Divided Attention Immediate Memory Recent Memory	Stroop RAVLT T RAVLT D	Rheumatic	53.9	NA	Case Contro-lled
Brown et al., 2013	15	NA	Hydrocortisone	2.50	Short Term	20	Immediate Memory	RAVLT	Healthy	25.3	18–50	RCT
Brunner et al., 2005	9	Acute Optic Neuritis	Methylprednisolone	5.00	Short Term	500	Divided Attention Immediate Memory Recent Memory Sustained Attention Working Memory	TAP Divide RAVLT RAVLT TAP Alert TAP WM	Acute Optic Neuritis	27.7	18–41	CBA
	21	Multiple Sclerosis					Divided Attention Immediate Memory	TAP Divide RAVLT	Multiple Sclerosis	33.1	20–48	

Table 1 (continued)

Study Name	Treatment Group n	Subgroup with Study (if Applicable)	Drug	Length of Drug Use (Days)	Length of Use (Classification)	Dose (mg per day)	Cognitive Domain	Cognitive Test	Participant Health Status	Mean Age	Age Range	Study Design
							Recent Memory	RAVLT				
							Sustained Attention	TAP Alert				
							Working Memory	TAP WM				
Buss et al., 2004	22	NA	Hydrocortisone	0.04	Acute	10	Very Long Term Memory	AMT	Healthy	26.27	NA	RCT
Groch et al., 2013	16	Fludrocortisone	Fludrocortisone	0.83	Acute	0.2	Immediate Memory	VPA	Healthy	23.25	19–29	RCT
							Recent Memory	VPA				
		Hydrocortisone	Hydrocortisone			22	Immediate Memory	VPA				
							Recent Memory	VPA				
Hájek et al., 2006	6	NA	Prednisone or Betamethasone	193.00	Chronic	24.2	Divided Attention	TMT B	Dermatological or Rheumatic Disorders	59	24–83	CBA
							Immediate Memory	RAVLT				
							Sustained Attention	TMT A				
							Working Memory	DS				
Henckens et al., 2011	23	NA	Hydrocortisone	0.17	Acute	10	Working Memory	N-Back	Healthy	NA	18–29	RCT
Keenan et al., 1996	25	NA	Prednisone	365.00	Chronic	5	Recent Memory	LM	Rheumatology and Neurology Patients	51	22–73	Cohort
							Sustained Attention	DSF				
Kuhlmann et al., 2005	16	NA	Hydrocortisone	0.04	Acute	30	Sustained Attention	DSF	Healthy	26.56	21–33	RCT
							Working Memory	DSB				
Montero-López et al., 2016	33	NA	Prednisone	365.00	Chronic	6.35	Divided Attention	TMTB/A	Systemic lupus erythematosus	36.48	NA	Case Contro-lled
							Executive Function	IGT				
Naber et al., 1996	50	Ocular Disease	Methylprednisolone or Fluocortolone	8.00	Short Term	150	Divided Attention	TMT B	Ocular Disease	42	NA	CBA
							Expressive Language	Verbal Fluency				
							Immediate Memory	BVRT				
							Processing Speed	DSST				
							Recent Memory	RAVLT				
							Sustained Attention	TMT A				
Newcomer et al., 1994	10	NA	Dexamethasone	11.00	Short Term	1	Immediate Memory	LM I	Healthy	33.85	NA	RCT
							Recent Memory	LM II				
							Sustained Attention	VT				
Newcomer et al., 1999	15	High Dose	Hydrocortisone	4.00	Short Term	160	Divided Attention	Stroop	Healthy	22.2	18–30	RCT
							Expressive Language	Verbal Fluency				
							Sustained Attention	CPT				
	16	Low Dose				40	Divided Attention	Stroop				
							Expressive Language	Verbal Fluency				
							Sustained Attention	CPT				
Otte et al., 2015	12	Healthy	Fludrocortisone	0.06	Acute	0.4	Divided Attention	TMT-B	Healthy	26.8	NA	RCT
							Recent Memory	RAVLT				
							Sustained Attention	DSF				
							Very Long Term Memory	AMT				

Table 1 (continued)

Study Name	Treatment Group n	Subgroup with Study (if Applicable)	Drug	Length of Drug Use (Days)	Length of Use (Classification)	Dose (mg per day)	Cognitive Domain	Cognitive Test	Participant Health Status	Mean Age	Age Range	Study Design
							Working Memory	DSB				
Schlosser et al., 2010	8	Healthy	Hydrocortisone	0.04	Acute	10	Very Long Term Memory	AMT	Healthy	34.1	NA	RCT
Terfehr et al., 2011	51	Healthy	Hydrocortisone	0.06	Acute	10	Recent Memory	LM II	Healthy	33.5	NA	RCT
Vaz et al., 2011	10	NA	Hydrocortisone	0.04	Acute	30	Divided Attention	TMT B	Healthy	23.35	18–35	RCT
							Executive Function	ZMP				
							Expressive Language	Verbal Fluency				
							Immediate Memory	Prose recall				
							Processing Speed	PASAT				
							Sustained Attention	DSF				
							Working Memory	DSB				
Wingenfeld et al., 2011	16	NA	Hydrocortisone	0.10	Acute	120	Executive Function	TAP CF	Healthy	38.4	31–50	RCT
							Working Memory	TAP WM				
Wolf et al., 2001	11	Old	Hydrocortisone	0.10	Acute	0.5 mg/kg	Divided Attention	Stroop	Healthy	69	59–76	RCT
							Immediate Memory	Prose recall				
							Processing Speed	Cancellation				
							Recent Memory	Prose recall				
	9	Young					Divided Attention	Stroop		24	19–30	
							Immediate Memory	Prose recall				
							Processing Speed	Cancellation				
							Recent Memory	Prose recall				
Young et al., 1999	20	NA	Hydrocortisone	10.00	Short Term	40	Executive Function	CANTB TOL	Healthy	33	21–44	RCT
							Immediate Memory	CANTAB PAL				
							Working Memory	CANTAB WM				

AMT, Autobiographic Memory Cueing Test; BVRT, Benton Visual Retention Test; CANTAB PAL, Cambridge Neuropsychological Test Automated Battery: Paired Associates Learning; CANTAB WM, Cambridge Neuropsychological Test Automated Battery: Spatial Working Memory; CANTB TOL, Cambridge Neuropsychological Test Automated Battery: Tower of London; CBA, Controlled before and after study; CPT, Continuous Performance Task; DS, Digit Span; DSB, Digit Span Backwards; DSF, Digit Span Forwards; DSST, Digit Symbol Substitution Test; IGT, Iowa Gambling Task; Isaacs, Isaacs Set Test; LM, Logical Memory; LM I, Logical Memory I; LM II, Logical Memory II; MMSE, Mini Mental state Exam; PASAT, Paced Auditory Serial Addition Test; RAVLT, Rey Auditory Verbal Learning Test; RAVLT D, Rey Auditory Verbal Learning Test Delayed; RAVLT T, Rey Auditory Verbal Learning Test Total; RCT, Randomised Controlled Trial; RVIP, Rapid Visual Information Processing; SS, Spatial Span; Stroop, Stroop Colour Word; TAP Alert, Test for Attentional Performance – Alertness; TAP CF, Test for Attentional Performance, Cognitive Flexibility; TAP Divide, Test for Attentional Performance Divided Attention; TAP WM, Test for Attentional Performance Working Memory; TMT A, Trail Making Test Part A; TMT B, Trail Making Test Part B; TMTB/A, Trail Making Test; VPA, Verbal Paired Associates; VSLT, Visuo-spatial Learning Test; VT, Vigilance Test; WMT, Weingartner Memory Test; ZMP, Zoo Map Test.

memory and working memory. Summary data for all studies included in the meta-analysis is presented in Table 2.

In order to investigate whether the effects of corticosteroids on cognition varied by duration of use, a subgroup analysis was conducted which compared acute, short term and chronic users for each cognitive domain.

Divided Attention

Eleven studies examined the effects of corticosteroid use on divided attention (Ancelin et al., 2012; Brown, Vera, Frol, Woolston, & Johnson, 2007; Brown et al., 2004; Brunner et al., 2005; Hájek, Kopeček, Preiss, Alda, & Höschl, 2006; Montero-López et al., 2016; Naber, Sand, & Heigl, 1996; Newcomer et al., 1999; Otte et al., 2015; Vaz, Pradella-Hallinan, Bueno, & Pompéia, 2011; Wolf et al., 2001). Of these studies, five evaluated more than one subgroup, providing a total of 17 independent effect sizes to pool. As shown in Fig. 2, overall, corticosteroids had a statistically non-significant effect on divided attention (SMD = 0.01, 95% CI = −0.14 to 0.35, z = 0.17, p = 0.86). Heterogeneity was low, Tau^2 = 0.15; Chi^2 = 20.33, df = 16 (p = 0.21), I^2 = 21.30%. Comparisons between duration of use revealed that corticosteroids had statistically non-significant effects on divided attention for acute, short term and chronic users (see Fig. 2). The pooled effect sizes between these three groups were not significantly different from each other, Chi^2 = 1.21, df = 2 (p = 0.55).

Executive Function

Four studies examined the effects of corticosteroid use on executive function (Montero-López et al., 2016; Vaz et al., 2011; Wingenfeld, Wolf, Krieg, & Lautenbacher, 2011; Young et al., 1999). As shown in Fig. 3, overall, corticosteroids had a statistically non-significant effect on executive function (SMD = −0.26, 95% CI = −0.86 to 0.35, z = −0.84 p = 0.40). Heterogeneity was moderate, Tau^2 = 0.15; Chi^2 = 7.05, df = 3 (p = 0.07), I^2 = 57.47%. Comparisons between duration of use revealed that corticosteroids had statistically non-significant effects on executive function for short term and chronic users, however steroids had a small but statistically significant negative effect on executive function for acute users (see Fig. 3). The pooled effect sizes between these three groups were significantly different from each other, Chi^2 = 6.29, df = 2 (p = 0.04).

Expressive Language

Four studies examined the effects of corticosteroid use on expressive language (Ancelin et al., 2012; Naber et al., 1996; Newcomer et al., 1999; Vaz et al., 2011). Of these studies, two evaluated more than one subgroup, providing a total of eight independent effect sizes to pool. As shown in Fig. 4, overall, corticosteroids had a statistically non-significant effect on expressive language (SMD = 0.18, 95% CI = −0.28 to 0.65, z = 0.77, p = 0.44). Heterogeneity was moderate, Tau^2 = 0.05; Chi^2 = 19.46, df = 7 (p = 0.01), I^2 = 64.02%. Comparisons between duration of use revealed that corticosteroids had statistically non-significant effects on expressive language for acute and chronic users, however steroids had a small but statistically significant positive effect on expressive language for short term users (see Fig. 4). The pooled effect sizes between these three groups were significantly different from each other, Chi^2 = 14.18, df = 2 (p = <0.01).

Immediate Memory

Fifteen studies examined the effects of corticosteroid use on immediate memory (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003; Bremner et al., 2004; Brown, Beard, Frol, & Rush, 2006; Ancelin et al., 2012; Brown et al., 2013; Brown et al., 2007; Brown et al., 2004; Brunner et al., 2005; Groch, Wilhelm, Lange, & Born, 2013; Hájek et al., 2006; Naber et al., 1996; Newcomer et al., 1994; Vaz et al., 2011; Wolf et al., 2001; Young et al., 1999). Of these studies, four evaluated more than one subgroup providing a total of 22 independent effect sizes to pool. As shown in Fig. 5, overall, corticosteroids had a statistically non-significant effect on immediate memory (SMD = −0.12, 95% CI = −0.26 to 0.04, z = −1.50, p = 0.13). Heterogeneity was low, Tau^2 = 0.04; Chi^2 = 38.14, df = 21 (p = 0.01), I^2 = 44.94%. Comparisons between duration of use revealed that corticosteroids had statistically non-significant effects on immediate memory for acute, short term and chronic users (see Fig. 5). The pooled effect sizes between these three groups were not significantly different from each other, Chi^2 = 0.68, df = 2 (p = 0.71).

Processing Speed

Four studies examined the effects of corticosteroid use on processing speed (Meieran, Reus, Webster, Shafton, & Wolkowitz, 2004; Naber et al., 1996; Vaz et al., 2011; Wolf et al., 2001) and investigated acute and short term users only. Of these studies, one evaluated more than one subgroup, providing a total of four independent effect sizes to pool. As shown in Fig. 6, overall, corticosteroids had a statistically non-significant effect on processing speed (SMD = 0.09, 95% CI = −0.34 to 0.50, z = 0.41, p = 0.68). Heterogeneity was low, Tau^2 = 0.00; Chi^2 = 2.55, df = 3 (p = 0.47), I^2 = 0.00%. Comparisons between duration of use revealed that corticosteroids had statistically non-significant effects on processing speed for acute and short term users (see Fig. 6). The pooled effect sizes between these two groups were not significantly different from each other, Chi^2 = 2.18, df = 1 (p = 0.14).

Table 2 Summary data for all studies

Study Name	Subgroup within Study (if Applicable)	Outcome		Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
Abercrombie et al., 2003	20 mg	Immediate Memory	Word List	4.66	2.40	29.00	3.95	2.66	28.00
	40 mg	Immediate Memory	Word List	4.41	2.46	30.00	3.95	2.66	28.00
				Odds Ratio	LL	UL	Confidence Level		
Ancelin et al., 2012	Men / Inhaled	Divided Attention	TMT B	0.81	0.46	1.40	0.95		
		Expressive Language	Isaacs	1.05	0.69	1.60	0.95		
		Global	MMSE	1.20	0.80	1.79	0.95		
		Immediate Memory	Benton	0.79	0.52	1.21	0.95		
		Sustained Attention	TMT A	1.09	0.65	1.83	0.95		
	Men / Oral	Divided Attention	TMT B	0.92	0.39	2.15	0.95		
		Expressive Language	Isaacs	1.42	0.70	2.87	0.95		
		Global	MMSE	1.18	0.60	2.33	0.95		
		Immediate Memory	Benton	1.08	0.54	2.18	0.95		
		Sustained Attention	TMT A	1.17	0.54	2.57	0.95		
	Women / Inhaled	Divided Attention	TMT B	1.65	1.10	2.47	0.95		
		Expressive Language	Isaacs	0.76	0.51	1.13	0.95		
		Global	MMSE	0.68	0.47	1.01	0.95		
		Immediate Memory	Benton	1.29	0.87	1.91	0.95		
		Sustained Attention	TMT A	0.78	0.49	1.25	0.95		
	Women / Oral	Divided Attention	TMT B	1.02	0.56	1.84	0.95		
		Expressive Language	Isaacs	1.14	0.70	1.87	0.95		
		Global	MMSE	1.05	0.65	1.70	0.95		
		Immediate Memory	Benton	1.19	0.72	1.97	0.95		
		Sustained Attention	TMT A	1.03	0.56	1.90	0.95		
				Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
Breitberg et al., 2013	High Dose	Sustained Attention	RVIP	430.75	64.22	22.00	437.00	51.78	22.00
		Working Memory	SS	7.10	1.17	22.00	7.20	1.26	22.00
	Low Dose	Sustained Attention	RVIP	450.85	102.27	22.00	433.85	64.97	22.00
		Working Memory	SS	6.85	1.09	22.00	6.85	1.49	22.00
Bremner et al., 2004	NA	Immediate Memory	LM I	50.00	12.00	13.00	52.00	14.00	15.00
		Recent Memory	LM II	44.00	14.00	13.00	54.00	16.00	15.00
Brown et al., 2004	NA	Divided Attention	TMT B	49.20	11.50	17.00	49.30	14.20	15.00
		Immediate Memory	RAVLT T	46.20	10.80	17.00	55.20	10.50	15.00
		Recent Memory	RAVLT D	48.70	8.50	17.00	55.90	10.20	15.00
		Sustained Attention	TMT A	51.80	9.80	17.00	49.10	10.20	15.00
				Mean Difference	SD of Difference	Sample Size			
Brown et al., 2006	NA	Immediate Memory	RAVLT T	1.60	7.90	30.00			
		Recent Memory	RAVLT D	2.10	3.20	30.00			
				Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
Brown et al., 2007	NA	Divided Attention	Stroop	43.10	6.80	6.00	52.60	9.70	6.00
		Immediate Memory	RAVLT T	47.40	9.90	6.00	59.40	7.20	6.00
		Recent Memory	RAVLT D	49.70	11.20	6.00	58.60	7.90	6.00
				Difference in Means	Sample Size	Paired Groups p Value			

Table 2 (continued)

Study Name	Subgroup within Study (if Applicable)	Outcome		Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
Brown et al., 2013	NA	Immediate Memory	RAVLT	4.25	15.00	0.10			
				Pre Mean	Pre SD	Post Mean	Post SD	Sample Size	
Brunner et al., 2005	Acute Optic Neuritis	Divided Attention	TAP Divide	28.90	4.00	29.70	2.50	9.00	
		Immediate Memory	RAVLT	11.70	3.30	10.80	3.60	9.00	
		Recent Memory	RAVLT	12.00	3.10	10.70	3.50	9.00	
		Sustained Attention	TAP Alert	241.90	16.70	232.90	14.50	9.00	
		Working Memory	TAP WM	11.30	4.30	11.40	4.80	9.00	
	Multiple Sclerosis	Divided Attention	TAP Divide	27.20	5.10	28.30	4.20	21.00	
		Immediate Memory	RAVLT	11.60	2.70	9.10	3.50	21.00	
		Recent Memory	RAVLT	11.20	2.90	9.20	3.30	21.00	
		Sustained Attention	TAP Alert	221.00	3.10	220.80	32.50	21.00	
		Working Memory	TAP WM	10.60	3.20	12.00	3.80	21.00	
				Difference in Means	Sample Size	Paired Groups p Value			
Buss et al., 2004	NA	Very Long Term Memory	AMT	4.45	22.00	0.00			
				Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
Groch et al., 2013	Fludrocortisone	Immediate Memory	VPA	29.81	4.00	16.00	30.50	2.44	16.00
		Recent Memory	VPA	30.50	3.80	16.00	28.88	3.96	16.00
	Hydrocortisone	Immediate Memory	VPA	28.63	4.08	16.00	27.69	2.64	16.00
		Recent Memory	VPA	27.31	5.20	16.00	27.25	4.48	16.00
				Pre Mean	Pre SD	Post Mean	Post SD	Sample Size	
Hájek et al., 2006	NA	Divided Attention	TMT B	99.90	32.40	122.20	69.80	6.00	
		Immediate Memory	RAVLT	51.50	9.20	48.20	5.10	6.00	
		Sustained Attention	TMT A	61.80	20.30	35.20	9.80	6.00	
		Working Memory	DS	10.00	4.00	13.00	3.70	6.00	
				Drug Sample Size	Placebo Sample Size	Independent t Value			
Henckens et al., 2011	NA	Working Memory	N-Back	23.00	23.00	3.59			
				Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
Keenan et al., 1996	NA	Recent Memory	LM	13.00	5.60	25.00	17.90	6.60	25.00
		Sustained Attention	DSF	7.20	1.90	25.00	8.10	2.10	25.00
Kuhlmann et al., 2005	NA	Sustained Attention	DSF	9.19	1.28	16.00	9.69	1.44	16.00
		Working Memory	DSB	7.94	1.88	16.00	8.13	1.76	16.00
Montero-López et al., 2016	NA	Divided Attention	TMTB/A	2.57	0.90	33.00	2.18	0.65	38.00
		Executive Function	IGT	−7.13	18.62	33.00	−9.00	23.35	38.00
				Pre Mean	Pre SD	Post Mean	Post SD	Sample Size	
Naber et al., 1996	Ocular Disease	Divided Attention	TMT B	90.40	40.00	87.00	32.30	50.00	
		Expressive Language	Verbal Fluency	9.40	3.60	11.80	4.30	50.00	
		Immediate Memory	BVRT	4.60	2.40	4.90	2.40	50.00	

Table 2 (continued)

Study Name	Subgroup within Study (if Applicable)	Outcome		Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
		Processing Speed	DSST	41.30	12.10	44.60	13.90	50.00	
		Recent Memory	RAVLT	9.50	2.40	7.90	2.40	50.00	
		Sustained Attention	TMT A	43.40	24.30	39.50	21.10	50.00	
				Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
Newcomer et al., 1994	NA	Immediate Memory	LM I	0.40	0.50	10.00	1.10	1.10	9.00
		Recent Memory	LM II	0.60	0.70	10.00	1.40	1.00	9.00
		Sustained Attention	VT	0.20	0.40	10.00	0.40	0.70	9.00
Newcomer et al., 1999	High Dose	Divided Attention	Stroop	31.60	5.40	15.00	30.00	5.60	20.00
		Expressive Language	Verbal Fluency	33.90	7.50	15.00	33.30	8.60	20.00
		Sustained Attention	CPT	440.00	57.00	15.00	425.00	37.00	20.00
	Low Dose	Divided Attention	Stroop	30.60	8.30	16.00	30.00	5.60	20.00
		Expressive Language	Verbal Fluency	39.00	8.10	16.00	33.30	8.60	20.00
		Sustained Attention	CPT	434.00	50.00	16.00	425.00	37.00	20.00
Otte et al., 2015	Healthy	Divided Attention	TMT-B	48.60	3.50	12.00	49.90	4.30	12.00
		Recent Memory	RAVLT	96.50	2.80	12.00	94.30	3.60	12.00
		Sustained Attention	DSF	10.00	0.40	12.00	10.00	0.50	12.00
		Very Long Term Memory	AMT	3.10	0.40	12.00	3.10	0.40	12.00
		Working Memory	DSB	8.30	0.50	12.00	8.00	0.50	12.00
Schlosser et al., 2010	Healthy	Very Long Term Memory	AMT	3.25	1.69	8.00	4.44	1.63	8.00
Terfehr et al., 2011	Healthy	Recent Memory	LM II	13.63	4.73	51.00	14.75	4.20	51.00
Vaz et al., 2011	NA	Divided Attention	TMT B	20.70	7.70	10.00	18.70	4.00	10.00
		Executive Function	ZMP	185.00	59.20	10.00	126.90	38.40	10.00
		Expressive Language	Verbal Fluency	46.80	8.90	10.00	48.10	8.00	10.00
		Immediate Memory	Prose recall	7.90	1.60	10.00	9.20	1.60	10.00
		Processing Speed	PASAT	50.30	6.00	10.00	52.90	7.00	10.00
		Sustained Attention	DSF	6.30	0.80	10.00	7.20	1.20	10.00
		Working Memory	DSB	5.70	1.40	10.00	6.20	1.90	10.00
Wingenfeld et al., 2011	NA	Executive Function	TAP CF	94.20	3.00	16.00	95.90	2.30	16.00
		Working Memory	TAP WM	13.10	1.60	16.00	13.10	1.70	16.00
Wolf et al., 2001	Old	Divided Attention	Stroop	2.00	4.64	11.00	−1.30	5.64	11.00
		Immediate Memory	Prose recall	20.40	5.97	11.00	22.50	5.30	11.00
		Processing Speed	Cancellation	49.00	10.61	11.00	47.50	11.94	11.00
		Recent Memory	Prose recall	20.10	5.30	11.00	19.10	4.64	11.00
	Young	Divided Attention	Stroop	9.30	6.90	9.00	9.30	7.20	9.00
		Immediate Memory	Prose recall	24.50	8.40	9.00	25.10	7.50	9.00
		Processing Speed	Cancellation	35.80	5.10	9.00	35.70	6.90	9.00
		Recent Memory	Prose recall	23.70	8.70	9.00	24.10	6.60	9.00
Young et al., 1999	NA	Executive Function	CANTB TOL	60.00	34.88	20.00	62.00	29.96	20.00
		Immediate Memory	CANTAB PAL	1.37	0.94	20.00	1.60	1.57	20.00

Table 2 (continued)

Study Name	Subgroup within Study (if Applicable)	Outcome		Drug Mean	Drug SD	Drug Sample Size	Placebo Mean	Placebo SD	Placebo Sample Size
		Working Memory	CANTAB WM	27.90	6.57	20.00	30.35	6.26	20.00

AMT, Autobiographic Memory Cueing Test; BVRT, Benton Visual Retention Test; CANTAB PAL, Cambridge Neuropsychological Test Automated Battery: Paired Associates Learning; CANTAB WM, Cambridge Neuropsychological Test Automated Battery: Spatial Working Memory; CANTB TOL, Cambridge Neuropsychological Test Automated Battery: Tower of London; CBA, Controlled before and after study; CPT, Continuous Performance Task; DS, Digit Span; DSB, Digit Span Backwards; DSF, Digit Span Forwards; DSST, Digit Symbol Substitution Test; IGT, Iowa Gambling Task; Isaacs, Isaacs Set Test; LL, Lower limit; LM, Logical Memory; LM I, Logical Memory I; LM II, Logical Memory II; MMSE, Mini Mental state Exam; PASAT, Paced Auditory Serial Addition Test; RAVLT, Rey Auditory Verbal Learning Test; RAVLT D, Rey Auditory Verbal Learning Test Delayed; RAVLT T, Rey Auditory Verbal Learning Test Total; RCT, Randomised Controlled Trial; RVIP, Rapid Visual Information Processing; SS, Spatial Span; Stroop, Stroop Colour Word; TAP Alert, Test for Attentional Performance – Alertness; TAP CF, Test for Attentional Performance, Cognitive Flexibility; TAP Divide, Test for Attentional Performance Divided Attention; TAP WM, Test for Attentional Performance Working Memory; TMT A, Trail Making Test Part A; TMT B, Trail Making Test Part B; TMTB/A, Trail Making Test; UL, Upper limit; VPA, Verbal Paired Associates; VSLT, Visuo-spatial Learning Test; VT, Vigilance Test; WMT, Weingartner Memory Test; ZMP, Zoo Map Test.

Recent Memory

Twelve studies examined the effects of corticosteroid use on recent memory (Bremner et al., 2004; Brown et al., 2006; Brown et al., 2007; Brown et al., 2004; Brunner et al., 2005; Groch et al., 2013; Keenan et al., 1996; Naber et al., 1996; Newcomer et al., 1994; Otte et al., 2015; Terfehr et al., 2011; Wolf et al., 2001). Of these studies, four evaluated more than one subgroup, providing a total of 15 independent effect sizes to pool. As shown in Fig. 7, overall, corticosteroids had a statistically non-significant effect on recent memory (SMD = −0.40, 95% CI = −0.91 to 0.11, $z = -1.53$, $p = 0.13$). Heterogeneity was moderate, $Tau^2 = 0.12$; $Chi^2 = 33.54$, df = 14 ($p = 0.33$), $I^2 = 58.25\%$. Comparisons between duration of use revealed that corticosteroids had a statistically non-significant effect on recent memory for acute users, however had small, significant negative effects on short term and chronic users (see Fig. 7). The pooled effect sizes between these three groups were significantly different from each other, $Chi^2 = 12.51$, df = 2 ($p = 0.01$).

Sustained Attention

Twelve studies examined the effects of corticosteroid use on sustained attention (Ancelin et al., 2012; Breitberg et al., 2013; Brown et al., 2004; Brunner et al., 2005; Hájek et al., 2006; Keenan et al., 1996; Kuhlmann, Kirschbaum, & Wolf, 2005; Naber et al., 1996; Newcomer et al., 1994; Newcomer et al., 1999; Otte et al., 2015; Vaz et al., 2011). Of these studies, four evaluated more than one subgroup, providing a total of 18 independent effect sizes to pool. As shown in Fig. 8, overall, corticosteroids had a statistically non-significant effect on sustained attention (SMD = −0.03, 95% CI = −0.20 to 0.14, $z = -0.30$, $p = 0.77$). Heterogeneity was low, $Tau^2 = 0.02$; $Chi^2 = 21.72$, df = 17 ($p = 0.20$), $I^2 = 21.74\%$. Comparisons between duration of use revealed that corticosteroids had statistically non-significant effects on sustained attention for acute, short term and chronic users (see Fig. 8). The pooled effect sizes between these three groups were not significantly different from each other, $Chi^2 = 2.02$, df = 2 ($p = 0.36$).

Very Long Term Memory

Three studies examined the effects of corticosteroid use on very long term memory (Buss, Wolf, Witt, & Hellhammer, 2004; Otte et al., 2015; Schlosser et al., 2010) and investigated acute users only. Each study contributed one effect size, providing a total of three independent effect sizes to pool. As shown in Fig. 9, corticosteroids had a statistically significant negative effect on very long term memory (SMD = −0.55, 95% CI = −1.00 to −0.08, $z = -2.31$, $p = 0.02$). Heterogeneity was low, $Tau^2 = 0.04$; $Chi^2 = 2.60$, df = 2 ($p = 0.27$), $I^2 = 23.00\%$.

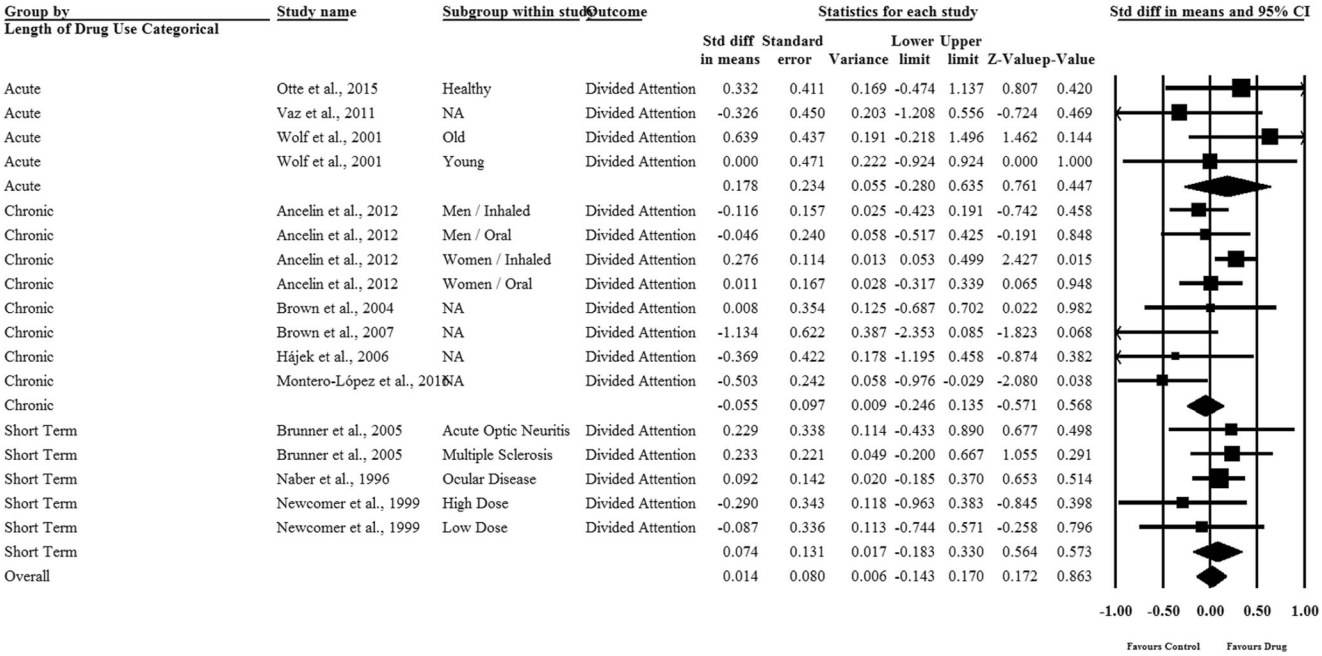

Fig. 2 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on divided attention, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.15$, $Chi^2 = 20.33$, df = 16 ($p = 0.45$), $I^2 = 21.30\%$. Test for subgroup differences: $Chi^2 = 1.21$, df = 2 ($p = 0.55$)

Working Memory

Nine studies examined the effects of corticosteroid use on working memory (Breitberg et al., 2013; Brunner et al., 2005; Hájek et al., 2006; Henckens et al., 2011; Kuhlmann et al., 2005; Otte et al., 2015; Vaz et al., 2011; Wingenfeld et al., 2011; Young et al., 1999). Of these studies, two evaluated more than one subgroup, providing a total of 11 independent effect sizes to pool. As shown in Fig. 10, overall, corticosteroids had a statistically non-significant effect on working memory (SMD = 0.18, 95% CI = −0.14 to 0.51, $z = 1.10$, $p = 0.27$). Heterogeneity was low, $Tau^2 = 0.09$; $Chi^2 = 17.83$, df = 10 ($p = 0.06$), $I^2 = 43.91\%$. Comparisons between duration of use revealed that corticosteroids had statistically non-significant effects on working memory for acute, short term and chronic users (see Fig. 10). The pooled effect sizes between these three groups were not significantly different from each other, $Chi^2 = 1.36$, df = 2 ($p = 0.51$).

Additional Moderator Analyses

In order to investigate the potential impact of study design on the overall pooled effect of corticosteroids on cognition, a meta-analysis was carried out which pooled the effect sizes across all cognitive domains. In order to ensure that each study did not contribute more than one effect size per outcome, where one study contributed more than one effect size (i.e., cognitive domain), the mean of those effect sizes was entered into the analysis. A subgroup analysis was then conducted comparing study designs. The analysis revealed that overall, corticosteroids did not have a statistically significant effect on this combined measure of cognitive function (SMD = −0.00, 95% CI = −0.20 to 0.03, $z = -1.51$, $p = 0.13$). Heterogeneity was low, $Tau^2 = 0.03$; $Chi^2 = 51.42$, df = 34 ($p = 0.03$), $I^2 = 33.88\%$. Sixteen RCTs were included. Of these, five evaluated more than one subgroup, providing a total of 22 independent effect sizes to pool. The subgroup analysis revealed that for RCTs, steroids did not have a

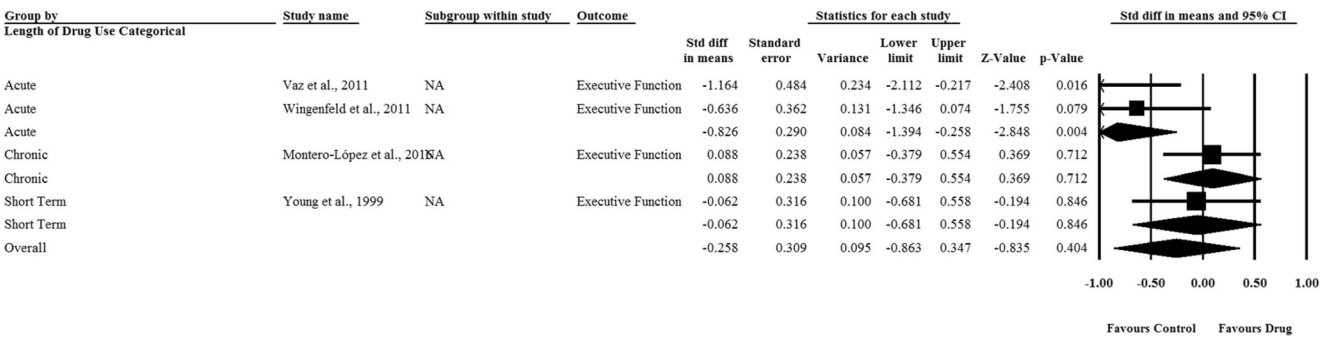

Fig. 3 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on executive function, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 7.05$, df = 3 ($p = 0.07$), $I^2 = 57.47\%$. Test for subgroup differences: $Chi^2 = 6.29$, df = 2 ($p = 0.04$)

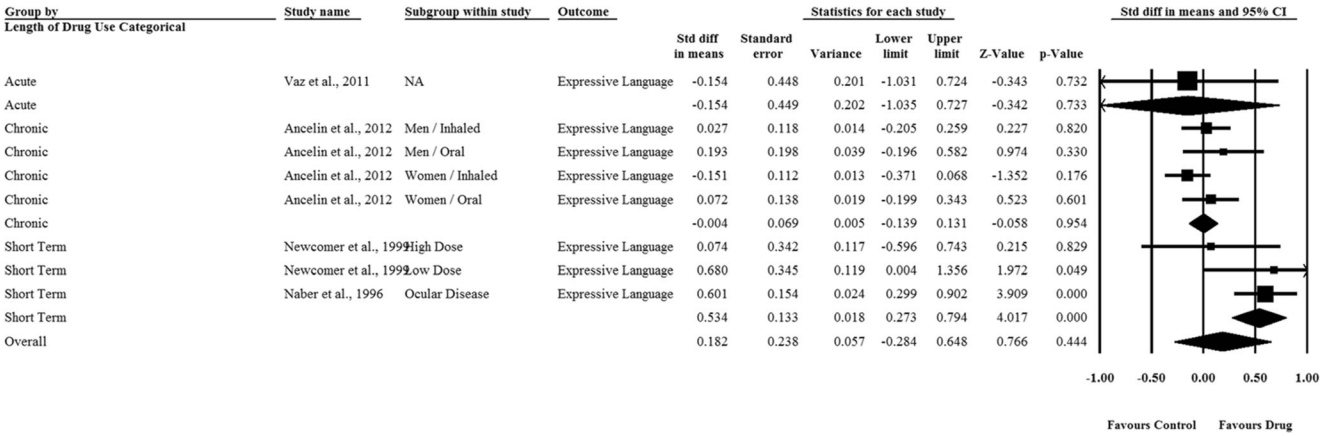

Fig. 4 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on expressive language, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 19.46$, df = 7 ($p = 0.01$), $I^2 = 64.02\%$. Test for subgroup differences: $Chi^2 = 14.18$, df = 2 ($p = <0.01$)

statistically significant effect on cognition (SMD = −0.07, 95% CI = −0.23 to 0.10, $z = -0.78$, $p = 0.43$). Two cohort studies were included. Of these, one evaluated more than one subgroup, providing a total of five independent effect sizes to pool. The sub-group analysis revealed that for cohort studies, corticosteroids did not have a statistically significant effect on cognition (SMD = −0.05, 95% CI = −0.28 to 0.18, $z = -0.43$, $p = 0.67$). Four CBA studies were included. Of these, one evaluated more than one subgroup, providing a total of five independent effect sizes to pool. The sub-group analysis revealed that for CBA's, corticosteroids did not have a statistically significant effect on cognition (SMD = -0.08, 95% CI = −0.36 to 0.20, $z = -0.58$, $p = 0.56$). Two case controlled studies were included. Of these, one evaluated more than one subgroup, providing a total of three independent effect sizes to pool. The sub-group analysis revealed that for case controlled studies, corticosteroids did not have a statistically significant effect on cognition (SMD = −0.41, 95% CI = −0.87 to 0.05, $z = -1.76$, $p = 0.08$). Results from the four included study designs were not significantly different from each other, $Chi^2 = 2.07$, df = 3 ($p = 0.56$).

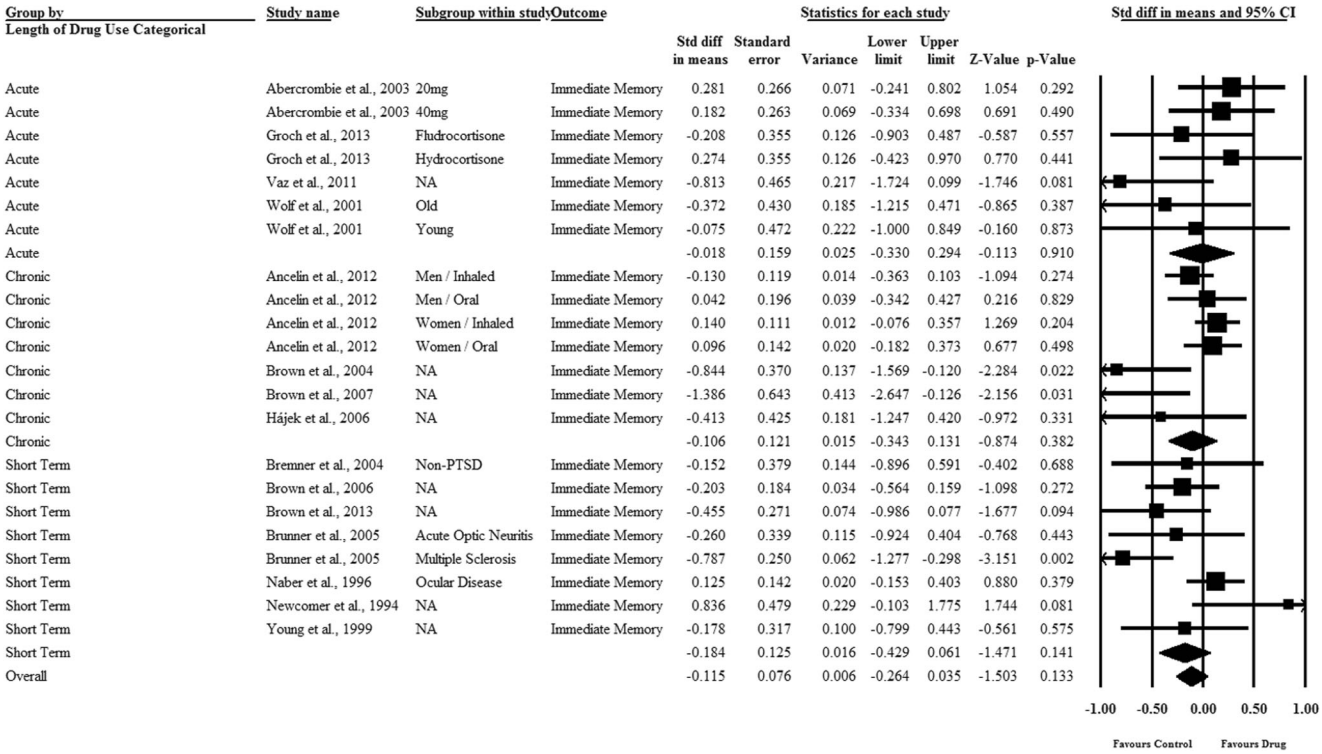

Fig. 5 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on immediate memory, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.04$, $Chi^2 = 38.14$, df = 21 ($p = 0.01$), $I^2 = 44.94\%$. Test for subgroup differences: $Chi^2 = 0.68$, df = 2 ($p = 0.71$)

Group by Length of Drug Use Categorical	Study name	Subgroup within study	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Acute	Vaz et al., 2011	NA	Processing Speed	-0.399	0.452	0.204	-1.284	0.486	-0.883	0.377
Acute	Wolf et al., 2001	Old	Processing Speed	-0.133	0.427	0.182	-0.969	0.704	-0.311	0.756
Acute	Wolf et al., 2001	Young	Processing Speed	-0.016	0.471	0.222	-0.940	0.907	-0.035	0.972
Acute				-0.185	0.259	0.067	-0.693	0.323	-0.715	0.475
Short Term	Naber et al., 1996	Ocular Disease	Processing Speed	0.252	0.144	0.021	-0.030	0.534	1.755	0.079
Short Term				0.252	0.144	0.021	-0.030	0.534	1.755	0.079
Overall				0.087	0.212	0.045	-0.329	0.502	0.408	0.683

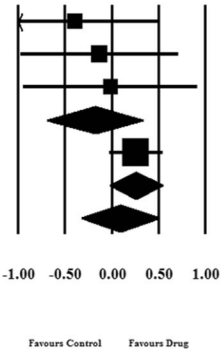

Fig. 6 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on processing speed, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 2.55$, df = 3 ($p = 0.47$), $I^2 = 0.00\%$. Test for subgroup differences: $Chi^2 = 2.18$, df = 1 ($p = 0.14$)

As the analysis included studies with healthy participants, as well as some clinical groups (e.g., acute optic neuritis, asthma, etc.), a meta-analysis was carried out which pooled the effect sizes across all cognitive domains and a subgroup analysis was then conducted comparing healthy and clinical participant groups. The analysis revealed that overall, corticosteroids did not have a statistically significant effect on either the clinical group (SMD = −0.17, 95% CI = −0.42 to 0.07, z = −1.40, $p = 0.16$), or the healthy group (SMD = −0.06, 95% CI = −0.19 to 0.07, z = −0.94, $p = 0.54$). Results revealed that the clinical and healthy groups were not significantly different from each other, $Chi^2 = 0.63$, df = 1 ($p = 0.43$).

Given that the studies included in the meta-analysis investigated cognition in participants of varying ages, a random effects meta-regression analysis was applied to estimate the relationship between SMD and the mean age of participants in each study. The meta-regression revealed that age was not significantly related to the overall pooled effect size, Q-Model was 4.55 with df = 1 and $p = 0.33$. A random effects meta-regression analysis was also applied to estimate the relationship between SMD and study year. Results revealed that study year was not significantly related to the overall pooled effect size, Q-Model was 0.08 with df = 1 and $p = 0.78$.

To investigate the potential impact of drug dose on the overall pooled effect of corticosteroids on cognition, drug

Group by Length of Drug Use Categorical	Study name	Subgroup within study	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Acute	Groch et al., 2013	Fludrocortisone	Recent Memory	0.417	0.357	0.128	-0.283	1.118	1.168	0.243
Acute	Groch et al., 2013	Hydrocortisone	Recent Memory	0.012	0.354	0.125	-0.681	0.705	0.035	0.972
Acute	Otte et al., 2015	Healthy	Recent Memory	0.682	0.420	0.176	-0.141	1.505	1.624	0.104
Acute	Terfehr et al., 2011	Healthy	Recent Memory	-0.250	0.199	0.040	-0.640	0.139	-1.260	0.208
Acute	Wolf et al., 2001	Old	Recent Memory	0.201	0.427	0.183	-0.637	1.039	0.470	0.639
Acute	Wolf et al., 2001	Young	Recent Memory	-0.052	0.471	0.222	-0.976	0.872	-0.110	0.913
Acute				0.082	0.160	0.025	-0.231	0.395	0.515	0.607
Chronic	Brown et al., 2004	NA	Recent Memory	-0.772	0.367	0.135	-1.491	-0.052	-2.101	0.036
Chronic	Brown et al., 2007	NA	Recent Memory	-0.918	0.607	0.368	-2.108	0.271	-1.513	0.130
Chronic	Keenan et al., 1996	NA	Recent Memory	-0.801	0.294	0.086	-1.377	-0.224	-2.724	0.006
Chronic				-0.808	0.245	0.060	-1.288	-0.328	-3.298	0.001
Short Term	Bremner et al., 2004	Non-PTSD	Recent Memory	-0.662	0.389	0.151	-1.424	0.101	-1.701	0.089
Short Term	Brown et al., 2006	NA	Recent Memory	-0.656	0.201	0.041	-1.051	-0.262	-3.260	0.001
Short Term	Brunner et al., 2005	Acute Optic Neuritis	Recent Memory	-0.392	0.346	0.120	-1.070	0.286	-1.133	0.257
Short Term	Brunner et al., 2005	Multiple Sclerosis	Recent Memory	-0.641	0.240	0.057	-1.111	-0.172	-2.676	0.007
Short Term	Naber et al., 1996	Ocular Disease	Recent Memory	-0.667	0.156	0.024	-0.973	-0.360	-4.264	0.000
Short Term	Newcomer et al., 1994	NA	Recent Memory	0.936	0.484	0.234	-0.012	1.885	1.935	0.053
Short Term				-0.522	0.133	0.018	-0.782	-0.262	-3.939	0.000
Overall				-0.397	0.260	0.067	-0.906	0.112	-1.530	0.126

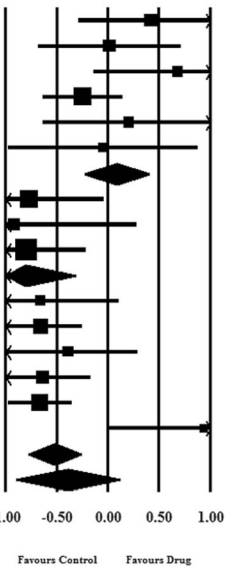

Fig. 7 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on recent memory, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.12$, $Chi^2 = 33.54$, df = 14 ($p = 0.01$), $I^2 = 58.25\%$. Test for subgroup differences: $Chi^2 = 12.51$, df = 2 ($p = 0.01$)

Group by Length of Drug Use Categorical	Study name	Subgroup within study	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Acute	Breitberg et al., 2013	High Dose	Sustained Attention	0.107	0.302	0.091	-0.484	0.699	0.355	0.723
Acute	Breitberg et al., 2013	Low Dose	Sustained Attention	-0.198	0.302	0.091	-0.791	0.394	-0.656	0.512
Acute	Kuhlmann et al., 2005	NA	Sustained Attention	-0.367	0.357	0.127	-1.066	0.332	-1.029	0.303
Acute	Otte et al., 2015	Healthy	Sustained Attention	0.000	0.408	0.167	-0.800	0.800	0.000	1.000
Acute	Vaz et al., 2011	NA	Sustained Attention	-0.883	0.468	0.219	-1.801	0.036	-1.884	0.060
Acute				-0.203	0.168	0.028	-0.533	0.127	-1.203	0.229
Chronic	Ancelin et al., 2012	Men / Inhaled	Sustained Attention	0.048	0.146	0.021	-0.238	0.333	0.326	0.744
Chronic	Ancelin et al., 2012	Men / Oral	Sustained Attention	0.087	0.219	0.048	-0.344	0.517	0.394	0.693
Chronic	Ancelin et al., 2012	Women / Inhaled	Sustained Attention	-0.137	0.132	0.017	-0.395	0.121	-1.040	0.298
Chronic	Ancelin et al., 2012	Women / Oral	Sustained Attention	0.016	0.172	0.030	-0.320	0.353	0.095	0.924
Chronic	Brown et al., 2004	NA	Sustained Attention	-0.270	0.356	0.127	-0.968	0.427	-0.760	0.447
Chronic	Hájek et al., 2006	NA	Sustained Attention	1.513	0.598	0.357	0.341	2.684	2.531	0.011
Chronic	Keenan et al., 1996	NA	Sustained Attention	-0.449	0.286	0.082	-1.011	0.112	-1.569	0.117
Chronic				-0.031	0.094	0.009	-0.215	0.153	-0.329	0.742
Short Term	Brunner et al., 2005	Acute Optic Neuritis	Sustained Attention	0.573	0.360	0.129	-0.132	1.278	1.592	0.111
Short Term	Brunner et al., 2005	Multiple Sclerosis	Sustained Attention	0.006	0.218	0.048	-0.421	0.434	0.030	0.976
Short Term	Naber et al., 1996	Ocular Disease	Sustained Attention	0.171	0.142	0.020	-0.109	0.450	1.197	0.231
Short Term	Newcomer et al., 1994	NA	Sustained Attention	0.356	0.463	0.214	-0.551	1.264	0.769	0.442
Short Term	Newcomer et al., 1999	High Dose	Sustained Attention	-0.322	0.344	0.118	-0.996	0.351	-0.938	0.348
Short Term	Newcomer et al., 1999	Low Dose	Sustained Attention	-0.208	0.336	0.113	-0.867	0.451	-0.619	0.536
Short Term				0.090	0.120	0.014	-0.146	0.325	0.747	0.455
Overall				-0.026	0.087	0.008	-0.196	0.144	-0.297	0.766

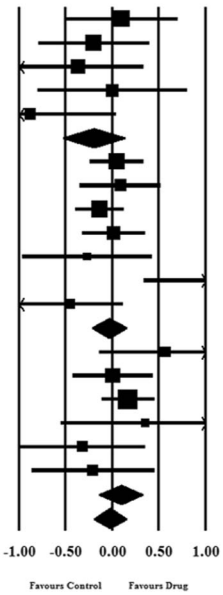

Fig. 8 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on sustained attention, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.02$, $Chi^2 = 21.72$, df = 17 ($p = 0.20$), $I^2 = 21.74\%$. Test for subgroup differences: $Chi^2 = 2.02$, df = 2 ($p = 0.36$)

doses were converted to prednisone equivalents (Meikle & Tyler, 1977; Webb & Singer, 2005). A random effects meta-regression analysis was then applied to estimate the relationship between SMD and the mean drug dose administered to participants in each study. Two studies were excluded from this analysis as the specific type of corticosteroid drug used in the study was not reported (Ancelin et al., 2012; Brown et al., 2007). When drug dose was reported as mg/kg (Wolf et al., 2001), the drug dose entered into the analysis was estimated based on average adult weight statistics published by the Australian Bureau of Statistics (ABS, 2012). The meta-regression revealed that drug dose was not significantly related to the overall pooled effect size, Q-Model was 0.39 with df = 1 and $p = 0.53$. Only 6% of the variance in true effects could be explained by dose alone, R^2 analog = 0.06.

Although duration of use was examined categorically using sub-group analyses, in order to investigate possible moderating effects of length of drug use on overall cognitive function, a random effects meta-regression analysis was applied to estimate the relationship between SMD and the mean duration of use (in days) for each study. The meta-regression revealed that duration of use was not significantly related to the overall pooled effect size, Q-Model was 1.94 with df = 1 and $p = 0.16$. Only 12% of the variance in true effects could be explained by age alone, R2 analog = 0.12.

Group by Length of Drug Use Categorical	Study name	Subgroup within study	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Acute	Buss et al., 2004	NA	Very Long Term Memory	-0.752	0.241	0.058	-1.225	-0.279	-3.114	0.002
Acute	Otte et al., 2015	Healthy	Very Long Term Memory	0.000	0.408	0.167	-0.800	0.800	0.000	1.000
Acute	Schlosser et al., 2010	Healthy	Very Long Term Memory	-0.717	0.516	0.266	-1.728	0.294	-1.390	0.165
Acute				-0.545	0.236	0.056	-1.008	-0.083	-2.313	0.021
Overall				-0.545	0.236	0.056	-1.008	-0.083	-2.313	0.021

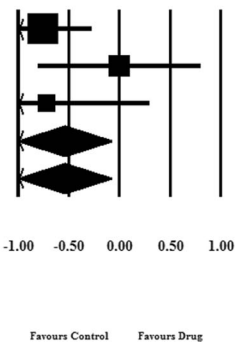

Fig. 9 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on very long term memory, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.04$, $Chi^2 = 2.60$, df = 2 ($p = 0.27$), $I^2 = 23.00\%$

Group by Length of Drug Use Categorical	Study name	Subgroup within study	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Acute	Breitberg et al., 2013	High Dose	Working Memory	-0.082	0.302	0.091	-0.673	0.509	-0.272	0.785
Acute	Breitberg et al., 2013	Low Dose	Working Memory	0.000	0.302	0.091	-0.591	0.591	0.000	1.000
Acute	Henckens et al., 2011	NA	Working Memory	1.059	0.315	0.099	0.442	1.676	3.362	0.001
Acute	Kuhlmann et al., 2005	NA	Working Memory	-0.104	0.354	0.125	-0.798	0.589	-0.295	0.768
Acute	Otte et al., 2015	Healthy	Working Memory	0.600	0.417	0.174	-0.218	1.418	1.438	0.151
Acute	Vaz et al., 2011	NA	Working Memory	-0.300	0.450	0.202	-1.181	0.582	-0.666	0.505
Acute	Wingenfeld et al., 2011	NA	Working Memory	0.000	0.354	0.125	-0.693	0.693	0.000	1.000
Acute				0.179	0.182	0.033	-0.178	0.536	0.983	0.326
Chronic	Hájek et al., 2006	NA	Working Memory	0.777	0.466	0.217	-0.136	1.691	1.669	0.095
Chronic				0.777	0.571	0.326	-0.341	1.896	1.362	0.173
Short Term	Brunner et al., 2005	Acute Optic Neuritis	Working Memory	0.022	0.333	0.111	-0.632	0.675	0.066	0.948
Short Term	Brunner et al., 2005	Multiple Sclerosis	Working Memory	0.396	0.227	0.051	-0.048	0.840	1.746	0.081
Short Term	Young et al., 1999	NA	Working Memory	-0.382	0.319	0.102	-1.007	0.244	-1.197	0.231
Short Term				0.049	0.254	0.064	-0.448	0.546	0.192	0.847
Overall				0.182	0.165	0.027	-0.142	0.506	1.100	0.271

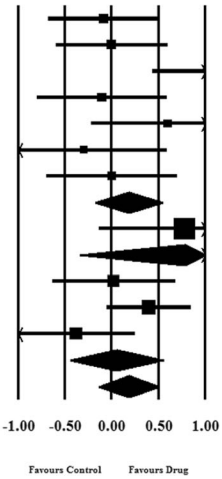

Fig. 10 Pooled effect (random effects model) for studies assessing the effects of corticosteroids on working memory, grouped by duration of use. *Note*: CI, confidence interval. Heterogeneity: $Tau^2 = 0.09$, $Chi^2 = 17.83$, df = 10 ($p = 0.06$), $I^2 = 43.91\%$. Test for subgroup differences: $Chi^2 = 1.36$, df = 2 ($p = 0.51$)

Bias of Included Studies

Assessment of bias is summarised in Table 3. None of the included studies were found to present a high risk of bias for sequence generation, sequence concealment, baseline outcomes, incomplete outcome data or selective outcome reporting; however several studies did present an unclear risk for these categories. One study (Ancelin et al., 2012) was denoted a high risk of bias for blinding and contamination. One study (Montero-López et al., 2016) was denoted a high risk for baseline characteristics. To compare the results of studies with different risk profiles, a meta-analysis was carried out which pooled the effect sizes across all cognitive domains and a subgroup analysis was then conducted comparing studies classified as low, unclear or high risk. To facilitate grouping, a study was categorised as high risk overall if one category in the risk of bias analysis was denoted high risk. A study was categorised as unclear risk of bias if more than one category for that study was denoted as unclear risk. The remaining studies were classes as low risk. The analysis revealed that overall, corticosteroids did not have statistically significant effects for the high risk (SMD = −0.01, 95% CI = −0.225 to 0.21, z = −0.08, p = 0.94), unclear risk (SMD = −0.08, 95% CI = −0.23 to 0.07, z = −1.06, $p = 0.29$) or low risk groups (SMD = −0.26, 95% CI = −0.55 to 0.03, z = −1.74, $p = 0.08$). Results revealed that the low, unclear and high risk groups were not significantly different from each other, $Chi^2 = 1.85$, df = 2 ($p = 0.40$).

Small sample bias was assessed using a funnel plot as shown in Fig. 11. Qualitative assessment of the funnel plot revealed no obvious signs of publication bias. As recommended by the *Cochrane Review Handbook* an Egger's test was used to test for funnel plot asymmetry and found the intercept (b) to be −0.33, with a 95% confidence interval from −1.37 to 0.71, and a one-tailed p value of 0.26, indicating the plot is symmetrical.

Discussion

This meta-analysis included 26 studies that examined the effects of corticosteroids on cognitive function. The studies investigated these effects using a range of participant groups and durations of drug use. Sub-group analyses based on duration of use revealed that corticosteroids had significant negative effects on executive function for acute users, recent memory for short term and chronic users, and very long term memory for acute users. Corticosteroids had a significant positive effect on expressive language for short term users. Corticosteroids had no significant effect on divided attention, immediate memory, processing speed, sustained attention and working memory. Heterogeneity varied across the cognitive domains assessed, but generally fell within the low to moderate ranges. Additional analyses of study design, duration of use, drug dose and participant age did not reveal significant relationships between these variables and the effects of corticosteroids on cognition.

The study found modest but significant negative effects of corticosteroids on executive function, recent memory and very long term memory. These findings align with the fact that the brain regions which primarily subserve these functions; that is the hippocampus, which is important for memory processing (Young & Preskorn, 2013) and the prefrontal cortex (Wolkowitz, Burke, Epel, & Reus, 2009), which is essential for executive functions (Miller & Cohen, 2001), contain high concentrations of corticosteroid receptors (McEwen, 2006). Newcomer and colleagues (Newcomer et al., 1999) have suggested that the negative effects of corticosteroids on these functions may be related to disrupted glucose transport into neurons in these regions. Also consistent with the current finding of negative effects of corticosteroids on recent and very long term memory, corticosteroid administration has

Table 3 Assessment of Bias of included studies

Study Name	Study Design	Sequence Generation	Concealment	Baseline Outcomes	Baseline Characteristics	Incomplete Outcome Data	Blinding	Contamination	Selective Outcome Reporting
Abercrombie et al., 2003	RCT	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low
Ancelin et al., 2012	Cohort	NA	NA	Low	Low	Low	High	High	Low
Breitberg et al., 2013	RCT	Unclear	Unclear	Unclear	Low	Low	Unclear	Low	Low
Bremner et al., 2004	RCT	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low
Brown et al., 2004	CC	NA	NA	Unclear	Low	Low	Low	Unclear	Low
Brown et al., 2006	CBA	NA	NA	Unclear	Low	Low	Low	Low	Low
Brown et al., 2007	CC	NA	NA	Unclear	Low	Low	Unclear	Low	Low
Brown et al., 2013	RCT	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Brunner et al., 2005	CBA	NA	NA	Low	Low	Low	Low	Low	Low
Buss et al., 2004	RCT	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Low
Groch et al., 2013	RCT	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low
Hájek et al., 2006	CBA	NA	NA	Low	Low	Low	Unclear	Low	Low
Henckens et al., 2011	RCT	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Keenan et al., 1996	Cohort	NA	NA	Low	Low	Low	Unclear	Low	Low
Kuhlmann et al., 2005	RCT	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Montero-López et al., 2016	CC	NA	NA	Unclear	High	Low	Unclear	Low	Low
Naber et al., 1996	CBA	NA	NA	Low	Unclear	Low	Unclear	Low	Low
Newcomer et al., 1994	RCT	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Newcomer et al., 1999	RCT	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Otte et al., 2015	RCT	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low
Schlosser et al., 2010	RCT	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Terfehr et al., 2011	RCT	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low
Vaz et al., 2011	RCT	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low
Wingenfeld et al., 2011	RCT	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low
Wolf et al., 2001	RCT	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low
Young et al., 1999	RCT	Unclear	Unclear	Low	Low	Low	Low	Low	Low

CBA, controlled before and after study; CC, Case Controlled; NA, not applicable; RCT, randomised controlled trial

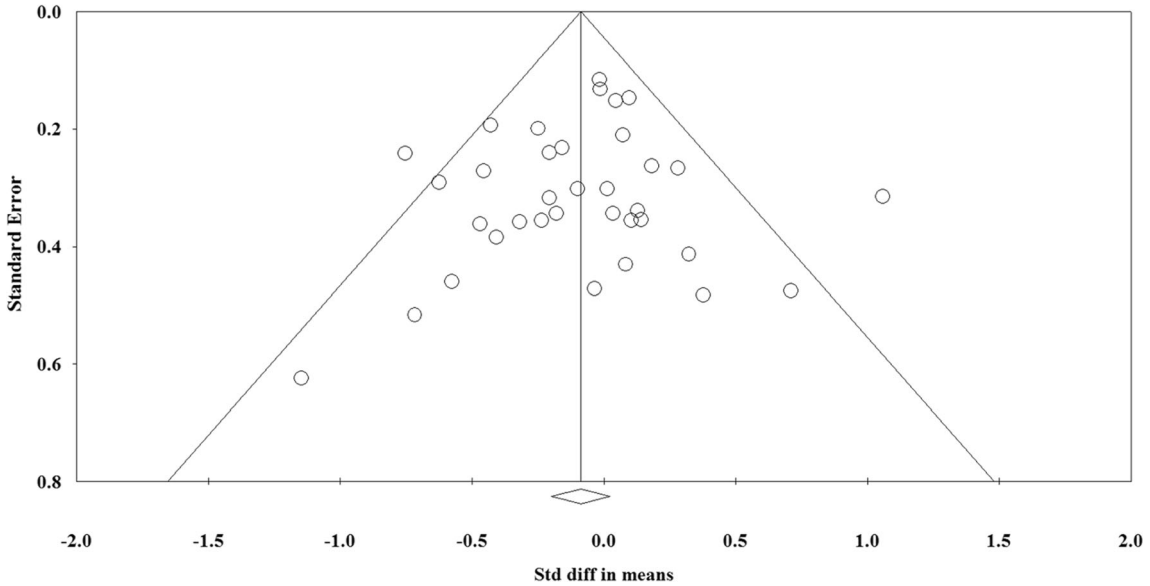

Fig. 11 Funnel plot of all studies. *Note*: Std Diff, standardised difference

been associated with functional changes in several related brain regions including decreased activity in the hippocampus and reduced cerebral blood flow in the posterior medial temporal lobe (De Quervain et al., 2003; Ganguli, Singh, Brar, Carter, & Mintun, 2002; Judd et al., 2014).

In contrast to the negative effects on recent and long term memory, the current data revealed no significant relationships between immediate memory and corticosteroid use. This finding may potentially be related to the two corticosteroid receptor systems, and the way in which these systems interact during memory formation. Although glucocorticoid receptors (GR) have been reported to be generally inactive during the acquisition phase of learning, these receptors promote the effects of corticosteroids on memory consolidation (Ferguson & Sapolsky, 2007; Lupien & McEwen, 1997). Conversely, high affinity mineralocorticoid receptors (MR) are thought to be related to the initial phase of memory encoding (de Kloet, Oitzl, & Joëls, 1999). Given that MR and GR have disparate affinity for corticosteroids, differential involvement of these receptors may underlie the disparate findings across measures of immediate, recent and very long term memory (Schaaf, De Kloet, & Vreugdenhil, 2000). Furthermore, previous research has indicated that corticosteroids influence memory processing in an inverted U-shaped relationship (Lupien & McEwen, 1997), with both low and high doses impairing memory consolidation, while moderate levels may improve consolidation (Roozendaal, 2000). Overall, while the current findings tend to support the theory that glucocorticoids can potentially impair recent memory, more research is required to better elucidate the mechanism of actions on the different aspects of memory formation (Jameison & Dinan, 2001).

A single positive effect was found for expressive language for short term users. Little research to date has specifically investigated the effects of corticosteroid use on language, and given the small number of studies included in the current analysis that examined this domain, the results should be interpreted with caution. However, there are some case reports of corticosteroids improving language function in children who are treated with the drugs in the context of progressive epileptic encephalopathies (Sinclair & Snyder, 2005), as well as reports of corticosteroids improving language function in children with pervasive developmental disorder (Stefanatos, Grover, & Geller, 1995). Further investigation of the mechanisms behind these effects is warranted to clarify the current findings.

Corticosteroids were not found to have any significant effects on divided attention, processing speed, sustained attention, or working memory. While researchers have found negative effects of corticosteroids in these domains (Lupien et al., 1999; Vaz et al., 2011), the effect sizes tend to be small and/or the studies employed small samples; furthermore contrasting findings of positive effects also exist (Henckens et al., 2011). Thus, although the current data suggest that corticosteroids do not influence these domains of cognition, further research that robustly investigates these areas of functioning is worthwhile to clarify the current findings.

The current data did not reveal a clear time dependent relationship between corticosteroid use and cognitive deficits. Although significant negative effects were found in several cognitive domains, there was no clear differentiation of effects across duration of use. However, these results should be interpreted with caution given the small number of studies available for inclusion per duration subgroup in some domains. This restricted breadth of data for some cognitive domains means that it is difficult to draw definitive conclusions regarding potential time dependent differences. Further

research that directly compares the cognitive effects of corticosteroids over time, particularly in short term and chronic users, would be of value.

Moderator analyses did not reveal study year or participant health status (healthy versus clinical groups) to be significantly related to the overall effect of corticosteroids on cognition. Similarly, meta-regression did not reveal age to be significantly related to the overall effect of corticosteroids on cognition. While these results appear to suggest that corticosteroids affect cognition similarly across ages, it remains possible that age and dose related factors may impact the relationship between corticosteroids and cognition at an individual level. It should be noted that the meta-regression technique applied to the current data is observational in nature and has been used to relate the SMD to an *averaged* characteristic (i.e., mean age per study) rather than individual level participant data, and as such may be impacted by ecological bias. That is, as noted by Petkova, Tarpey, Huang, and Deng (2013), the relationship between the SMD and mean age may not be equal to the relationship between the outcome and the covariate in the individual studies.

Meta regression indicated that drug dose was not significantly related to the overall effect of corticosteroids on cognition. This finding is surprising, given that medications with cognitive side effects are frequently demonstrated to influence cognitive functioning in a dose-dependent manner (Federico et al., 2017; Mula, 2012; Newcomer et al., 1999; Warrington & Bostwick, 2006). This finding is also inconsistent with previous research which has demonstrated the dose-dependent effect of corticosteroids on a range of neuropsychiatric outcomes, including psychiatric symptoms (Brown & Chandler, 2001), working memory function (Lupien et al., 1999), associative learning (Brown, 2009) and memory (Beckwith et al., 1986). It is possible that the studies included in the current analysis did not include sufficient breadth of data to adequately compare dose-dependent effects on cognition, particularly at low versus high doses. In addition, several included studies did not clearly state the drug dose that was administered to participants, or administered a dose that varied between participants, further limiting the dose data available for interrogation. Additional research investigating the dose-dependent effects of corticosteroids on cognitive functioning would be worthwhile to clarify these findings.

Pragmatically, the current findings suggest that clinicians and patients who require treatment with corticosteroids should not be overly concerned that such treatment will necessarily result in severe cognitive difficulties, particularly since there is strong evidence to suggest that cognitive side effects of corticosteroids remit once treatment is ceased (Kenna, Poon, de los Angeles, & Koran, 2011; Oliveri et al., 1998). When considering the way in which corticosteroid use may influence performance in a neuropsychological assessment setting, the results from the current meta-analysis suggest that it would be pertinent for clinicians to enquire as to an individual's use of corticosteroids, and consider this in the context of poor memory, and to a lesser extent executive function, performance. With that said, based on the magnitude of the effect sizes found in the analysis, in general, the use of corticosteroid medication is unlikely to lead to erroneous diagnostic conclusions of cognitive impairment as a consequence of appropriate therapeutic use of such drugs. Of note however, the current findings are based on group data and when formulating opinion at the individual patient level the integration of multiple factors that modulate medication-induced neurocognitive effects, such as dose, chronicity of treatment, tolerance, age, interactions with other medications, and other medical history for the individual patient is important (Stein & Strickland, 1998).

Limitations

There are several limitations of this meta-analysis that should be noted when considering the findings. Although a moderator analysis was conducted using the available data which revealed that drug dose was not significantly related to the overall effect of corticosteroids on cognition, further detailed investigation of this relationship is warranted to further explore and clarify this finding. Also, the results from a range of studies with differing methodologies were pooled. While it is acknowledged that the 'gold standard' of research is considered to be RCTs, there is currently insufficient literature of this type to allow for detailed consideration of the effects of corticosteroids on individual cognitive domains. Furthermore, a sensitivity analysis which investigated the different types of study designs included in the current analysis did not reveal significantly different results between study types. Also, although the current analysis was able to investigate several different domains of cognition, in the case of executive function (for short term and chronic users), expressive language (for acute users) and working memory (for chronic users) there was only one study that contributed data to one subgroup based on duration of use. Further investigation of these domains would be worthwhile to generate sufficient data to enable calculation of a pooled effect. In addition, many studies were denoted as having an 'unclear' risk of bias for several categories (see Table 3). This was mostly due to a lack of detailed explanation regarding methodology in the published papers, particularly regarding sequence generation and concealment. This highlights the need for future researchers to clearly detail study procedures to allow a comprehensive risk of bias to be carried out.

Another limitation relates to the various cognitive tests that were used to assess each cognitive domain. This is a common problem when attempting to pool data on cognition due to the lack of a standard, widely administered testing protocol. Nevertheless, stringent inclusion criteria were employed

which carefully considered the psychometric properties and standardised administration of tests used in potential studies. This was intended to increase the validity of the pooled effects for each cognitive domain. Furthermore, while the allocation of tests to cognitive domains were carefully considered and based on relevant sources, many of the included tests require a range of cognitive functions to be recruited in order to successfully undertake the task. Also, there remains a lack of consensus in the literature regarding the underlying constructs some neuropsychological tests measure, which results in differences in classification of some tests (Chaytor & Schmitter-Edgecombe, 2003). As such, it is plausible that the categorisation of tests to alternative cognitive domains may impact the current findings.

Moderate heterogeneity was identified when pooling the effects for executive function, expressive language and recent memory. This may have been caused by the pooling of studies that employed different methodologies, used different types of corticosteroid drugs, and included studies with different durations of treatment as shown in Table 2. However, this heterogeneity was explored using moderation, regression and sensitivity analyses in an attempt to clarify the extent that these variables may have impacted upon the current findings. Lastly, several closely related pharmacological agents were used in the included studies, however previous research has demonstrated that these have comparable effects. For example when Cortisol and Dexamethasone were administered in identical experimental designs, similar results were found for both agents (Newcomer et al., 1994; Newcomer et al., 1999).

Conclusions

The current meta-analysis investigated the effects of corticosteroids on various domains of cognitive functioning. Results revealed that corticosteroids have a modest, negative effect on executive function for acute users, recent memory for short term and chronic users, and very long term memory for acute users. Corticosteroids had a significant positive effect on expressive language for short term users.

Compliance with Ethical Standards

Conflict of Interest None.

References

Abercrombie, H. C., Kalin, N. H., Thurow, M. E., Rosenkranz, M. A., & Davidson, R. J. (2003). Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behavioral Neuroscience, 117*, 505–516. https://doi.org/10.1037/0735-7044.117.3.505

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Ancelin, M.-L., Carrière, I., Helmer, C., Rouaud, O., Pasquier, F., Berr, C., … Ritchie, K. (2012). Steroid and nonsteroidal anti-inflammatory drugs, cognitive decline, and dementia. *Neurobiology of Aging, 33*, 2082–2090. https://doi.org/10.1016/j.neurobiolaging.2011.09.038

Australian Bureau of Statistics. (2012). Profiles of Health, Australia, 2011–13, viewed 17/01/19, www.abs.gov.au/ausstats/abs@.nsf/lookup/4338.0main+features212011-13. Accessed 17 Jan 2019

Barnes, P. J., & Pedersen, S. (1993). Efficacy and safety of inhaled corticosteroids in asthma. *American Review of Respiratory Disease, 148,* 1-26. DOI:Org/https://doi.org/10.1164/ajrccm/148.4_Pt_2.S1

Beckwith, B. E., Petros, T. V., Scaglione, C., & Nelson, J. (1986). Dose-dependent effects of hydrocortisone on memory in human males. *Physiology & Behavior, 36*, 283–286. https://doi.org/10.1016/0031-9384(86)90017-X

Belanoff, J. K., Gross, K., Yager, A., & Schatzberg, A. F. (2001). Corticosteroids and cognition. *Journal of Psychiatric Research, 35*, 127–145. https://doi.org/10.1016/S0022-3956(01)00018-8

Bender, B., Lerner, J., & Poland, J. (1991). Association between corticosteroids and psychologic change in hospitalized asthmatic children. *Annals of Allergy, 66*, 414–419.

Bhangle, S. D., Kramer, N., & Rosenstein, E. D. (2013). Corticosteroid-induced neuropsychiatric disorders: Review and contrast with neuropsychiatric lupus. *Rheumatology International, 33*, 1923–1932. https://doi.org/10.1007/s00296-013-2750-z

Borenstein, M., Hedges, L. V., Higgins, J., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods, 1*, 97–111. https://doi.org/10.1002/jrsm.12

Breitberg, A., Drevets, W. C., Wood, S. E., Mah, L., Schulkin, J., Sahakian, B. J., & Erickson, K. (2013). Hydrocortisone infusion exerts dose-and sex-dependent effects on attention to emotional stimuli. *Brain and Cognition, 81*, 247–255. https://doi.org/10.1016/j.bandc.2012.10.010

Bremner, J. D., Vythilingam, M., Vermetten, E., Afzal, N., Nazeer, A., Newcomer, J. W., & Charney, D. S. (2004). Effects of dexamethasone on declarative memory function in posttraumatic stress disorder. *Psychiatry Research, 129*, 1–10. https://doi.org/10.1016/j.psychres.2004.08.004

Brown, E. S. (2009). Effects of glucocorticoids on mood, memory, and the hippocampus. *Annals of the New York Academy of Sciences, 1179*, 41–55. https://doi.org/10.1111/j.1749-6632.2009.04981.x

Brown, E. S., Beard, L., Frol, A. B., & Rush, A. J. (2006). Effect of two prednisone exposures on mood and declarative memory. *Neurobiology of Learning and Memory, 86*, 28–34. https://doi.org/10.1016/j.nlm.2005.12.009

Brown, E. S., & Chandler, P. A. (2001). Mood and cognitive changes during systemic corticosteroid therapy. *Primary Care Companion to the Journal of Clinical Psychiatry, 3*, 17–21.

Brown, E. S., Jeon-Slaughter, H., Lu, H., Jamadar, R., Issac, S., Shad, M., … Thomas, B. P. (2015). Hippocampal volume in healthy controls given 3-day stress doses of hydrocortisone. *Neuropsychopharmacology, 40*, 1216. https://doi.org/10.1038/npp.2014.307

Brown, E. S., Khan, D. A., & Nejtek, V. A. (1999). The psychiatric side effects of corticosteroids. *Annals of Allergy, Asthma & Immunology, 83*, 495–504. https://doi.org/10.1016/S1081-1206(10)62858-X

Brown, E. S., Lu, H., Denniston, D., Uh, J., Thomas, B. P., Carmody, T. J., … Tamminga, C. (2013). A randomized, placebo-controlled proof-of-concept, crossover trial of phenytoin for hydrocortisone-induced declarative memory changes. *Journal of Affective Disorders, 150*, 551–558. https://doi.org/10.1016/j.jad.2013.01.038

Brown, E. S., Vera, E., Frol, A. B., Woolston, D. J., & Johnson, B. (2007). Effects of chronic prednisone therapy on mood and memory.

Journal of Affective Disorders, 99, 279–283. https://doi.org/10.1016/j.jad.2006.09.004

Brown, E. S., Woolston, D. J., Frol, A., Bobadilla, L., Khan, D. A., Hanczyc, M., … Cullum, C. M. (2004). Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. *Biological Psychiatry, 55*, 538–545. https://doi.org/10.1016/j.biopsych.2003.09.010

Brunner, R., Schaefer, D., Hess, K., Parzer, P., Resch, F., & Schwab, S. (2005). Effect of corticosteroids on short-term and long-term memory. *Neurology, 64*, 335–337. https://doi.org/10.1212/01.WNL.0000149523.35039.4C

Buchanan, T. W., & Lovallo, W. R. (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology, 26*, 307–317. https://doi.org/10.1016/S0306-4530(00)00058-5

Buss, C., Wolf, O. T., Witt, J., & Hellhammer, D. H. (2004). Autobiographic memory impairment following acute cortisol administration. *Psychoneuroendocrinology, 29*, 1093–1096. DOI: Org/https://doi.org/10.1016/j.psyneuen.2003.09.006

Cameron, C., Fireman, B., Hutton, B., Clifford, T., Coyle, D., Wells, G., … Toh, S. (2015). Network meta-analysis incorporating randomized controlled trials and non-randomized comparative cohort studies for assessing the safety and effectiveness of medical treatments: Challenges and opportunities. *Systematic Reviews, 4*, 147. https://doi.org/10.1186/s13643-015-0133-0

Chaytor, N., & Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological tests: A review of the literature on everyday cognitive skills. *Neuropsychology Review, 13*, 181–197. https://doi.org/10.1023/B:NERV.0000009483.91468.fb

Cottrell, G., & Nakajima, S. (1977). Effect of corticosteroids in the hippocampus on passive avoidance behavior in the rat. *Pharmacology Biochemistry and Behavior, 7*, 277–280. https://doi.org/10.1016/0091-3057(77)90146-0

Daffner, K. R., Gale, S. A., Barrett, A., Boeve, B. F., Chatterjee, A., Coslett, H. B., … Hart, J. J. (2015). Improving clinical cognitive testing report of the AAN behavioral neurology section workgroup. *Neurology, 85*, 910–918. https://doi.org/10.1212/WNL.0000000000001763

de Kloet, E. R. (1991). Brain corticosteroid receptor balance and homeostatic control. *Frontiers of Neuroendocrinology, 12*, 95–164.

de Kloet, E. R., Oitzl, M. S., & Joëls, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends in Neurosciences, 22*, 422–426. https://doi.org/10.1016/S0166-2236(99)01438-1

de Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joels, M. (1998). Brain corticosteroid receptor balance in health and disease. *Endocrine Reviews, 19*, 269–301.

de Quervain, D. J. F., Henke, K., Aerni, A., Treyer, V., McGaugh, J. L., Berthold, T., … Hock, C. (2003). Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. *European Journal of Neuroscience, 17*, 1296–1302. https://doi.org/10.1046/j.1460-9568.2003.02542.x

Denburg, S. D., Carbotte, R. M., & Denburg, J. A. (1994). Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. *Arthritis & Rheumatology, 37*, 1311–1320. https://doi.org/10.1002/art.1780370907

Effective Practice and Organisation of Care (EPOC) (2015) Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors. Oslo: Norwegian Knowledge Centre for the Health Services. Available at: http://epoc.cochrane.org/epoc-specific-resources-review-authors

Faber, T., Ravaud, P., Riveros, C., Perrodeau, E., & Dechartres, A. (2016). Meta-analyses including non-randomized studies of therapeutic interventions: A methodological review. *BMC Medical Research Methodology, 16*, 35. https://doi.org/10.1186/s12874-016-0136-0

Federico, A., Tamburin, S., Maier, A., Faccini, M., Casari, R., Morbioli, L., & Lugoboni, F. (2017). Multifocal cognitive dysfunction in high-dose benzodiazepine users: A cross-sectional study. *Neurological Sciences, 38*, 137–142. https://doi.org/10.1007/s10072-016-2732-5

Fehm-Wolfsdorf, G., Soherr, U., Arndt, R., Kern, W., Fehm, H. L., & Nagel, D. (1993). Auditory reflex thresholds elevated by stress-induced cortisol secretion. *Psychoneuroendocrinology, 18*, 579–589. https://doi.org/10.1016/0306-4530(93)90035-J

Ferguson, D., & Sapolsky, R. (2007). Mineralocorticoid receptor overexpression differentially modulates specific phases of spatial and non-spatial memory. *Journal of Neuroscience, 27*, 8046–8052. https://doi.org/10.1523/JNEUROSCI.1187-07.2007

Follmann, D., Elliott, P., Suh, I., & Cutler, J. (1992). Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology, 45*, 769–773. https://doi.org/10.1016/0895-4356(92)90054-Q

Freyne, A. (2005). Neuropsychiatric complications of corticosteroids in older people. *Irish Journal of Psychological Medicine, 22*, 22–25. https://doi.org/10.1017/S0790966700008752

Ganguli, R., Singh, A., Brar, J., Carter, C., & Mintun, M. (2002). Hydrocortisone induced regional cerebral activity changes in schizophrenia: A PET scan study. *Schizophrenia Research, 56*, 241–247. https://doi.org/10.1016/S0920-9964(01)00219-5

Gil, T., Calev, A., Greenberg, D., Kugelmass, S., & Lerer, B. (1990). Cognitive functioning in Post-Traumatic Stress Disorder. *Journal of Traumatic Stress, 3*(1), 29–45. https://doi.org/10.1002/jts.2490030104

Groch, S., Wilhelm, I., Lange, T., & Born, J. (2013). Differential contribution of mineralocorticoid and glucocorticoid receptors to memory formation during sleep. *Psychoneuroendocrinology, 38*, 2962–2972. https://doi.org/10.1016/j.psyneuen.2013.08.006

Hájek, T., Kopeček, M., Preiss, M., Alda, M., & Höschl, C. (2006). Prospective study of hippocampal volume and function in human subjects treated with corticosteroids. *European Psychiatry, 21*, 123–128. https://doi.org/10.1016/j.eurpsy.2005.01.005

Hall, R. C., Popkin, M. K., Stickney, S. K., & Gardner, E. R. (1979). Presentation of the steroid psychoses. *Journal of Nervous and Mental Disease*, *167*, 229–236. https://doi.org/10.1097/00005053-197904000-00006

Harvey, S. T., & Taylor, J. E. (2010). A meta-analysis of the effects of psychotherapy with sexually abused children and adolescents. *Clinical Psychology Review, 30*, 517–535. https://doi.org/10.1016/j.cpr.2010.03.006

Henckens, M. J., van Wingen, G. A., Joëls, M., & Fernández, G. (2011). Time-dependent corticosteroid modulation of prefrontal working memory processing. *Proceedings of the National Academy of Sciences, 108*, 5801–5806. https://doi.org/10.1073/pnas.1019128108

Het, S., Ramlow, G., & Wolf, O. (2005). A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology, 30*, 771–784. https://doi.org/10.1016/j.psyneuen.2005.03.005

Higgin, J., Thompson, S., Deeks, J., & Altman, D. (2003). Measuring inconsistency in meta-analysis. *British Medical Journal, 327*, 557–560. https://doi.org/10.1136/bmj.327.7414.557

Higgins, J. P., & Green, S. (2011). *Cochrane handbook for systematic reviews of interventions* (Vol. 4). John Wiley & Sons.

Jameison, K., & Dinan, T. G. (2001). Glucocorticoids and cognitive function: From physiology to pathophysiology. *Human Psychopharmacology: Clinical and Experimental, 16*, 293–302. https://doi.org/10.1002/hup.304

Joëls, M., Pu, Z., Wiegert, O., Oitzl, M. S., & Krugers, H. J. (2006). Learning under stress: How does it work? *Trends in Cognitive Sciences, 10*, 152–158. https://doi.org/10.1016/j.tics.2006.02.002

Judd, L. L., Schettler, P. J., Brown, E. S., Wolkowitz, O. M., Sternberg, E. M., Bender, B. G., … Fardet, L. (2014). Adverse consequences of glucocorticoid medication: Psychological, cognitive, and behavioral effects. *American Journal of Psychiatry, 171*, 1045–1051. https://doi.org/10.1176/appi.ajp.2014.13091264

Keenan, P., Jacobson, M., Soleymani, R., Mayes, M., & Yaldoo, D. (1996). The effect on memory of chronic prednisone treatment in patients with systemic disease. *Neurology, 47*, 1396-1402. https://doi.org/10.1212/WNL.47.6.1396

Keenan, P., Jacobson, M., Soleymani, R., & Newcomer, J. (1995). Commonly used therapeutic doses of glucocorticoids impair explicit memory. *Annals of the New York Academy of Sciences, 761*, 400–402. https://doi.org/10.1111/j.1749-6632.1995.tb31402.x

Kenna, H. A., Poon, A. W., de los Angeles, C. P., & Koran, L. M. (2011). Psychiatric complications of treatment with corticosteroids: Review with case report. *Psychiatry and Clinical Neurosciences, 65*, 549–560. DOI:org/https://doi.org/10.1111/j.1440-1819.2011.02260.x

Kirschbaum, C., Wolf, O. T., May, M., Wippich, W., & Hellhammer, D. H. (1996). Stress-and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sciences, 58*, 1475–1483. https://doi.org/10.1016/0024-3205(96)00118-X

Kuhlmann, S., Kirschbaum, C., & Wolf, O. T. (2005). Effects of oral cortisol treatment in healthy young women on memory retrieval of negative and neutral words. *Neurobiology of Learning and Memory*, 158–183, 162. https://doi.org/10.1016/j.nlm.2004.09.001

Kusljic, S., Manias, E., & Gogos, A. (2016). Corticosteroid-induced psychiatric disturbances: It is time for pharmacists to take notice. *Research in Social and Administrative Pharmacy*, *12*, 355–360. https://doi.org/10.1016/j.sapharm.2015.05.012

Lau, J., Ioannidis, J. P., & Schmid, C. H. (1998). Summing up evidence: One answer is not always enough. *The Lancet, 351*, 123–127. https://doi.org/10.1016/S0140-6736(97)08468-7

Lezak, M., Howieson, D., Bigler, E., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). New York, NY: Oxford University Press.

Ling, M. H., Perry, P. J., & Tsuang, M. T. (1981). Side effects of corticosteroid therapy: Psychiatric aspects. *Archives of General Psychiatry, 38*, 471–477. https://doi.org/10.1001/archpsyc.1981.01780290105011

Liu, D., Ahmet, A., Ward, L., Krishnamoorthy, P., Mandelcorn, E. D., Leigh, R., … Kim, H. (2013). A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy, Asthma & Clinical Immunology, 9*, –30. https://doi.org/10.1186/1710-1492-9-30

Lupien, S. J., Gillin, C. J., & Hauger, R. L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose–response study in humans. *Behavioral Neuroscience, 113*, 420–430.

Lupien, S. J., & McEwen, B. S. (1997). The acute effects of corticosteroids on cognition: Integration of animal and human model studies. *Brain Research Reviews, 24*, 1–27. https://doi.org/10.1016/S0165-0173(97)00004-0

Lupien, S. J., Wilkinson, C. W., Brière, S., Ménard, C., Kin, N. N. Y., & Nair, N. (2002). The modulatory effects of corticosteroids on cognition: Studies in young human populations. *Psychoneuroendocrinology, 27*, 401–416.

McEwen, B. S. (2006). Protective and damaging effects of stress mediators: Central role of the brain. *Dialogues in Clinical Neuroscience, 8*, 367–381.

Meieran, S. E., Reus, V. I., Webster, R., Shafton, R., & Wolkowitz, O. M. (2004). Chronic pregnenolone effects in normal humans: Attenuation of benzodiazepine-induced sedation. *Psychoneuroendocrinology, 29*, 486–500. https://doi.org/10.1016/S0306-4530(03)00056-8

Meikle, A. W., & Tyler, F. H. (1977). Potency and duration of action of glucocorticoids: Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. *The American Journal of Medicine, 63*, 200–207. https://doi.org/10.1016/0002-9343(77)90233-9

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Montero-López, E., Santos-Ruiz, A., Navarrete-Navarrete, N., Ortego-Centeno, N., Pérez-García, M., & Peralta-Ramírez, M. I. (2016). The effects of corticosteroids on cognitive flexibility and decision-making in women with lupus. *Lupus, 25*, 1470–1478. https://doi.org/10.1177/0961203316642313

Mula, M. (2012). Topiramate and cognitive impairment: Evidence and clinical implications. *Therapeutic Advances in Drug Safety, 3*, 279–289. https://doi.org/10.1177/2042098612455357

Naber, D., Sand, P., & Heigl, B. (1996). Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. *Psychoneuroendocrinology, 21*, 25–31. https://doi.org/10.1016/0306-4530(95)00031-3

Newcomer, J. W., Craft, S., Hershey, T. E., Askins, K., & Bardgett, M. (1994). Glucocorticoid-induced impairment in declarative memory performance in adult humans. *Journal of Neuroscience, 14*, 2047–2053. https://doi.org/10.1523/JNEUROSCI.14-04-02047.1994

Newcomer, J. W., Selke, G., Melson, A. K., Hershey, T., Craft, S., Richards, K., & Alderson, A. L. (1999). Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of General Psychiatry, 56*, 527–533. https://doi.org/10.1001/pubs.Archgenpsychiatry-ISSN-0003-990x-56-6-yoa8291

Oliveri, R., Sibilia, G., Valentino, P., Russo, C., Romeo, N., & Quattrone, A. (1998). Pulsed methylprednisolone induces a reversible impairment of memory in patients with relapsing-remitting multiple sclerosis. *Acta Neurologica Scandinavica, 97*, 366–369. https://doi.org/10.1111/j.1600-0404.1998.tb05967.x

Otte, C., Wingenfeld, K., Kuehl, L. K., Kaczmarczyk, M., Richter, S., Quante, A., … Wiedemann, K. (2015). Mineralocorticoid receptor stimulation improves cognitive function and decreases cortisol secretion in depressed patients and healthy individuals. *Neuropsychopharmacology, 40*, 386–393. https://doi.org/10.1038/npp.2014.181

Peinemann, F., Tushabe, D. A., & Kleijnen, J. (2013). Using multiple types of studies in systematic reviews of health care interventions–a systematic review. *PLoS One, 8*, e85035. https://doi.org/10.1371/journal.pone.0085035

Petkova, E., Tarpey, T., Huang, L., & Deng, L. (2013). Interpreting meta-regression: Application to recent controversies in antidepressants' efficacy. *Statistics in Medicine, 32*, 2875–2892. https://doi.org/10.1002/sim.5766

Prado, C. E., Watt, S., & Crowe, S. F. (2018). A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples, 1–*Neuropsychology Review*, 41. https://doi.org/10.1007/s11065-018-9369-5

Rock, P., Roiser, J., Riedel, W., & Blackwell, A. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine, 44*, 2029. https://doi.org/10.1017/S0033291713002535

Rome, H. P., & Braceland, F. J. (1952). The psychological response to ACTH, cortisone, hydrocortisone, and related steroid substances. *American Journal of Psychiatry, 108*, 641–651. https://doi.org/10.1176/ajp.108.9.641

Roozendaal, B. (2000). Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology, 25*, 213–238. https://doi.org/10.1016/S0306-4530(99)00058-X

Sandi, C., Loscertales, M., & Guaza, C. (1997). Experience-dependent facilitating effect of corticosterone on spatial memory formation in the water maze. *European Journal of Neuroscience, 9*, 637–642. https://doi.org/10.1111/j.1460-9568.1997.tb01412.x

Sandi, C., & Rose, S. P. (1994). Corticosterone enhances long-term retention in one-day-old chicks trained in a weak passive avoidance learning paradigm. *Brain Research, 647*, 106–112. https://doi.org/10.1016/0006-8993(94)91404-4

Sapolsky, R. M., Krey, L. C., & McEwen, B. (1985). Prolonged glucocorticoid exposure reduces hippocampal neuron number: Implications for aging. *Journal of Neuroscience, 5*, 1222–1227. https://doi.org/10.1523/JNEUROSCI.05-05-01222.1985

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (2002). The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. *Science's SAGE KE, 2002*, 21 sageke.sciencemag.org/cgi/content/abstract/sageke;2002/38/cp21

Sapolsky, R. M., Uno, H., Rebert, C. S., & Finch, C. E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience, 10*, 2897–2902. https://doi.org/10.1523/JNEUROSCI.10-09-02897.1990

Schaaf, M., De Kloet, E., & Vreugdenhil, E. (2000). Corticosterone effects on BDNF expression in the hippocampus implications for memory formation. *Stress, 3*, 201–208. https://doi.org/10.3109/10253890009001124

Scheel, M., Ströhle, A., & Bruhn, H. (2010). Effects of short-term stress-like cortisol on cerebral metabolism: A proton magnetic resonance spectroscopy study at 3.0 T. *Journal of Psychiatric Research, 44*, 521–526. DOI:org/https://doi.org/10.1016/j.jpsychires.2009.11.010

Schlosser, N., Wolf, O. T., Fernando, S. C., Riedesel, K., Otte, C., Muhtz, C., … Wingenfeld, K. (2010). Effects of acute cortisol administration on autobiographical memory in patients with major depression and healthy controls. *Psychoneuroendocrinology, 35*, 316–320. https://doi.org/10.1016/j.psyneuen.2009.06.015

Schwabe, L., Schächinger, H., de Kloet, E. R., & Oitzl, M. S. (2010). Corticosteroids operate as a switch between memory systems. *Journal of Cognitive Neuroscience, 22*, 1362–1372. https://doi.org/10.1162/jocn.2009.21278

Shrier, I., Boivin, J.-F., Steele, R. J., Platt, R. W., Furlan, A., Kakuma, R., ... Rossignol, M. (2007). Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *American Journal of Epidemiology, 166*, 1203–1209. https://doi.org/10.1093/aje/kwm189

Sinclair, D. B., & Snyder, T. J. (2005). Corticosteroids for the treatment of Landau-Kleffner syndrome and continuous spike-wave discharge during sleep. *Pediatric Neurology, 32*, 300–306. https://doi.org/10.1016/j.pediatrneurol.2004.12.006

Stefanatos, G. A., Grover, W., & Geller, E. (1995). Case study: Corticosteroid treatment of language regression in pervasive developmental disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 1107–1134, 1111. https://doi.org/10.1097/00004583-199508000-00022

Stein, R. A., & Strickland, T. L. (1998). A review of the neuropsychological effects of commonly used prescription medications. *Archives of Clinical Neuropsychology, 13*, 259–284. https://doi.org/10.1016/S0887-6177(97)00027-9

Strauss, E., Sherman, E. M., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*: American Chemical Society.

Tendal, B., Higgins, J. P., Jüni, P., Hróbjartsson, A., Trelle, S., Nüesch, E., … Ilsøe-Kristensen, S. (2009). Disagreements in meta-analyses using outcomes measured on continuous or rating scales: Observer agreement study. *BMJ, 339*, b3128. https://doi.org/10.1136/bmj.b3128

Terfehr, K., Wolf, O. T., Schlosser, N., Fernando, S. C., Otte, C., Muhtz, C., … Löwe, B. (2011). Effects of acute hydrocortisone administration on declarative memory in patients with major depressive disorder: A placebo-controlled, double-blind crossover study. *Journal Clininical Psychiatry, 72*, 1644–1650.

Tessner, K. D., Walker, E. F., Dhruv, S. H., Hochman, K., & Hamann, S. (2007). The relation of cortisol levels with hippocampus volumes under baseline and challenge conditions. *Brain Research, 1179*, 70–78. https://doi.org/10.1016/j.brainres.2007.05.027

Uno, H., Eisele, S., Sakai, A., Shelton, S., Baker, E., DeJesus, O., & Holden, J. (1994). Neurotoxicity of glucocorticoids in the primate brain. *Hormones and Behavior, 28*, 336–348. https://doi.org/10.1006/hbeh.1994.1030

Uno, H., Tarara, R., Else, J. G., Suleman, M. A., & Sapolsky, R. M. (1989). Hippocampal damage associated with prolonged and fatal stress in primates. *Journal of Neuroscience, 9*, 1705–1711. https://doi.org/10.1523/JNEUROSCI.09-05-01705.1989

Vaz, L. J., Pradella-Hallinan, M., Bueno, O. F. A., & Pompéia, S. (2011). Acute glucocorticoid effects on the multicomponent model of working memory. *Human Psychopharmacology: Clinical and Experimental, 26*, 477–487. https://doi.org/10.1002/hup.1230

Wagner, S., Müller, C., Helmreich, I., Huss, M., & Tadić, A. (2015). A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *European Child & Adolescent Psychiatry, 24*(1), 5–19. https://doi.org/10.1007/s00787-014-0559-2

Waljee, A. K., Rogers, M. A., Lin, P., Singal, A. G., Stein, J. D., Marks, R. M., … Nallamothu, B. K. (2017). Short term use of oral corticosteroids and related harms among adults in the United States: Population based cohort study. *BMJ, 357*, j1415. https://doi.org/10.1136/bmj.j1415

Warrington, T. P., & Bostwick, J. M. (2006). Psychiatric adverse effects of corticosteroids. *Mayo Clinic Proceedings, 81*, 1361–1367. https://doi.org/10.4065/81.10.1361

Webb, R., & Singer, M. (2005). *Oxford handbook of critical care*. New York: Oxford University Press.

Wingenfeld, K., Wolf, S., Krieg, J.-C., & Lautenbacher, S. (2011). Working memory performance and cognitive flexibility after dexamethasone or hydrocortisone administration in healthy volunteers. *Psychopharmacology, 217*, 323–329. https://doi.org/10.1007/s00213-011-2286-4

Wolf, O., Convit, A., McHugh, P., Kandil, E., Thorn, E., De Santi, S., … De Leon, M. (2001). Cortisol differentially affects memory in young and elderly men. *Behavioral Neuroscience, 115*, 1002. https://doi.org/10.1037/0735-7044.115.5.1002

Wolkowitz, O. M., Burke, H., Epel, E. S., & Reus, V. I. (2009). Glucocorticoids. *Annals of the New York Academy of Sciences, 1179*, 19–40. https://doi.org/10.1111/j.1749-6632.2009.04980.x

Wolkowitz, O. M., Lupien, S. J., Bigler, E., Levin, R. B., & Canick, J. (2004). The "steroid dementia syndrome": An unrecognized complication of glucocorticoid treatment. *Annals of the New York Academy of Sciences, 1032*, 191–194. https://doi.org/10.1196/annals.1314.018

Wolkowitz, O. M., Reus, V. I., Canick, J., Levin, B., & Lupien, S. (1997). Glucocorticoid medication, memory and steroid psychosis in medical illness. *Annals of the New York Academy of Sciences, 823*, 81–96.

Wolkowitz, O. M., Reus, V. I., Weingartner, H., Thompson, K., & Breier, A. (1990). Cognitive effects of corticosteroids. *The American Journal of Psychiatry, 147*, 1297–1303.

Young, A., Sahakian, B., Robbins, T., & Cowen, P. (1999). The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology, 145*, 260–266. https://doi.org/10.1007/s002130051057

Young, K. D., & Preskorn, S. H. (2013). Neuroscientific basis of corticosteroid-induced changes in human cognitive and emotional processing: Implications for affective illness. *Journal of Psychiatric Practice, 19*, 309–315. https://doi.org/10.1097/01.pra.0000432601.09514.12